Gastric Cancer
Risk factors and Common Presentations

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Gastric cancer (GC)

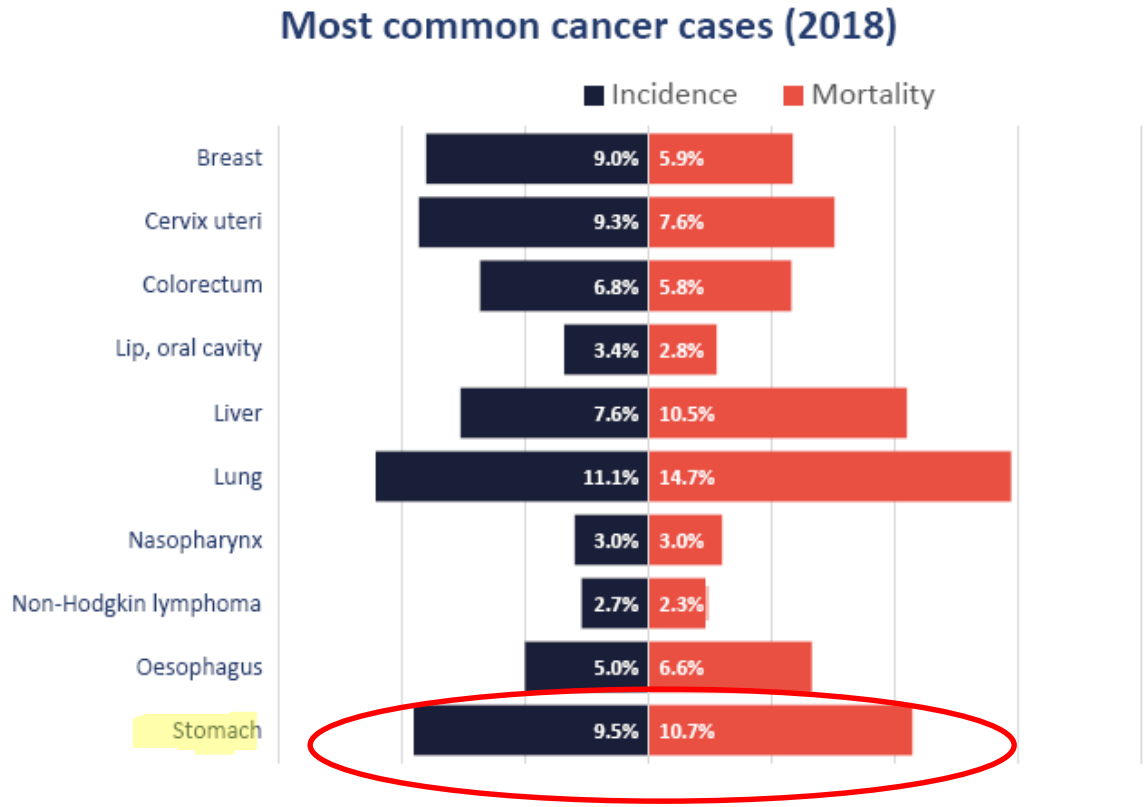
- ranks fifth for cancer incidence
- fourth for cancer related mortality
- with over 1 million new cases worldwide in 2020

Ferlay, J et al (2021) *Int. J. Cancer* , 149, 778–789.

Myanmar Data

- **Cancer as 25.3 % of NCD premature deaths**
- > 51,000 cancer deaths in 2018

Ferlay *et al*., (2020). Cancer Myanmar - country profile WHO 2020



Gastric Cancer stands for 2nd most common cause of malignancies and also the 2nd most common cause of cancer related deaths

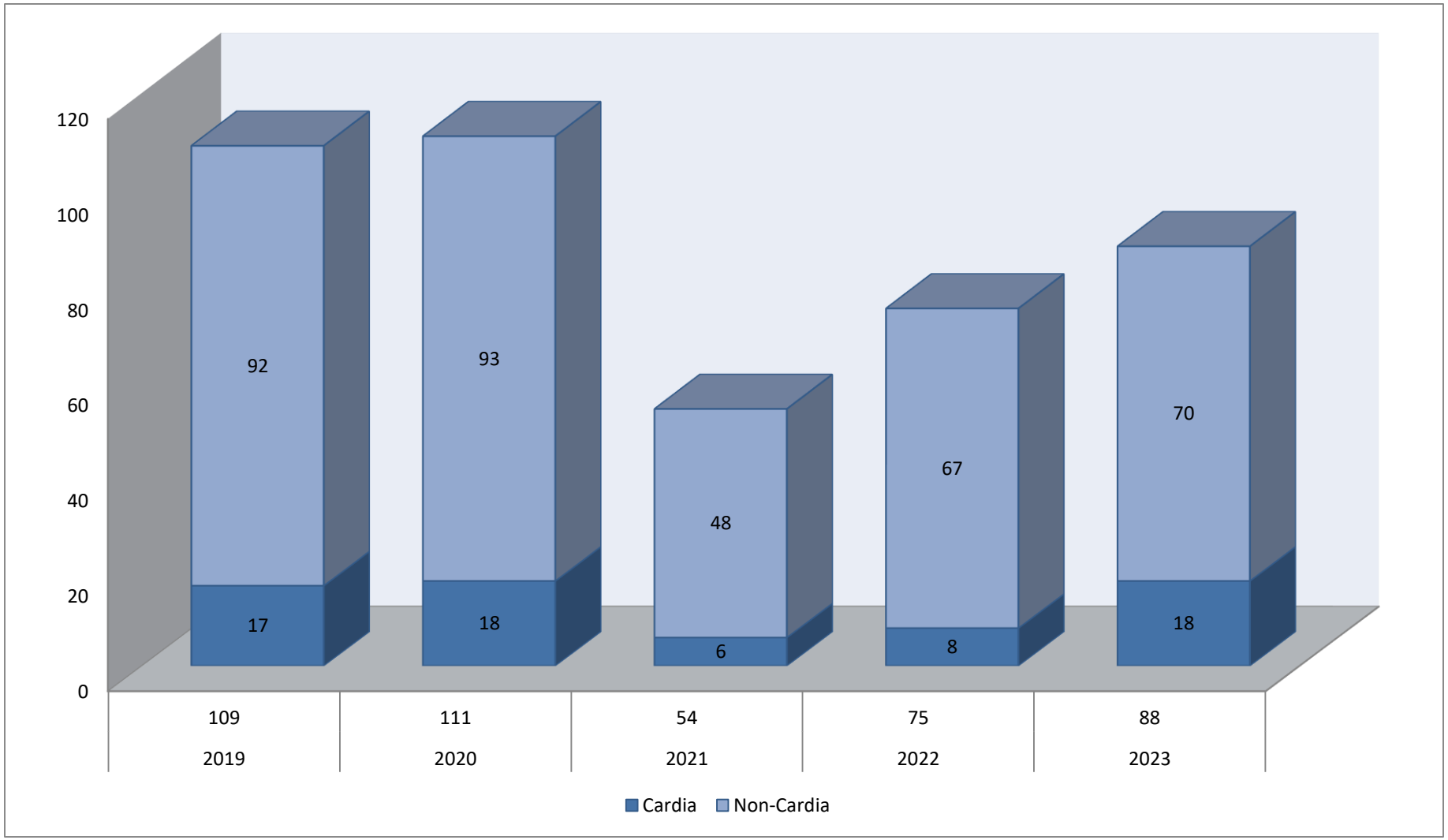
Cancer Myanmar - country profile WHO 2020

Departmental Data (TGH)

- detection rate of new cases of gastric cancer increased
- 4.3 % (109 out of 2507 EGD patients) in 2019
- 6.5 % (75 out of 1153 EGD patients) in 2022
- 5.2 % (88 out of 1700 EGD patients) in 2023

(TGH Registry, 2019-2023)

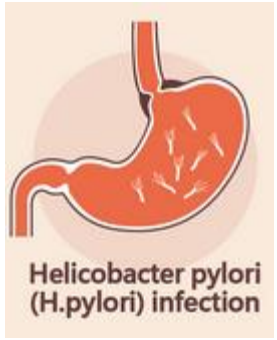
New cases of Gastric cancer (2019-2023)

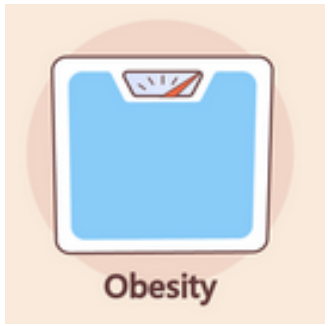


I. Risk Factors

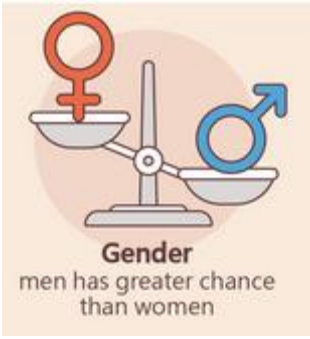
- Gastric cancer is a multifactorial disease, with both environmental and genetic factors play a role in its pathogenesis.

- Risk Factors
  - (1) strengths of associations between risk factors and gastric cancer
  - (2) reduction of known risk factors





- The main risk factors for GC are
  - Helicobacter pylori (Hp) infection
  - Tobacco smoking
  - Alcohol consumption
  - High intake of meat
  - High salt intake
  - Obesity
  - Family History
  - Gastric Premalignant conditions
    - Atrophic Gastritis
    - Intestinal Metaplasia
    - Dysplasia



Conti CB et al (2023) *Int. J. Environ. Res. Public Health* 20, 2149

Risk factors for gastric cancer

Cardia	Noncardia
Age	Age
Male sex	Male sex
Tobacco smoking	Tobacco smoking
Race	Race
Family history	Family history
Low physical activity	Low physical activity
Fiber intake	Fiber intake
Radiation	Radiation
—	*H. pylori*
—	Low socioeconomic status
—	High intake of salty and smoked food
—	Low consumption of fruits and vegetables
Obesity	—
GERD	—

Karimi P *et al (2014)* Gastric Cancer: *Prev*; 23(5) May 2014

Non-modifiable risk factors

Age

Male sex (4:1 for Cardia and 2.1:1 for Non-Cardia GC)

Family History

- Hereditary diffuse gastric cancer syndrome (HDGC)
- Lynch syndrome (LS)
- Li–Fraumeni syndrome (LFS)
- Familial adenomatous polyposis (FAP)
- Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS),
- Peutz–Jeghers syndrome (PJS)
- Juvenile polyposis syndrome (JPS)
- Familial intestinal gastric cancer (FIGC)
- Seppälä TT et al (2023) *BJS Open*. Jun; 7(3)

Helicobacter pylori

- Class I carcinogen and main environmental risk factor for GC
- Up to 89% of non-cardia gastric cancer (NCGC) can be attributed to chronic *H pylori* infection
- Chronic *H pylori* infection can lead to both
  - Gastric adenocarcinoma, by modifying the epithelial-mesenchymal transition, cell migration and cell invasion
  - MALT lymphoma, which is often reversible only with *H pylori* eradication

Morgan, A.D et al (2022). *Cancers* 2022, 14, 4886.

Helicobacter pylori

- Once infected and without a proper diagnosis and treatment, chronic infection will increase the risk of developing GC 1.4 to 4.2 times more than for the general population.

- Eradication definitely reduces GC incidence and mortality

- If all *H pylori* infections were eradicated, approximately 89%, 29% and 74% of NCGC, CGC and gastric non-Hodgkin lymphoma, respectively, would be prevented.

Ford, A.C et al (2020). *Gut* 69, 2113–2121

Tobacco smoking

- classified as a group 1 carcinogen for GC.
- Higher association with cardia GC
- the risk increases with amount and duration of smoking
  - by 32% for more than 20 cigarettes/day and
  - by 33% for smoking duration of ≥ 40 years as compared to never smokers
- The probability of developing GC is similar to that of non-smokers about 10 years after quitting.

Praud, D et al.(2018) Eur. J. Cancer Prev. 2018, 27, 124–133.

Alcohol drinking

- associated with an increased risk of GC, especially ≥30 g/day
- An OR of 1.30 was found in the subset of heavy drinkers
- Increased gastric cancer risk may be attributed by Acetaldehyde
  - the first metabolite of ethanol which could induce DNA lesions by the inhibition of DNA methylation
  - ALDH2 rs671, a polymorphism of an enzyme involved in alcohol metabolism, seems to increase the concentration of acetaldehyde after drinking
-

Deng, W. et al (2021) *Chem.Interactions* 2021, 336, 109365.

Diet – Processed meat and red meat

- Consumption of red meat and processed meat (smoked and salted) is associated with the development of non-cardia GC.

- Meta-analysis of dose-response demonstrates a 26% increased risk of GC for 100 g/day of red meat intake and a 72% increased risk for 50 g/day of additional processed meat intake

- Factors play a role in gastric carcinogenesis
  - carcinogen compounds such as heme iron and N-nitroso compounds
  - Heterocycles amine and polycyclic hydrocarbons released on high temperature cooking
  - presence of bacterial plasmids (DNA) from meat

Kim, S.R (2019 *Nutrients* 2019, 11, 826.

High Salt Intake

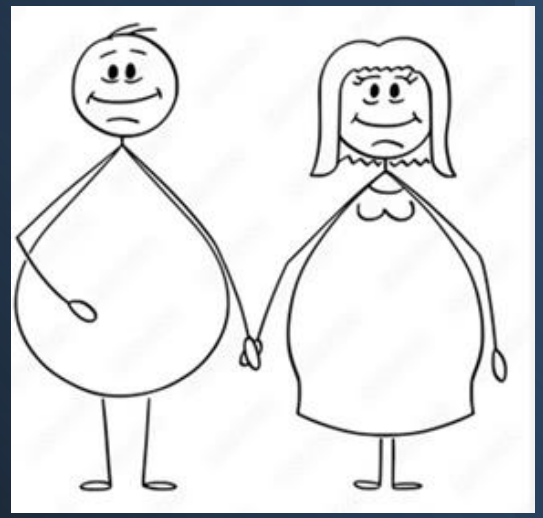
- Excessive salt intake can generate carcinogenic substances called **N-nitrosamines**, leading to damage to the gastric cell walls, inflammation, and atrophy, which increases the colonization of *H. pylori*

- A pooled analysis including > 30000 participants showed that highest salt-containing food consumption group had a 1.24-fold increased risk of GC compared to that in the lowest consumption group.

Morais S et al. (2022). *Cancer Causes Control* ;33:779-791.

Obesity

- There is a linear association between BMI and the risk of GC.
- It is more closely related to cardia GC.
- Obesity may increase the incidence of gastro-esophageal reflux, which is a recognized cause of Barrett's esophagus and, eventually, esophageal adenocarcinoma and cardia GC.



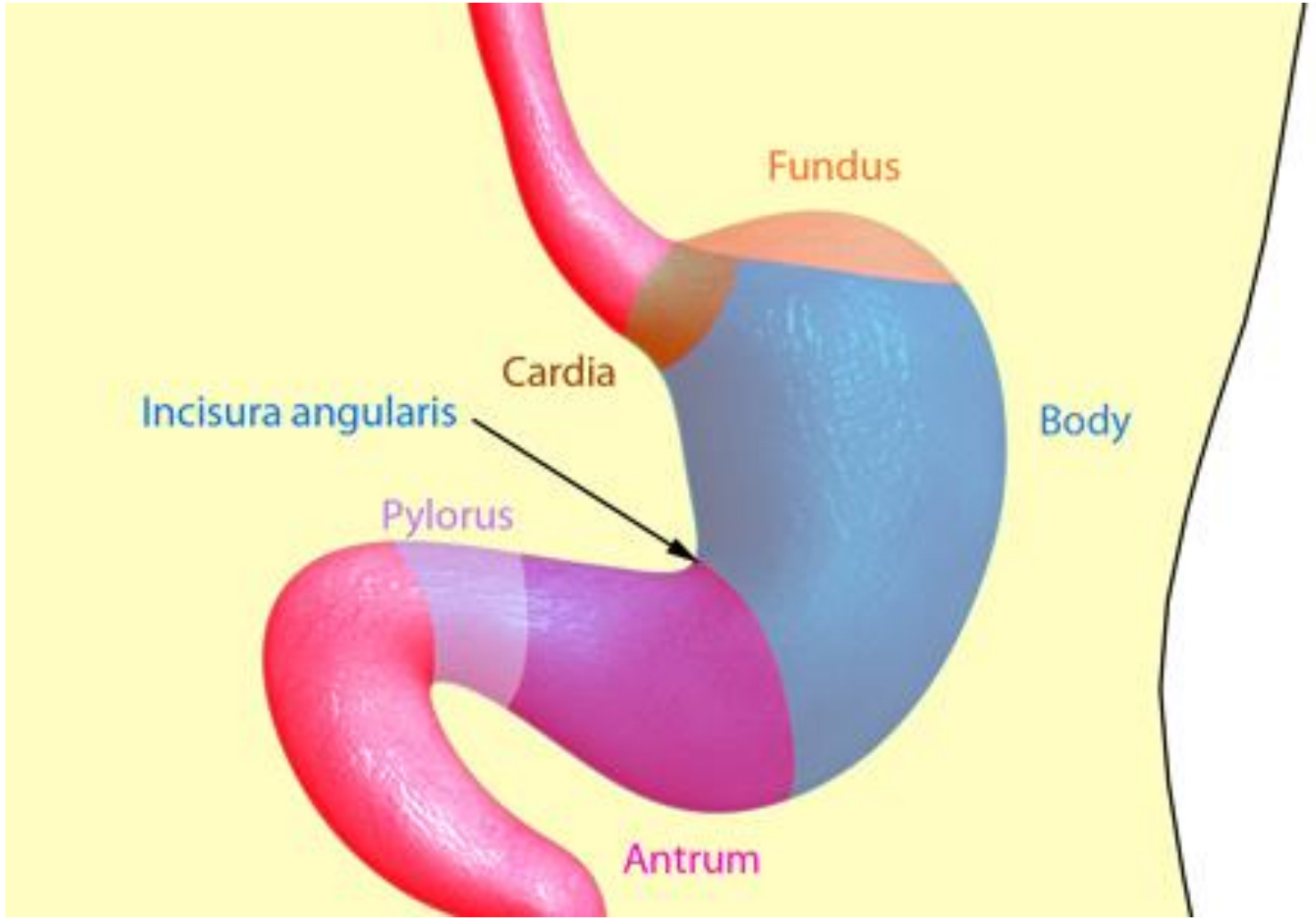
- Wu, A.H et al (2003) Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer* 98, 940–948.

Premalignant conditions – risks for developing GC

- Atrophic Gastritis (AG)
- Intestinal Metaplasia (IM)
- Dysplasia

- The risk of GC with these conditions depends on their
  (I) Extent
  (II) Severity

Different parts of the stomach

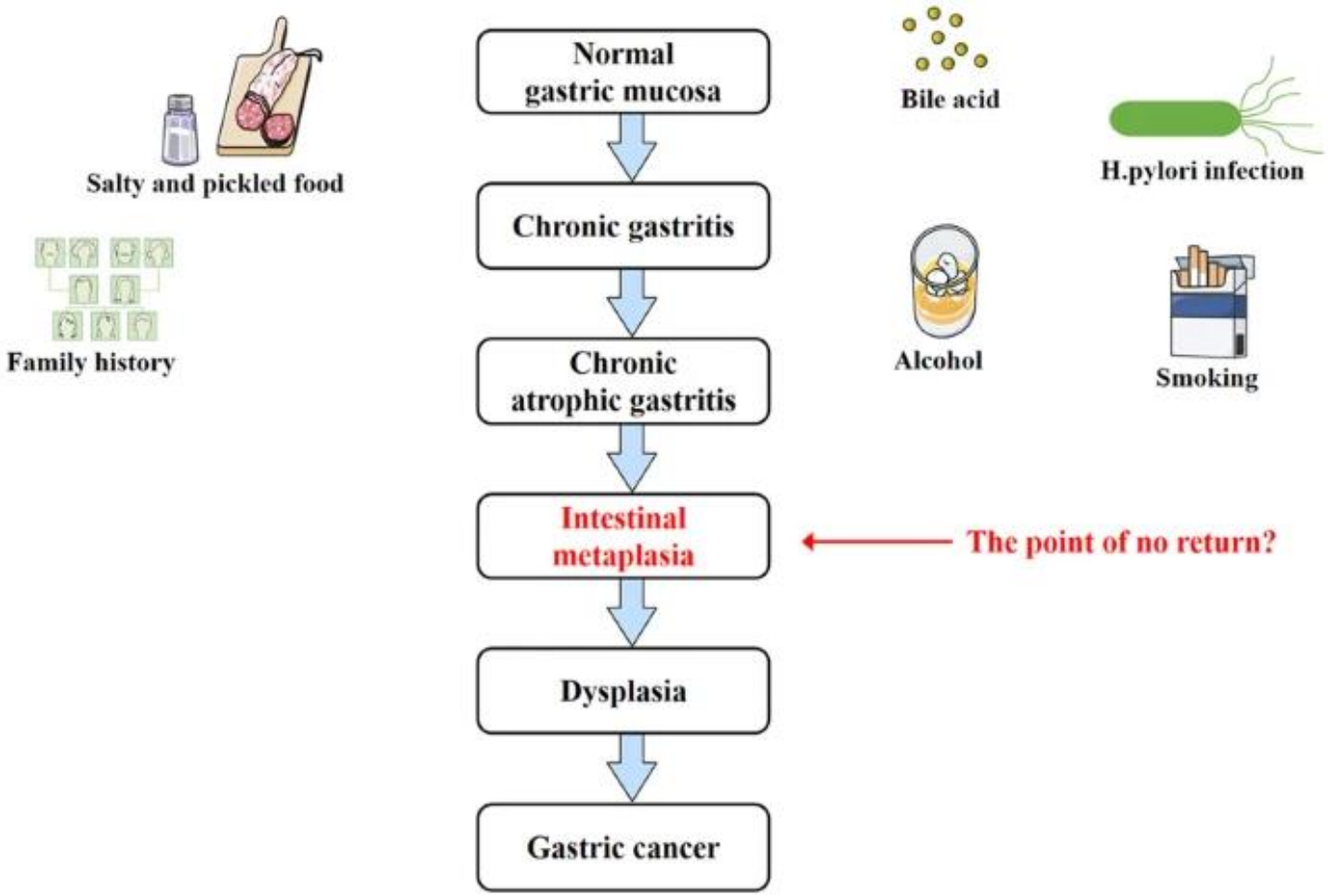


- According to Correa's multistep and multifactorial carcinogenesis pathway of the intestinal type gastric cancers;

- In a subset of patients infected with *H. pylori*, the inflammatory process leads to the development of atrophic gastritis (with loss of glandular tissue) followed by progression to intestinal metaplasia, dysplasia, early gastric cancer, and, eventually, advanced gastric cancer.

Correa, P. (1992) *Cancer Res*: **52;** p.6735-40.

GC development following the Correa's cancer cascade



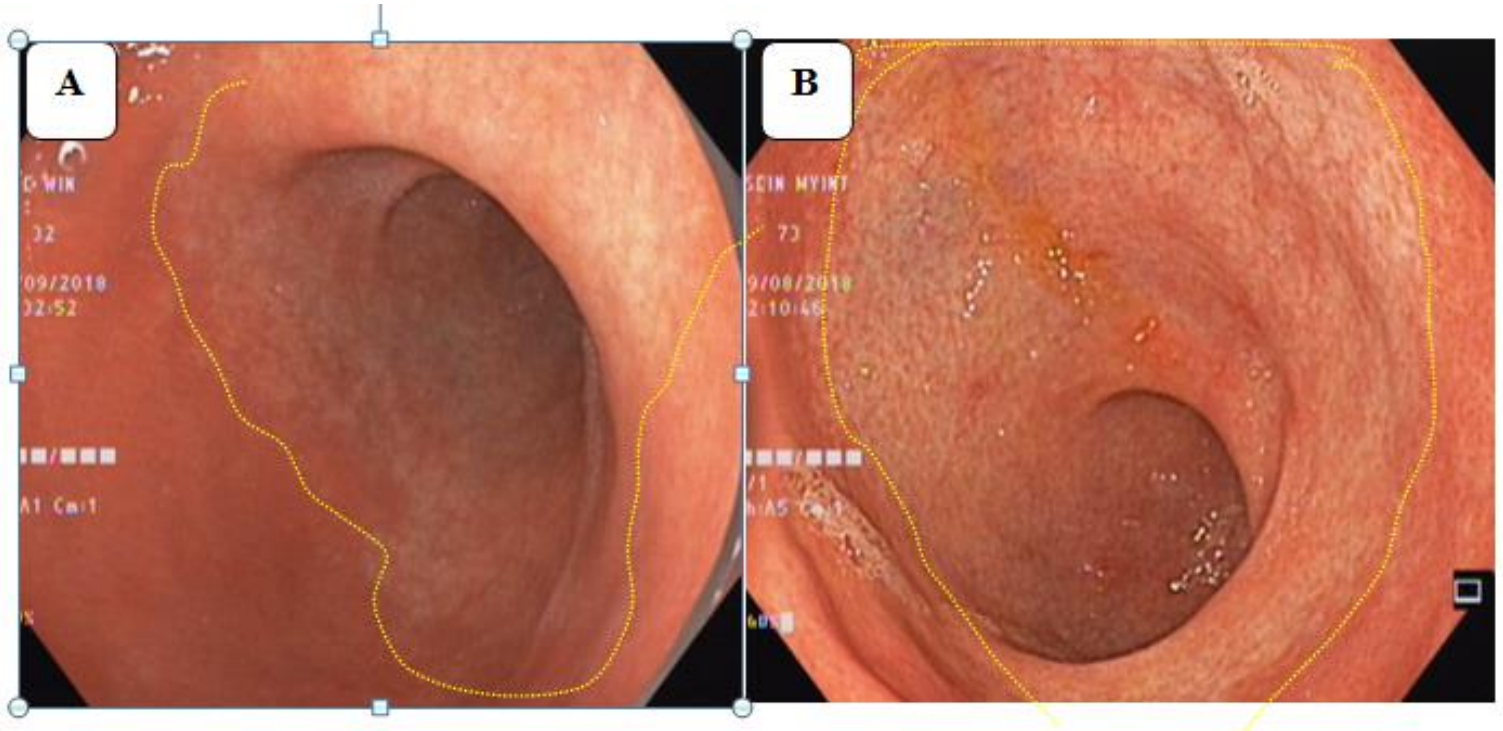
He Q *et al* (2022) *Cell Death Discovery* (2022) 8:158

- **<u>Atrophic Gastritis</u>**

- Pathologically, it is defined as a loss of glandular tissue

- Endoscopically, gastric atrophy appears as pale gastric mucosa, increased visibility of the surface vasculature due to thinning of the gastric mucosa and loss of gastric folds

Kimura K, Takemoto T. (1969) *Endoscopy* ; 3: 87-97



- Figure Atrophic gastritis on white light examination showing the atrophic borders (A) Closed Type 2 AG with involvement beyond the incisura (B) Open Type 2 AG with involvement of the anterior and posterior walls of the gastric corpus

Atrophic Gastritis

- Typically begins at the antrum and expand to the corpus
- Once developed, progression of AG to gastric adenocarcinoma ranges from 0.1 % to 0.3 % per year

Vannella L *et al.* (2010) *Aliment Pharmacol Ther* 31:1042–1050.

Atrophic Gastritis

- Recent Meta-analysis in 2020
- > 650,000 participants and 2,794 patients with gastric cancer were analyzed.
- The pooled results suggested that gastric atrophy was associated with an elevated risk for gastric cancer [pooled risk ratio (RR) =2.91, 95% confidence interval (CI): 2.58–3.27].

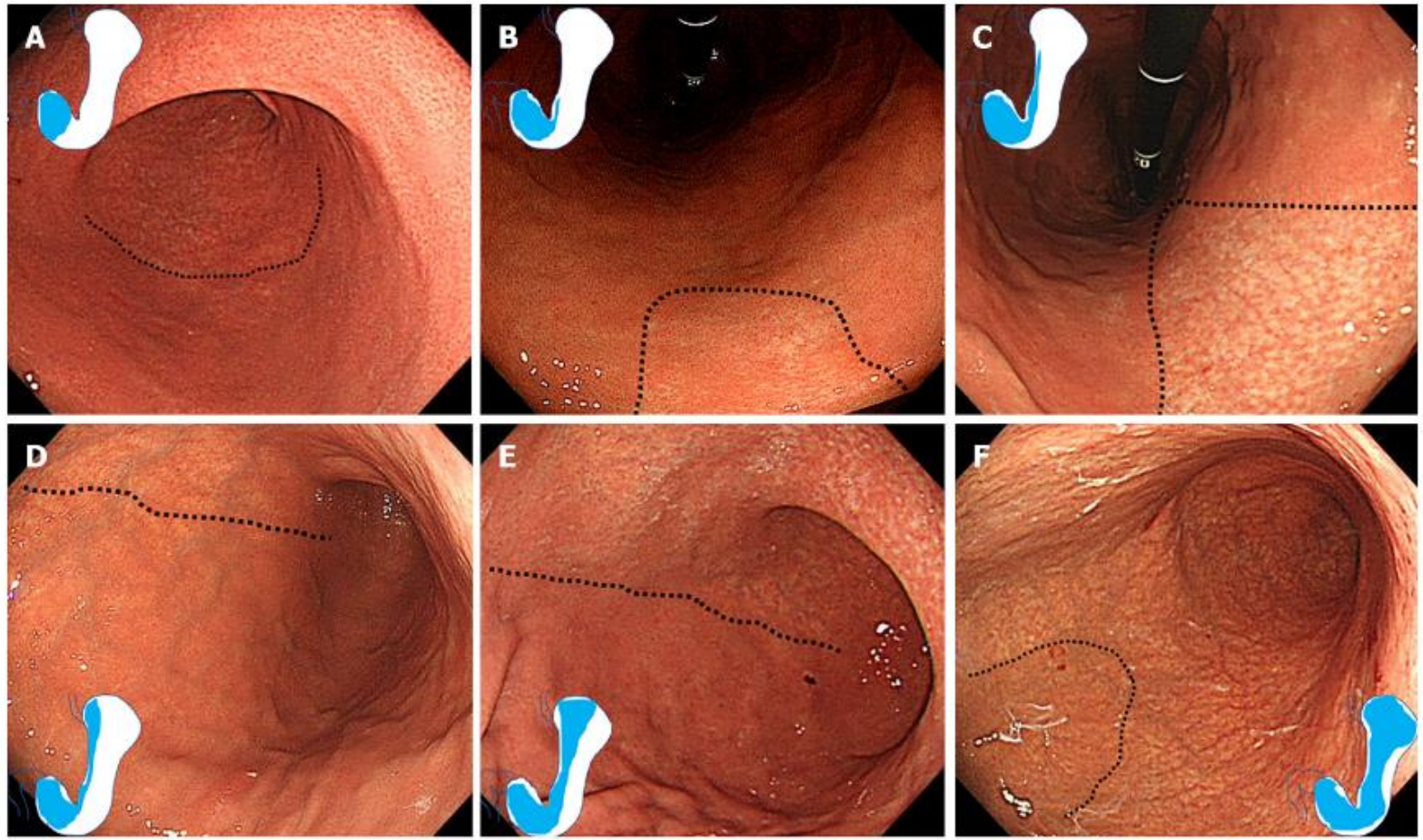
Sui Z et al (2020) *Transl Cancer Res* 2020;9(3):1618-1

Gastric cancer risk for pre-malignant stomach

Pre-malignant mucosa	Annual Incidence	5 yr cancer incidence	References
Severe gastric atrophy		**10%**	Zullo et al. [2012]
Mild gastric atrophy		0.7%	de Vries et al. [2008]
All grades of gastric atrophy	<0.5%	<2%	de Vries et al. [2008] Song et al. [2015] (49)
Antral & corpus intestinal metaplasia		**10%**	Shichijo et al. [2016]
Antral intestinal metaplasia		5%	Shichijo et al. [2016]
All grades of intestinal metaplasia	<0.4%		Spence et al. [2017]
		4 months to 2-year interval	
High grade **dysplasia**	6%	**60-85%**	de Vries et al. [2008]
Low grade dysplasia	0.6%	**0-23%**	de Vries et al. [2008] Song et al. [2015]

Banks M et al. (2019). *Gut* 68:1545-7

Kimura-Takemoto classification of endoscopic atrophy



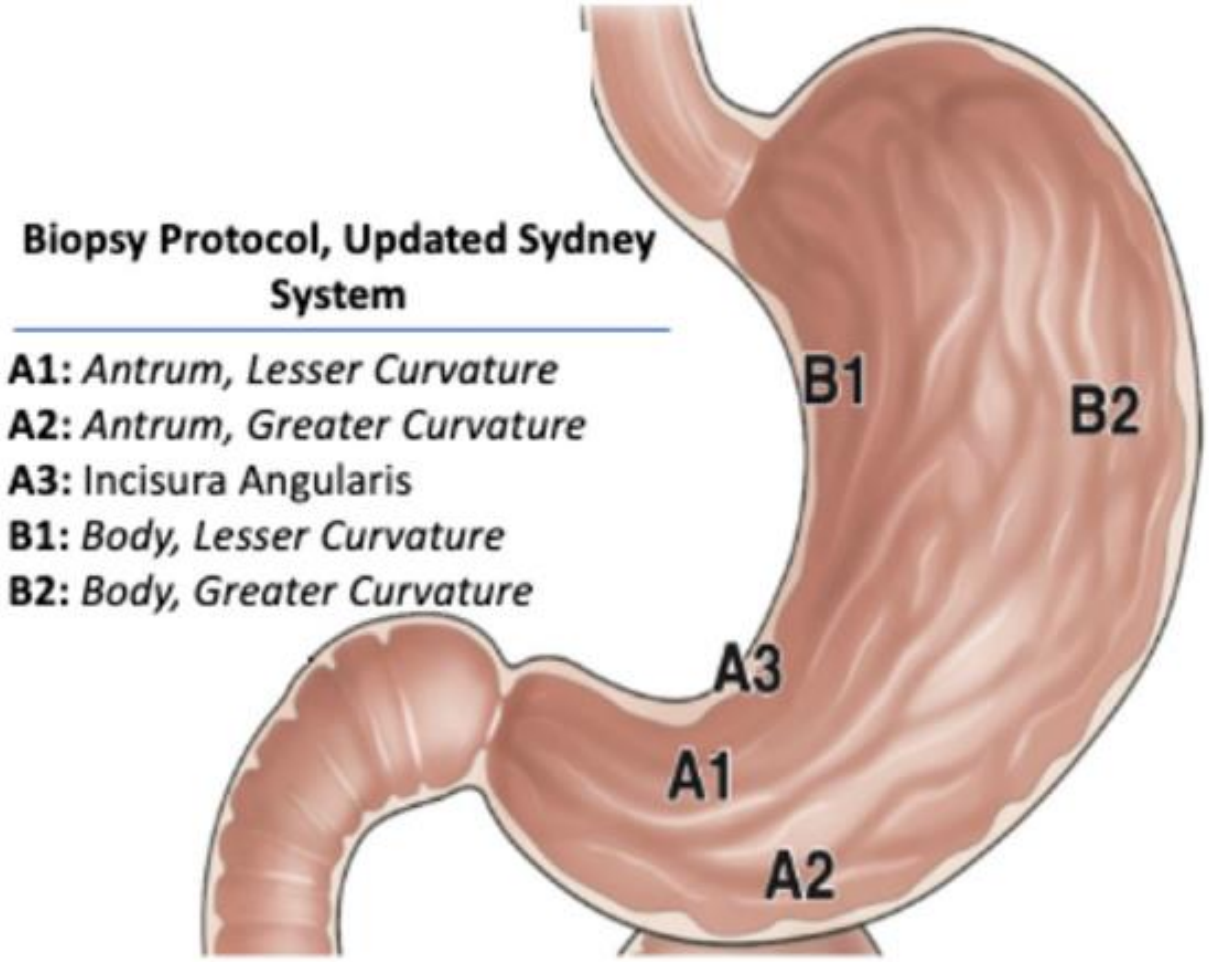
Toyoshima O et al (2020) *World J Gastroenterol* 26(5): 466-477

- While Kimura-Takemoto classification describe the extent of atrophic gastritis, Operative Link on Gastritis Assessment (**OLGA**) define the severity of atrophic gastritis and risk of Gastric cancer.

- OLGA system uses
  - gastric biopsy sampling protocol defined by Sydney System
  - the histological grading system recommended by the updated Sydney System.

Rugge, M eet al (2010) *AlimentPharmacol Ther*: **31**; p. 1104-11.

Updated Sydney System



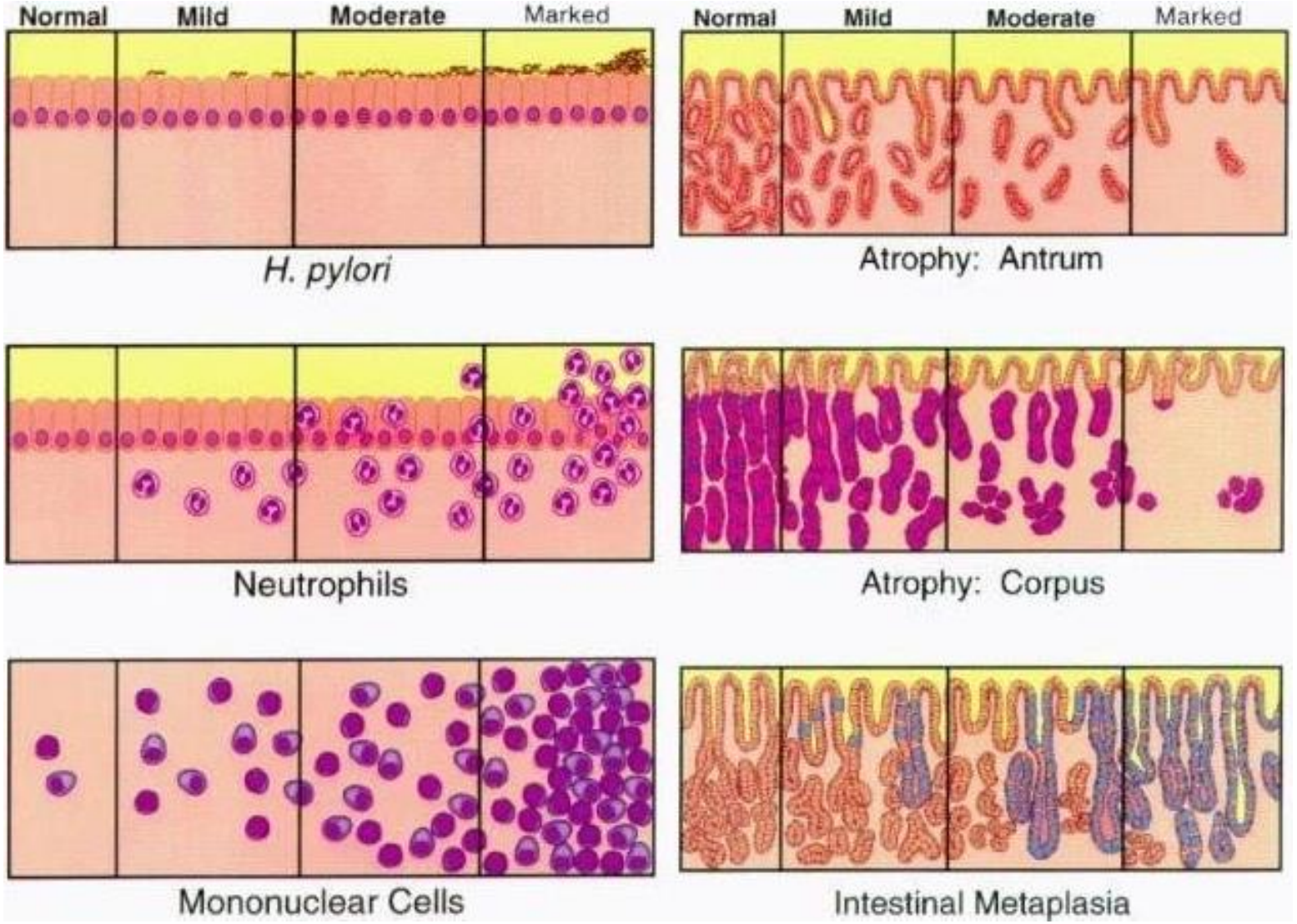


Figure : Visual analogue scale for grading of chronic gastritis: The Up-dated Sydney System

OLGA: Operative link on gastritis assessment staging system;

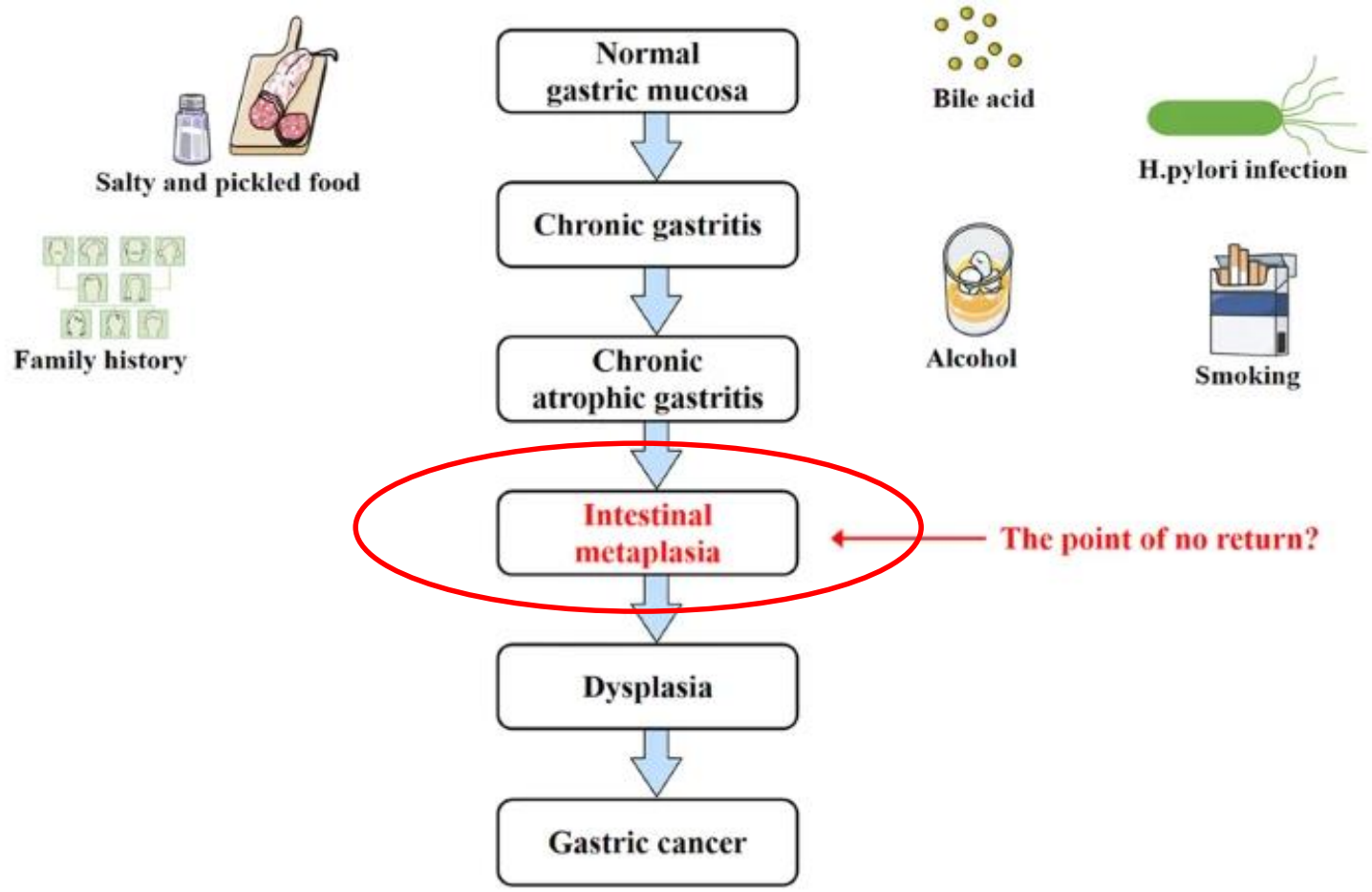
Atrophy score		Corpus			
		No atroph (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum (Including incisura angularis)	No atroph (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2)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

- Weng CY et al (2021) *World J Gastroenterol* 21; 27(31): 5152-5170

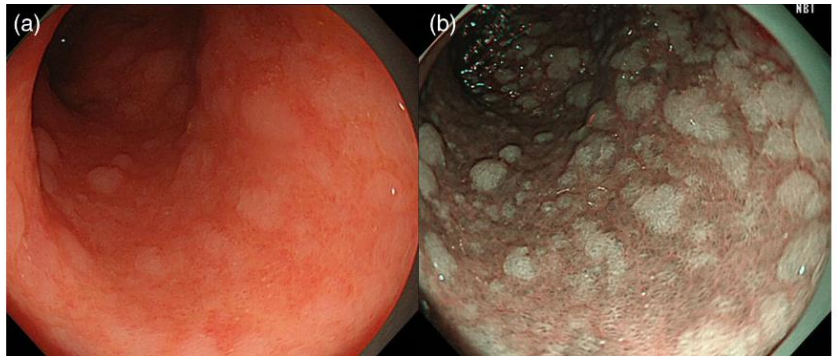
- Patients with higher OLGA stages (Stages III and IV) should be considered definitely candidates for endoscopic surveillance.

Rugge, M eet al (2010) *AlimentPharmacol Ther*: **31**; p. 1104-11.

Gastric Intestinal Metaplasia in GC development following the Correa's cancer cascade



He Q *et al* (2022) Roles and action mechanisms of bile acid-induced gastric intestinal metaplasia: a review *Cell Death Discovery* (2022) 8:158



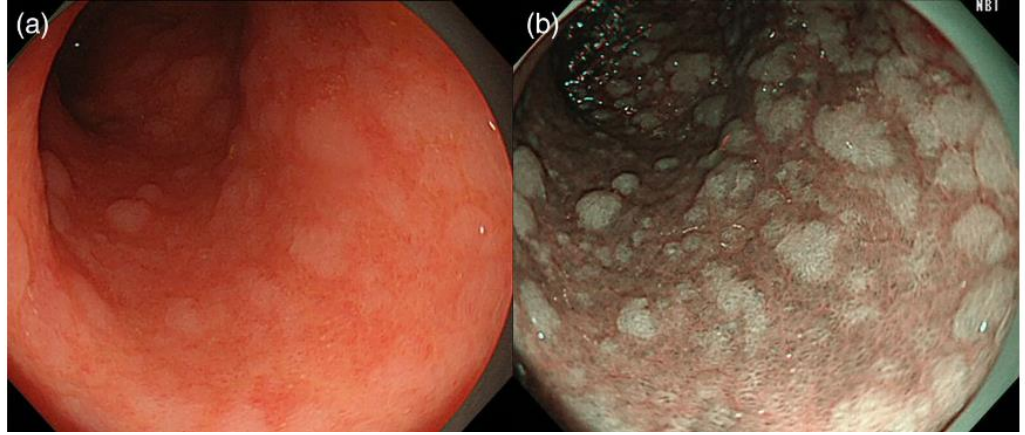
Intestinal Metaplasia

- Is defined as the appearance of intestinal epithelium in the stomach.

- At white light endoscopy (WLE), intestinal metaplasia typically appears as small, grey-white, elevated plaques surrounded by mixed patchy pink and pale areas of mucosa causing an irregular uneven surface.

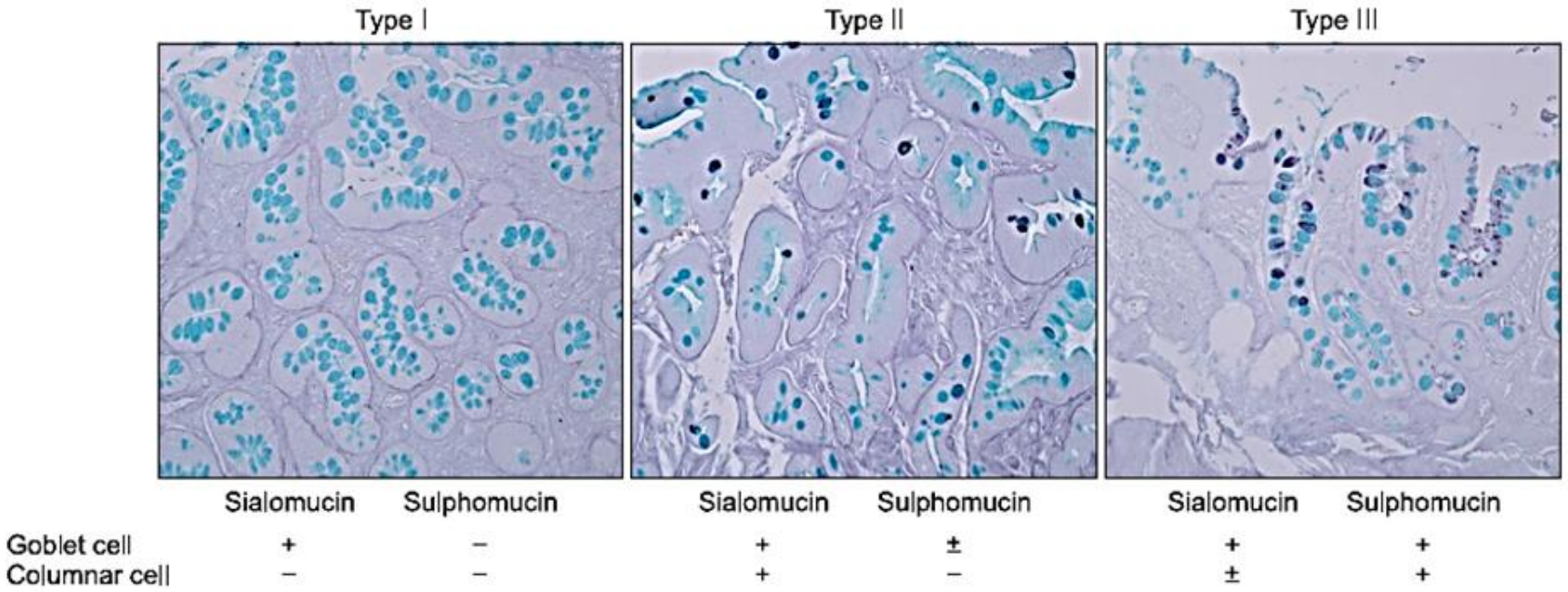
- The finding can be enhanced in narrow-band imaging (NBI) mode.

Waddingham W et al (2018) F1000 Research 2018



Intestinal Metaplasia

- IM can be subdivided into three categories
  - Type I is the complete form of IM and does not raise the risk of gastric cancer.
  - Type II or incomplete metaplasia contains few absorptive cells, few columnar intermediate cells, and goblet cells that express sialomucins.
  - Type III is intermediate between type I and type II and contains properties of both



- **Figure Phenotype of intestinal metaplasia (IM) classifying by mucin:** type I IM expresses only sialomucins (bright blue) and type II, III express sialomucins (bright blue) and sulfomucins (black) (High iron diamine and akian blue (pH 2.5) (HID-AB 2.5) staining x 400) (Kang *et al*,2009)

- Recent meta-analysis including 402,636 participants and 4535 GC patients, IM patients were at a higher risk of GC (pooled OR = 3.58, 95% CI 2.71–4.73)

- especially when
  - incomplete type pooled OR = 9.48, 95% CI 4.33–20.78) and
  - in the corpus (pooled OR = 7.39, 95% CI 4.94–11.06)

Shao, L et al. (2018) *Int. J. Cancer* 143, 1671–1677

OLGIM: Operative link on gastric intestinal metaplasia assessment

IM score		Corpus			
		No IM (score 0)	Mild IM (score 1)	Moderate IM (score 2)	Severe IM (score 3)
Antrum (Including incisura angularis)	No IM (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate IM (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

Weng CY et al (2021) *World J Gastroenterol* 21; 27(31): 5152-5170

(2) Reduction of Risk factors

Risks control

- Smoking
- Alcohol
- Diet
- H pylori eradication
- Screening of gastric premalignant conditions and early gastric cancer

Lifestyle modification

(1) Smoking cessation

(2) Limiting alcohol consumption -

American Cancer Society recommends that people who do choose to drink alcohol should have

- no more than 1 standard drink per day for women
- or 2 standard drinks per day for men
- although it is best not to drink alcohol

Rock CL et al.(2020) *CA Cancer J Clin* 2020;70:245-271.

Lifestyle modification – (3) Dietary patterns

- Reducing salt intake - < 5 g/day salt intake (WHO)
- daily consumption of fruits and vegetables
- reduced intake of salted and smoked food and red meat
- consumption of white meat
    - negatively associated with GC
    - contains less heme iron
    - a source of polyunsaturated fatty acids (PUFAs) with a lower level of cholesterol than red meat

Conti CB (2023) Int. J. Environ. Res. Public Health 20, 2149

***(4) H pylori* eradication**

- Meta-analysis in 2020 from seven RCTs
- GC developed in
  - 1.6% of 4206 individuals who received Hp eradication therapy,
  - 3% of 4117 subjects allocated placebo or no treatment
- (RR 0.54, 95% CI 0.4–0.72)

Ford, A.C. et al (2020). *Gut* 2020, 69, 2113–2121

***(4) H pylori* eradication**

- Many countries in Asia have developed screening programs to detect H pylori and increase its eradication.

Chiang, T.-H.; et al.(2022) *J. Formos. Med. Assoc*, 121, 2378–2392.

Available Screening Programs for H pylori infection in Asian Countries

Country	Screening Age	Beginning of Screening	Screening Interval	Strategy	Expected or Demonstrated Benefits
Japan	20 years	2013	Once	Hp infection diagnosed at endoscopic screening	**6% reduction in GC mortality** in 2016
Republic of Korea	40-65 years	2014	Once	Urea breath test (UBT) screening	To reduce the incidence of GC through Hp eradication
China	18 years	2022	Once	Through UBT screening for parents; reach children for Hp testing.	To prevent Hp spread among family members and thus reduce GC incidence and related costs.
Taiwan	30 years	2004	Every 2 years	Urea breath test (UBT) screening	**53% reduction in GC incidence and 25% reduction in GC mortality**

Conti CB *et al* (2023) *Int. J. Environ. Res. Public Health*, 20, 2149

(5) Endoscopic surveillance of gastric premalignant lesions (GPL) and screening for early gastric cancer (EGC)

While 5-year survival rates for advanced gastric cancer are less than 20%, early gastric cancer (EGC) has a good prognosis with 5-year survival rates over 90% to 95%

Thus, detection of the gastric precancerous conditions and the surveillance of EGC become an important issue around the world especially at the Asian countries like Japan and Korea where the prevalence of gastric cancer is high

Park, J.M. et al (2006) *Cancer Res Treat*: **38**; p. 13-8.

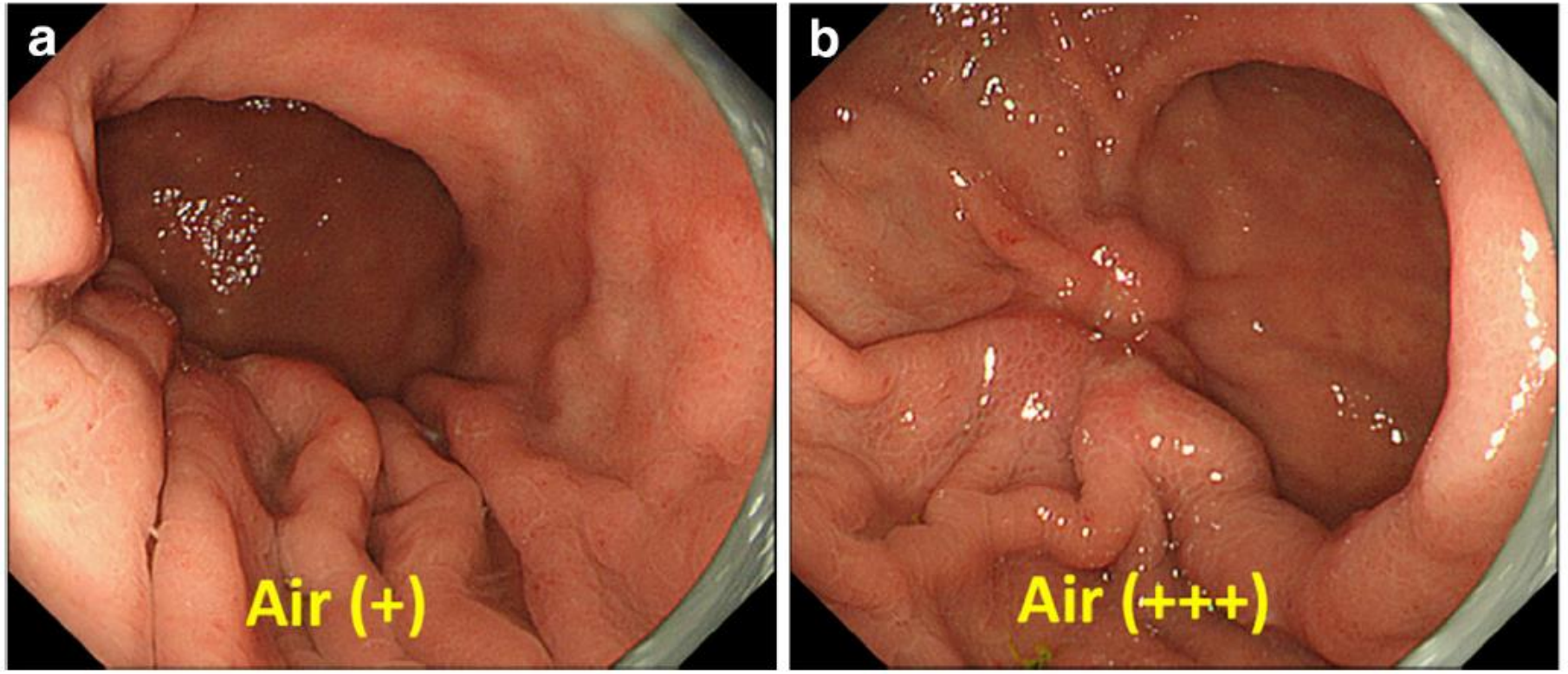
Gastric Premalignant Lesions (GPL) surveillance

Adequate air insufflations

Adequate mucosal cleansing

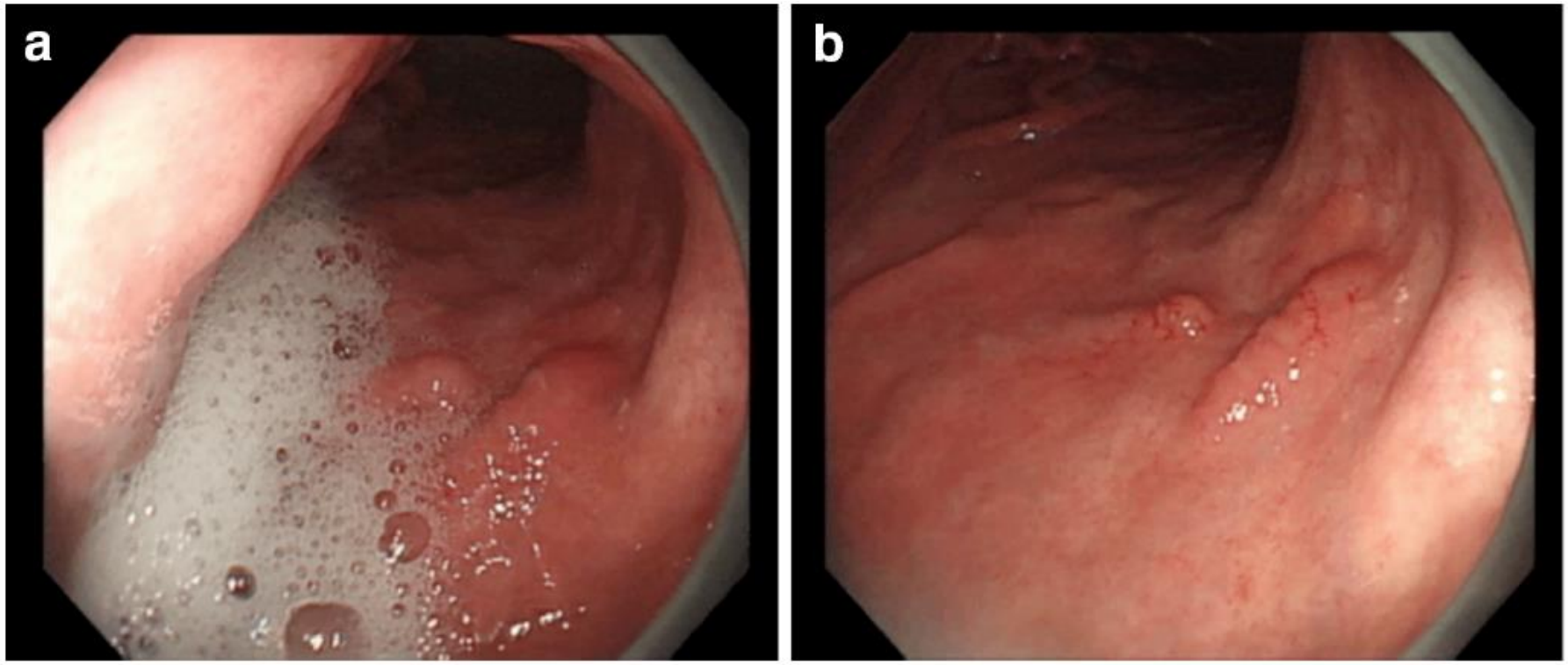
Sufficient examination time

Adequate insufflations with a large amount of air to flatten the mucosal folds



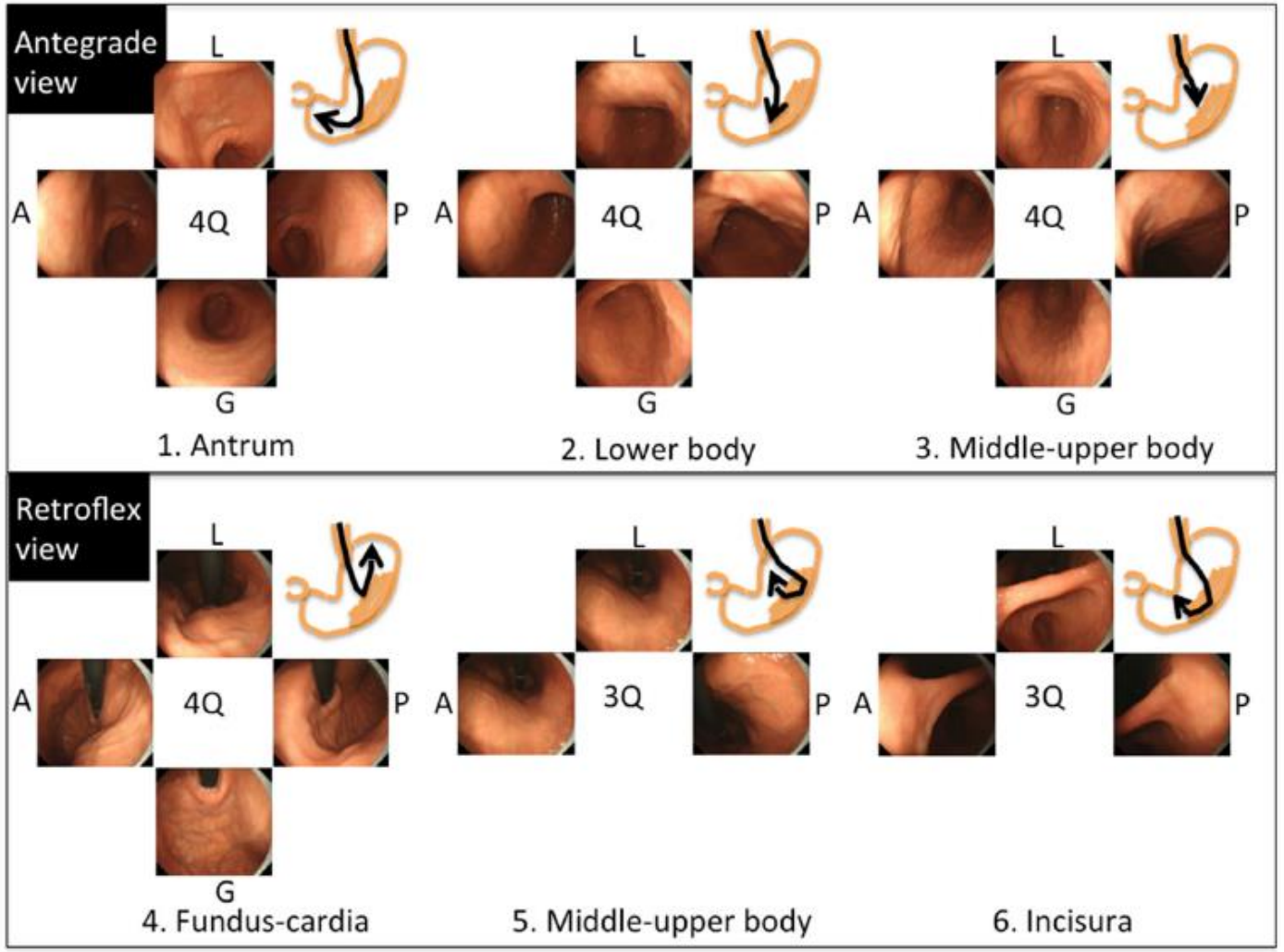
Yao K et al (2017) *Gastric Cancer* 20 (Suppl 1):S28–S38

Adequate Rinsing of mucus and froth off the mucosal surface



- Yao K et al (2017) *Gastric Cancer* 20 (Suppl 1):S28–S38

Systematic screening protocol for the stomach (SSS)

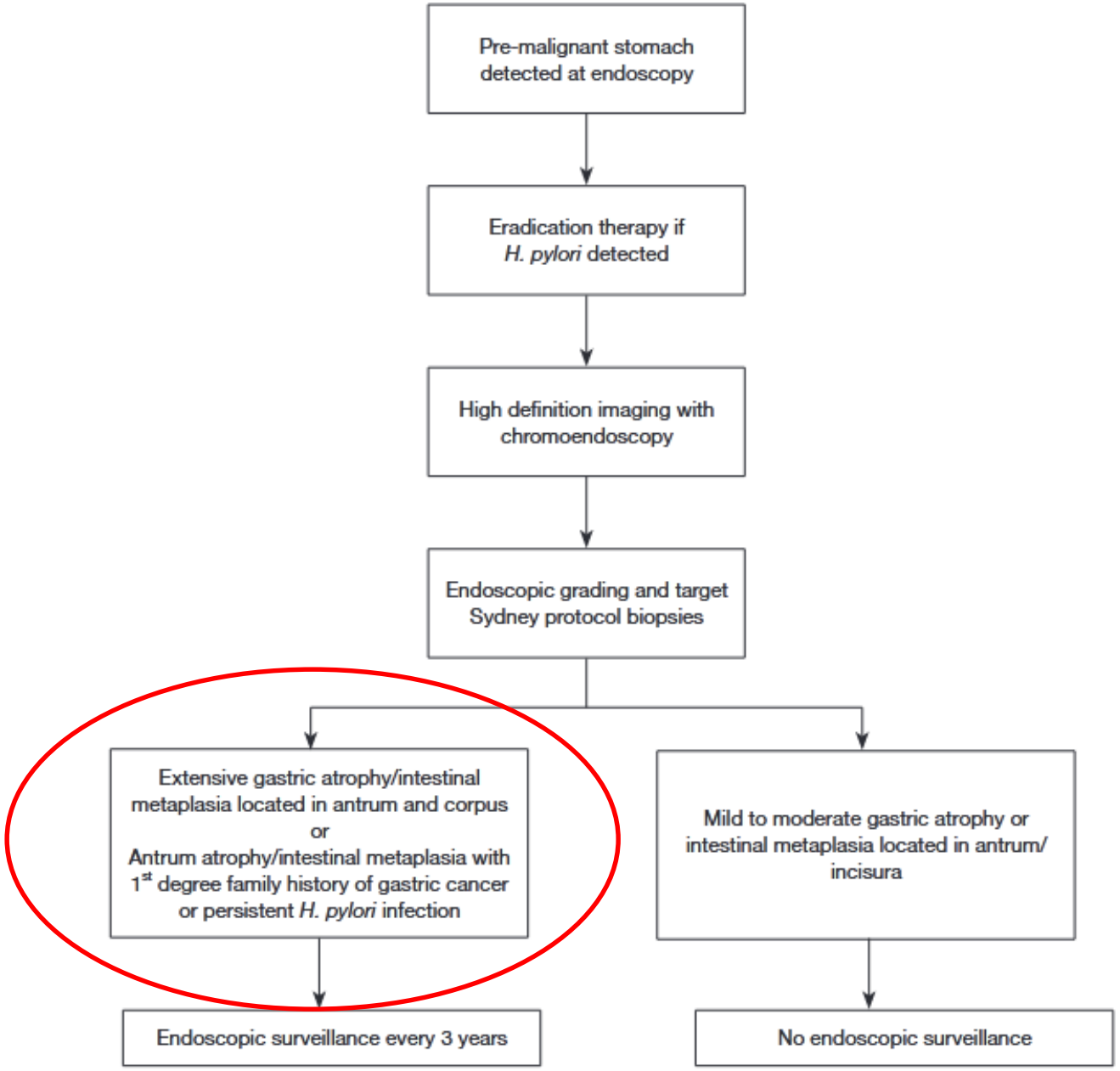


Yao K et al (2017) *Gastric Cancer* 20 (Suppl 1):S28–S38

AGA Clinical Practice Update on Atrophic Gastritis (2021)

- A surveillance endoscopy every 3 years should be considered in individuals with advanced atrophic gastritis, defined based on anatomic extent and histologic grade.

Shah SC et al (2021) Expert Review *Gastroenterology.* October ; 161(4):



Banks M et al. **(2019) British Society of Gastroenterology guidelines** on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut* 68:1545-7

Singapore Guideline (2022) for GPLs

- Surveillance of GPLs depends on
  (1) OLGIM Stage
  (2) additional risk factors such as
  - significant smoking history (20 pack-years)
  - age >50 years
  - incomplete intestinal metaplasia
  - persistent *H. pylori infection*
  - *first-degree family history of gastric cancer*

Namasivayam V *et al* (2022) *Ann Acad Med Singap* ;51:417-35

Singapore Guideline (2022) for GPLs

OLGIM and Endoscopic Surveilance

- stage I + No risk factors – Surveillance is not justified
- stage I + additional risk factors - surveillance every 3 years

- stage II - surveillance every 5 years

- Stage III–IV – every 3 years
- Stage III–IV + ≥2 risk factors - surveillance endoscopy may be offered in 2 years.

- Namasivayam V *et al* (2022) *Ann Acad Med Singap* ;51:417-35

Singapore Guideline (2022) for GPLs

- In cases of dysplasia detected incidentally from random biopsies, when there is still no focal lesion(s) identified on repeat endoscopy, a surveillance endoscopy should be carried out
  - once every 6 months in the case of high grade dysplasia and
  - annually for low grade dysplasia,
  - both for a minimum period of 5 years.

- Namasivayam V *et al* (2022) Singapore clinical guideline on endoscopic surveillance and management of gastric premalignant lesions. *Ann Acad Med Singap* ;51:417-35

II. Common Presentations

- Early cases are mostly asymptomatic.
- Most symptoms of gastric cancer reflect advanced disease
  - Indigestion
  - Nausea or vomiting
  - Dysphagia
  - Postprandial fullness
  - Loss of appetite
  - GI Bleeding – Hematamesis and Melaena
  - Weight loss

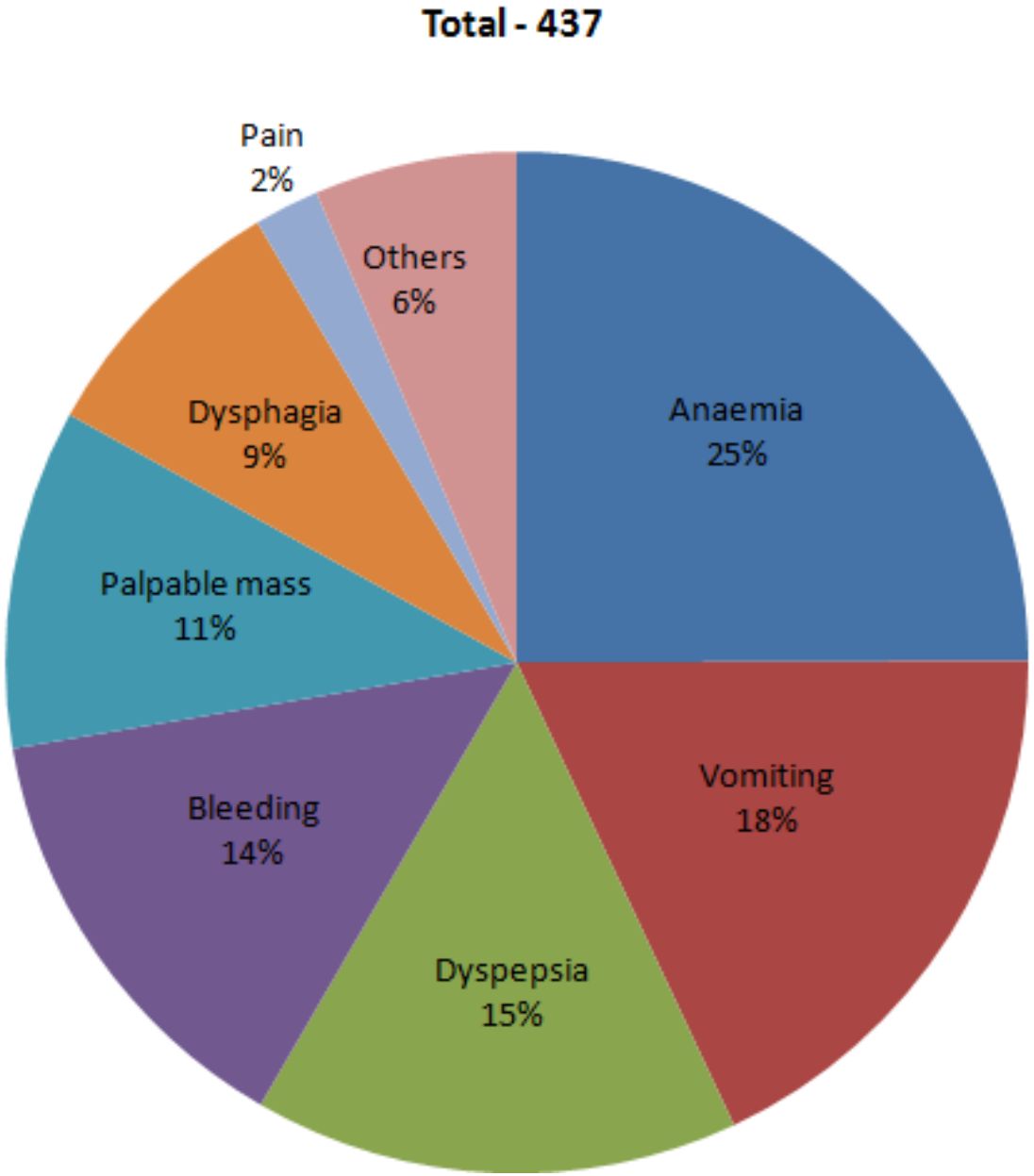
Cabebe EC (2023) Gastric Cancer Clinical Presentation *Medscape Education* ***8 -2023***

May also present with late complications

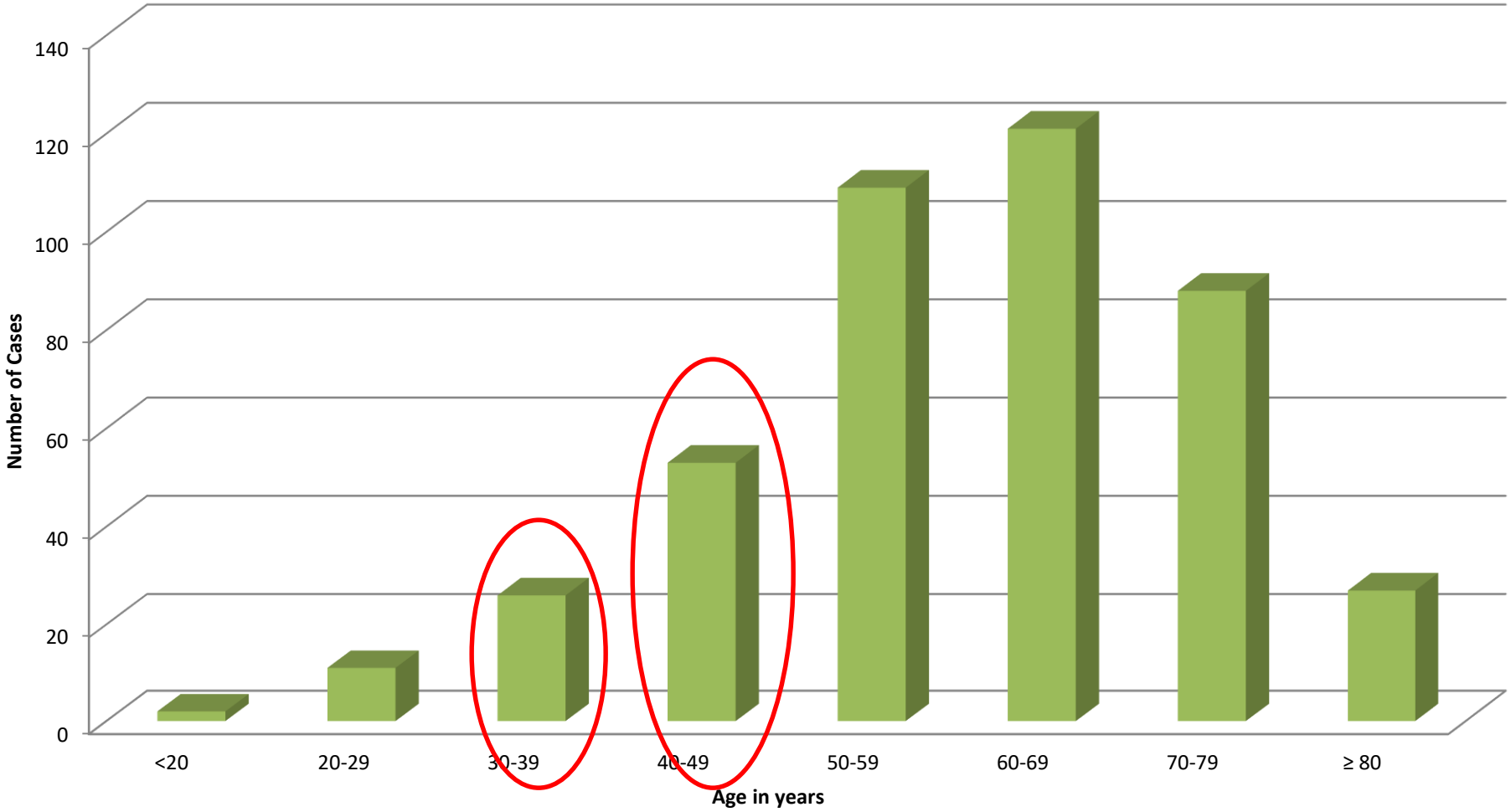
- Peritoneal and pleural effusions
- Obstruction of the gastric outlet, gastroesophageal junction, or small bowel
- Intrahepatic jaundice caused by hepatomegaly
- Extrahepatic jaundice by lymphnodes compression
- Inanition resulting from starvation or cachexia of tumor origin

- Cabebe EC (2023) Gastric Cancer Clinical Presentation *Medscape Education* ***8 -2023***

Common presentations (TGH Data)

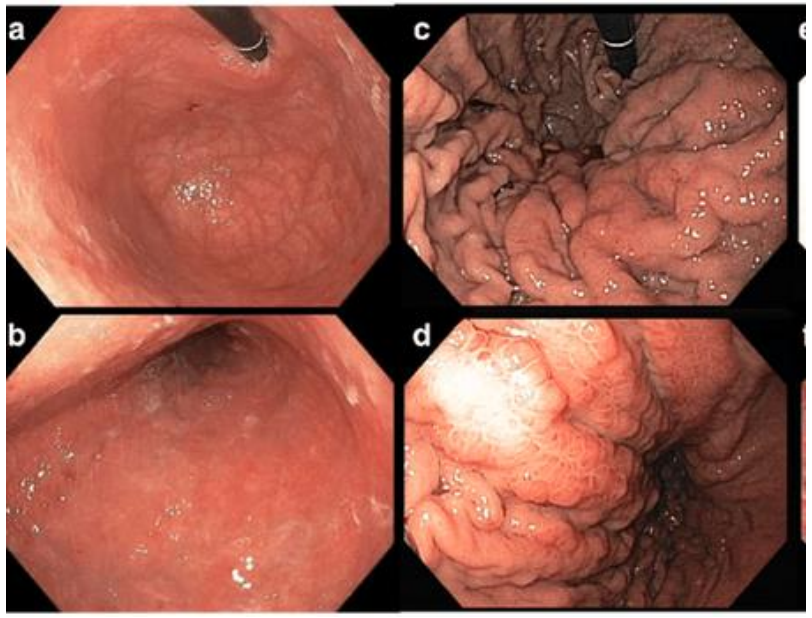


TGH Data – Age Distribution of Gastric Cancer (2019-2023)



TGH Data – Age Distribution of Gastric Cancer (2019-2023)

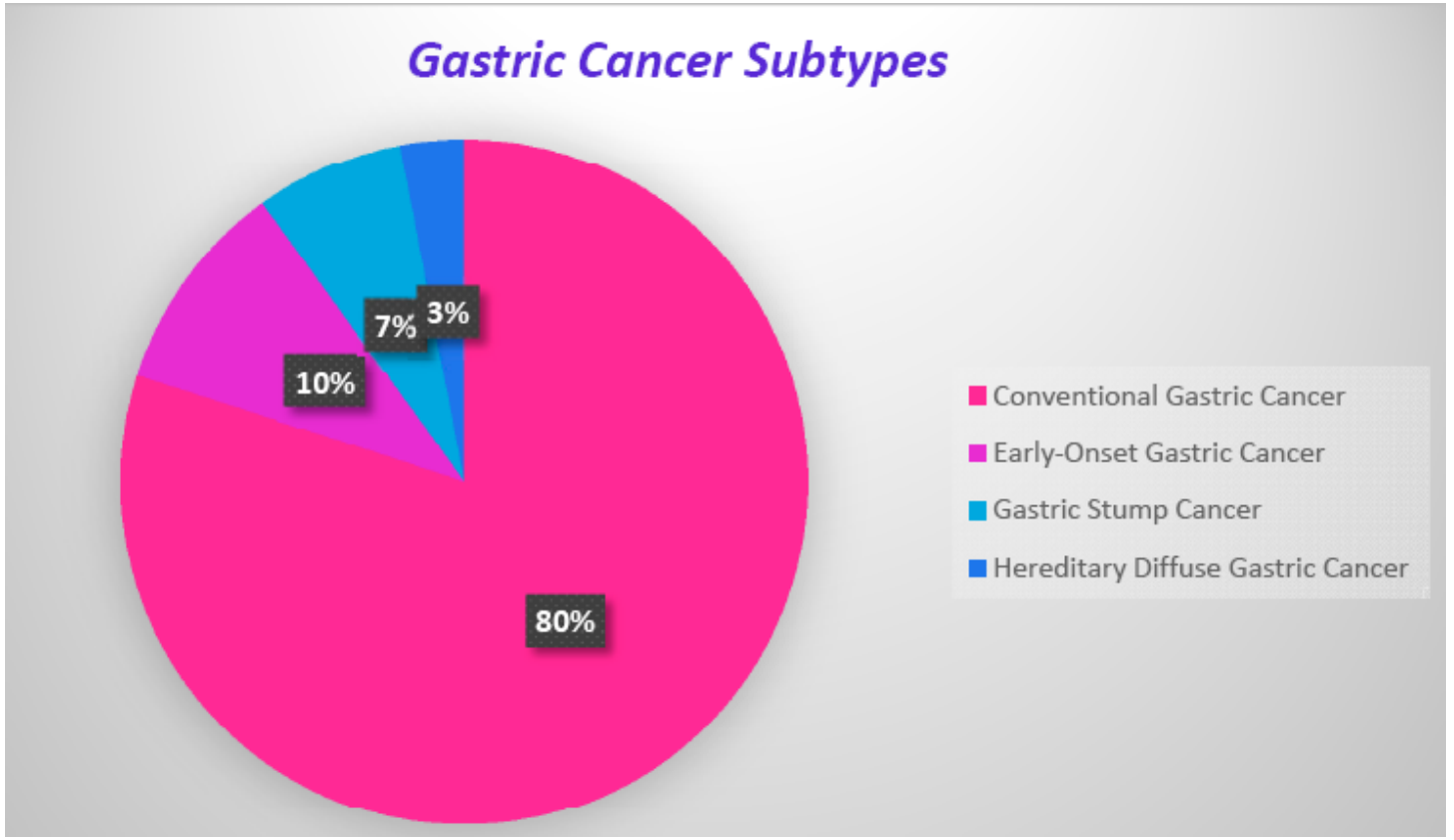
- Highest incidence in 60-69 years age group
- Youngest – 19 yrs
- Oldest – 94 yrs
- One third of the patients in 30-50 years of age represents diffuse type gastric cancer



Endoscopic aspect of (a, b) a normal stomach (c,d) diffuse type GC

- TGH Registry

- Age of symptoms onset is also determined by the type of gastric cancer.



Machlowska Jet al (2020) *Int. J. Mol. Sci.,* 21, 4012

I . Conventional Gastric Cancer (80%)

- diagnosed between 60 -80 years of age with M:F -2:1

II. Early-Onset Gastric Cancer (10%)

- age ≤ 45 years with **diffuse lesions**
- around 10% of EOGCs have a positive family history

III. Gastric Stump Cancer (7%)

- GC in the gastric remnant after partial gastric resection for PUD

IV. Hereditary Diffuse Gastric Cancer -HDGC (3%)

- autosomal dominant inheritance with **diffuse GC**
- Median age of onset is around 38 years (range of 14–69 yrs)

Machlowska Jet al (2020) Gastric cancer:

HDGC Screening should be considered when there is

≥ 2 documented cases of diffuse GC in 1st /2nd - degree relatives with at least one diagnosed before the age of 50

(or) ≥ 3 cases of documented diffuse GC in 1st /2nd - degree relatives, independent of the age of onset

Machlowska Jet al (2020) *Int. J. Mol. Sci*., 21, 4012

Conclusion

- Both environmental and genetic factors have an impact on gastric carcinogenesis.
- Physicians should focus on lifestyle modification and the reduction of risk factors.
- Eradication of *H pylori* should be encouraged, when possible.
- Great difference between 5-year survival rates for advanced gastric cancer (20%) and early gastric cancer (95%) makes diagnosis and surveillance of the gastric precancerous conditions an important issue.
- Surveillance intervals for gastric premalignant lesions should be based on
  (1) risk factors
  (2) extent and severity of these lesions (OLGA – OLGIM) .
- Although rare, diffuse GC in young patients alerts physicians for family screening.

Thank You
for the kind
attention.