Pre-malignant conditions of the stomach and gastric cancer

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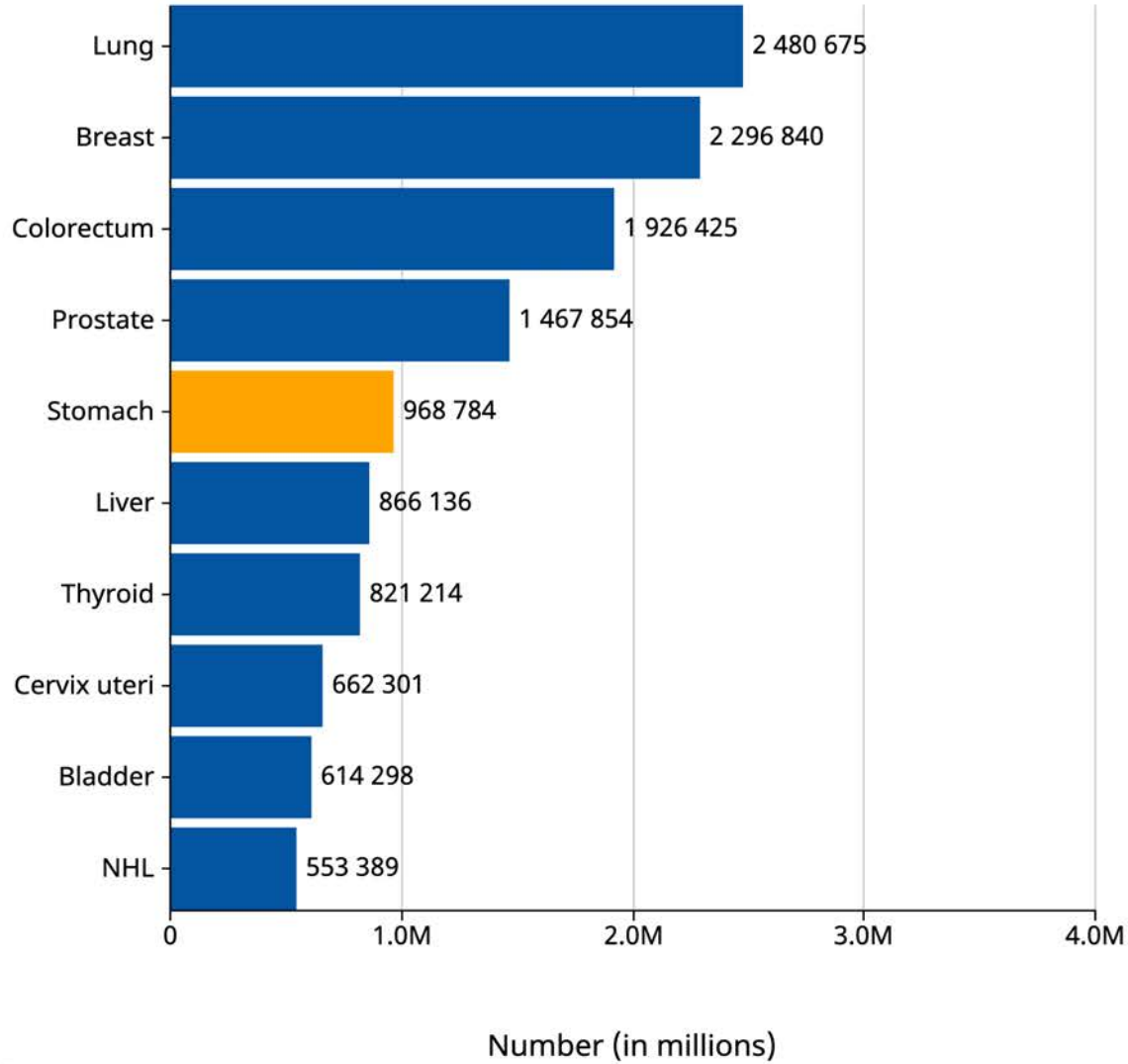
Introduction

- Gastric cancer is one of the most common malignant diseases which has a significant impact on morbidity and mortality
- It has traditionally been associated with poor outcomes and limited therapeutic options by the time patients present
- The fifth leading cause of cancer worldwide with marked geographic variability in incidence

Absolute numbers, Incidence, Both sexes, in 2022
World
(Top 10 cancer sites)



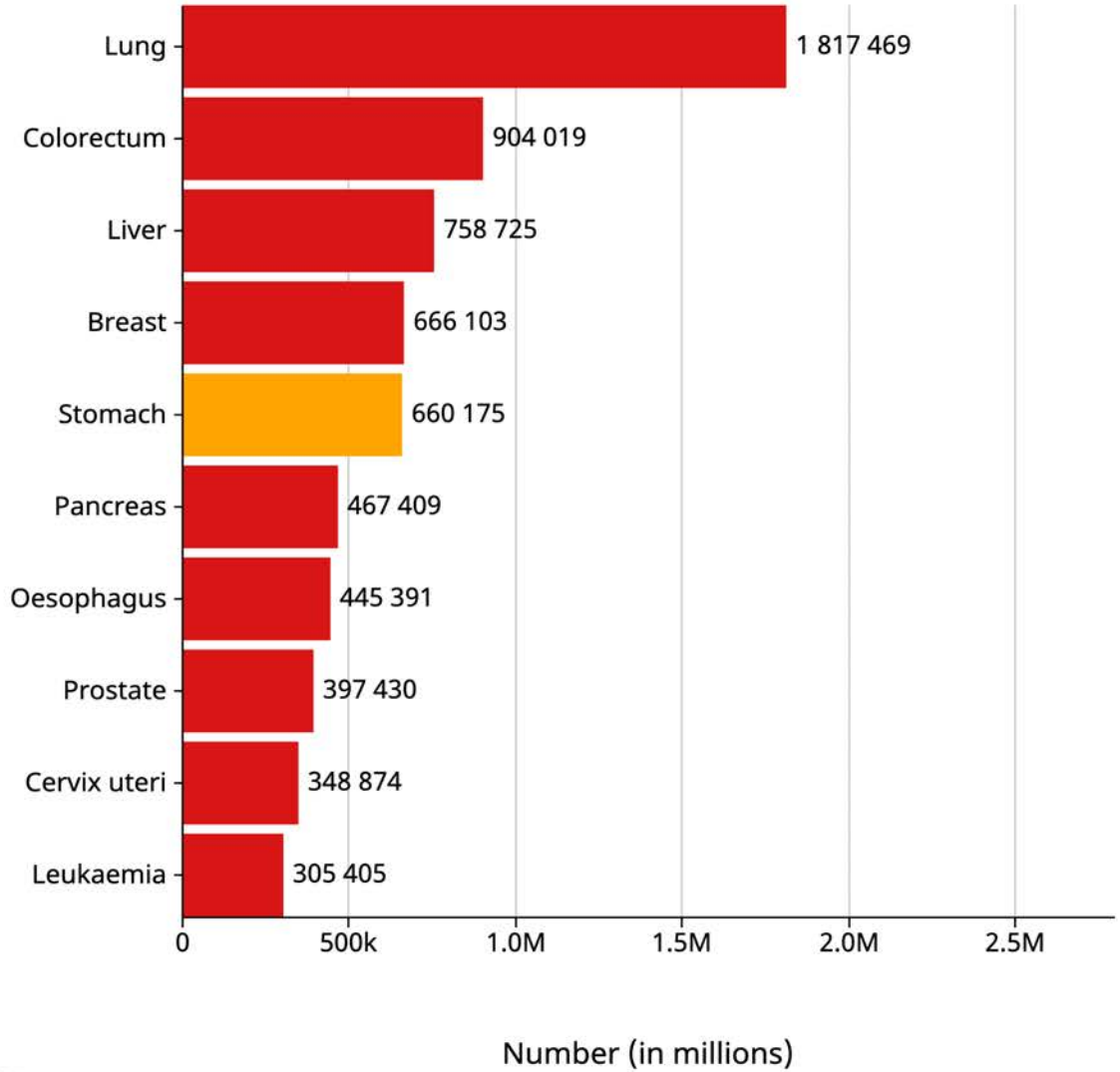
Cancer TODAY | IARC - https://gco.iarc.who.int/today
Data version : Globocan 2022 (version 1.1)

International Agency for Research on Cancer
World Health Organization

Absolute numbers, Mortality, Both sexes, in 2022

World

(Top 10 cancer sites)

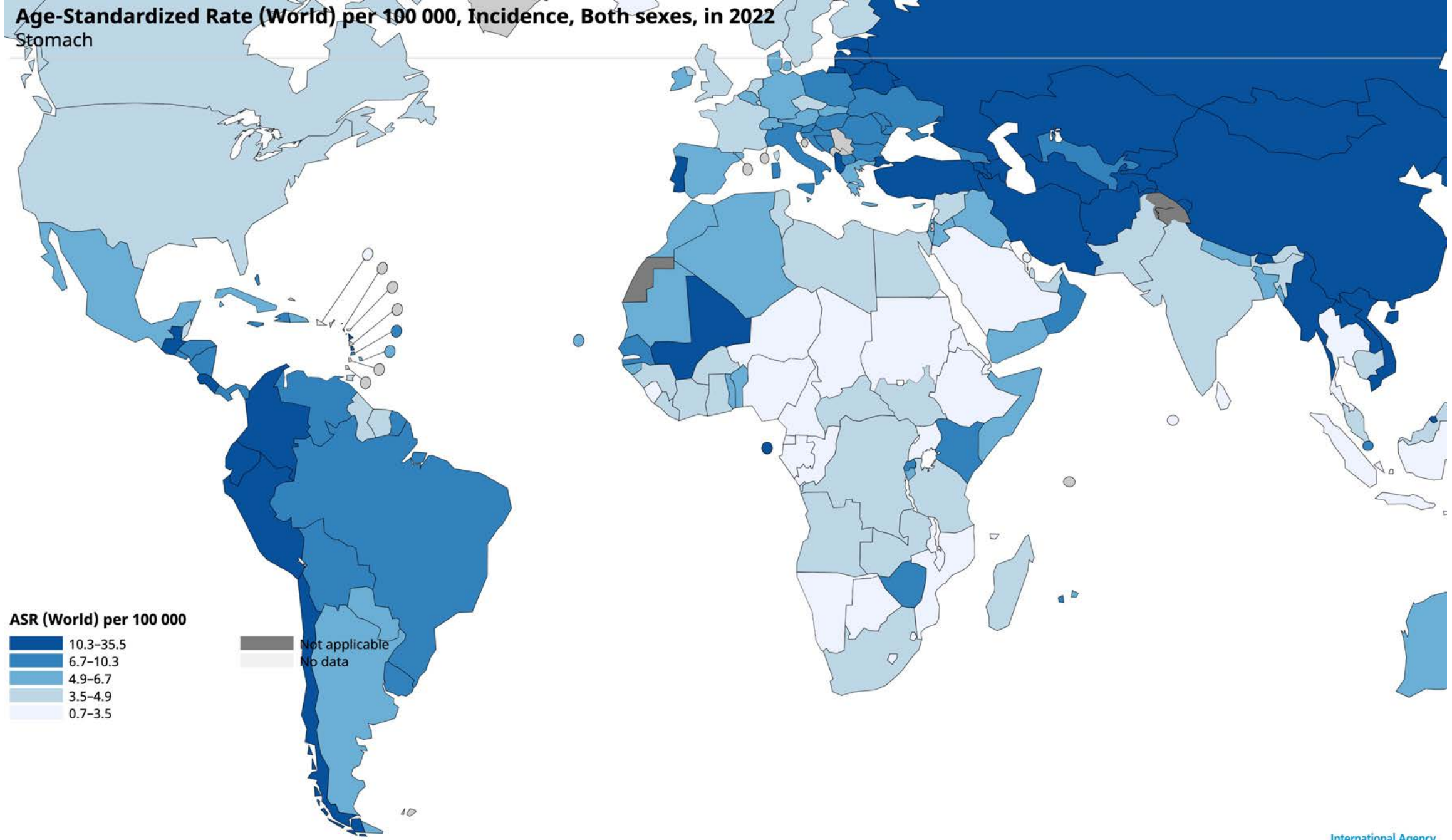


International Agency for Research on Cancer

World Health Organization

Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, in 2022

Stomach



Cancer TODAY | IARC
https://gco.iarc.who.int/today
Data version: Globocan 2022 - 08.02.2024

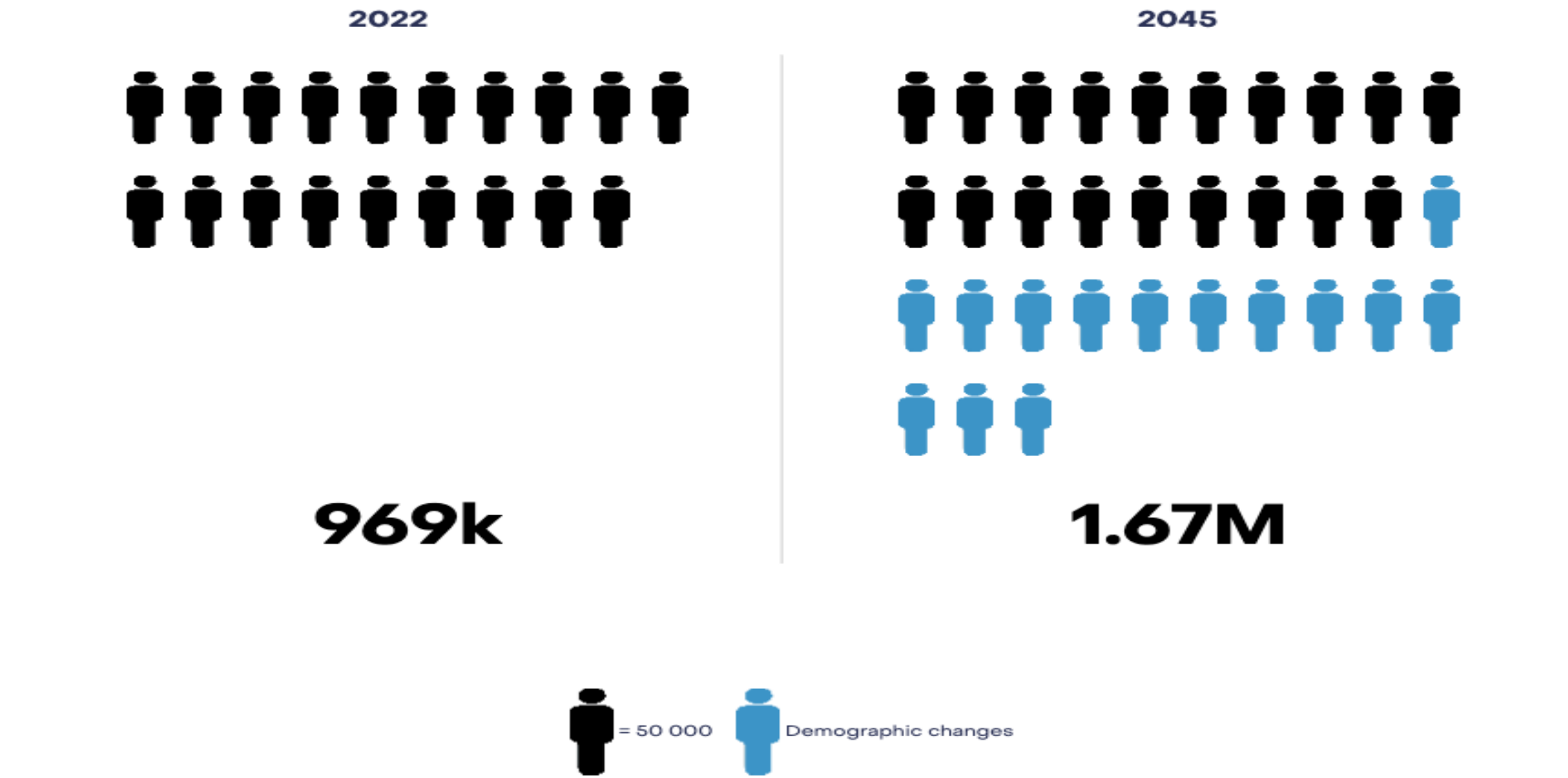
International Agency for Research on Cancer
World Health Organization

Estimated number of new cases from 2022 to 2045, Both sexes, age [0–85+]

Stomach

World

GLOBAL CANCER OBSERVATORY



Cancer Tomorrow | **IARC** – https://gco.iarc.who.int

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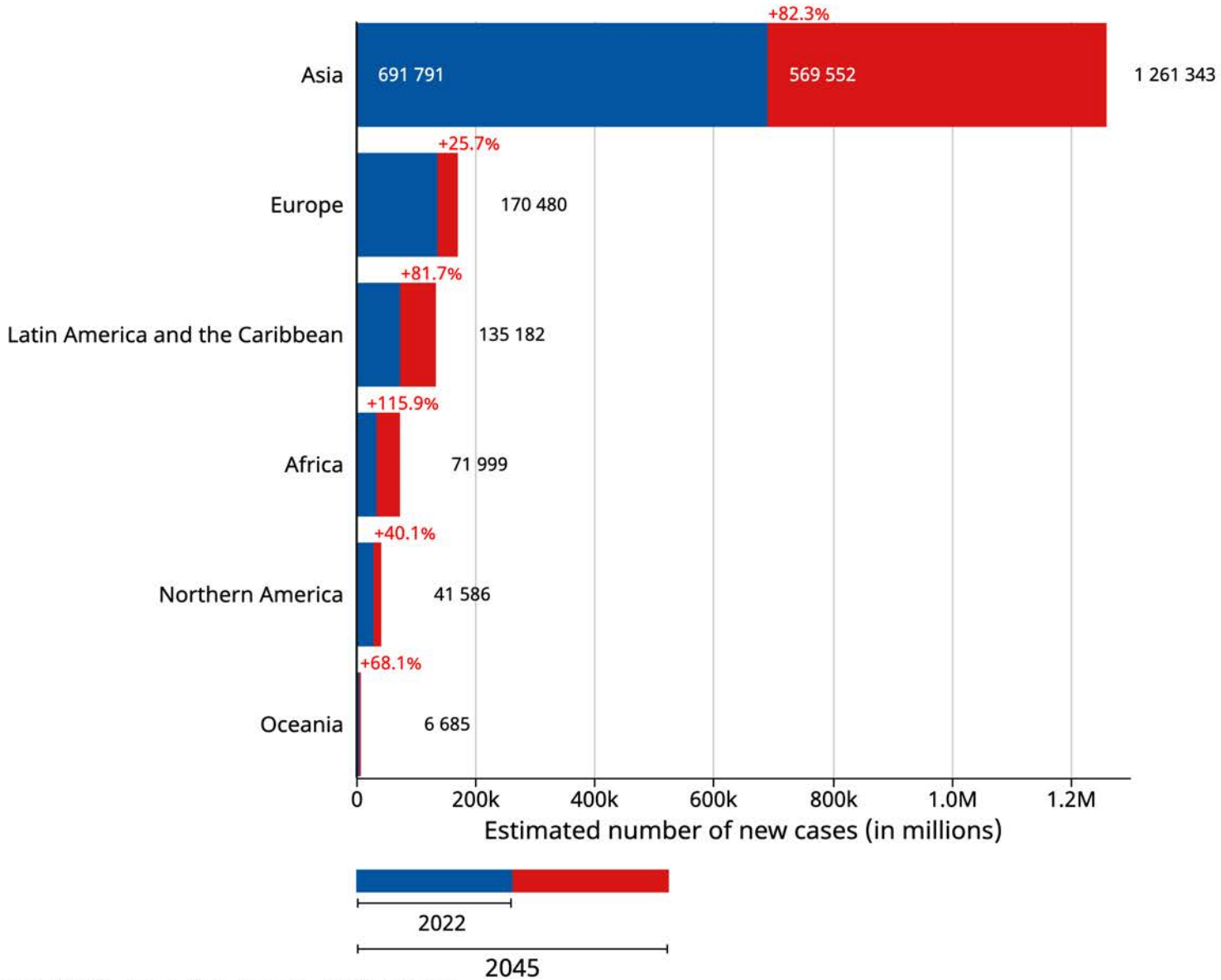


Cancer Tomorrow | IARC - https://gco.iarc.who.int/tomorrow
Data version : Globocan 2022 (version 1.1)

International Agency for Research on Cancer
World Health Organization

Classification

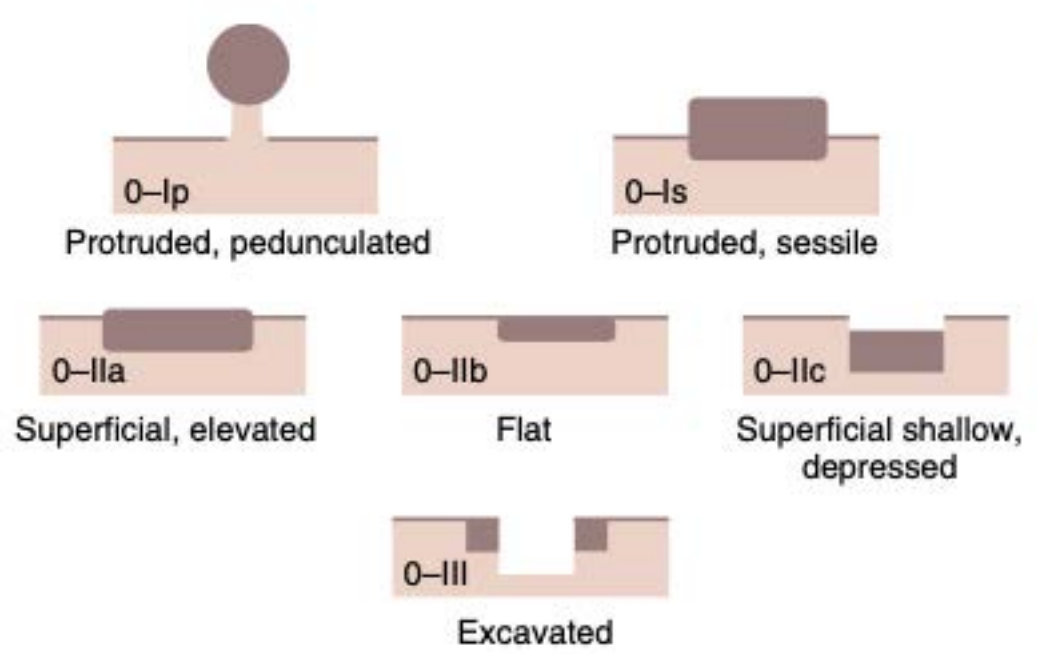
- **Gastric adenocarcinoma** makes up most of gastric cancer

- **Gastric epithelial tumors**: **> 95 % adenocarcinoma**,
- Other gastric epithelial malignancies include:
  - squamous,
  - adenosquamous,
  - undifferentiated carcinomas,
  - medullary carcinoma with lymphoid stroma and
  - neuroendocrine tumors
- **Nonepithelial primary gastric malignancies** include:
  - lymphomas and
  - mesenchymal tumors

Piazuelo MB et al *Colomb Med 2013*

- # Paris Classification

- Based on macroscopic features, early gastric carcinomas are sub-classified into three main types according to the Endoscopic Classification Review Group (Paris classification):
- 0-I (protruded)
- 0-II (superficial)
- 0-III (excavated)

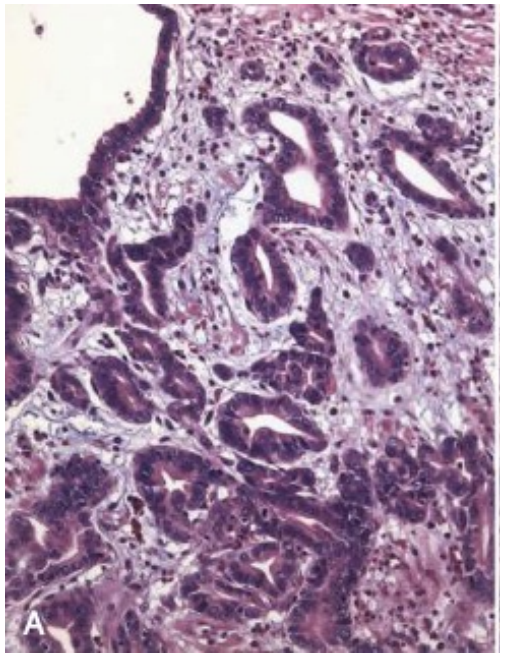


Lordick F et al. Ann Oncol 2022
Sleisenger and Fordtran's Gastroenterlogy and Liver Disease , Elsevier 2021

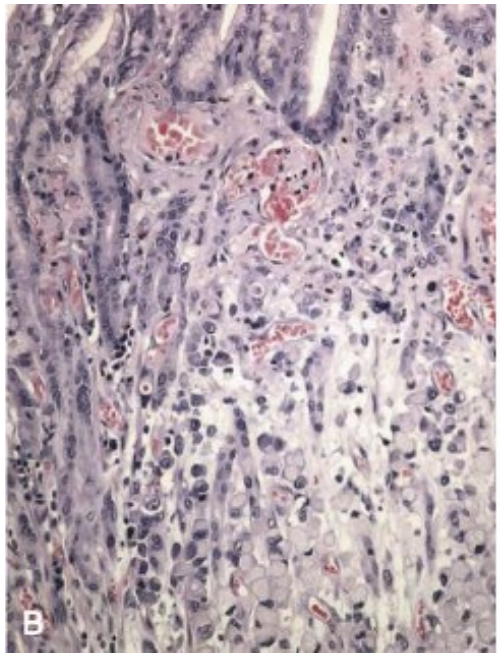
- Borrmann classification
- locally advanced gastric carcinomas are macroscopically sub-classified according to the
- Typer I: polypoid/fungating without ulceration ,
- Type II: ulcerated with elevated borders and sharp margins
- Type III: ulcerated with diffuse infiltration at the base
- Type IV: diffusely infiltrative with thickening of the wall

Lordick F et al. Ann Oncol 2022

- Laurén classification:
  - Intestinal type of cancer
  - Diffuse type
  - Mixed



Intestinal type



Diffuse type

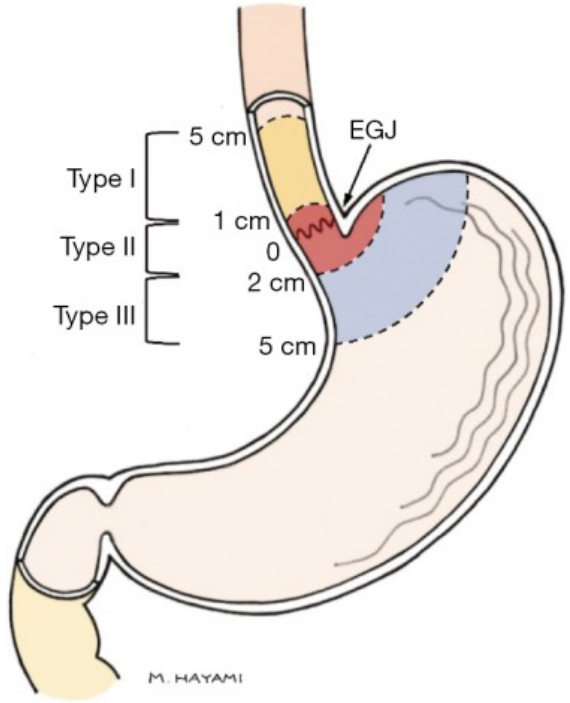
- **The WHO classification**
- five main histological subtypes:
  - tubular,
  - papillary,
  - poorly cohesive (including signet ring cell and other subtypes),
  - mucinous and
  - mixed ACs.

Lordick F et al. Ann Oncol 2022

- **Anatomical Classification**
- Proximal tumors (EGJ and gastric cardia)
- Distal or non-junctional tumors (fundus, body, and antrum)

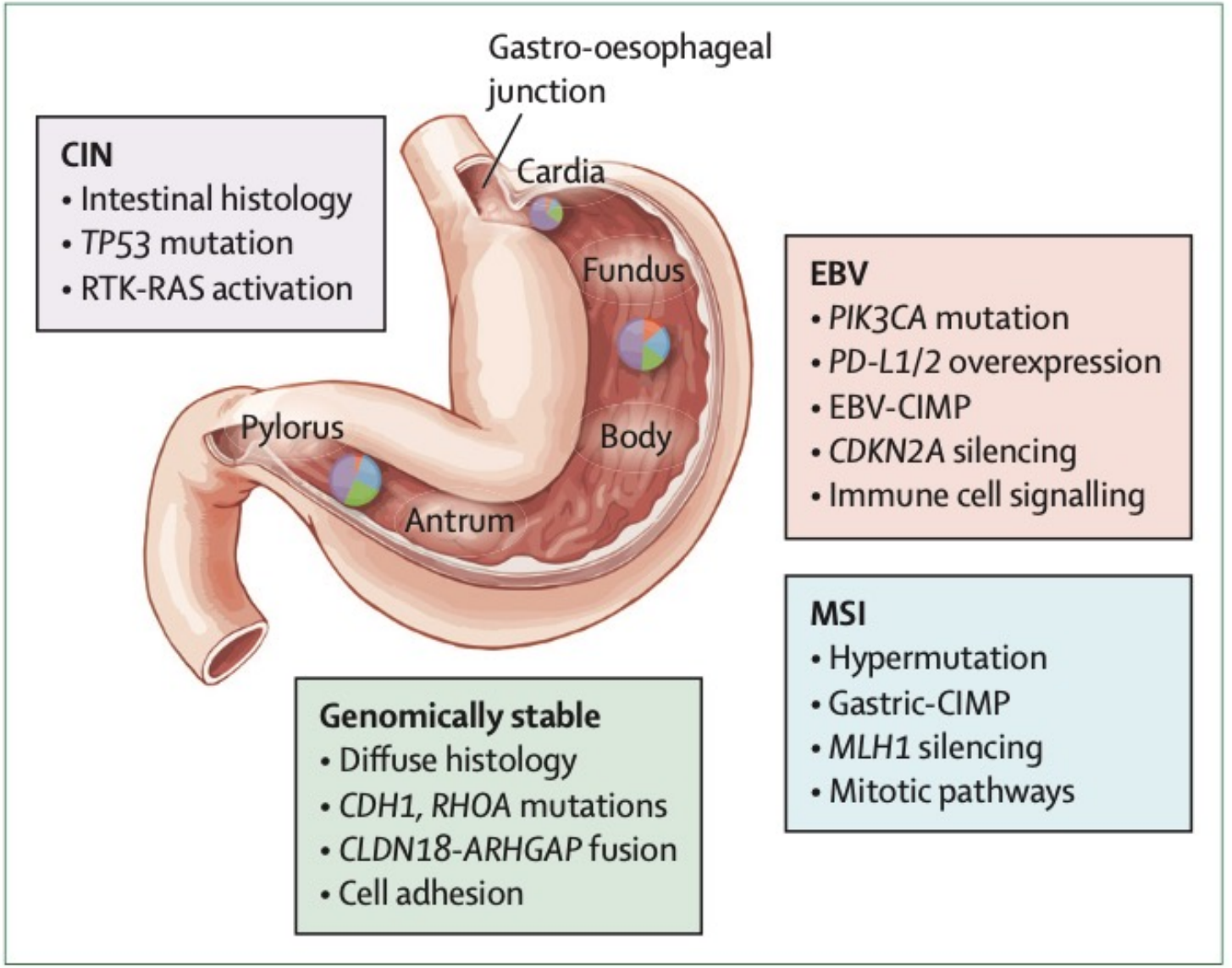
Saliba et al. Annals of Esophagus 2020

- **Gastrooesophageal-junction cancers** are widely categorised according to the **Siewert classification**
  - **Type I**: 1-5cm above the EGJ
  - **Type II**: from 1cm above to 2cm below EGJ)
  - **Type III**: 2- 5cm below the junction



Saliba et al. Annals of Esophagus 2020

- **The Cancer Genome Atlas (CTGA):**
  - Positive for Epstein-Barr virus (9%)
  - microsatellite unstable tumours (22%
  - genomically stable tumours (20%)
  - chromosomally unstable tumours (50



Van Cutsem et al The Lancet 2016

Risk Factors of Gastric Adenocarcinoma

- **DEFINITE**
- Adenomatous gastric polyps
- Chronic atrophic gastritis
- Cigarette smoking
- Dysplasia
- EBV
- History of gastric surgery (esp. Billroth II)
- Hp infection
- Intestinal metaplasia

- **GENETIC FACTORS**
- Family history of gastric cancer (first-degree relative)
- Familial adenomatous polyposis (with fundic gland polyps)
- Hereditary nonpolyposis colorectal cancer
- Juvenile polyposis
- Peutz-Jeghers syndrome

Sleisenger and Fordtran's Gastroenterlogy and Liver Disease Elsevier 2021

Risk Factors of Gastric Adenocarcinoma

- **PROBABLE**
- High salt intake
- History of gastric ulcer
- Obesity (adenocarcinoma of the cardia only
- Pernicious anemia
- Regular aspirin or other NSAID use (protective)
- Snuff tobacco use

- **POSSIBLE**
- Diet high in nitrates
- Heavy alcohol use
- High ascorbate intake (protective)
- High intake of fresh fruits and vegetables (protective)
- Low socioeconomic status
- Ménétrier disease
- Statin use (protective)

- **QUESTIONABLE**
- High green tea consumption (protective)
- Hyperplastic and fundic gland polyps

Sleisenger and Fordtran's Gastroenterlogy and Liver Disease Elsevier 2021

Premalignant conditions

- Chronic Atrophic Gastritis
- Intestinal Metaplasia
- Dysplasia
- Gastric Polyps
- Previous Gastrectomy
- PUD
- Ménétrier disease

Sleisenger and Fordtran's Gastroenterlogy and Liver Disease Elsevier 2021

Chronic Atrophic Gastritis

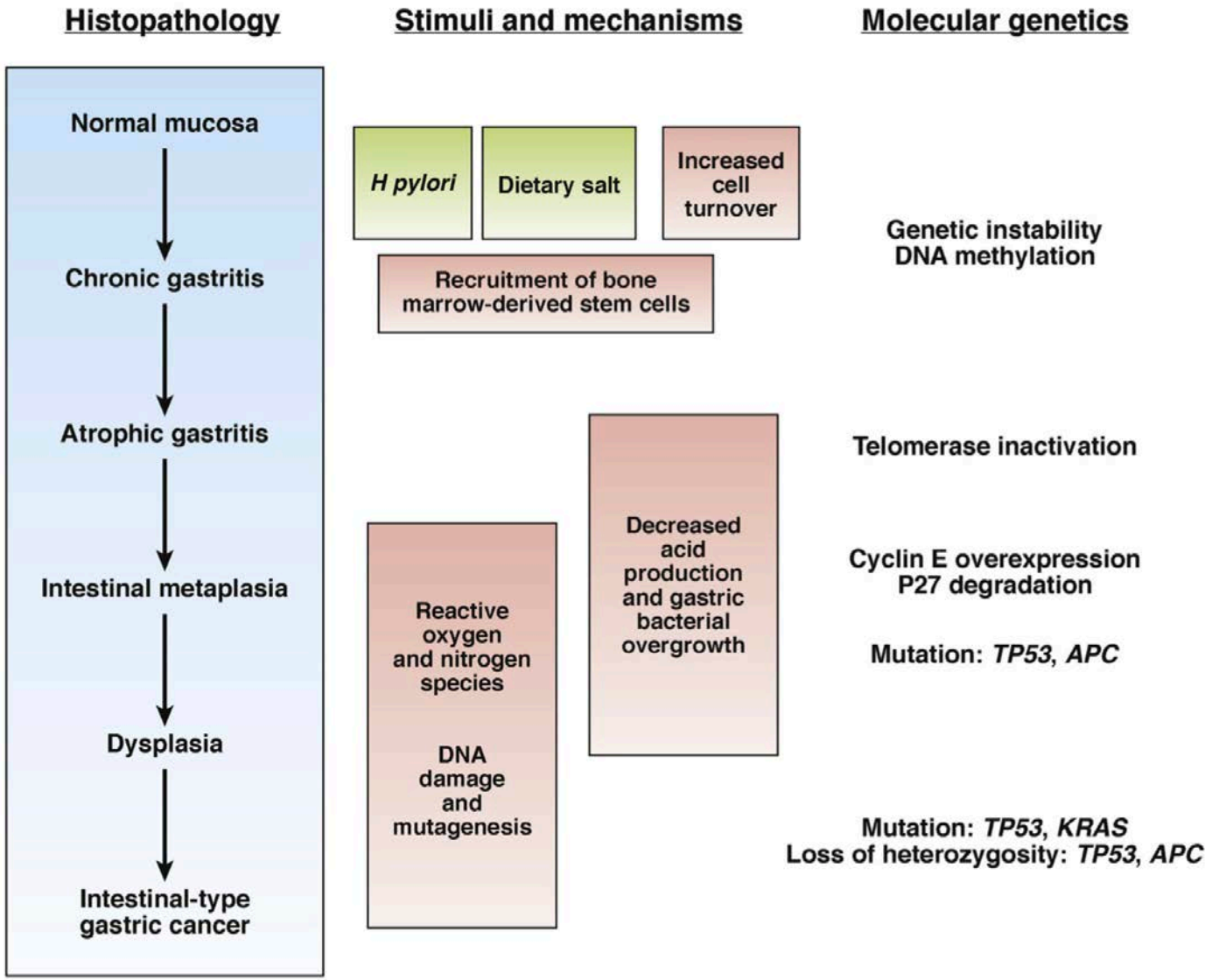
- Normal gastric mucosa is divided into *two compartments*:
  - Gastrin and mucus-secreting glands of the **antrum**
  - Acid and pepsinogen-secreting oxyntic glands of the **corpus**

- **Atrophic gastritis** is defined by *replacement* of appropriate gastric glandular structures with *connective tissue (nonmetaplastic atrophy*) or a *different, non-native epithelium (metaplastic atrophy)* on a background of chronic inflammation

- AG is considered the first of a multistep precancerous cascade

Banks M et al Gut 2019
Shah et al Gastroenterology 2021

Correa cascade

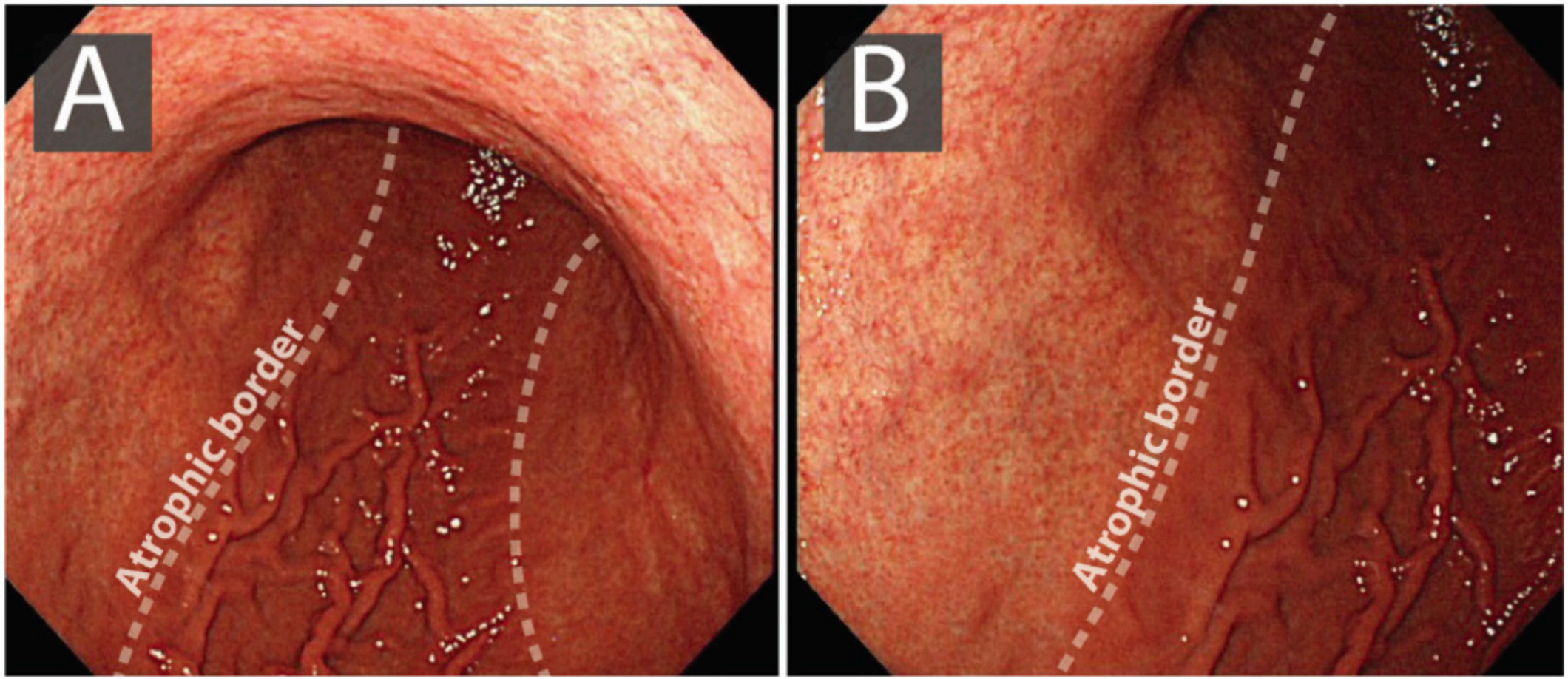


Moss , CMGH 2017

- The 2 most common etiologies of AG are chronic infection with Helicobacter pylori and autoimmunity
- Autoimmune gastritis (AIG) is significantly less common than H pylori-associated AG (HpAG).
- The prevalence has been estimated to approximate 0.5%–2%

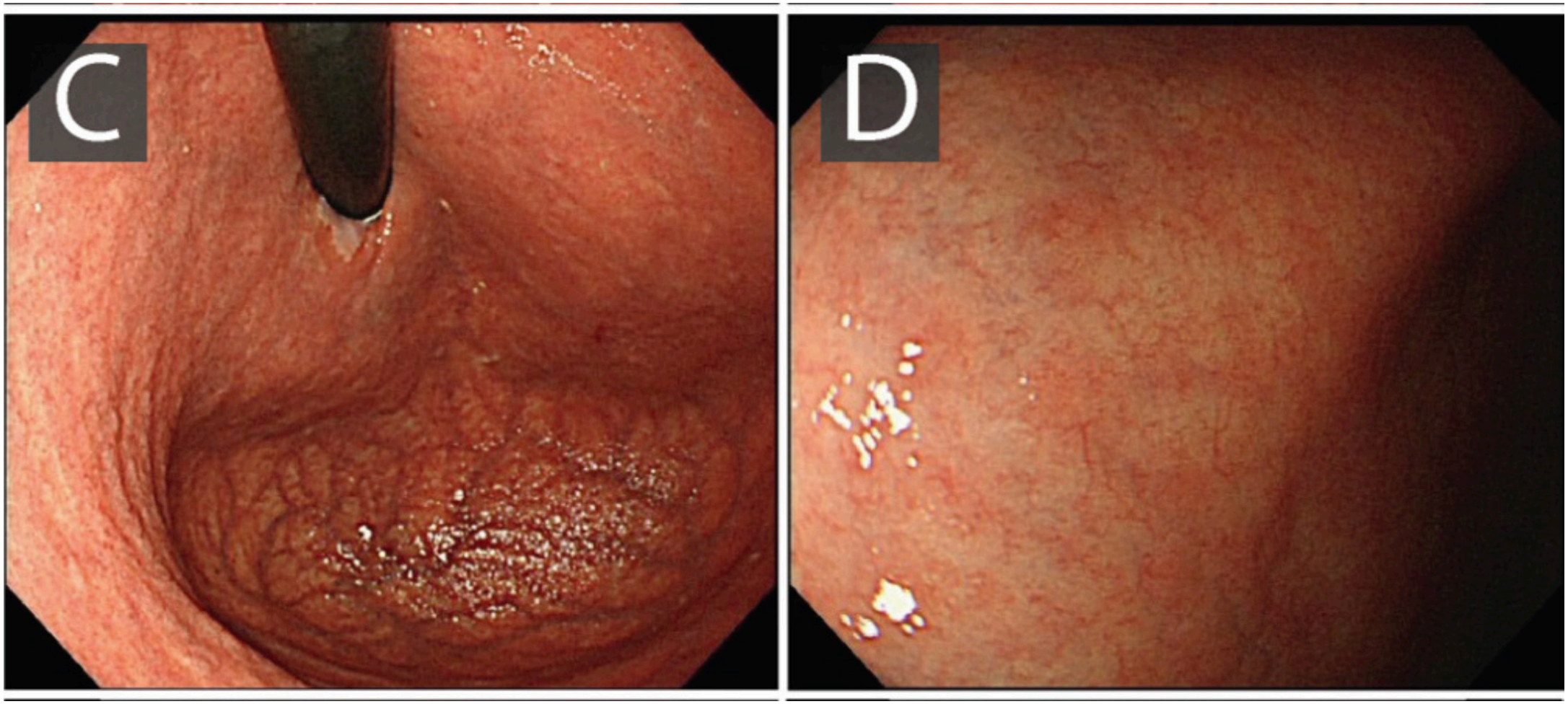
- **H pylori-associated AG (HpAG)**
- multifocal, more likely to be associated with metaplasia
- considerable regional variation in the prevalence of atrophic gastritis in Hp-infected individuals, with a roughly 3-fold increase in Asia compared to Western countries

- **Autoimmune gastritis (AIG)**
- associated with anti-parietal cell and intrinsic factor antibodies
- Confined to the body and fundus
- Autoimmune metaplastic atrophic gastritis is associated with pernicious anemia
- an increased gastric cancer risk, albeit not as high as that seen with Hp-induced MAG, owing most likely to a lesser degree of inflammation



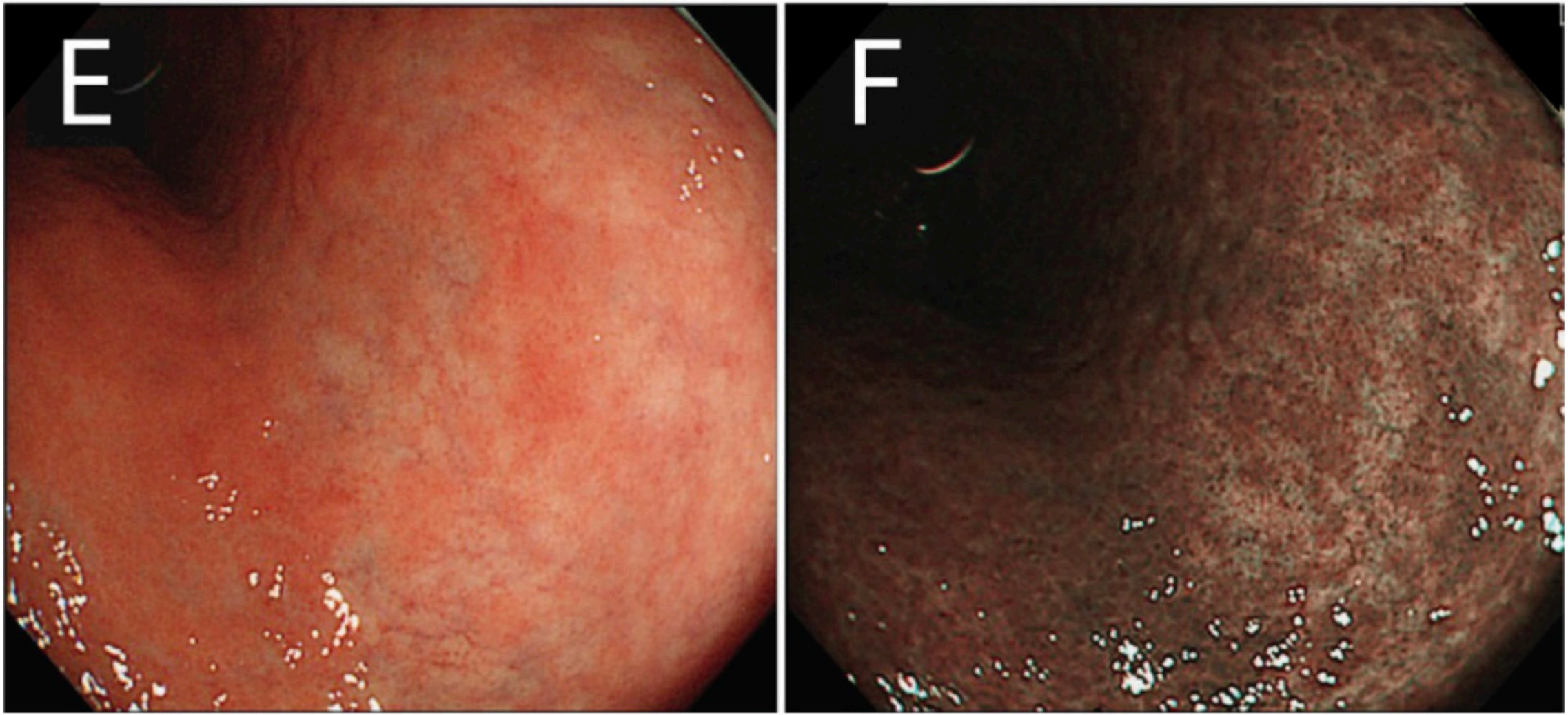
Chronic atrophic gastritis (CAG) and the atrophic border on white light endoscopy.
Four principle endoscopic features of CAG: **palor**, **loss of gastric folds**, **prominence of the vessels** and the **atrophic border**

Banks M *et al Gut 2019*



Chronic atrophic gastritis (CAG) on white light enhanced endoscopy.

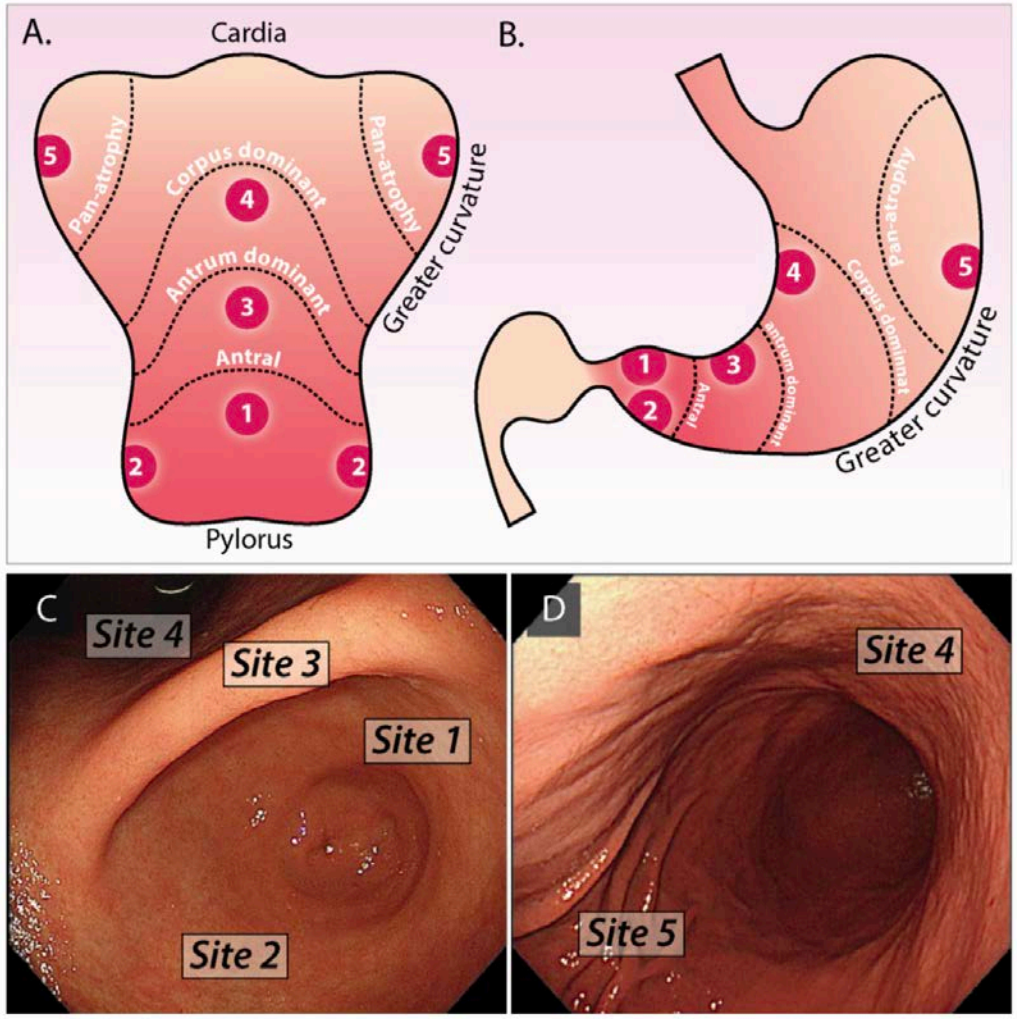
Banks M *et al Gut 2019*



Chronic atrophic gastritis (CAG) on white light and image enhanced endoscopy.

Banks M *et al Gut 2019*

The Integrated and Modified Kimura & Sydney Biopsy System



Banks M *et al Gut 2019*

Chronic atrophic gastritis (CAG) suspected on white light endoscopy

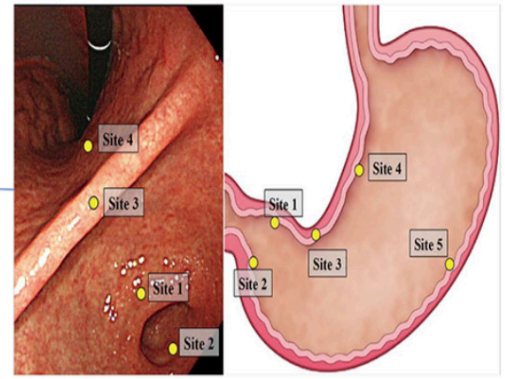
Eradicate H. pylori

Systematic endoscopy with image enhancement

Endoscopic grading of atrophy and intestinal metaplasia with Sydney protocol biopsies directed to areas of GIM or atrophy

Distal CAG Antrum Incisura	**Low risk**
Extensive CAG Corpus	**High risk**

Sydney protocol biopsies



1. Antrum 1
2. Antrum 2
3. Incisura
4. Lesser curve
5. Greater curve

CAG with dysplasia
(See guidance)

High risk CAG

Low risk CAG

Family history of gastric cancer or persistent *H.pylori* infection

3 yearly endoscopic surveillance
(with image enhancement)

No surveillance

Banks M *et al Gut 2019*

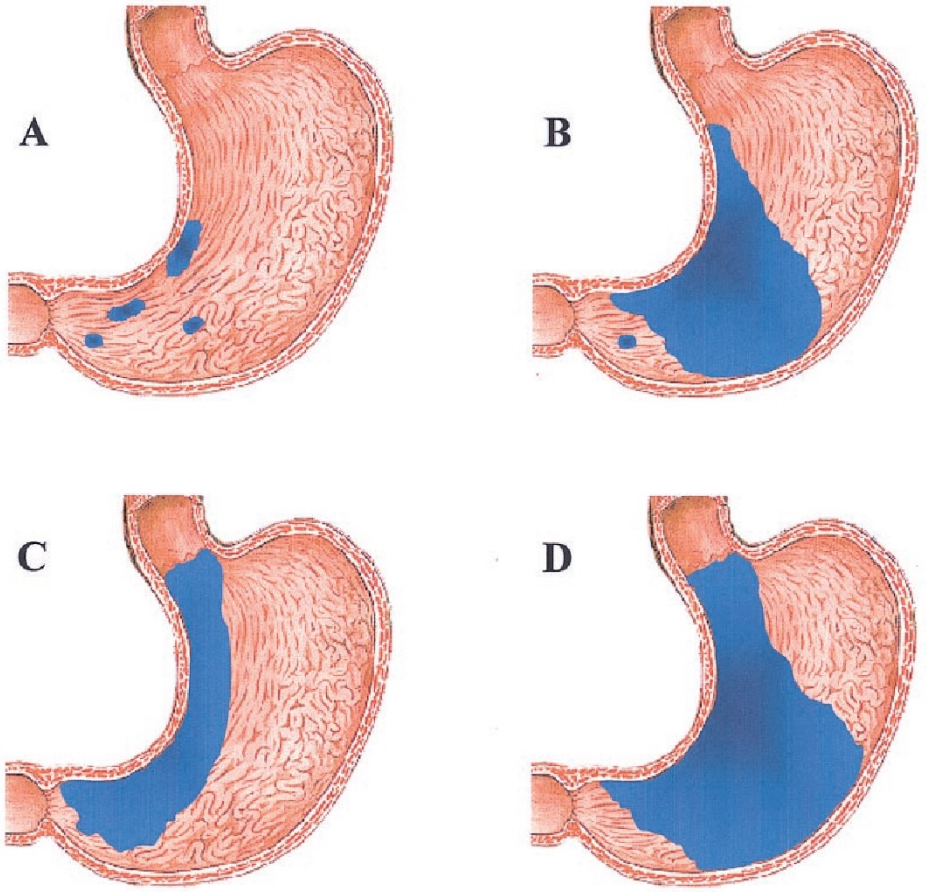
Intestinal Metaplasia

- GIM is the *replacement of normal gastric epithelium* with *epithelium resembling the intestine* as and adaptive response to chronic injury.
- Intestinal metaplasia (IM) can be subdivided into 3 histological categories
- ***Type I* (complete)** IM contains goblet cells and mature, nonsecretory absorptive cells.
- ***Type II* (incomplete**) IM contains few if any absorptive cells, columnar "intermediate" cells in various stages of differentiation and goblet cells
- ***Type III* (incomplete)** is less differentiated than type II, with the intermediate cells and the goblet cells
- *Type II* or *III* IM is associated with an *approximately 20-fold* increased risk of gastric cancer

- A large nationwide cohort study from the Netherlands on individuals identified a 0.25% annual progression rate toward cancer of in patients with gastric IM

- Although it is generally accepted that IM is associated with an increased risk for the intestinal type gastric cancer, patients with diffuse type tumors also show a high prevalence of IM in the nontumorous gastric mucosa

- The extent of the distribution of GIM appears to be of key importance
- Four patterns of GIM distribution have been described
    A. ‘focal’ GIM, consists of scattered foci, mostly in the lesser curvature and incisura
    B. ‘antrum-predominant’ GIM, involves most of the antrum and incisura angularis
    C. ‘magenstrasse’ GIM spreads throughout the lesser curvature from the cardia to the pylorus, also involving the greater curvature of the prepyloric antrum.
    D. ‘diffuse’ GIM involves the entire gastric mucosa, with the exception of the fundic areas



Cassaro, et al. *American Journal of Gastroenterology 2000*

The OLGA-staging system

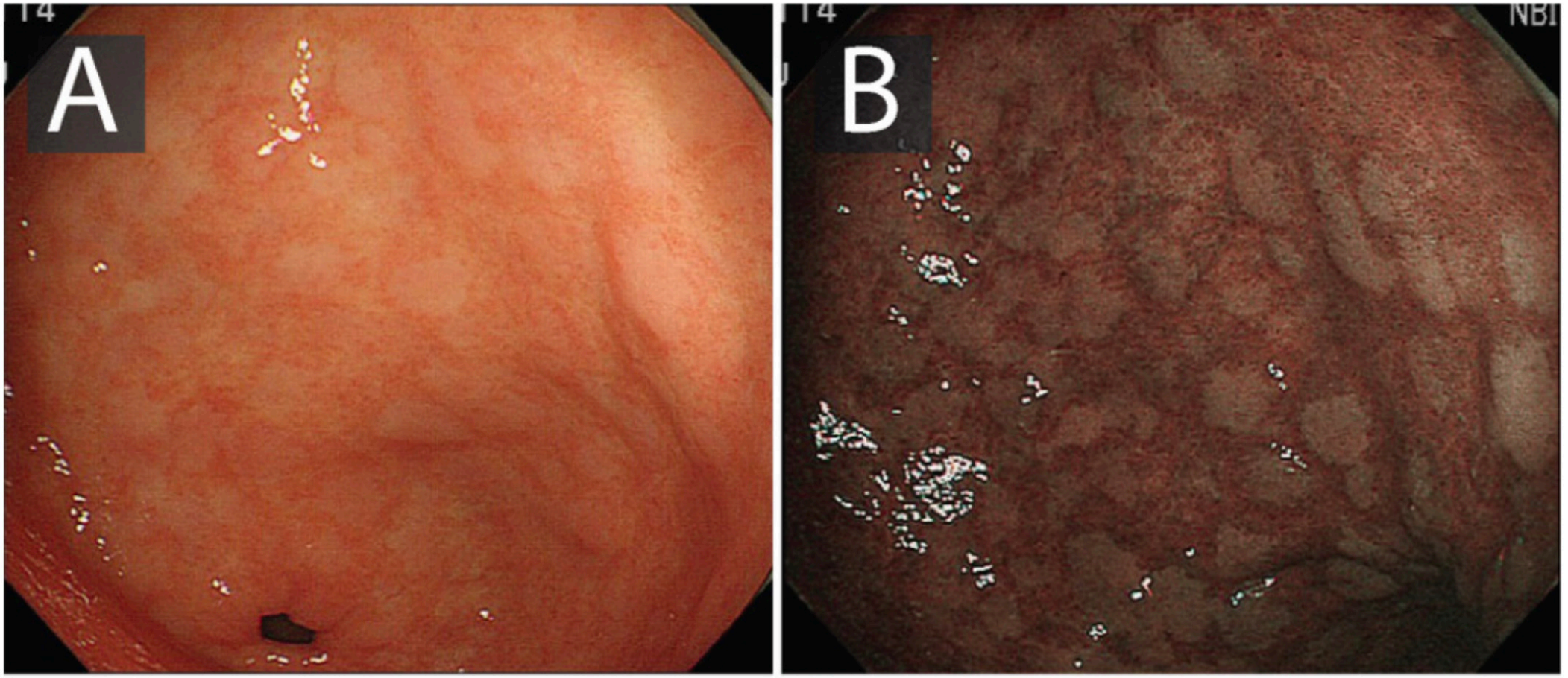
		Corpus			
	Atrophy score	No atrophy (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum	No atrophy (score 0) (including *incisura angularis*)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score 1) (including *incisura angularis*)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2) (including *incisura angularis*)	Stage II	Stage II	Stage III	Stage IV
	Severe atrophy (score 3) (including *incisura angularis*)	Stage III	Stage III	Stage IV	Stage IV

Aliment Pharmacol Ther, Volume: 31, Issue: 10, Pages: 1104-1111, First published: 20 April 2010, DOI: (10.1111/j.1365-2036.2010.04277.x)

The OLGIM staging system

Table 2. Operative Link on Gastric Intestinal Metaplasia Staging

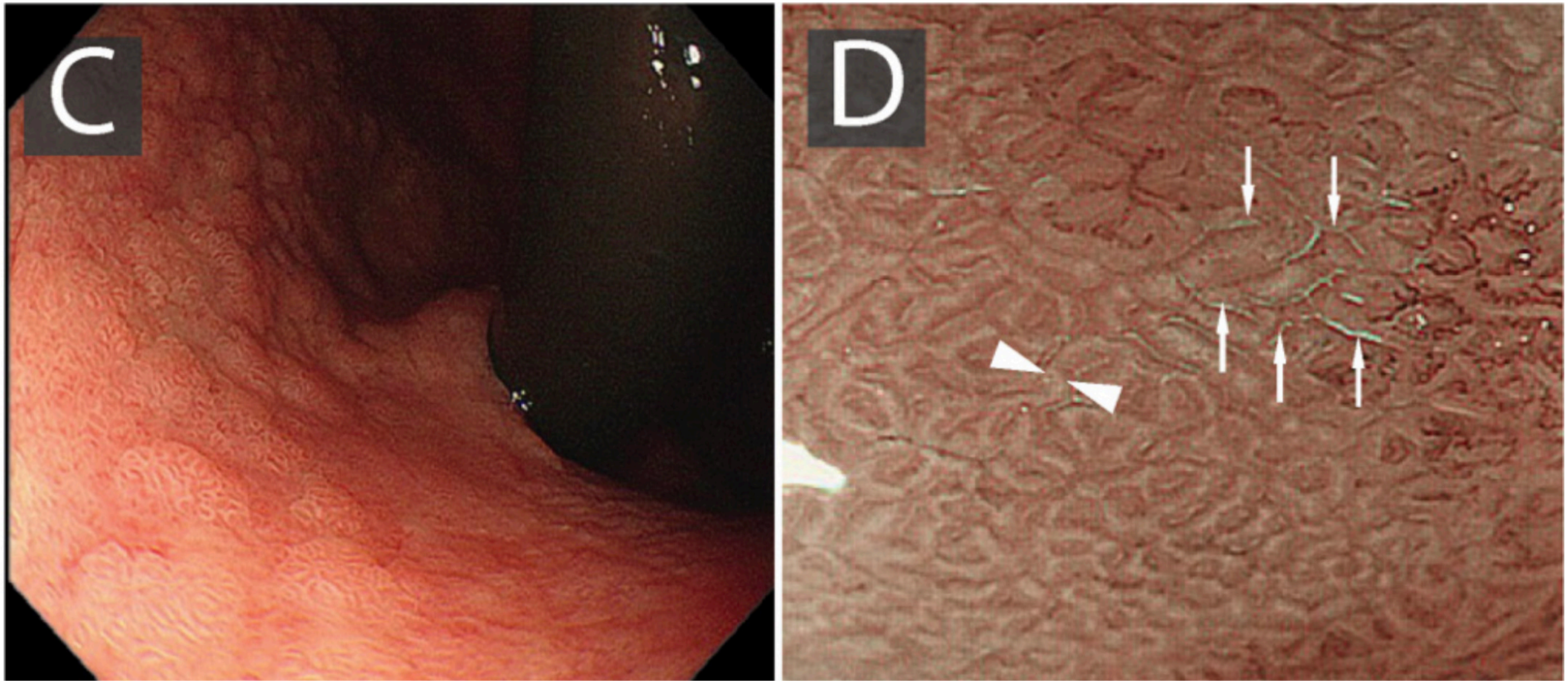
		Corpus			
Intestinal Metaplasia Score		No	Mild	Moderate	Severe
Antrum	No	Stage 0	Stage I	Stage II	Stage II
	Mild	Stage 1	Stage I	Stage II	Stage III
	Moderate	Stage II	Stage II	Stage III	Stage IV
	Severe	Sage III	Stage III	Stage IV	Stage IV



Gastric intestinal metaplasia under white light, image enhanced and magnification endoscopy.

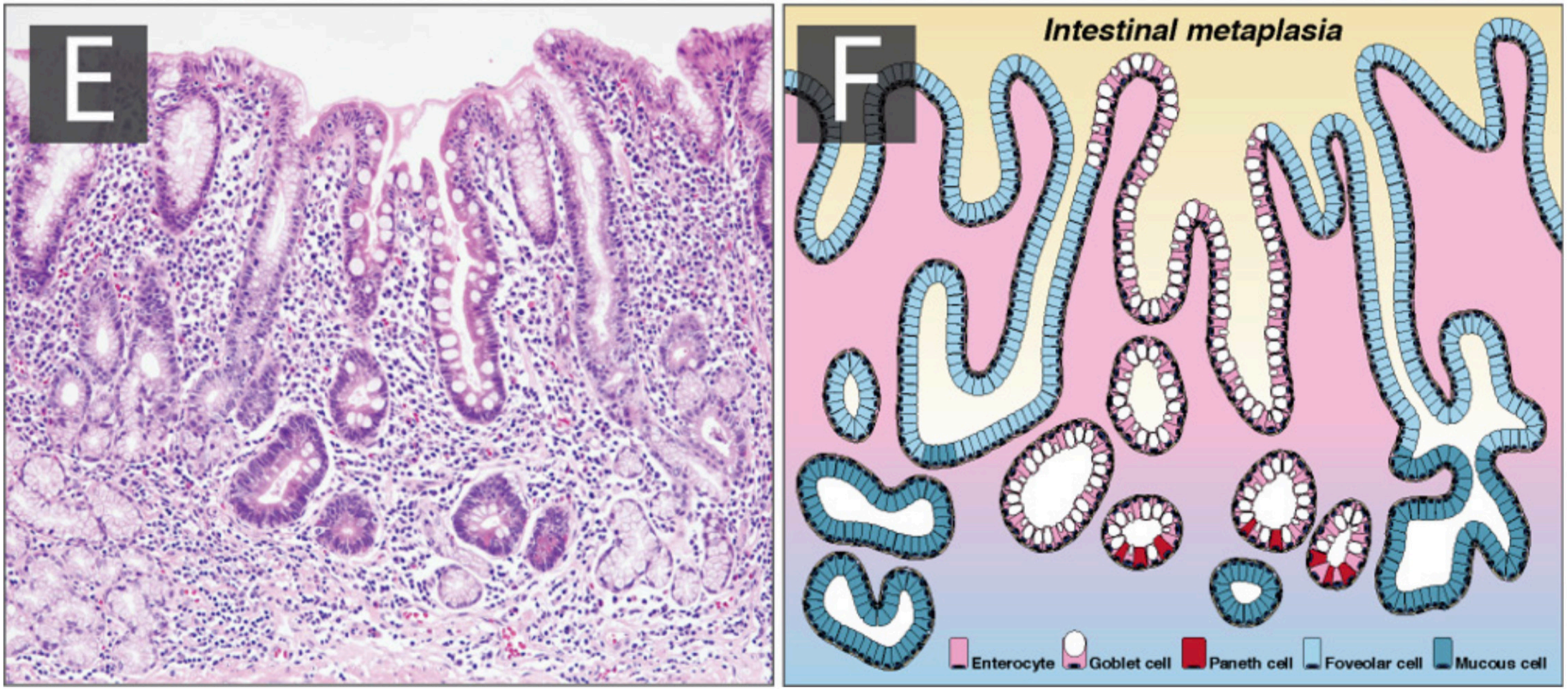
Small grey-white slightly elevated plaques surrounded by patchy pink and pale mucosa

Banks M *et al Gut 2019*



Corpus GIM can be distinguished from the normal straight/tubular glands of the corpus by a ‘groove type pattern’ similar to that of the antrum or villiform pattern of the intestine and may be appreciated with higher resolution technology on white light endoscopy (C). GIM in the antrum is more difficult to characterize as the normal glands are oblique. Additional features of GIM to aid diagnosis in the antrum include the **light blue crest** (LBC) and the **marginal turbid band** (MTB) (D) The LBC is a fine, blue-white line on the crest of the epithelial surface seen with NBI enhancement (Fine arrows in D). The MTD can be seen between the broad arrows.

Banks M *et al Gut 2019*



The numerous goblet cells characterise GIM (E & F)

Banks M *et al Gut 2019*

Gastric dysplasia

- Endoscopic prevalence of gastric dysplasia varies from 0.5% -3.7% in low-risk western countries to 9-20% in areas with high incidence of gastric adenocarcinoma

- HGD: rate of malignant progression or synchronous malignant lesion of 60-80% over a median interval of 4-48 months

- 1 in 19 patients with dysplasia progress to gastric adenocarcinoma in 20 years

Sung et al Korean J Intern Med 2016
Song et al BMJ 2015
Banks M *et al Gut 2019*

- The risk of progression of LGD is less clear
- LGD will regress in 38-75% of patients and persists in 19-50% of patients
- LGD that persists, risk of malignant progression ranges from 0- 23% over 10-48 months

Sung et al Korean J Intern Med 2016

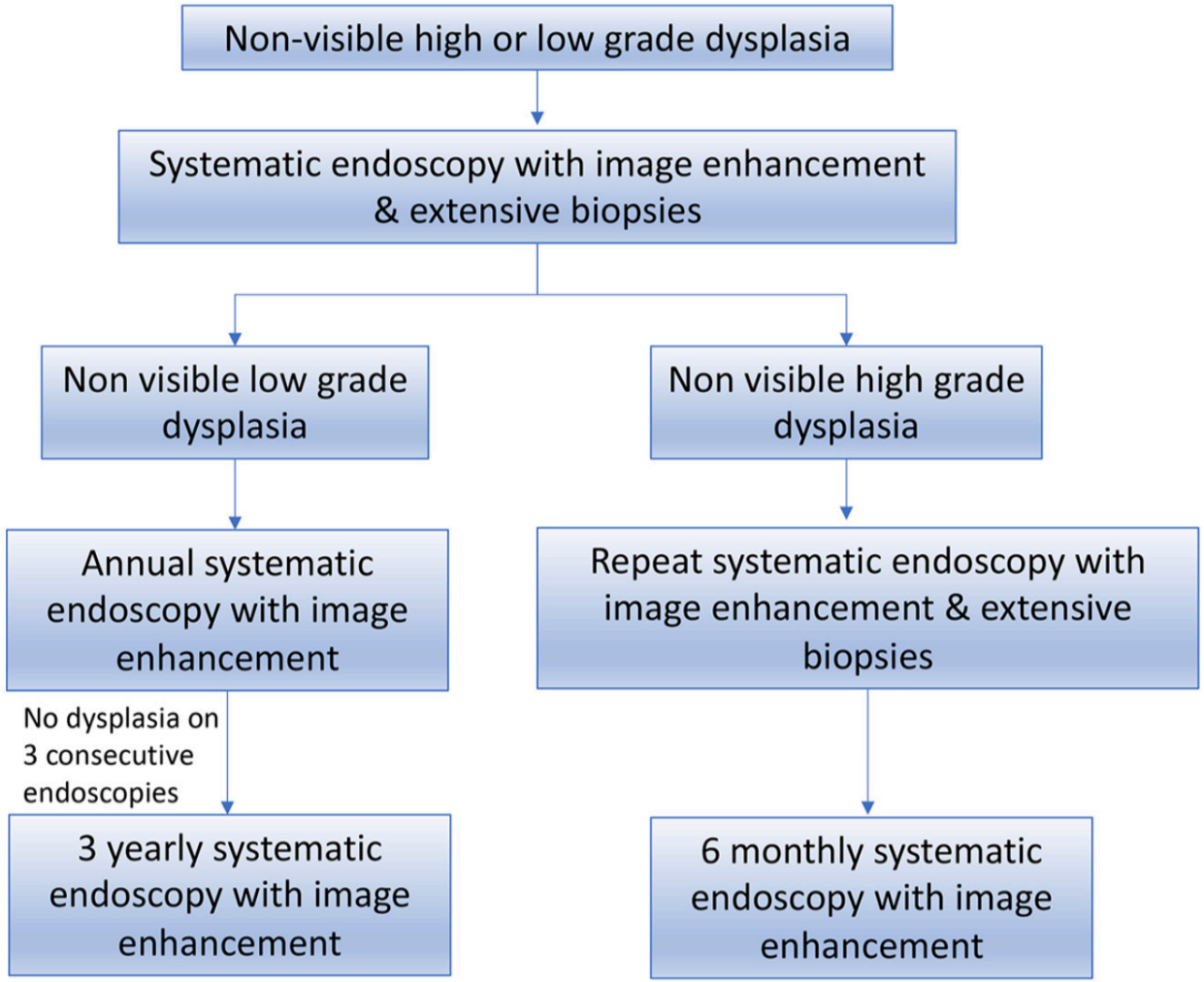
Table 3 The risk of cancer for patients with gastric atrophy and intestinal metaplasia

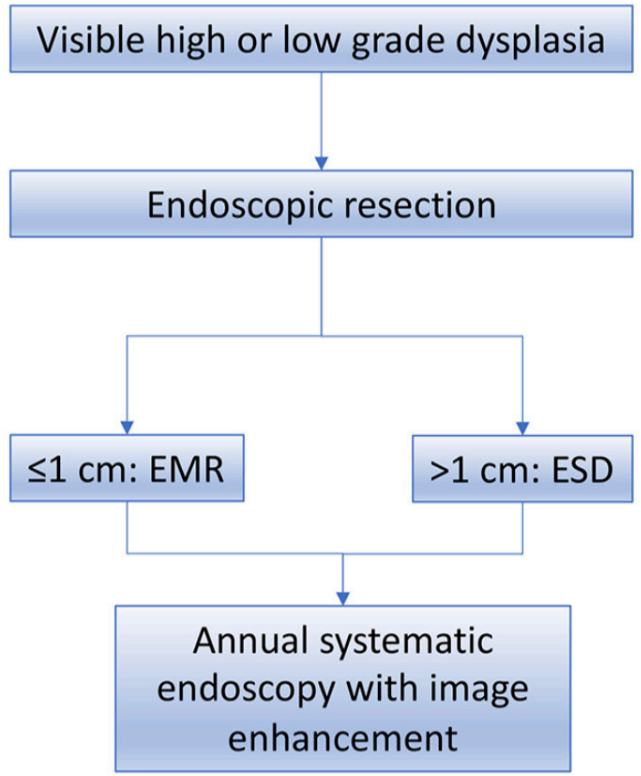
	5-Year incidence of gastric cancer (%)	Annual incidence (%)
All GA	1.9	0.1–0.5
Mild GA	0.7	
Severe GA	10	
All GIM		0.15–0.4 0.25
Antral GIM	5.3	
Antral and corpus GIM	9.8	
	Interval of 4–48 months	
Low-grade dysplasia	0–23	0.6
High-grade dysplasia	60–85	6

GA, gastric atrophy; GIM, gastric intestinal metaplasia.

Banks M *et al Gut 2019*

Endoscopic Management of Gastric Dysplasia





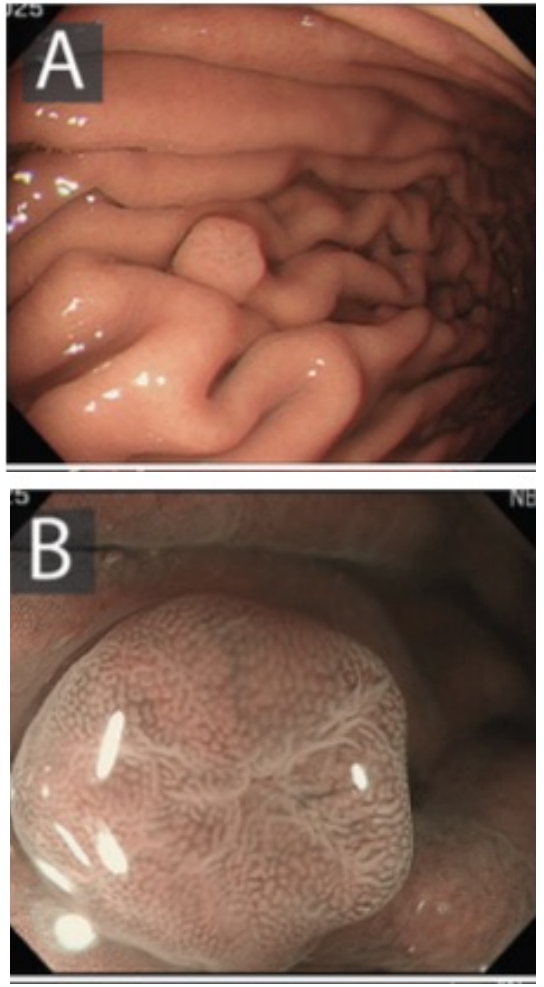
EMR: endoscopic mucosal resection
ESD: endoscopic submucosal dissection
NVLGD: non-visible low grade dysplasia
NVHGD: non-visible high grade dysplasia

Banks M *et al Gut 2019*

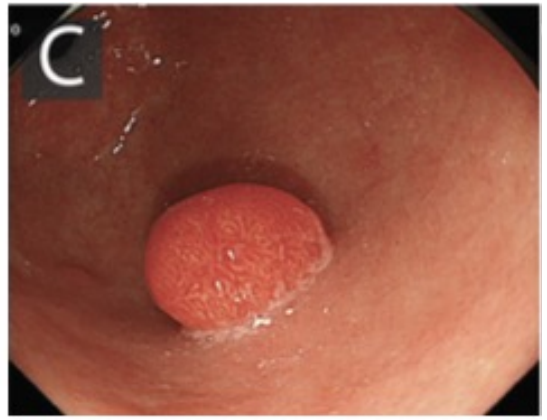
Gastric polyps

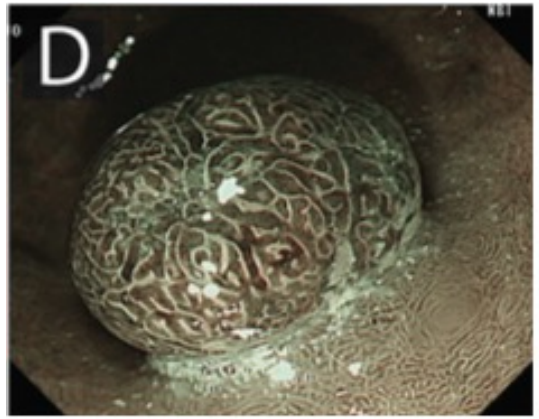
- The prevalence of gastric polyps in the general population is approximately 0.8% to 2.4%
- Gastric polyps consist predominantly of fundic gland polyps (≈50%), hyperplastic polyps (≈40%), and adenomatous polyps (≈10%)

- Fundic gland polyps
- Typically multiple, small (<1cm)
- Located in the fundus and corpus
- Appear: pale, smooth, glassy, and transparent or translucent, colour is either lighter or the same as the surrounding mucosa
- lacy blood vessels are seen through the translucent surface and the surface shows a pattern of fine grey dots
- Usually not associated with an increased risk of cancer, unless in the context of FAP syndrome
- larger FGPs (>1 cm) have been shown to be dysplastic in 1.9% and contain focal cancer also in 1.9%

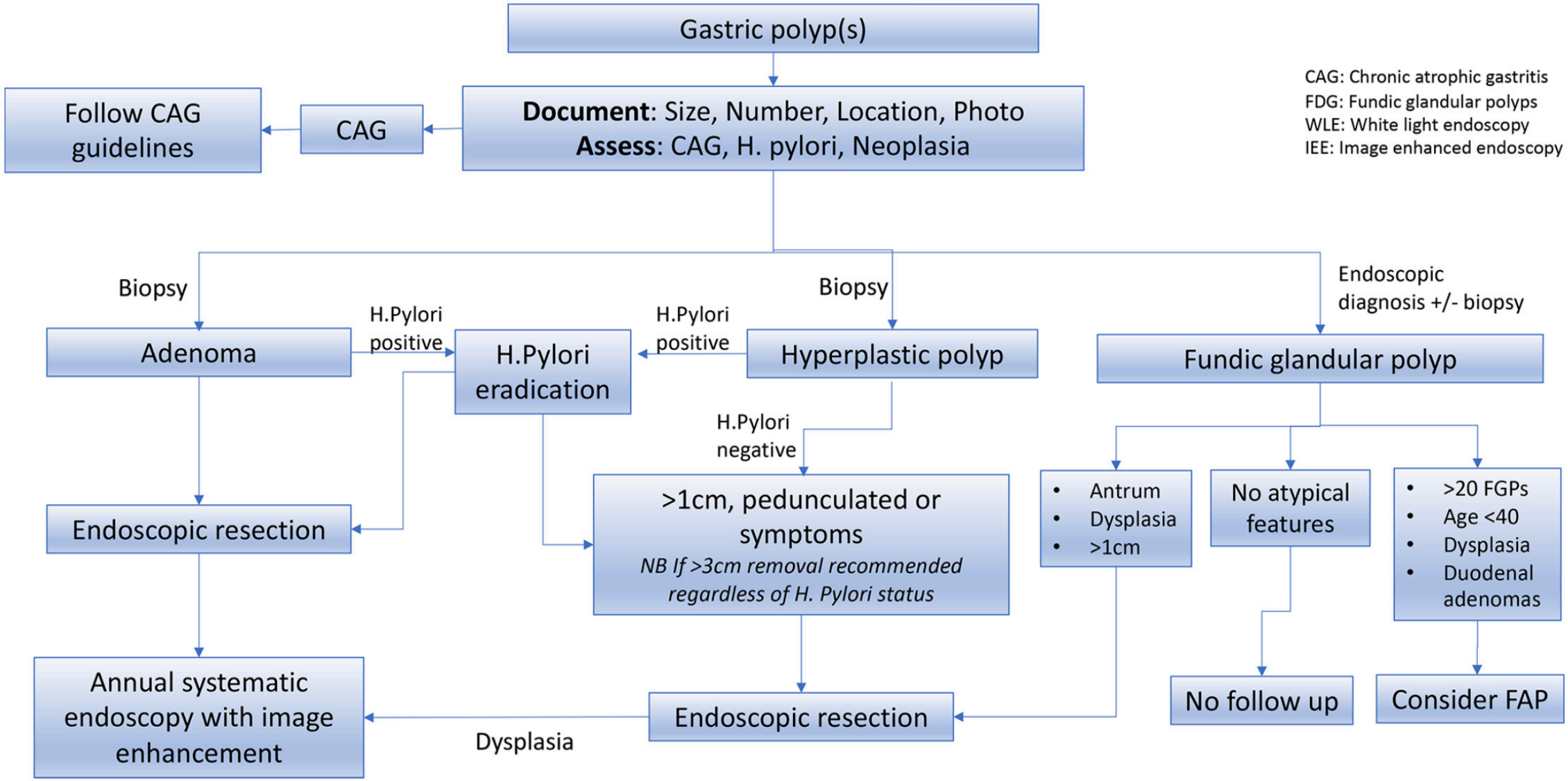


- Hyperplastic polyps
- usually single or few in number
- more frequently observed in the antrum or adjacent to ulcers, stomas and gastrectomy sites
- appear as smooth, red buttered with whitish exudates (fibrin) and are dome-shaped
- usually small (0.5–1.5cm), but may be larger and present as lobulated and pedunculated masses covered with superficial erosions.
- typically associated with *H. pylori* gastritis (25%), GA and GIM.
- Regression generally occurs after eradication of *H. pylori* (up to 70%)
- Gastric hyperplastic polyps can reveal dysplasia (1.9–19%) and malignant transformation (0.6–2.1%) especially when >1cm and in the postgastrectomy stomach





- **Adenomatous polyps**
- Adenomatous polyps are usually single (82%),
- Usually small (<2cm)
- located in the antrum and incisura angularis
- Endoscopically they have a velvety pink lobulated appearance and can be sessile or pedunculated
- In Western countries their prevalence varies between 0.5% and 10%
- They are normally associated with a background of GA and GIM
- Coexistence of a synchronous gastric adenocarcinoma has been found in up to 30% of patients with an adenomatous polyp.
- 50% of adenomatous polyps >2 cm contain foci of adenocarcinoma



Banks M *et al Gut 2019*

Previous Gastrectomy

- Gastric surgery for benign conditions can predispose patients to a higher risk of gastric cancer, beginning 20 years after the surgery
- The risk is greatest for those who underwent surgery before the age of 50 years, perhaps reflecting the long lag period necessary between the operation and the development of cancer
- The cancers tend to occur at or near the surgical anastomosis on the gastric side;
- Hypochlorhydria → bacterial overgrowth → increased production of nitrites
- chronic enterogastric reflux of bile salts and pancreatic enzymes (which are potent gastric irritants), and
- atrophy of the remaining fundic mucosa due to low levels of antral hormones, including gastrin
- The Billroth II operation with gastrojejunostomy predisposes to the development of cancer at a 4-fold higher rate than a Billroth I procedure with gastroduodenostomy, suggesting that bile reflux may be a significant predisposing factor

PUD

- Large epidemiologic studies have demonstrated a consistently increased risk of gastric cancer in patients with a history of a gastric ulcer
- In a cohort study, Swedish adults who were followed for an average of 9 years, a history of gastric ulcer was associated with a 1.8-fold increased risk of gastric cancer
- Interestingly, a history of duodenal ulcer was associated with a reduced risk of gastric cancer.
- The associations were confined to noncardia gastric cancer; there was no association between history of gastric ulcer and cardia cancer

- Ménétrier Disease
- In a review of case reports, 15% of patients with Ménétrier disease had associated gastric cancer, including several cases that documented a progression from dysplasia to cancer
- Because of the rarity of Ménétrier disease, it has been difficult to study its relationship with gastric cancer in any controlled fashion, and no recommendations regarding endoscopic surveillance can be made.

PREVENTION

- Eradication of H.Pylori
- H. Pylori eradication heals non-atrophic gastritis
- May lead to regression of atrophic gastritis
- Eradicating Hp leads to a decrease of the subsequent risk of gastric cancer

Kong YJ, et al 2014 World J Gastroenterol
Choi IJ et al 2020 NEJM
Ford AC et al, 2020 Cochrane Database Syst Rev.
Fukase K, 2008 Lancet.

Table 1. Selected Risk Factors for Gastric Cancer.

Risk factor	Associated risk	95% Confidence interval	Reference
Helicobacter pylori			
H. pylori infection	OR 3.8	2.3-6.2	Forman et al[29]
Presence of CagA gene	OR 2.87	1.71-3.05	Huang et al[31]
Tobacco use			
Current cigarette use	OR 1.26	1.12-1.41	Ferro et al[44]
< 10 cigarettes per day	OR 1.08	0.91-1.28	
10-20 cigarettes per day	OR 1.30	1.16-1.45	
> 20 cigarettes per day	OR 1.31	1.09-1.58	
Former cigarette use	OR 1.14	0.99-1.31	
Alcohol consumption			
Alcohol use	OR 1.20	1.12-1.27	Deng et al[49]
4-6 drinks per day	OR 1.26	1.08-1.48	Rota et al[50]
> 6 drinks per day	OR 1.48	1.29-1.7	Rota et al[50]
Dietary factors			
Salty taste preferences	OR 1.59	1.25-2.03	Morais et al[53]
Always using table salt	OR 1.33	1.16-1.54	Morais et al[53]
Highest tertile of high-salt and salt-preserved food intake	OR 1.24	1.01-1.51	Morais et al[53]
Intake of citrus fruits	OR 0.87	0.76-0.99	Bae and Kim[56]
Weight			
Obesity	OR 1.13	1.03-1.24	Lin et al[58]
Males with obesity	OR 1.27	1.09-1.48	
Females with obesity	OR 1.04	0.7-1.39	
Diabetes	OR 1.01	0.94-1.07	Dabo et al[62]
Medications			
Statin use ever	aHR 0.83	0.74-0.92	Spence et al[64]
Aspirin	OR 0.64	0.58-1.02	Win et al[65]
First-degree relative with gastric cancer (USA)	RR 2.2	1.5-3.3	Yaghoobi et al[73]

Note. *H. pylori* = *Helicobacter pylori*; OR = odds ratio; aHR = adjusted hazard ratio; RR = relative risk; USA = United States of America.

Pham et al Foregut 2023

World Journal of Gastroenterology

World J Gastroenterol. 2014 May 21; 20(19): 5903–5911.
Published online 2014 May 21. doi: 10.3748/wjg.v20.i19.5903

PMCID: PMC4024801
PMID: 24914352

Histological changes of gastric mucosa after *Helicobacter pylori* eradication: A systematic review and meta-analysis

Yan-Jun Kong, Hong-Gang Yi, Jun-Cheng Dai, and Mu-Xin Wei

RESULTS: The results of the meta-analysis showed that the pooled weighted mean difference (WMD) with 95%CI was 0.23 (0.18-0.29) between eradication and non-eradication of *H. pylori* infection in antral IM with a significant overall effect ($Z = 8.19$; $P < 0.00001$) and no significant heterogeneity ($\chi^2 = 27.54$, $I^2 = 16\%$). The pooled WMD with 95%CI was -0.01 (-0.04-0.02) for IM in the corpus with no overall effect ($Z = 0.66$) or heterogeneity ($\chi^2 = 14.87$, $I^2 = 0\%$) (fixed effects model). In antral GA, the pooled WMD with 95% CI was 0.25 (0.15-0.35) with a significant overall effect ($Z = 4.78$; $P < 0.00001$) and significant heterogeneity ($\chi^2 = 86.12$, $I^2 = 71\%$; $P < 0.00001$). The pooled WMD with 95% CI for GA of the corpus was 0.14 (0.04-0.24) with a significant overall effect ($Z = 2.67$; $P = 0.008$) and significant heterogeneity ($\chi^2 = 44.79$, $I^2 = 62\%$; $P = 0.0003$) (random effects model).

CONCLUSION: *H. pylori* eradication strongly correlates with improvement in IM in the antrum and GA in the corpus and antrum of the stomach.

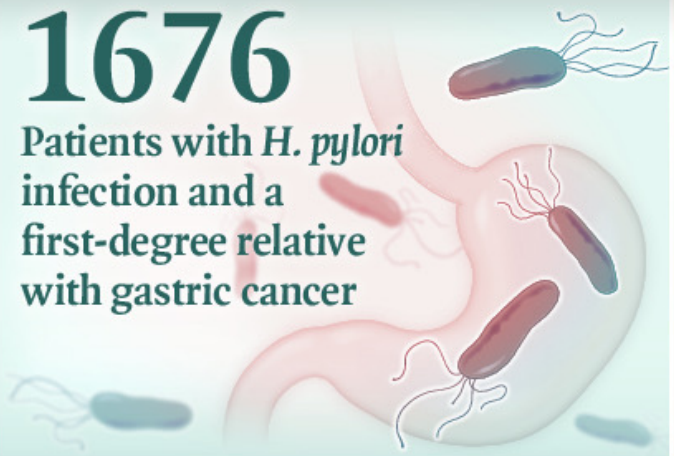
The NEW ENGLAND JOURNAL of MEDICINE

Family History of Gastric Cancer and *Helicobacter pylori* Treatment

SINGLE-CENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

1676

Patients with *H. pylori* infection and a first-degree relative with gastric cancer



	H. pylori Treatment	Placebo
	Lansoprazole (30 mg) + Amoxicillin (1000 mg) + Clarithromycin (500 mg)	
	Twice daily for 7 days	
Incidence of gastric cancer (median follow-up, 9.2 yr)	1.2% (10/832) (5/10 had persistent infection)	2.7% (23/844)
	HR, 0.45; 95% CI, 0.21–0.94; P=0.03	

H. pylori treatment reduced the risk of gastric cancer

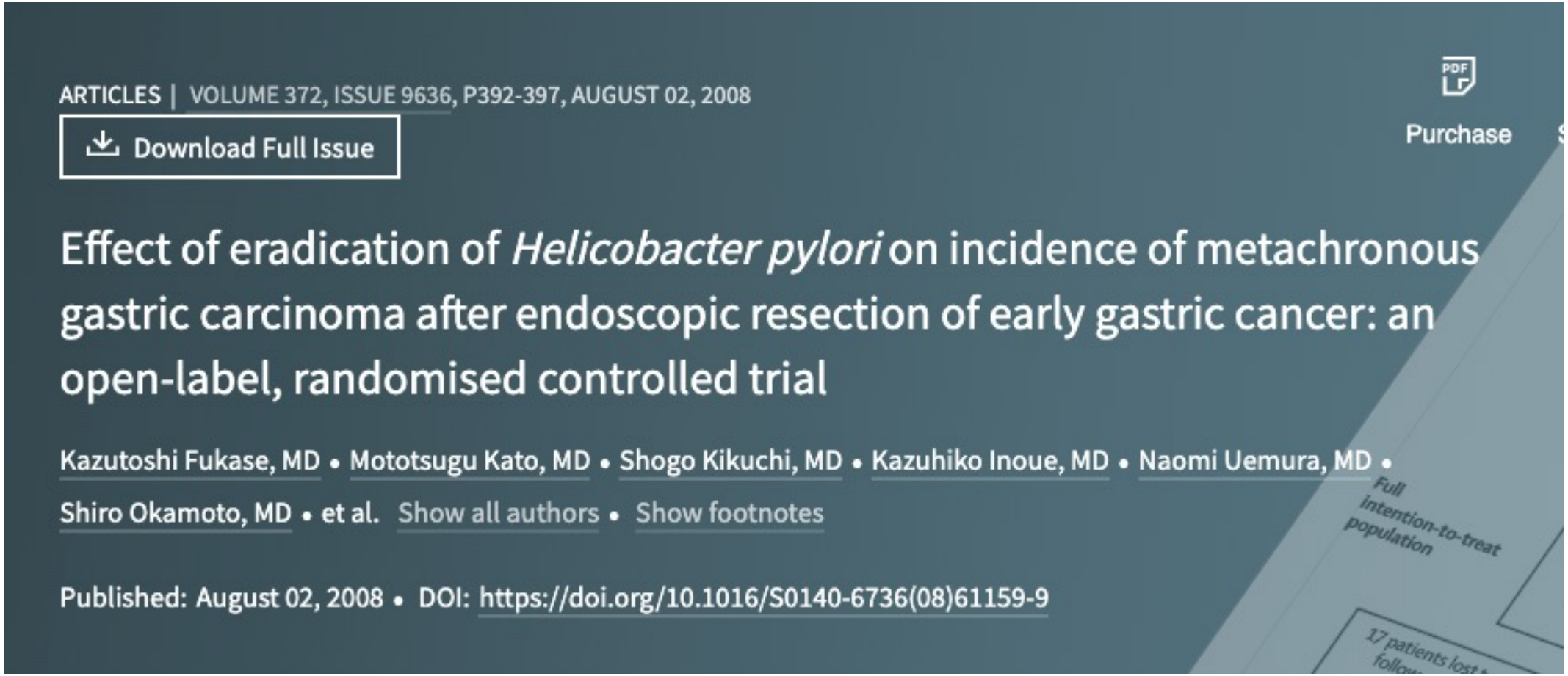
I.J. Choi et al. 10.1056/NEJMoa1909666

Cochrane Database Syst Rev. 2020; 2020(7): CD005583.
Published online 2020 Jul 6. doi: 10.1002/14651858.CD005583.pub3
PMCID: PMC7389270
PMID: 32628791

Helicobacter pylori eradication for the prevention of gastric neoplasia

Monitoring Editor: Cochrane Gut Group, Alexander C Ford, Yuhong Yuan, David Forman, Richard Hunt, and Paul Moayyedi

We found moderate certainty evidence that searching for and eradicating *H. pylori* reduces the incidence of gastric cancer and death from gastric cancer in healthy asymptomatic infected Asian individuals, but we cannot necessarily extrapolate this data to other populations.

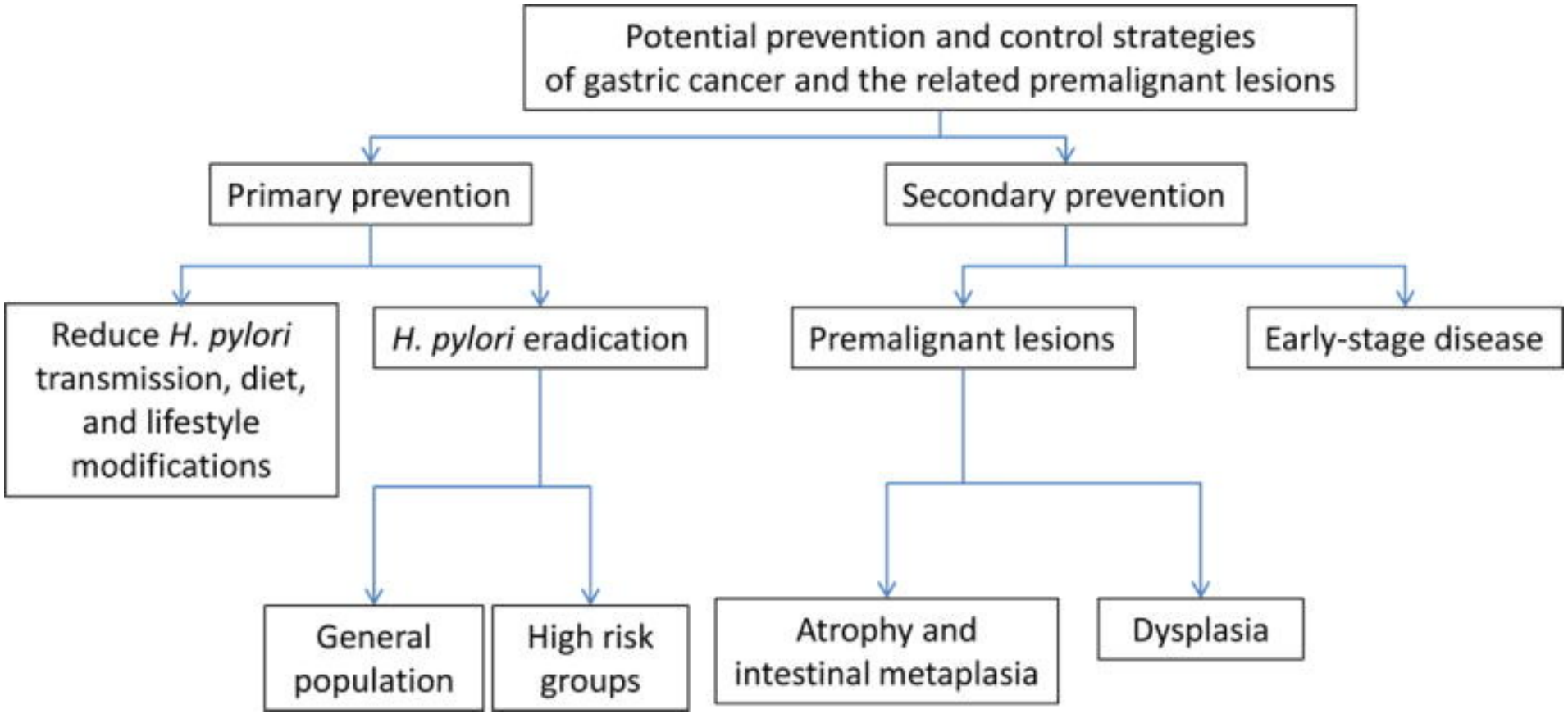


Findings

At 3-year follow-up, metachronous gastric carcinoma had developed in nine patients in the eradication group and 24 in the control group. In the full intention-to-treat population, including all patients irrespective of length of follow-up (272 patients in each group), the odds ratio for metachronous gastric carcinoma was 0·353 (95% CI 0·161–0·775; p=0·009

- **NSAIDs, Aspirin and COX-2 inhibitors**
- These are thought to reduce carcinogenesis by inhibiting cancer-associated prostaglandins, cytokines and angiogenic factors
- there is limited evidence to support their use because of low-quality studies performed in heterogeneous populations in countries with a high incidence of gastric cancer.
- **Antioxidants**
- A limited number of trials have explored the use of antioxidants for chemoprevention of gastric premalignant lesions but no evidence to support

SCREENING AND SURVEILLANCE



Leja M et al Best Pract Res Clin Gastroenterol. 2014

Clinical Features of Gastric Ca

- **Early gastric cancers**
- Often asymptomatic in early gastric cancers
- When symptoms occur, tend to mimic PUD

- **Advanced disease**:
- Weight loss (60%)
- Abdominal pain (50%)
- Nausea/vomiting, anorexia
- melena and early satiety

- Gastric outlet obstruction in tumors of antrum and pylorus
- Dysphagia in tumors of cardia
- Paraneoplastic syndromes

- Physical examination is usually unremarkable
- Cachectic
- Occasionally, epigastric mass, hepatomegaly, ascites and lower extremity edema

- Laboratory investigations are usually unremarkable until advanced stages
- Anemia
- Hypoproteinemia
- Elevated liver enzymes

- Gastric cancer is metastatic at the time of diagnosis in 33% of cases
- Liver (40%) of cases and peritoneum
- Other sites
- Periumblical lymph nodes (Sister Joseph nodule)
- Left supraclavicular sentinel nodes
- The pouch of Douglas
- Ovaries

Diagnosis

- Endoscopic examination and biopsies are the gold standard method for diagnosing gastric cancer
- Multiple (5- 8) biopsies should be carried out to provide adequately sized material for histological and molecular interpretation, especially in the setting of ulcerated lesions

Lordick F et al. Ann Oncol 2022

Staging of the disease

Table 2. Diagnostic and staging investigations in gastric cancer.

Procedure	Purpose
FBC	Assess for iron deficiency anaemia
Renal and liver function	Assess renal and liver function to determine appropriate therapeutic options
Endoscopy and biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. HER2 status
CT of thorax + abdomen ± pelvis	Staging of tumour – to detect local/distant lymphadenopathy and metastatic disease or ascites
EUS	Accurate assessment of T and N stage in potentially operable tumours Determine the proximal and distal extent of tumour
Laparoscopy + washings	Exclude occult metastatic disease involving peritoneum/diaphragm
PET, if available	May improve detection of occult metastatic disease in some cases. Often negative in diffuse-type gastric cancer
Assessment of nutritional status	May detect relevant dietary and nutritional deficiencies in both localised and advanced disease settings

CT, computed tomography; EUS, endoscopic ultrasound; FBC, full blood count; HER2, human epidermal growth factor receptor 2; N, node; PET, positron emission tomography; T, tumour.

Lordick F et al. Ann Oncol 2022

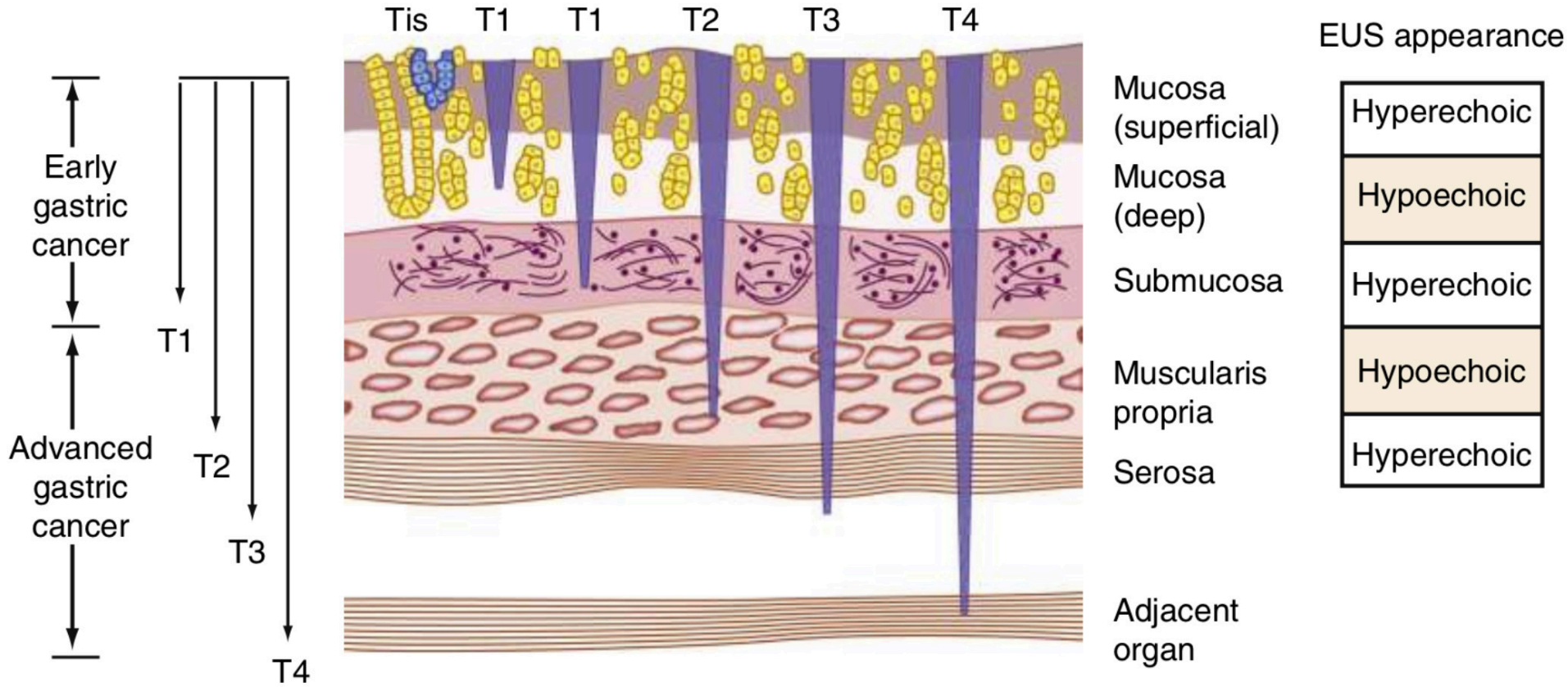


Fig. 54.8 Classification of gastric adenocarcinoma by depth of invasion (T classification). In the TNM classification, T denotes depth of invasion: Tis designates carcinoma in situ; T1 tumors are confined to the mucosa (T1a) and submucosa (T1b); T2 tumors invade the muscularis propria but not the serosa; T3 tumors penetrate the subserosal connective tissue without involving the visceral peritoneum or contiguous structures; and T4 tumors invade the serosa (visceral peritoneum) and may involve adjacent organs and tissues. In early gastric cancer, the disease is confined to the mucosa and submucosa (T1), regardless of nodal involvement.

- In the TNM staging system,
- **T (Tumor)** indicates the depth of penetration
  - T1a denotes a tumor that invades the lamina propria or mucosa,
  - T1b denotes invasion of the submucosa,
  - T2 denotes invasion of the muscularis propria,
  - T3 denotes invasion of the subserosal connective tissue,
  - T4a denotes invasion of the serosa (visceral peritoneum), and
  - T4b denotes invasion into adjacent organs or structures.
- **N (Nodes**) indicates the amount of lymph node invasion:
  - N0 denotes no lymph node involvement,
  - N1 denotes involvement of 1 to 2 lymph nodes,
  - N2 denotes involvement of 3 to 6 lymph nodes, and
  - N3 denotes involvement of 7 or more lymph nodes.
- **M (Metastasis)** indicates the presence of metastases, with
  - M0 denoting no metastases and
  - M1 denoting distant metastases, including positive peritoneal cytology

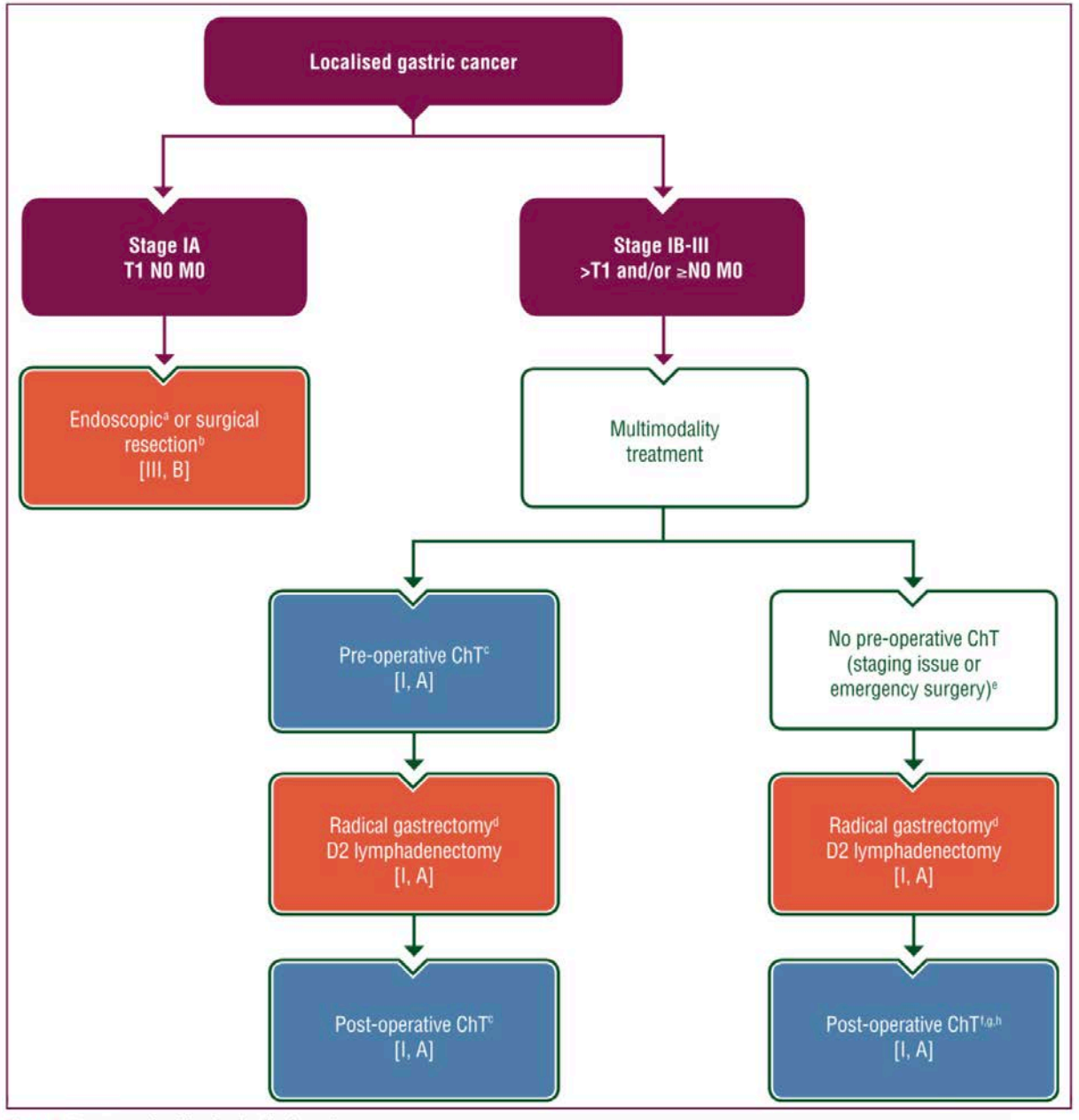
TABLE 54.4 Clinical Staging of Gastric Cancer Based on the TNM Classification

	N0	N1	N2	N3	M1 (Any N)
Tis	0	—	—	—	—
T1	IA	IB	IIA	IIB	IV
T2	IB	IIA	IIB	IIIA	IV
T3	IIA	IIB	IIIA	IIIB	IV
T4a	IIB	IIIA	IIIB	IIIC	IV
T4b	IIIB	IIIB	IIIC	IIIC	IV

is, in situ; M, metastases; *N*, node involvement; *T*, tumor.

*From Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM Classification of Malignant Tumours. 8th ed. Hoboken, NJ: Wiley-Blackwell; 2017.

Treatment algorithm for localised GCa



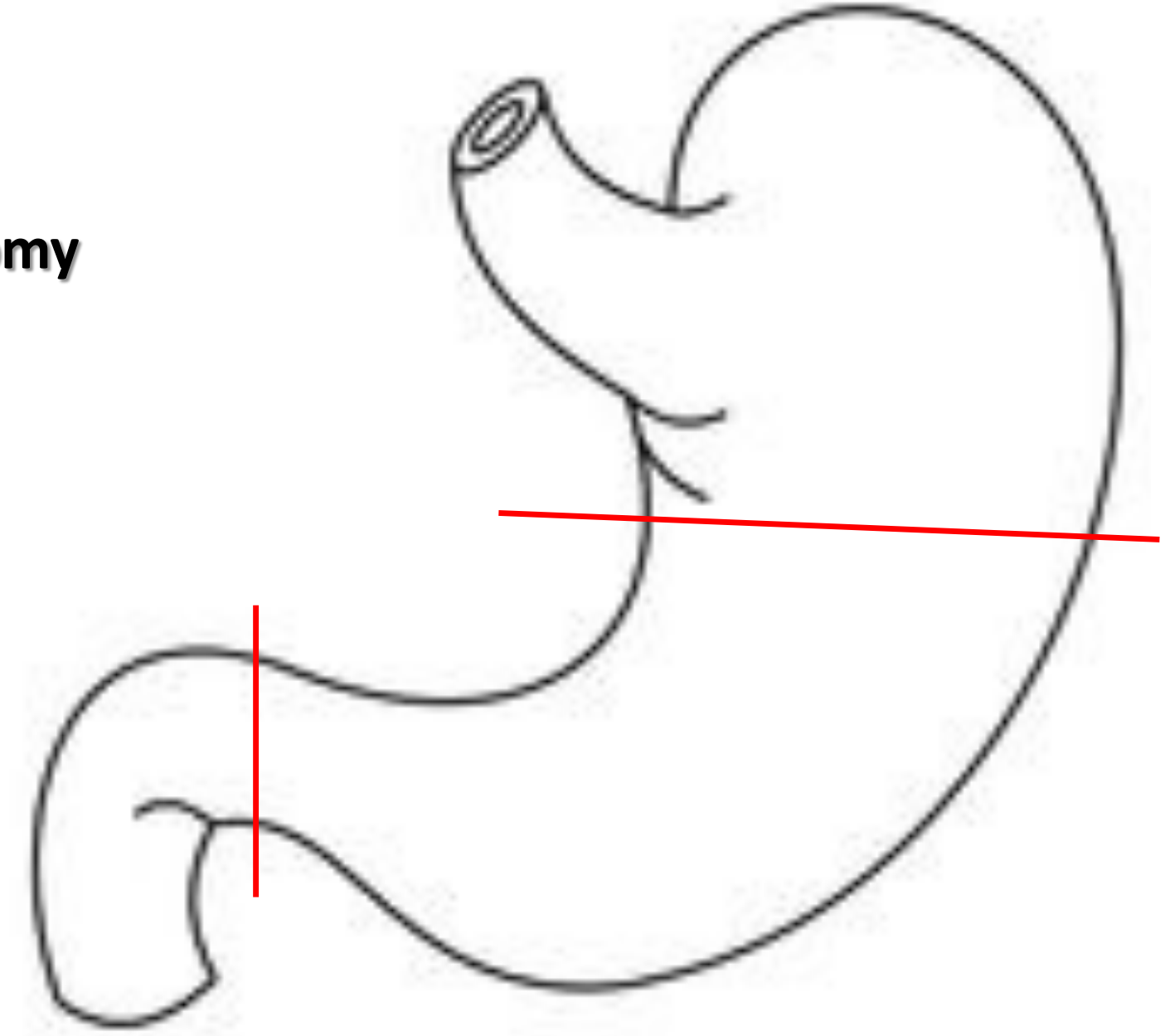
Surgery

- Choice in Operation:
  - **Approach:**
    - Open
    - Minimally-invasive
    - Robotic
  - **Resection:**
    - Distal/partial Gastrectomy
    - Subtotal Gastrectomy
    - Total Gastrectomy
  - **Reconstruction:**
    - Roux-en-Y/Billroth II
    - Retro-/antecolic
    - Anterior/posterior gastric wall
  - **Lymphadenectomy**

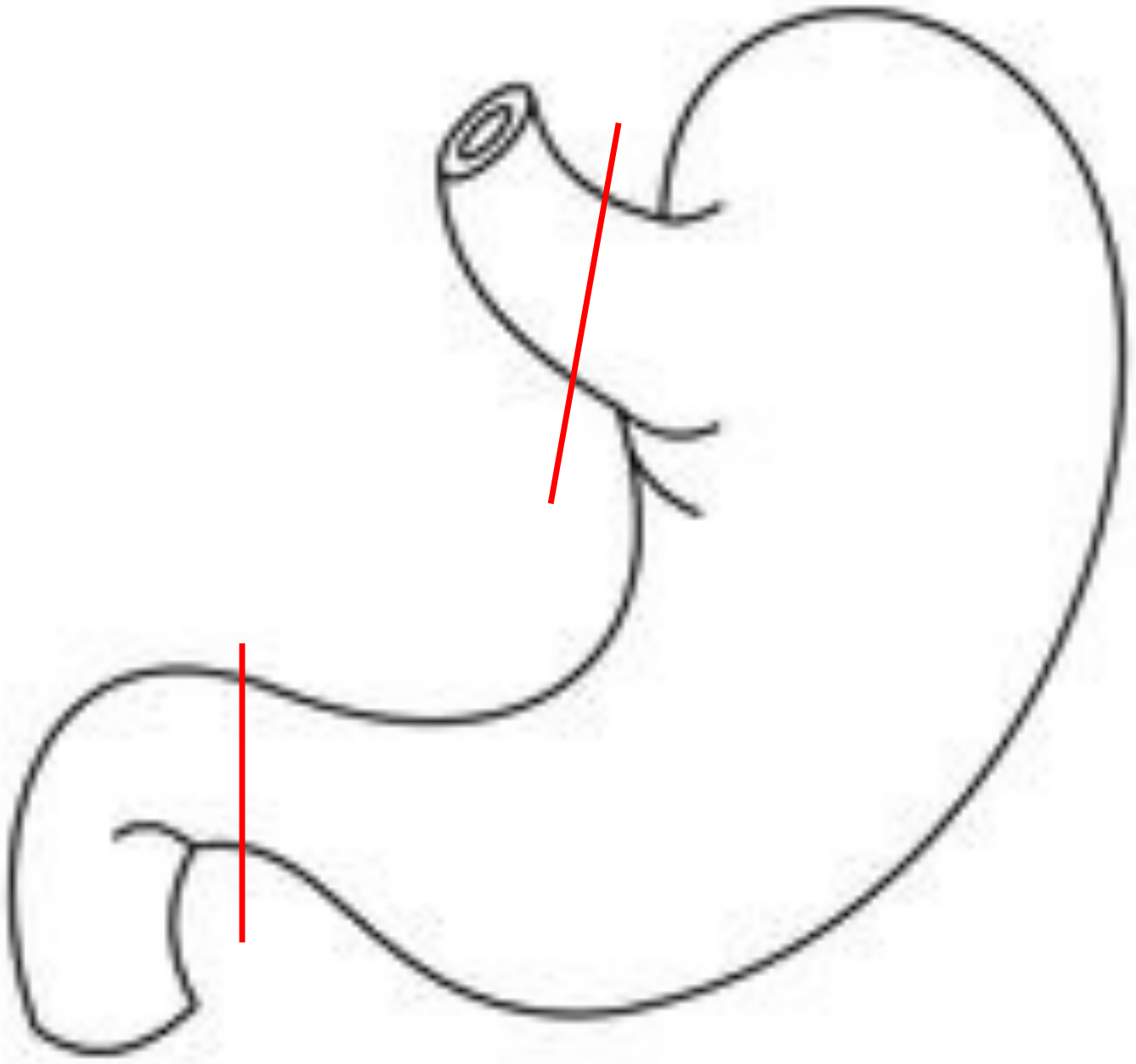
Resections

- Partial Gastrectomy
- Subtotal Gastrectomy
- Total Gastrectomy

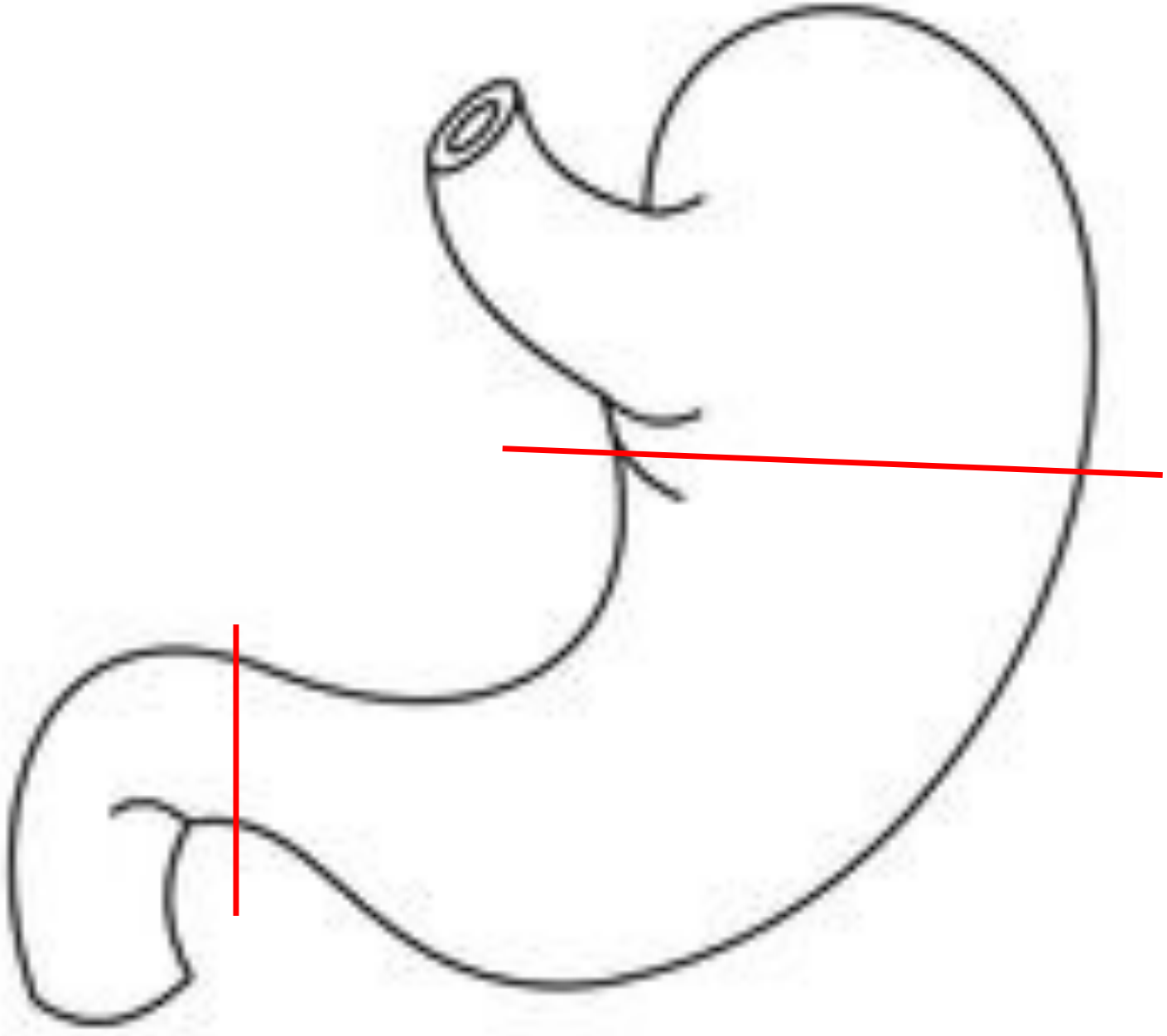
- **Partial/Distal Gastrectomy**



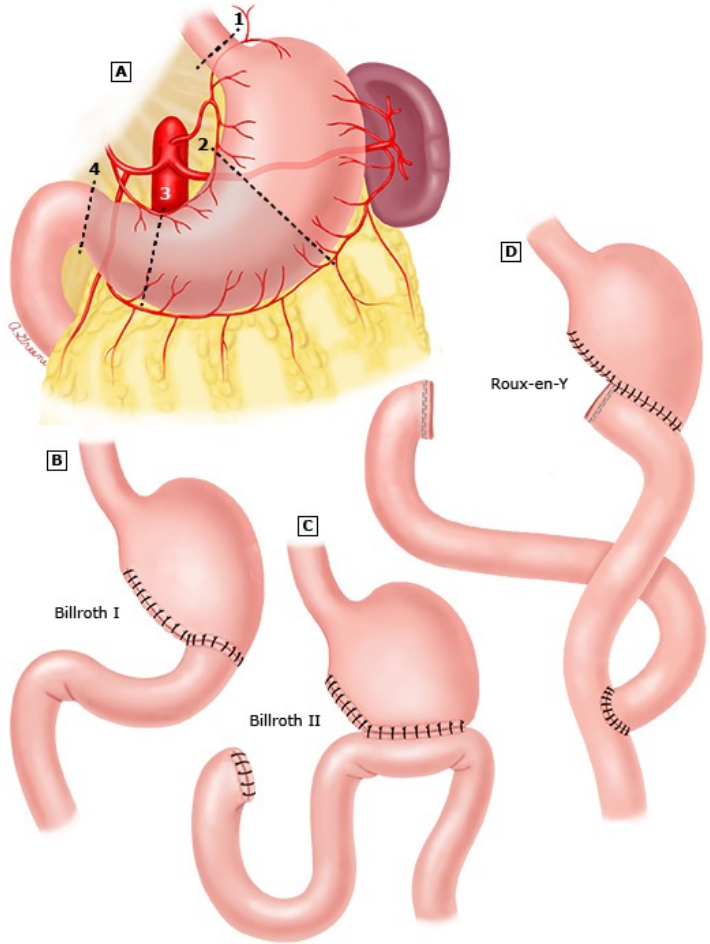
- **Total Gastrectomy**



- **Subtotal Gastrectomy**



Partial gastrectomy and reconstruction



Distal (partial) gastrectomy is performed by removing the distal portion of the stomach (A, shaded region between line 2 and line 4). Gastrointestinal continuity can be restored using one of three techniques. The first (B), known as a Billroth I reconstruction, anastomoses the stomach to the duodenal remnant. The Billroth II reconstruction (C) brings up a loop of proximal jejunum to create an end-to-side gastrojejunostomy. Another option is a Roux-en-Y gastrojejunostomy (D), in which the more distal jejunum is anastomosed to the stomach in an end-to-side fashion.

Take home message

- Gastric cancer is a major health problem, making fifth for incidence and cancer-related mortality globally
- Even though early recognition is possible, most cases are diagnosed late
- Important to recognize premalignant conditions and regular surveillance and to intervene to prevent advanced malignancy

THANK YOU