THE PREVENTION and REDUCTION of and SCREENING for GASTRIC CANCER

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CanMEDS Roles Covered

SCMD Semaine canadienne des maladies digestives[MC] | CDDW Canadian Digestive Diseases Week™

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
X	**Communicator** (as *Communicators*, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
	Collaborator (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
	Health Advocate (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
	Scholar (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	**Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Conflict of Interest Disclosure

SCMD
Semaine canadienne des maladies digestives^MC

CDDW
Canadian Digestive Diseases Week™

(Over the past 24 months)

Commercial or Non-Profit Interest	Relationship
Organization	
Paladin	Consultant
Pfizer	Speaker
Allergan	Advisory Board
AbbVie	Advisory Board

Objectives

- Learn about epidemiology of gastric cancer
- Learn about the importance of intestinal metaplasia and its relationship to *Helicobacter pylori*
- Learn about management of subgroups of patients at increased risk for gastric cancer

Case 45 Year old male

- Healthy
- Father died Gastric cancer age 53

- What would you advise ?

Gastric Cancer risk factors

- Age
- Diet
- Smoking
- Helicobacter
- Pernicious anemia
- Genetic factors → E-cadherin
- Family History Gastric Cancer

Gastric Cancer in Canada

In 2019:

- **4100 Canadians will be diagnosed with stomach cancer.**
- **1950 Canadians will die from stomach cancer.**
  - **2600 men, 1200 will die**
  - **1450 women, 760 will die**

Canadian Cancer Statistics

New Cancer Cases

FIGURE 1.2 Percent distribution of projected new cancer cases, by sex, Canada, 2019

Males
113,000
New cases

Prostate	20.3%
Lung and bronchus	13.2%
Colorectal	12.9%
Bladder	8.1%
Non-Hodgkin lymphoma	5.0%
Kidney and renal pelvis	4.2%
Melanoma	3.8%
Leukemia	3.5%
Oral	3.3%
Pancreas	2.7%
Stomach	2.3%
Liver	1.9%
Thyroid	1.9%
Multiple myeloma	1.7%
Esophagus	1.6%
Brain/CNS	1.5%
Testis	1.0%
Larynx	0.9%
Hodgkin lymphoma	0.5%
Breast	0.2%
All other cancers	9.7%

Females
107,400
New cases

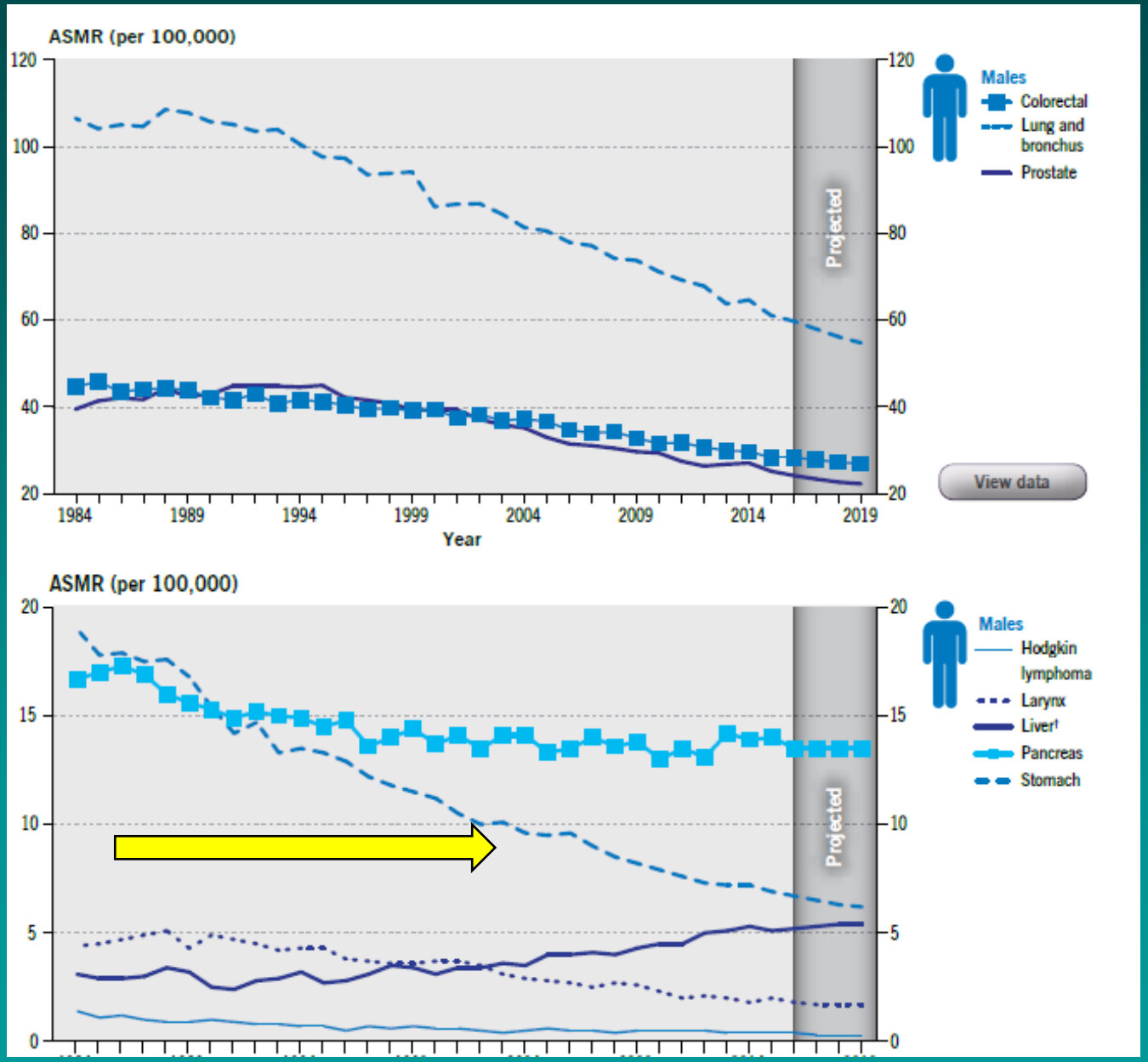
Breast	25.0%
Lung and bronchus	13.5%
Colorectal	10.9%
Uterus (body, NOS)	6.7%
Thyroid	5.7%
Non-Hodgkin lymphoma	4.1%
Melanoma	3.3%
Ovary	2.8%
Pancreas	2.6%
Leukemia	2.5%
Bladder	2.5%
Kidney and renal pelvis	2.3%
Oral	1.5%
Stomach	1.4%
Multiple myeloma	1.3%
Cervix	1.3%
Brain/CNS	1.2%
Liver	0.7%
Esophagus	0.5%
Hodgkin lymphoma	0.4%
Larynx	0.2%
All other cancers	9.6%

Stomach 2.3%

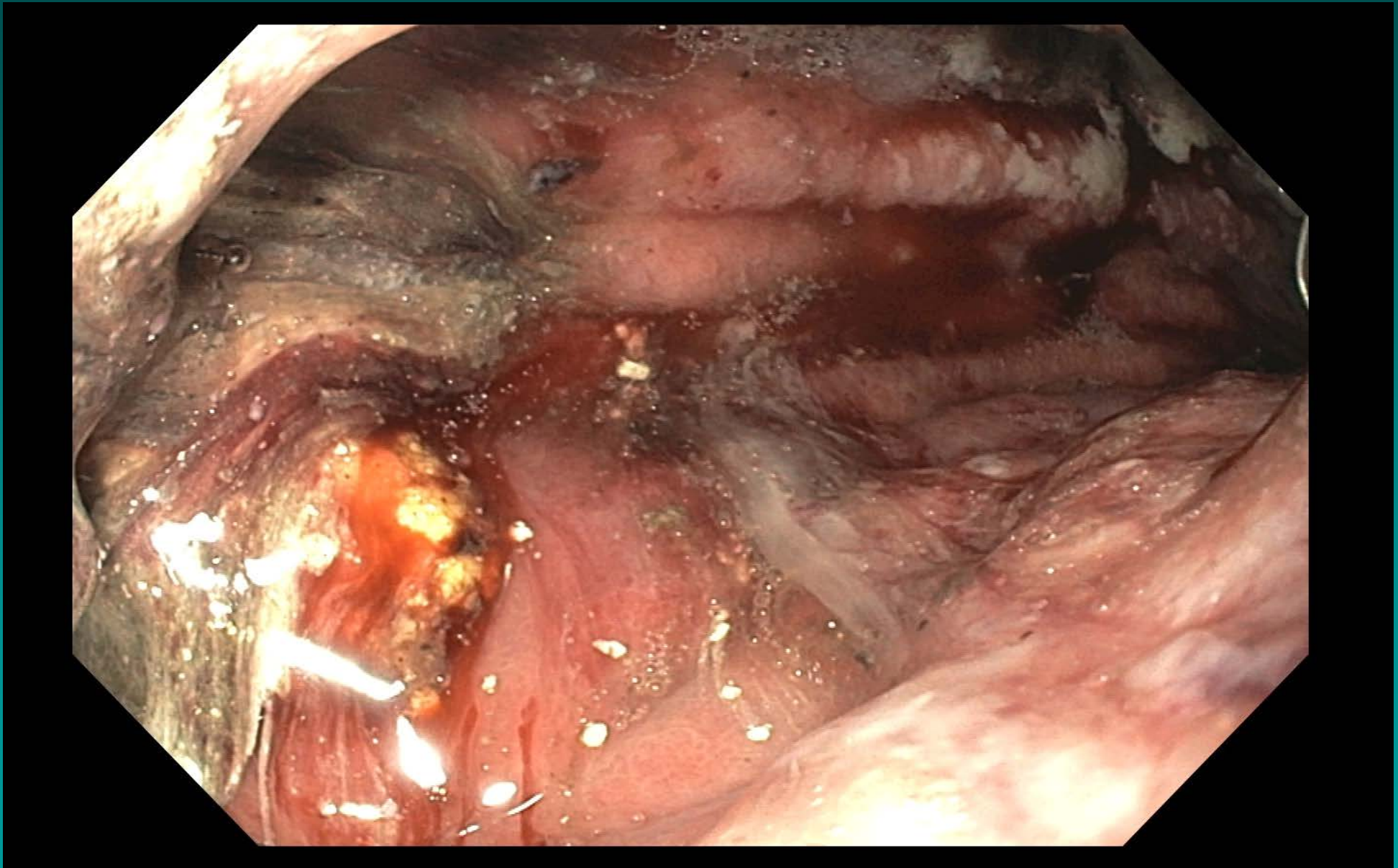
Stomach 1.4%

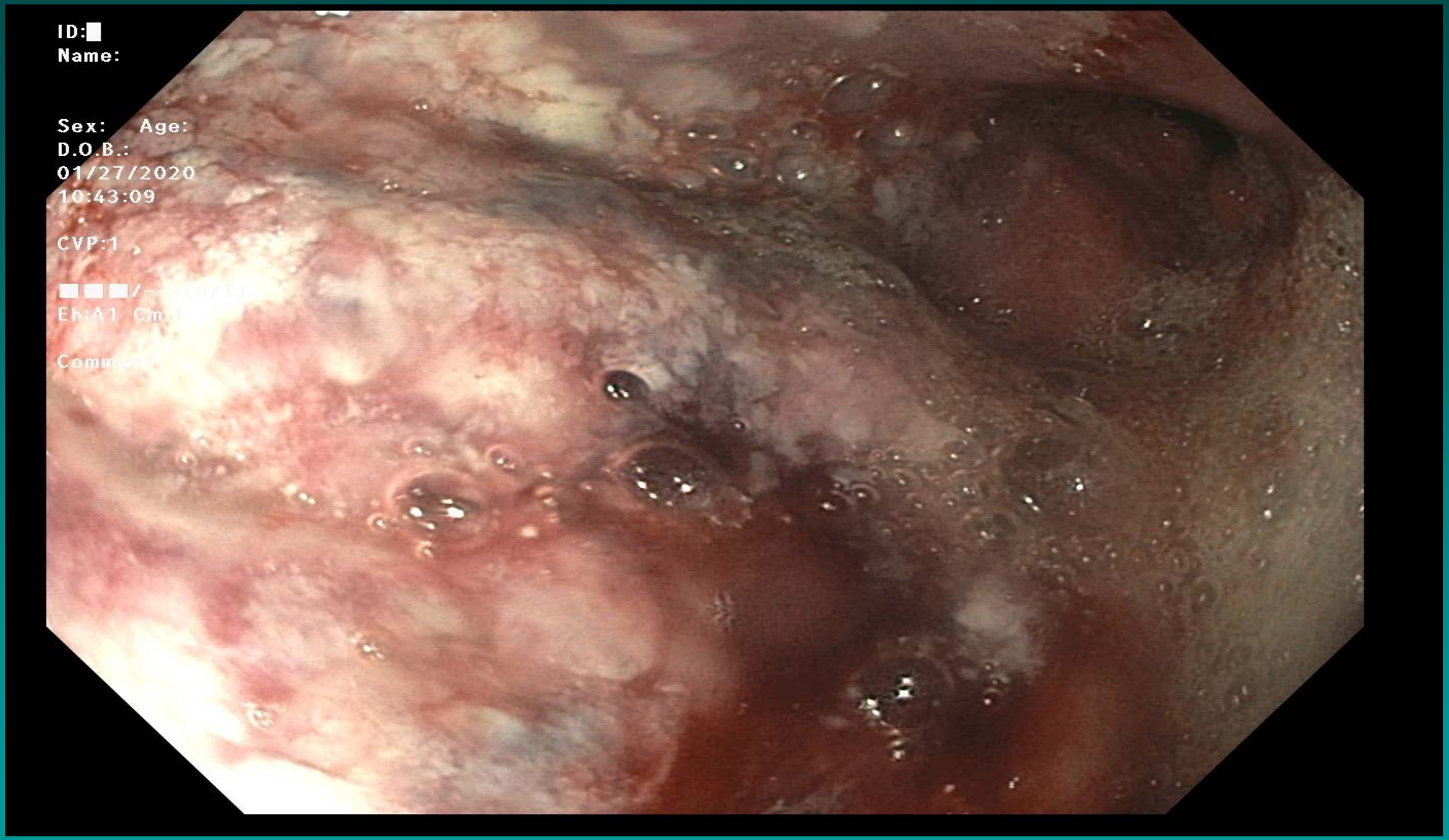
Canadian Cancer Statistics

Cancer Age Standardized Mortality



31 year old Male Signet cell Ring Gastric Cancer

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Sex: Age:
D.O.B.:
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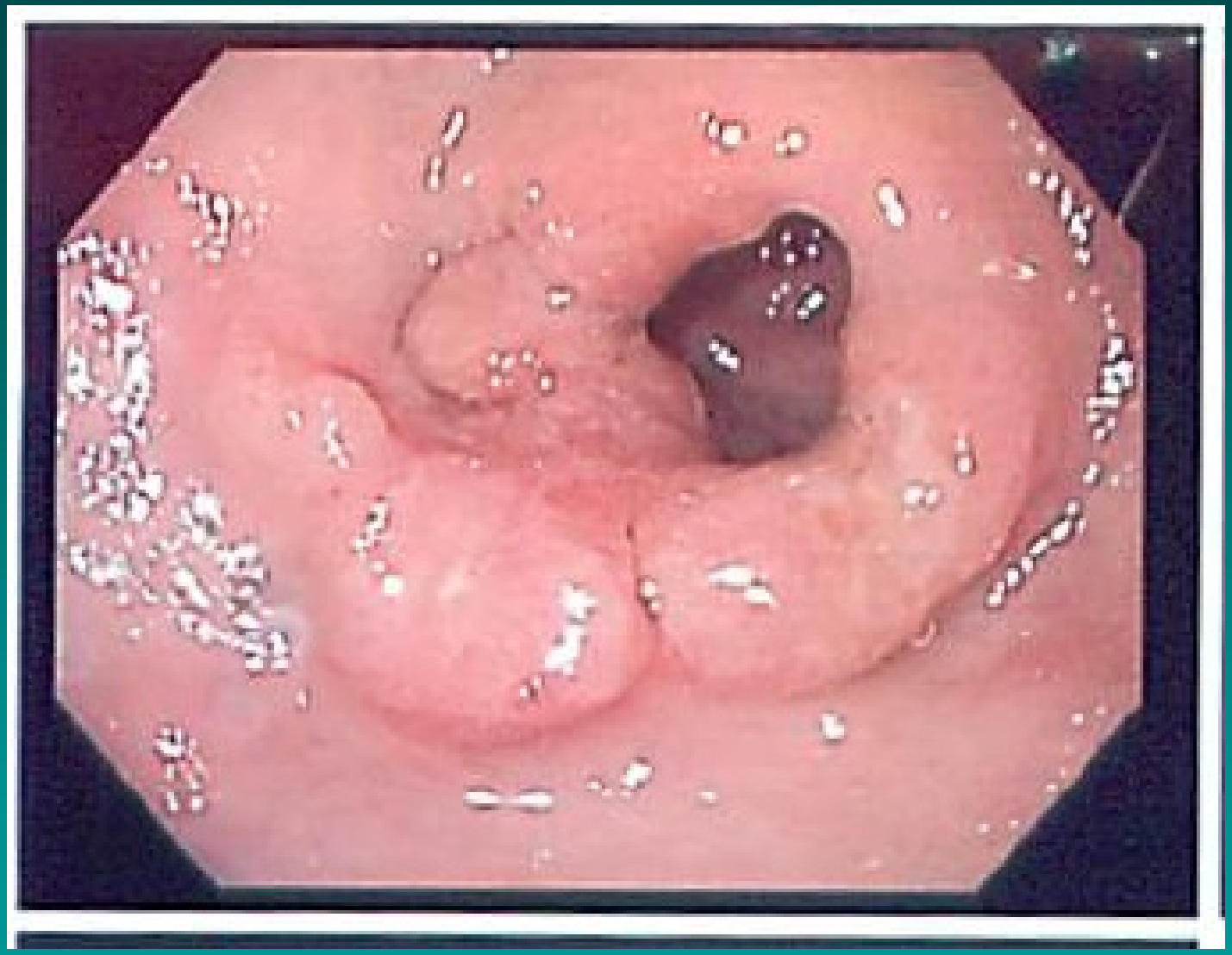
CVP:1



Gastric Cancer Subtypes

- Non Cardia type Gastric Cancer
- Cardia type Gastric Cancer

- Diffuse Type Gastric Cancer
- Gastric Malt Lymphoma

Non-Cardia Gastric Cancer

- "intestinal-type" gastric cancer
- *H. pylori* primary risk factor
- Attributable risk up to 60-80%

GE 2020;158:693-78

Hp and Cancer

- Intestinal type gastric cancer
- Diffuse type gastric cancer

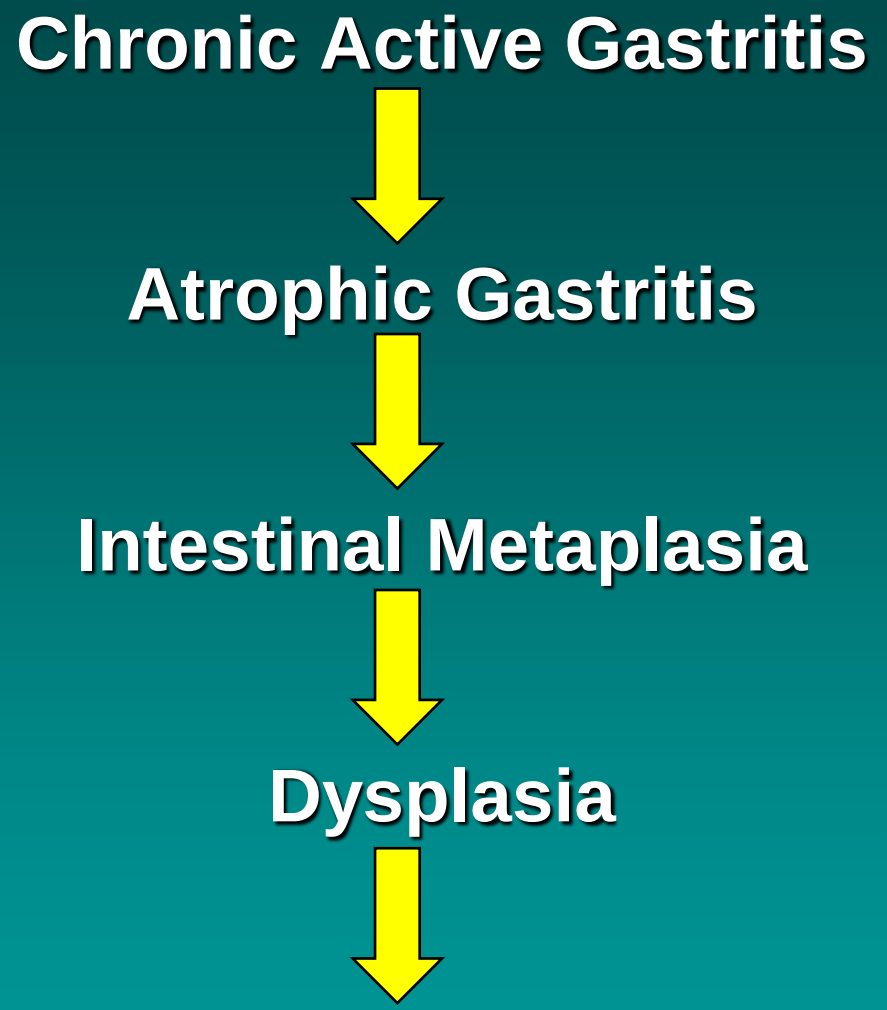
- Gastric MALT Lymphoma

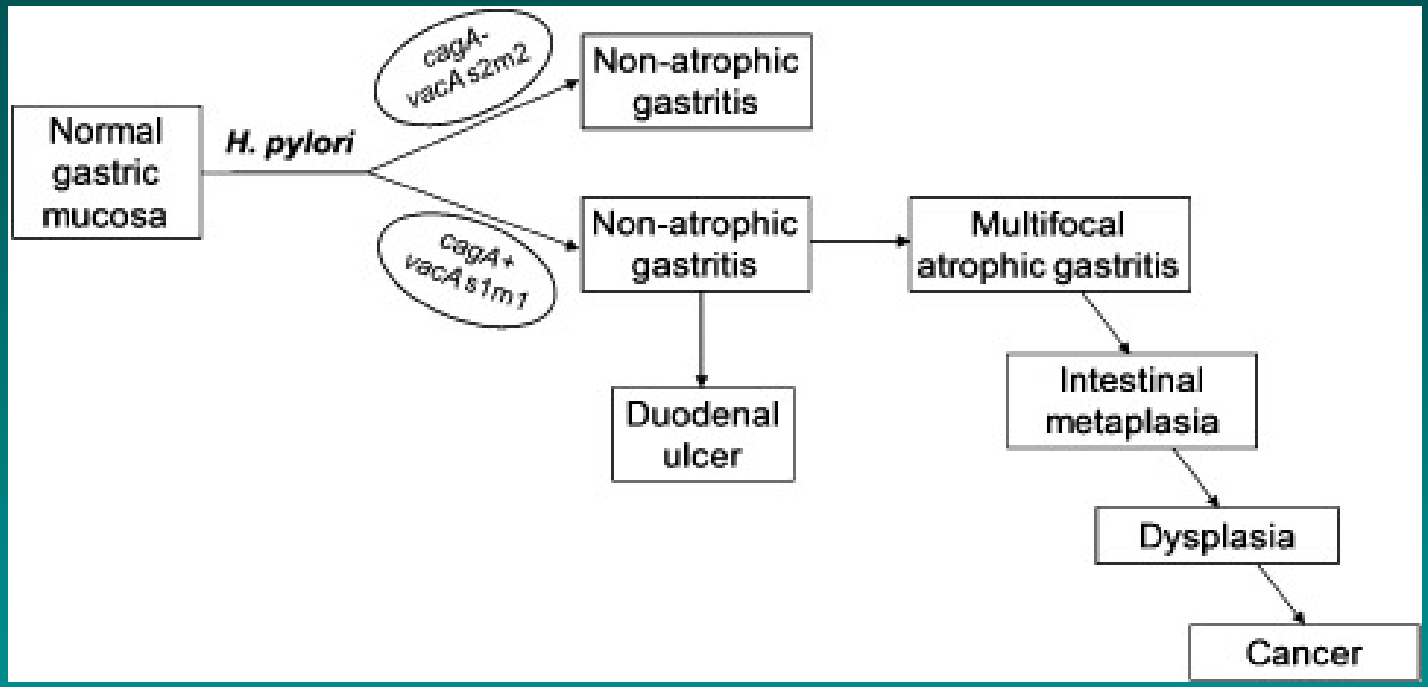
Gastritis is the Disease

Ulcers and Cancer are secondary phenomena

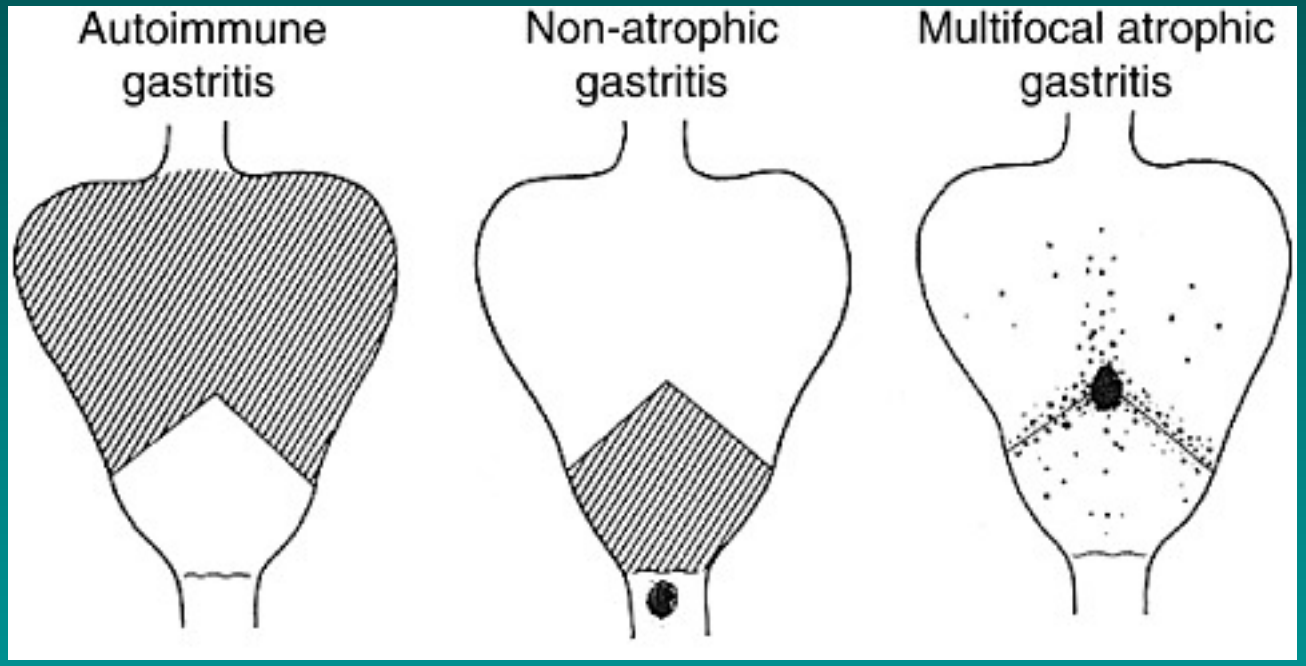
Whitehead , British pathologist

Correa Hypothesis



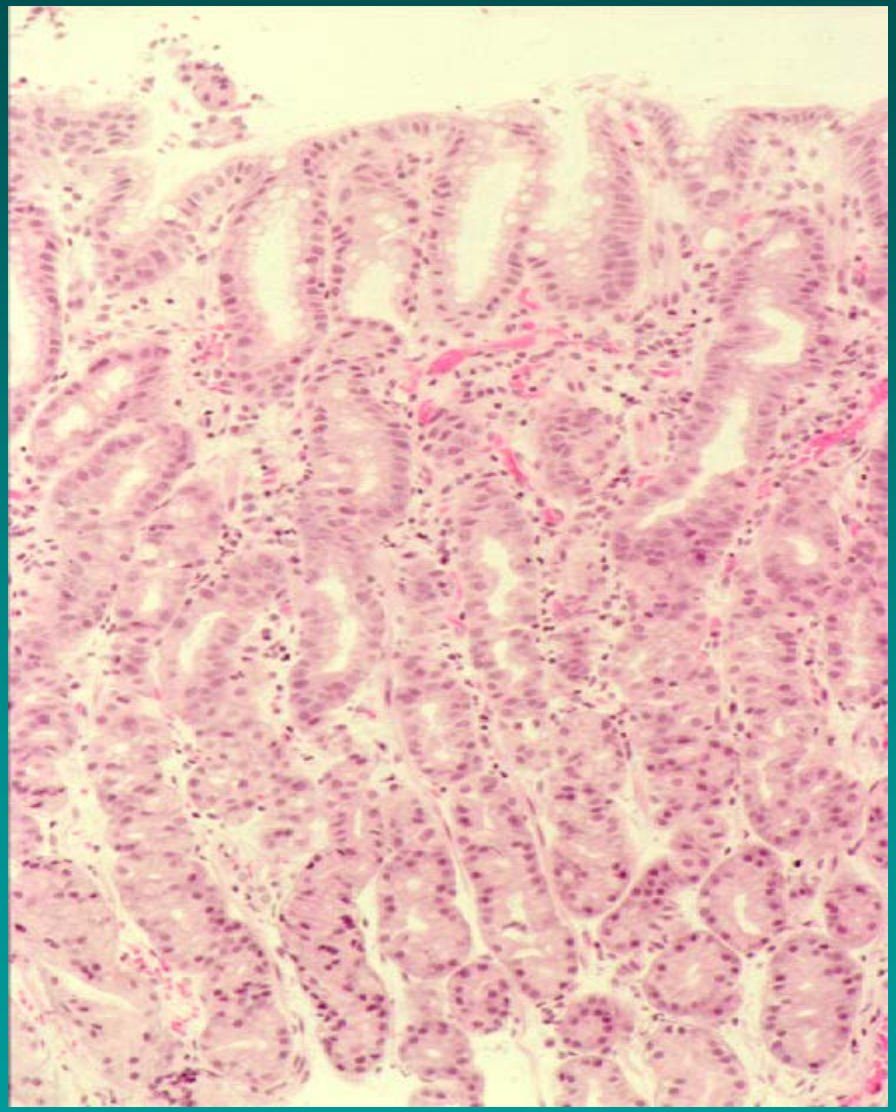

Normal gastric mucosa
H. pylori
cagA- vacA s2m2
Non-atrophic gastritis
cagA+ vacA s1m1
Non-atrophic gastritis
Multifocal atrophic gastritis
Duodenal ulcer
Intestinal metaplasia
Dysplasia
Cancer

Correa et al

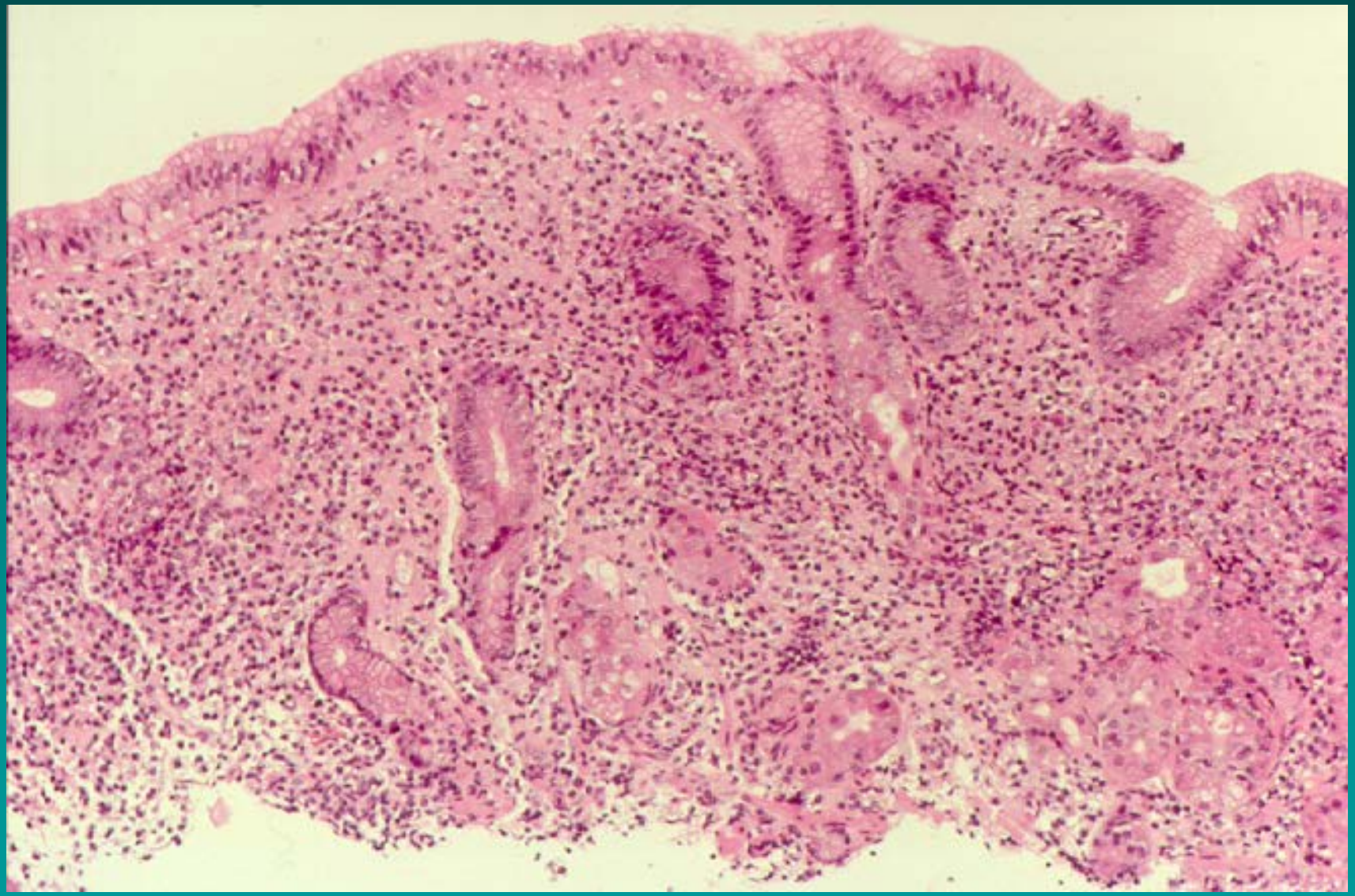


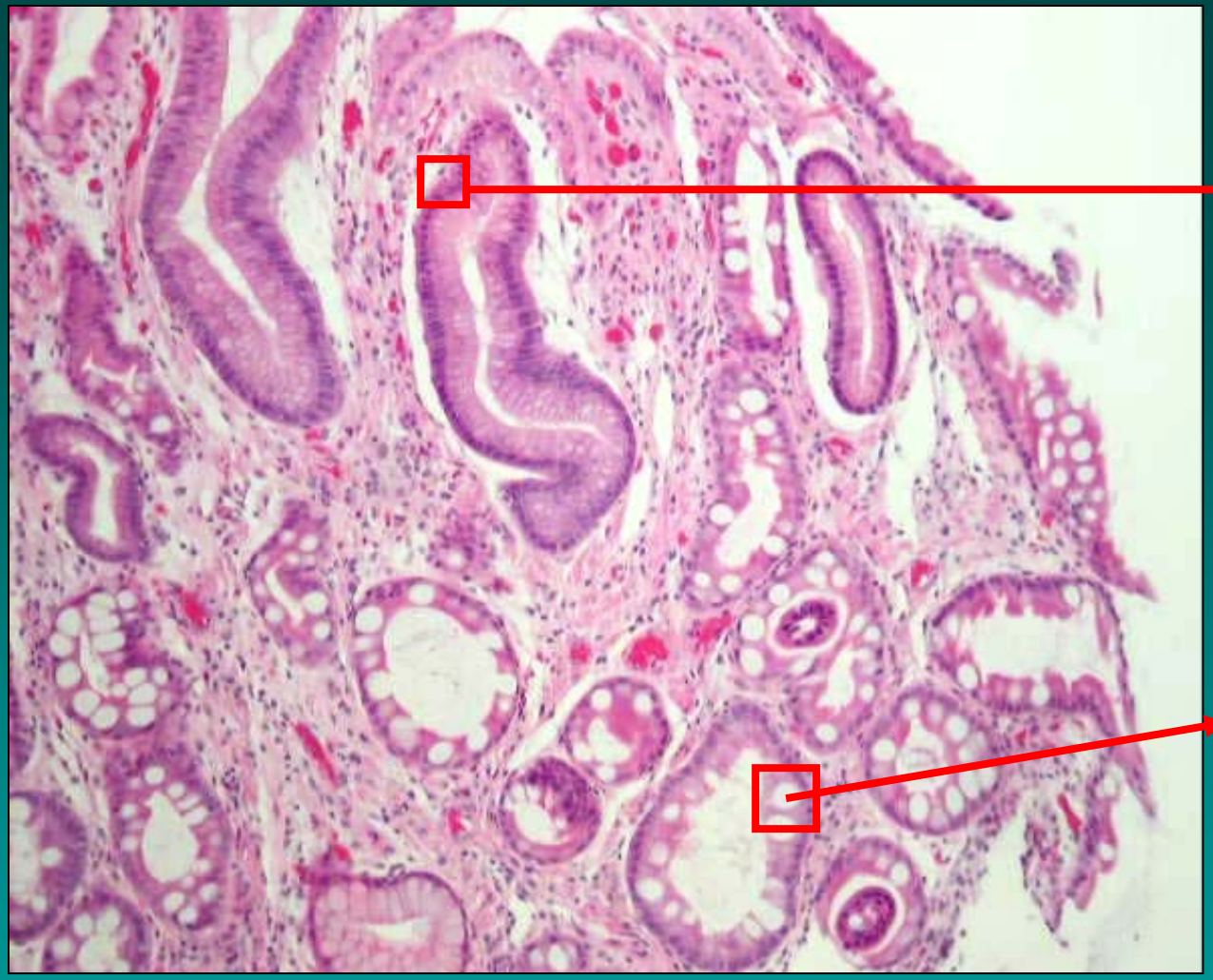
Correa, Piazuelo Journal of Digestive Diseases 2012; 13; 2–9

Normal Body Mucosa



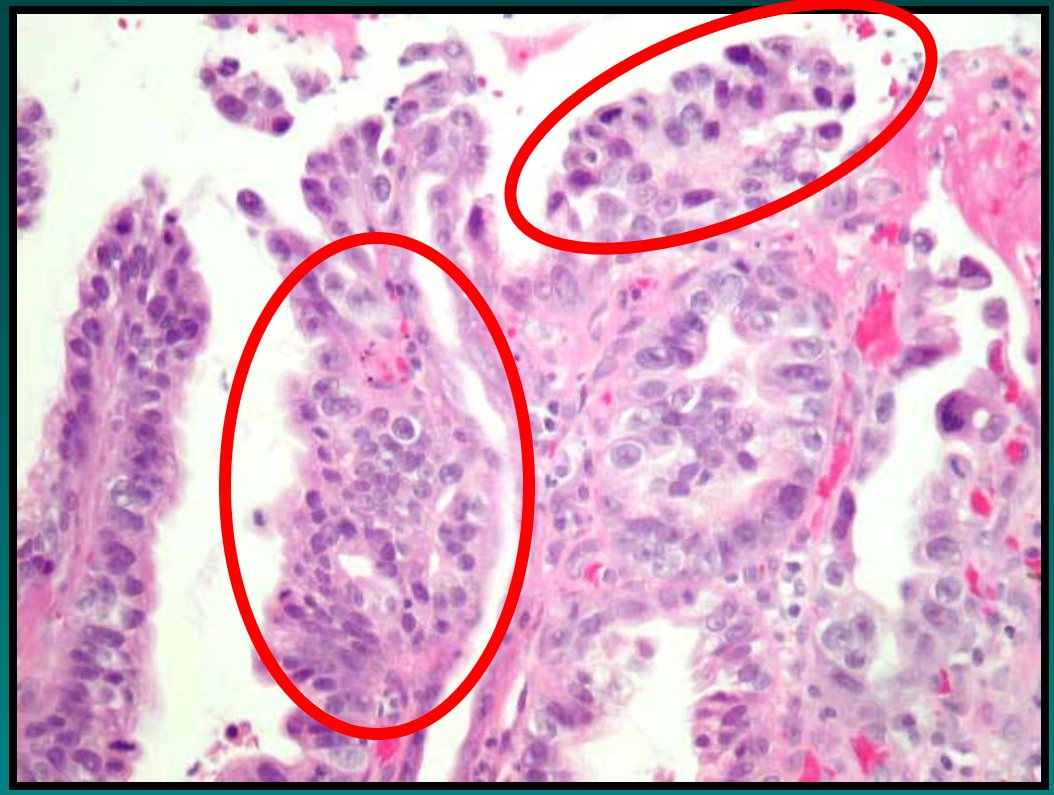
Body Gastritis with Atrophic Gastritis

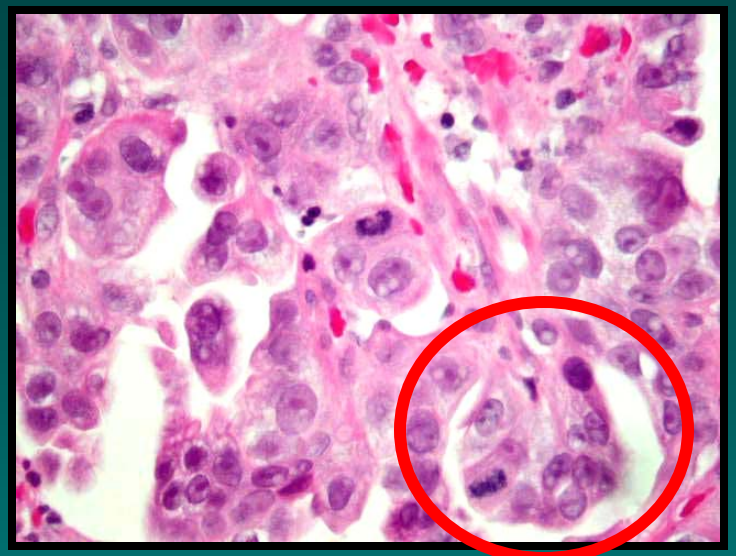


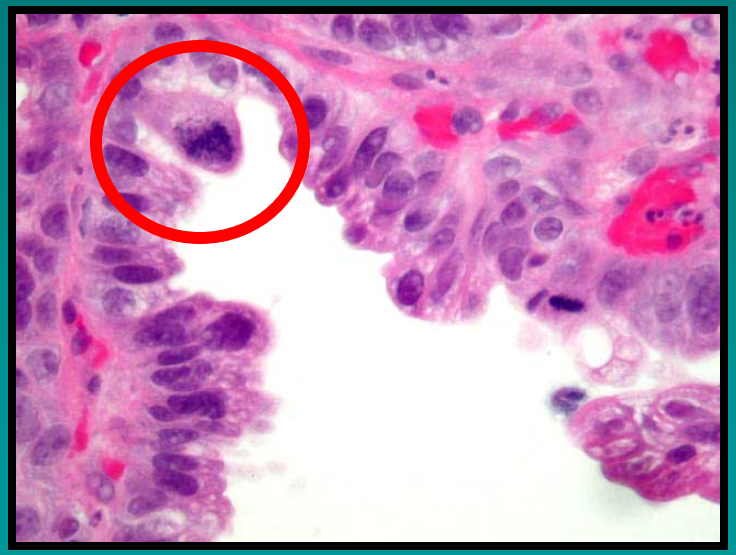


Normal gastric epithelial cells.

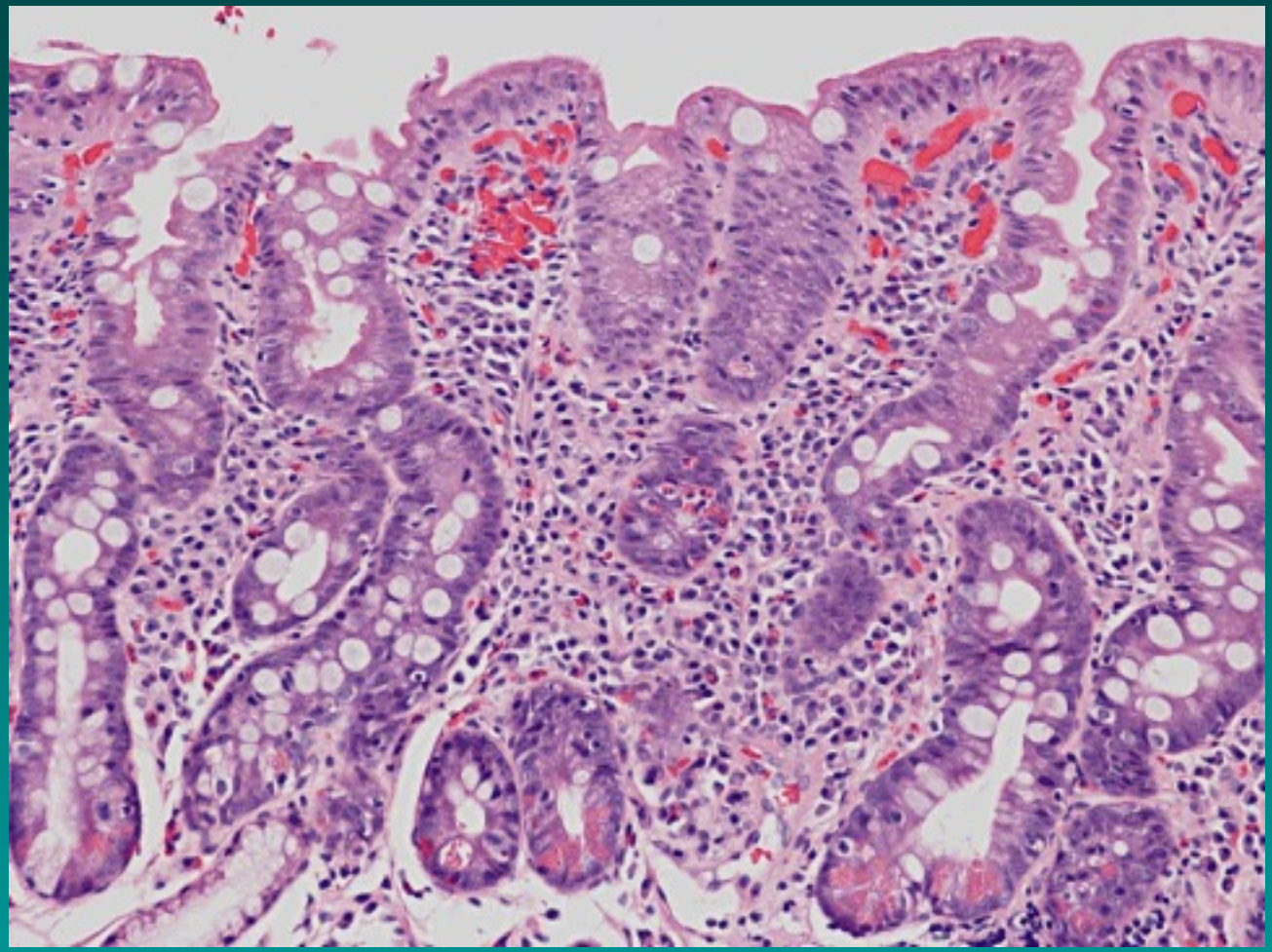
Intestinal (goblet cell) metaplasia



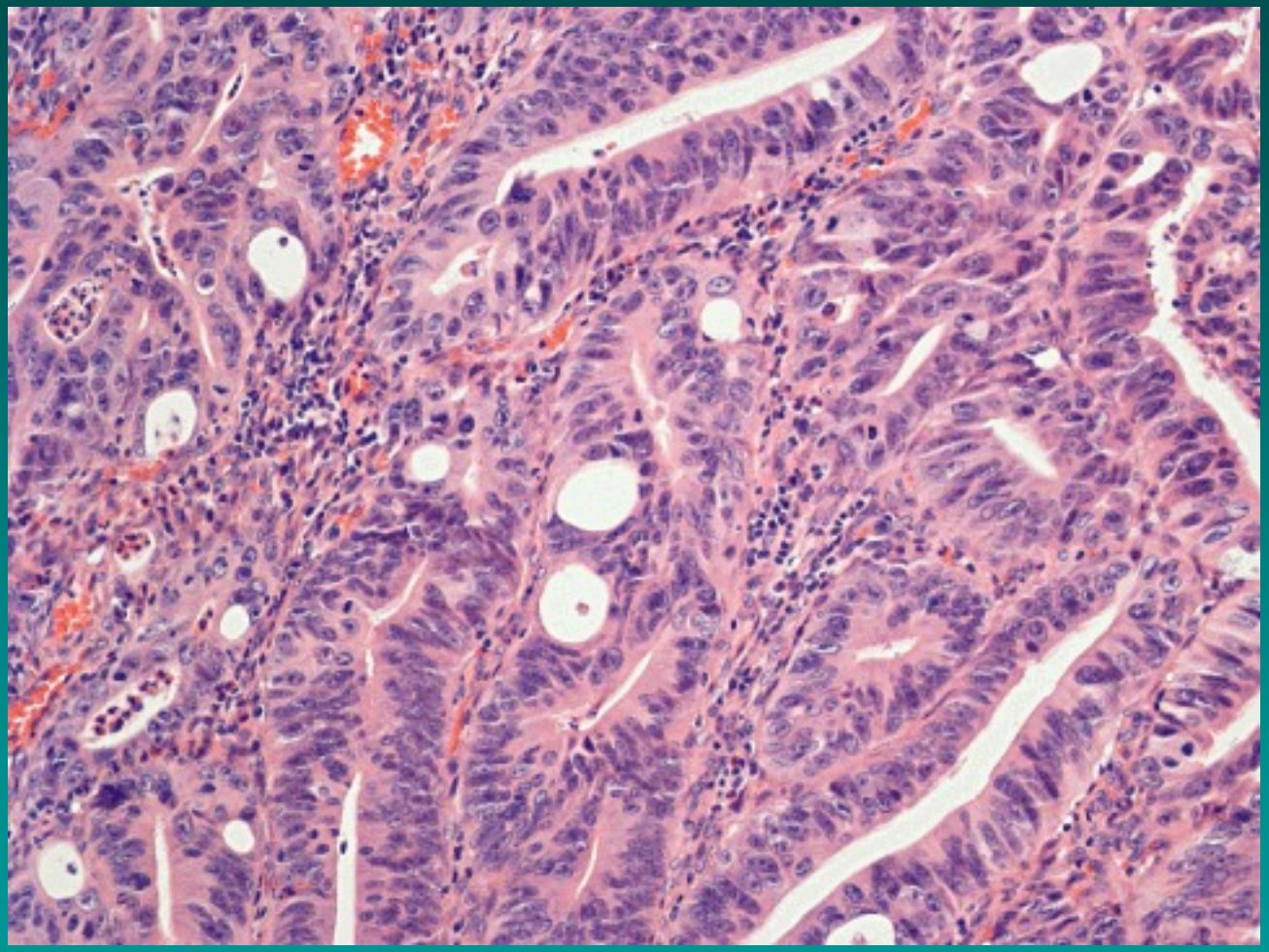




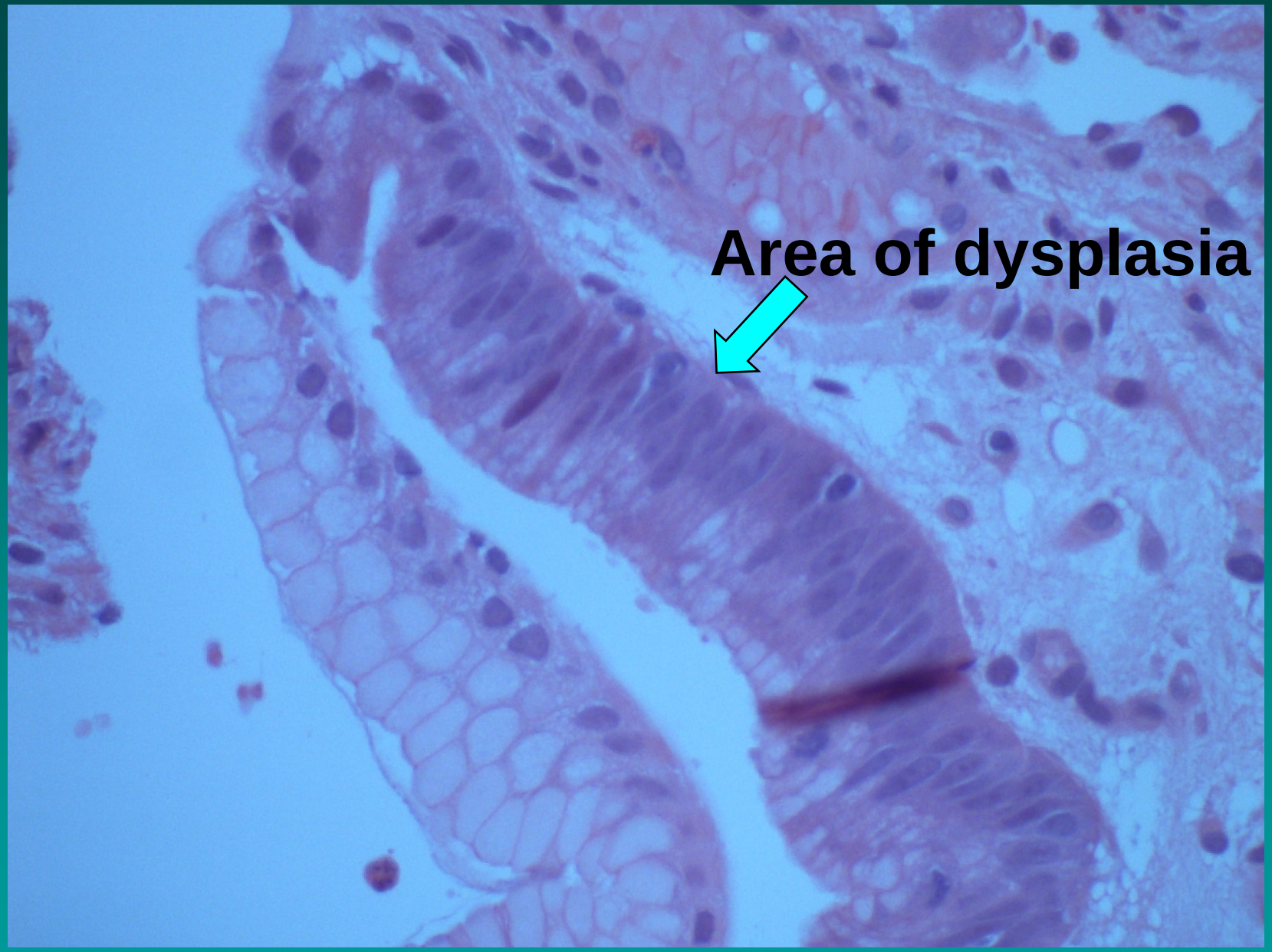
High Grade Dysplasia
(Early Gastric Cancer)



From Correa et al

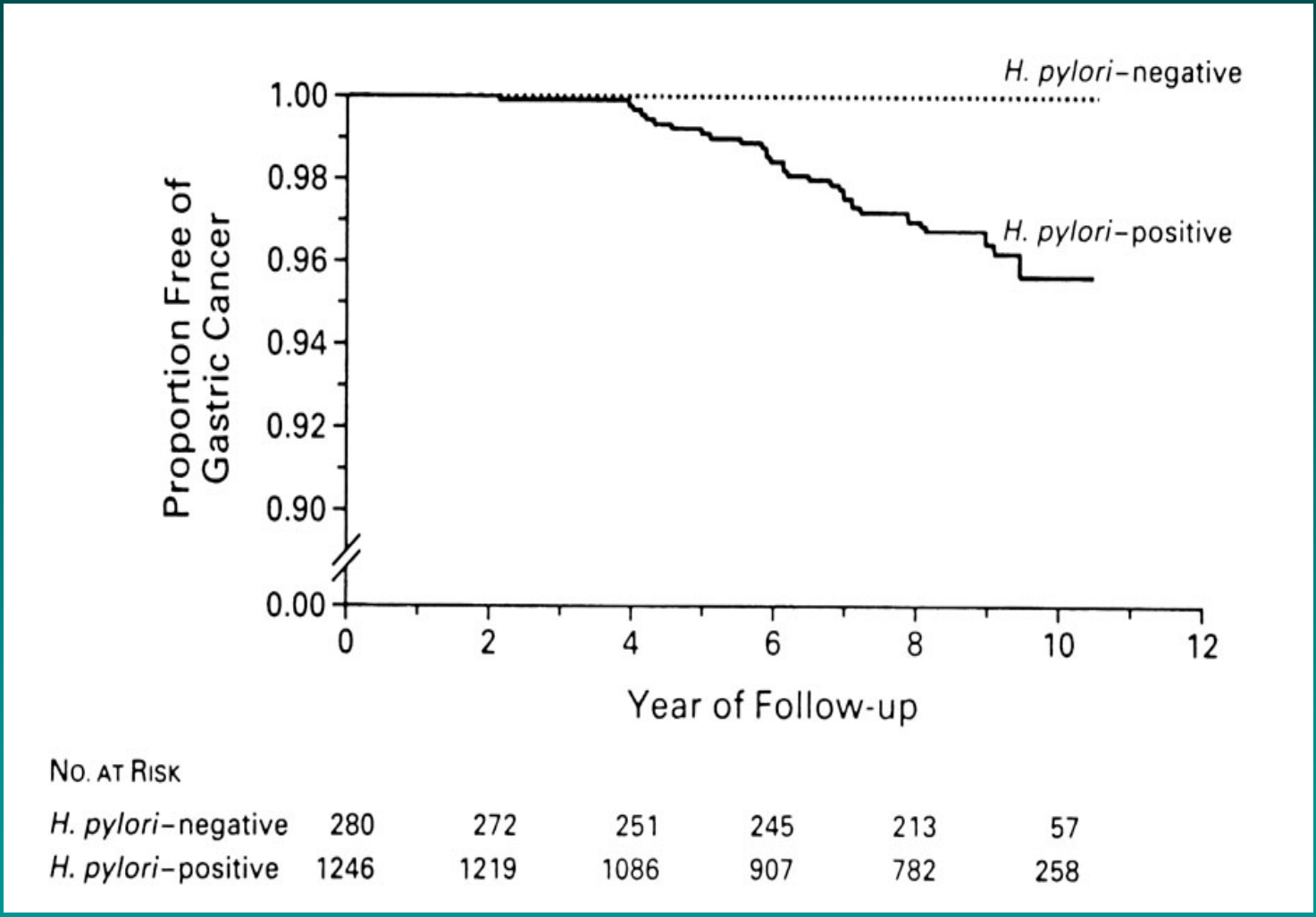


From Correa et al


Area of dysplasia

Hp infection Life Time Risk

- Antral predominant gastritis > 85%
- DU and GU 5-15%
- Gastric cancer < 1%
- Dyspepsia, epigastric pain dominant



Uemura, NEJM 2001

Hp-Gastric Cancer Relative Risk

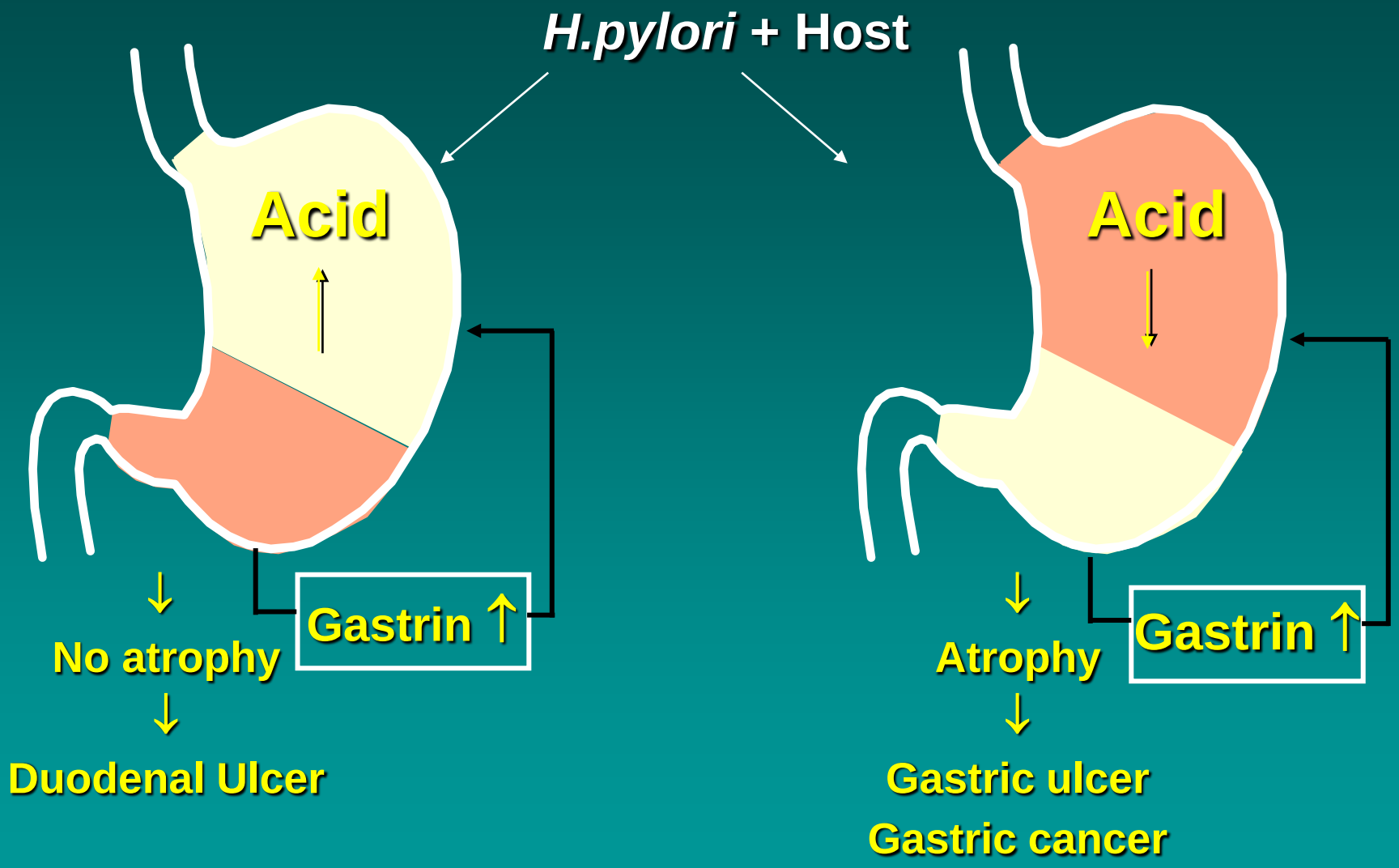
ATROPHY	
none/mild	1.0
moderate	1.7
severe	4.9

Gastritis Distribution	
antral predominant	1.0
pangastritis	15.6
corpus predominant	34.5

Intestinal metaplasia	
absent	1.0
present	6.5

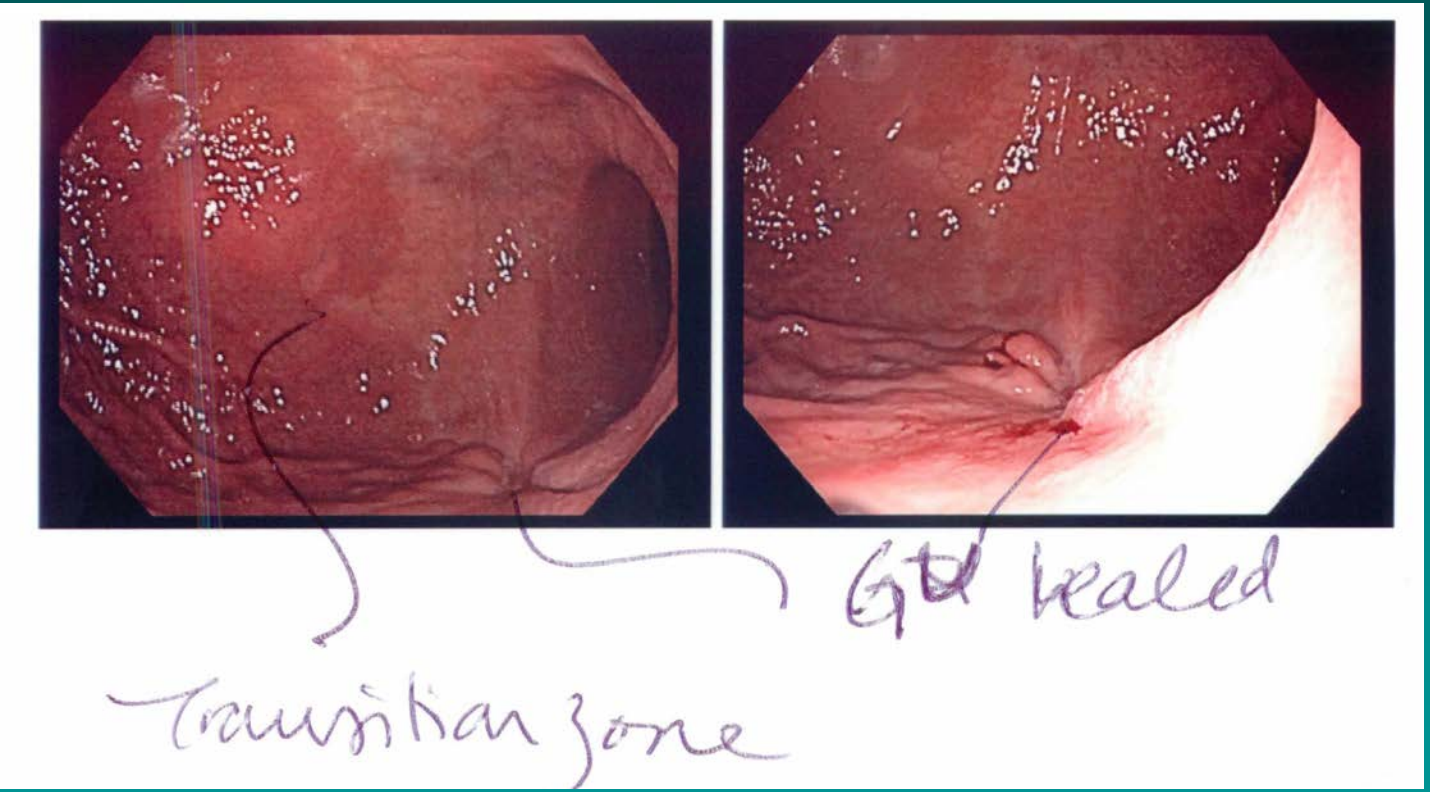
Uemura et al, NEJM 2001:345:784-9.

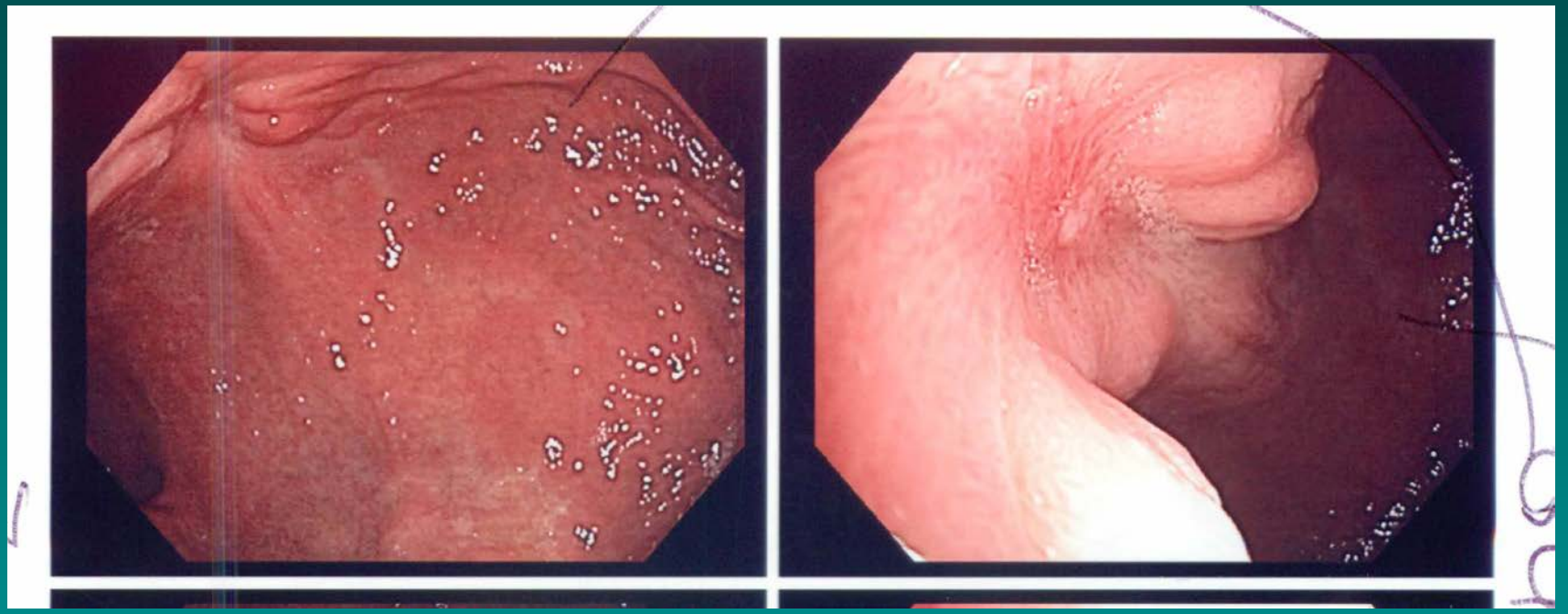
Outcomes of *H.pylori* colonization



Transition Zone

Most Gastric Ulcers and Cancer are located at site of worst gastritis



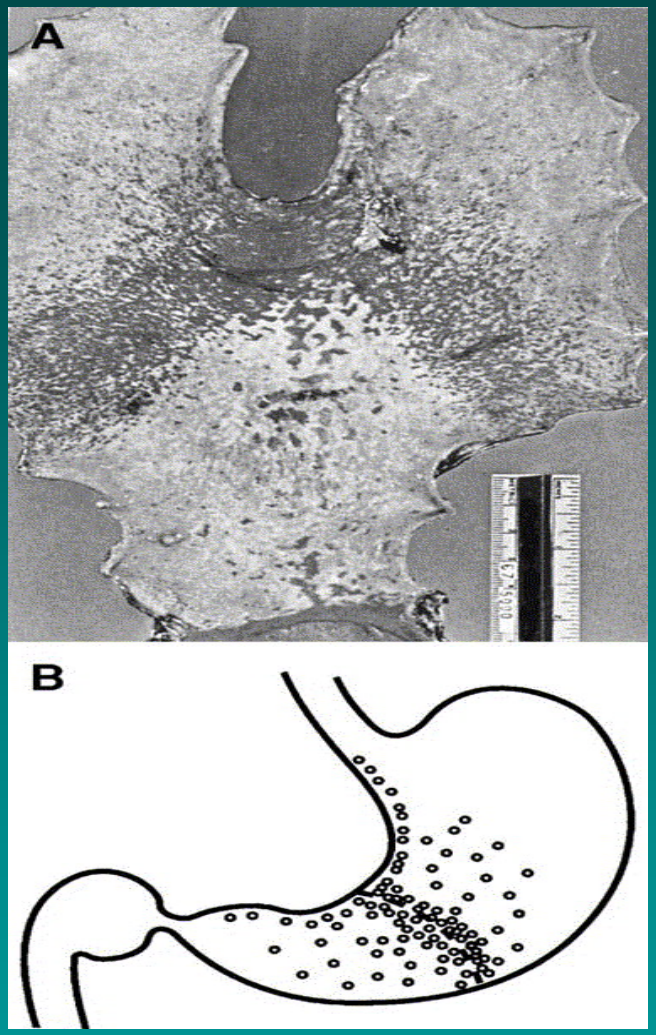


Concern about Gastric Cancer

- 2% of GUs are malignant
- Usually can tell by aspect of ulcer
- sometimes requires repeat biopsies
- slow healing of benign ulcers does occur

F/U gastric ulcers

- if you are concerned → keep taking biopsies
- take biopsies even in healed areas, esp. when you see scar
- Look at gastritis pattern



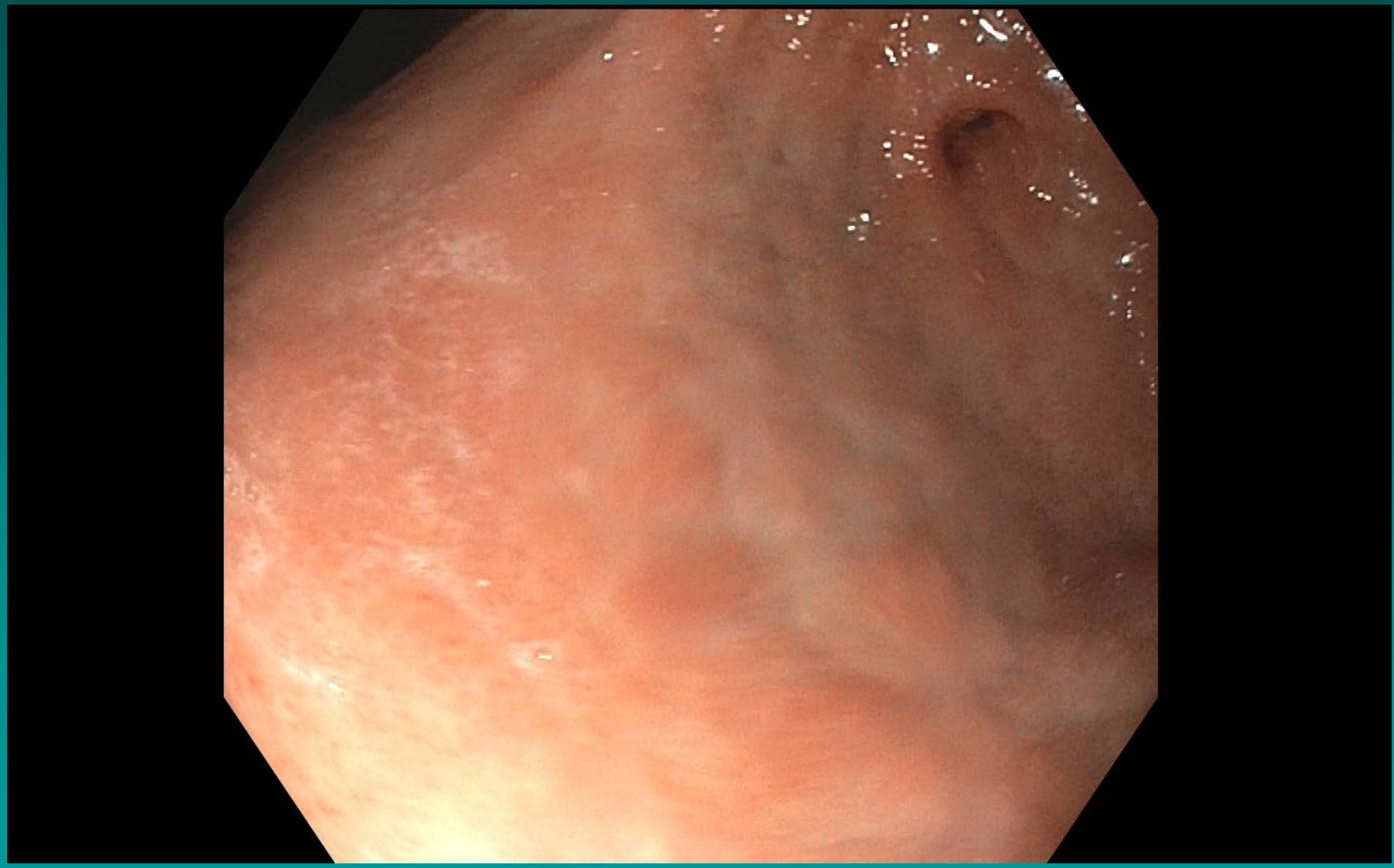
Reprinted from JNCI 1968

Note: correlation with transitional zone and incisura

Resected stomach: location Intestinal metaplasia

Van Zanten et al, GE 1999;116:1217-29

Endoscopic Intestinal Metaplasia



Endoscopic Intestinal Metaplasia

Hazard ratios for gastric cancer among patients with different lesions in the stomach compared with normal group

Mucosal status at baseline*	Hazard ratio (95% CI)†		
	Cardia gastric cancer	Non-cardia gastric cancer	All gastric cancer
Normal	Reference	Reference	Reference
Minor mucosal change	1.1 (0.4 to 2.9)	1.9 (1.3 to 2.8)	1.8 (1.2 to 2.5)
Gastritis	1.8 (1.2 to 2.9)	2.8 (2.3 to 3.5)	2.6 (2.2 to 3.2)
Atrophic gastritis	2.4 (1.1 to 4.8)	5.0 (3.8 to 6.7)	4.5 (3.5 to 5.8)
Intestinal metaplasia	4.7 (2.3 to 9.5)	6.5 (4.8 to 8.9)	6.2 (4.7 to 8.2)
Dysplasia	6.0 (2.3 to 15.9)	12.1 (8.3 to 17.6)	10.9 (7.7 to 15.4)

Song et al, BMJ 2015;351:h3867

How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis

- 10 studies, 181.662 upper GI endoscopies, 3 year follow-up
- 3.787 upper GI cancers diagnosed, 467 (12.3%) were originally missed
- 88% of missed cancers of gastric origin

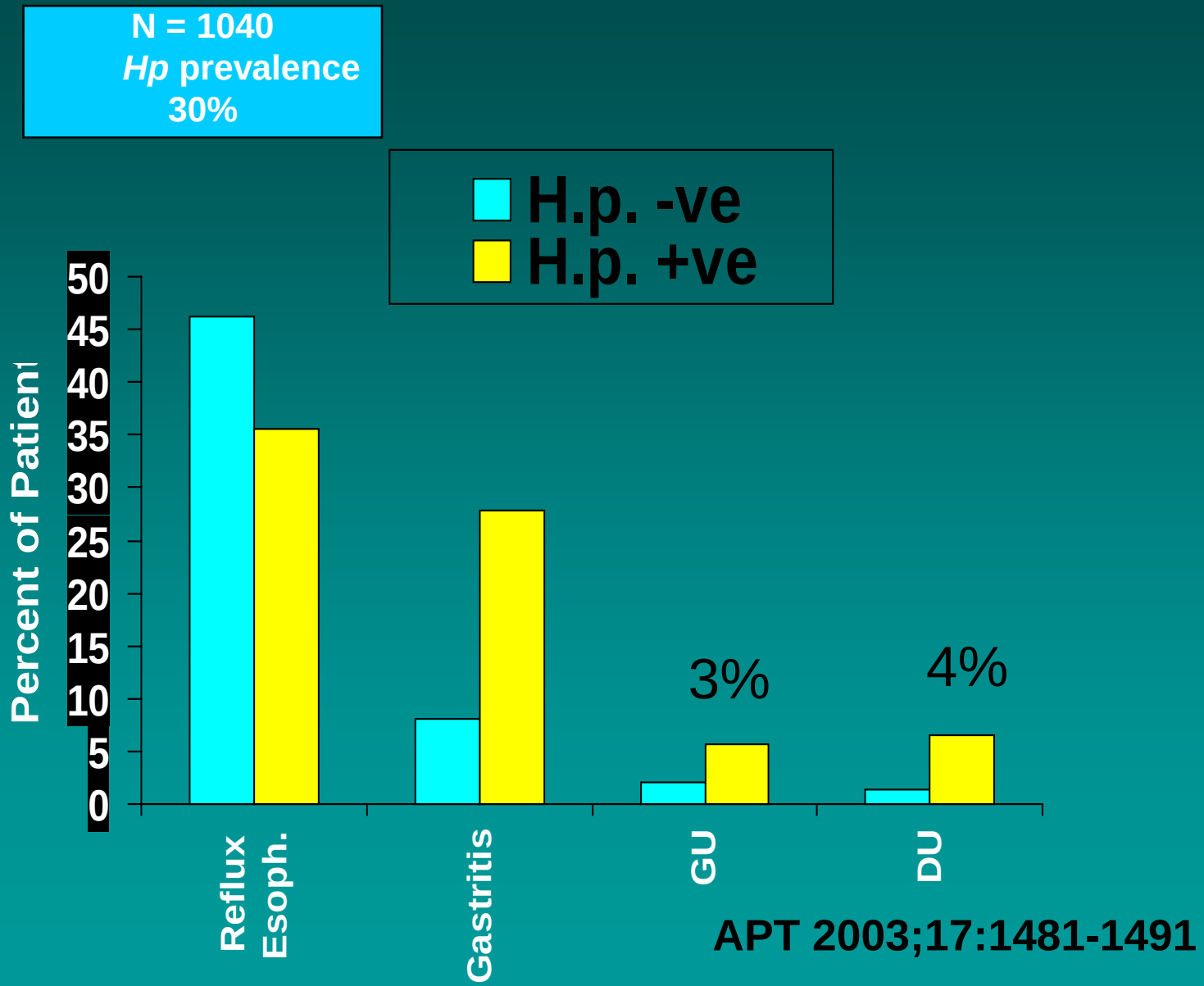
- Conclusion: missed gastric cancer 1 in 398

Menon S et al. Endosc Int Open 2014; 2: E46-50

Normal Endoscopy

- What is your definition ?
- What proportion of patients is on PPI at time of Gastroscopy ?
- In Dyspepsia (or GERD) do you take biopsies for *Hp* if it looks normal ?

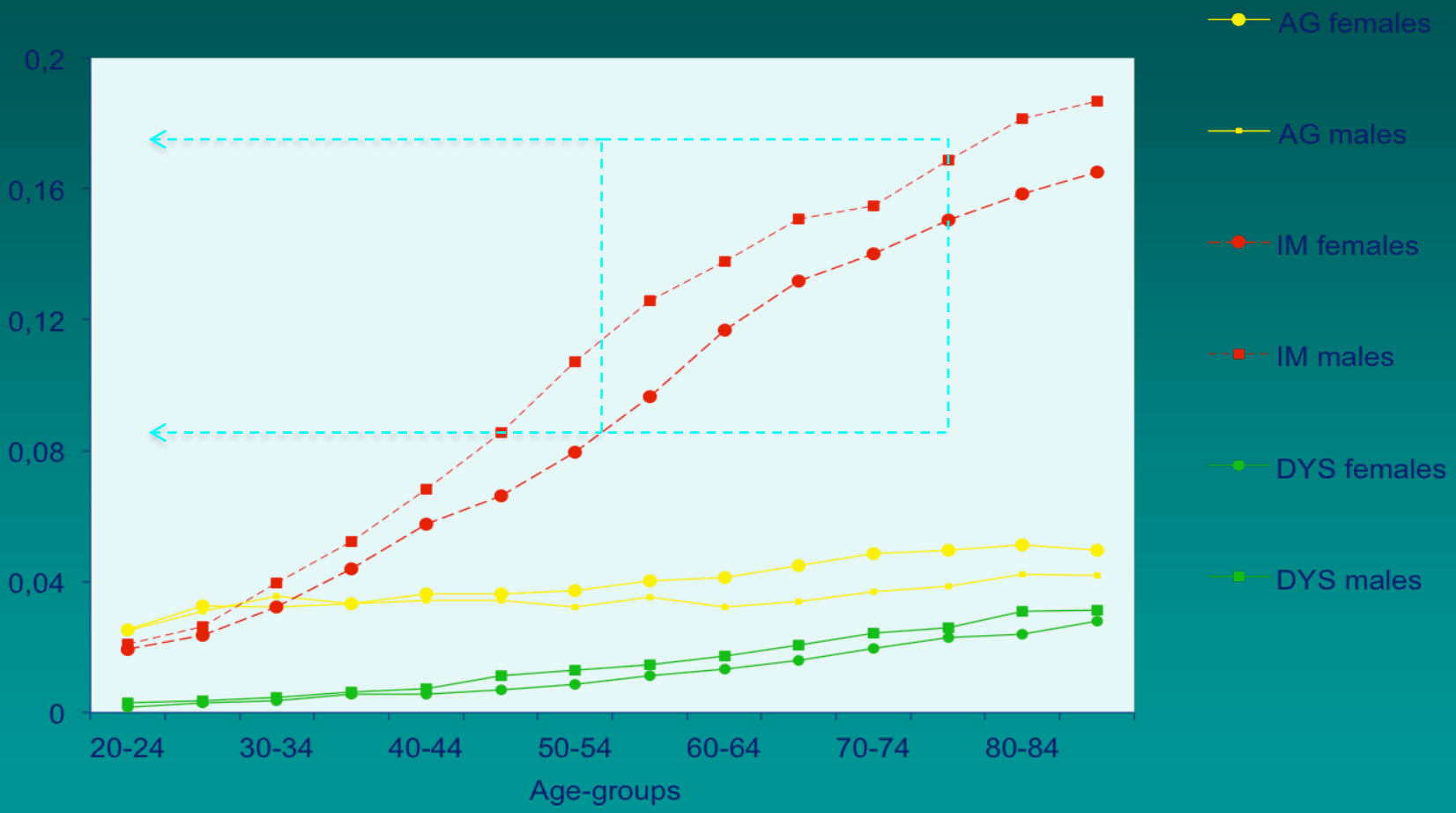
CADET-PE (prompt endoscopy): Endoscopic Findings by *Hp* Status



APT 2003;17:1481-1491

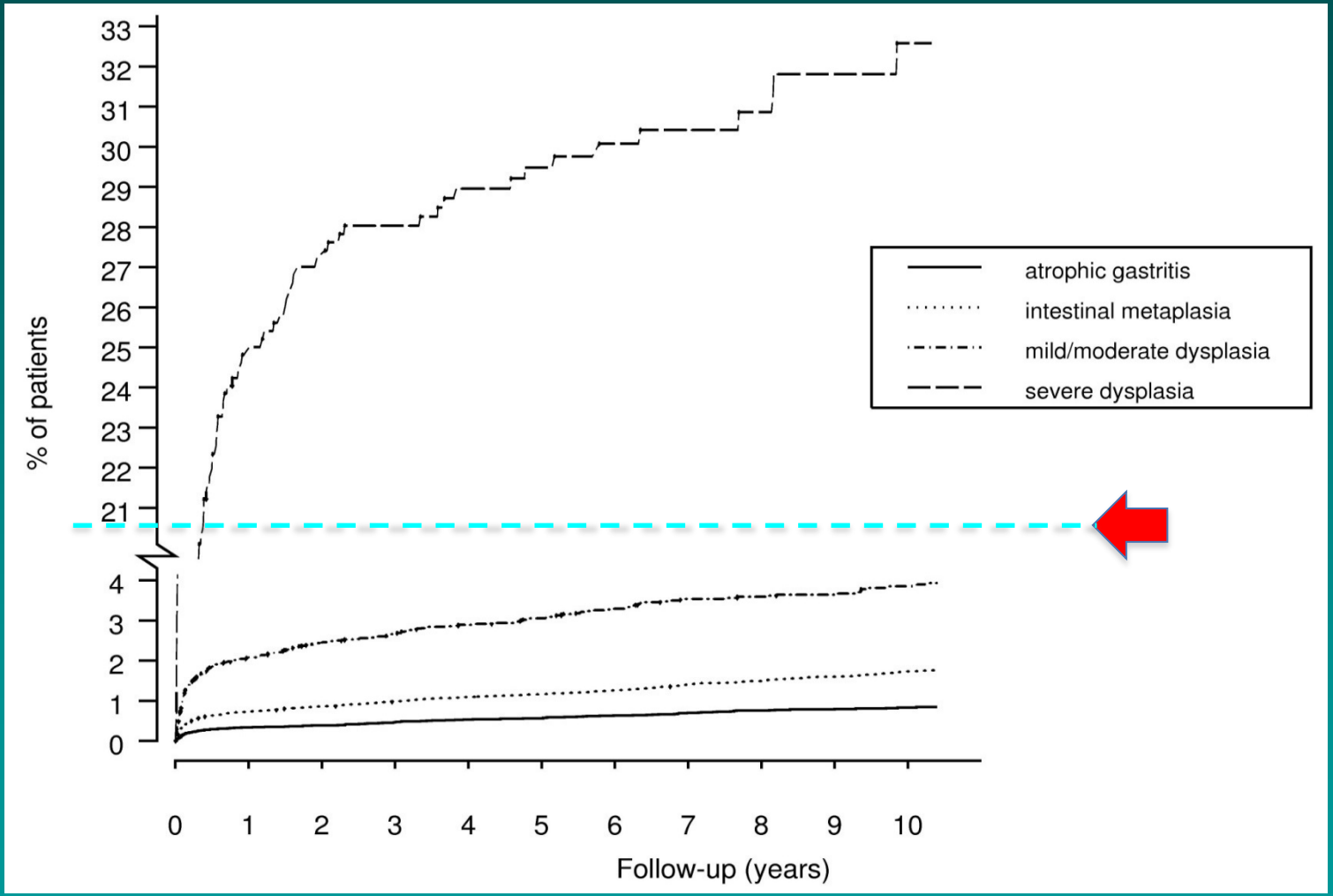
Does presence of Intestinal Metaplasia warrant follow-up ?

Age-related prevalence of pre-malignant gastric lesions in 97.837 Dutch subjects



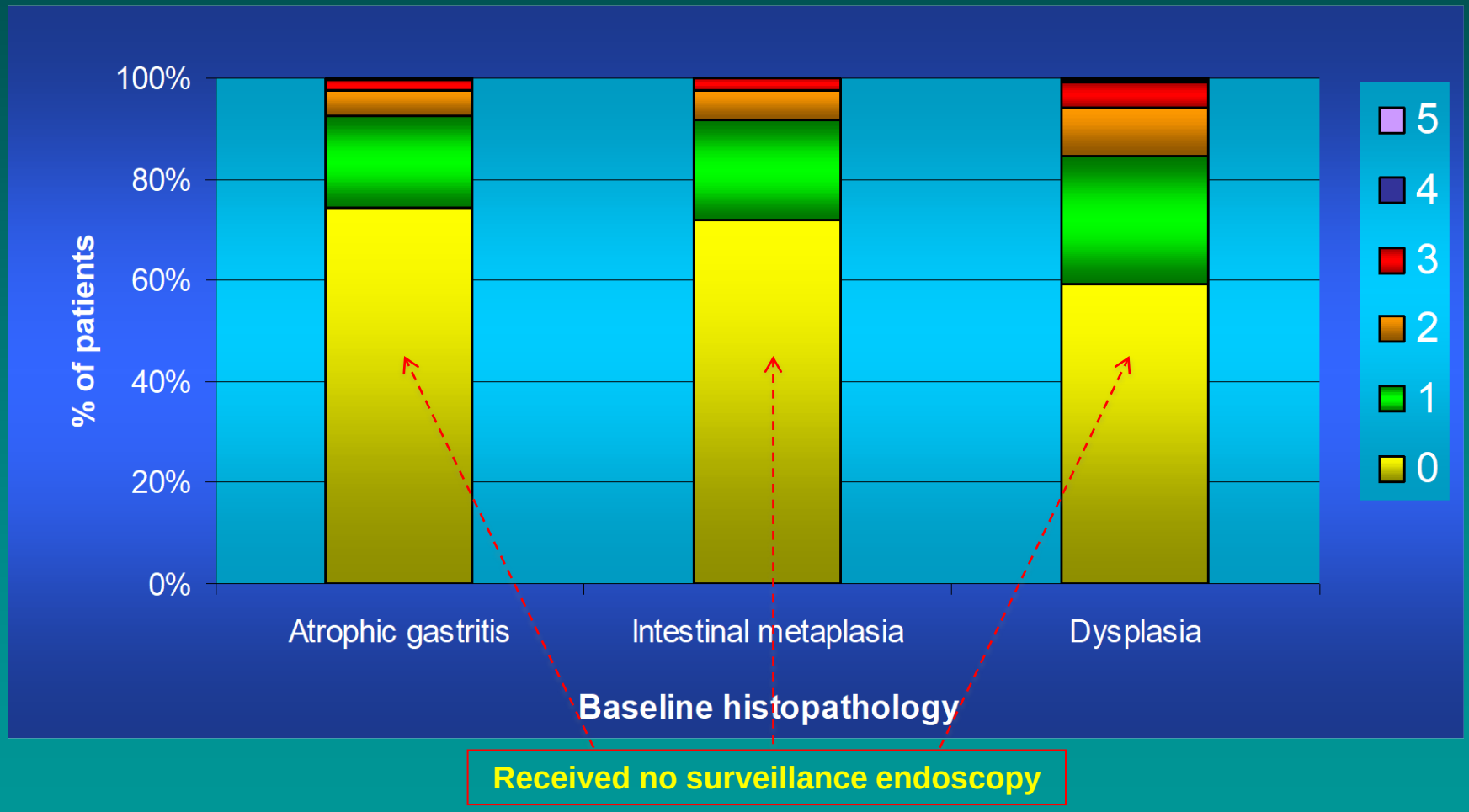
de Vries et al. Gut 2007

Time-related progression of pre-malignant lesions to gastric cancer in 92.250 Dutch subjects with atrophy/IM



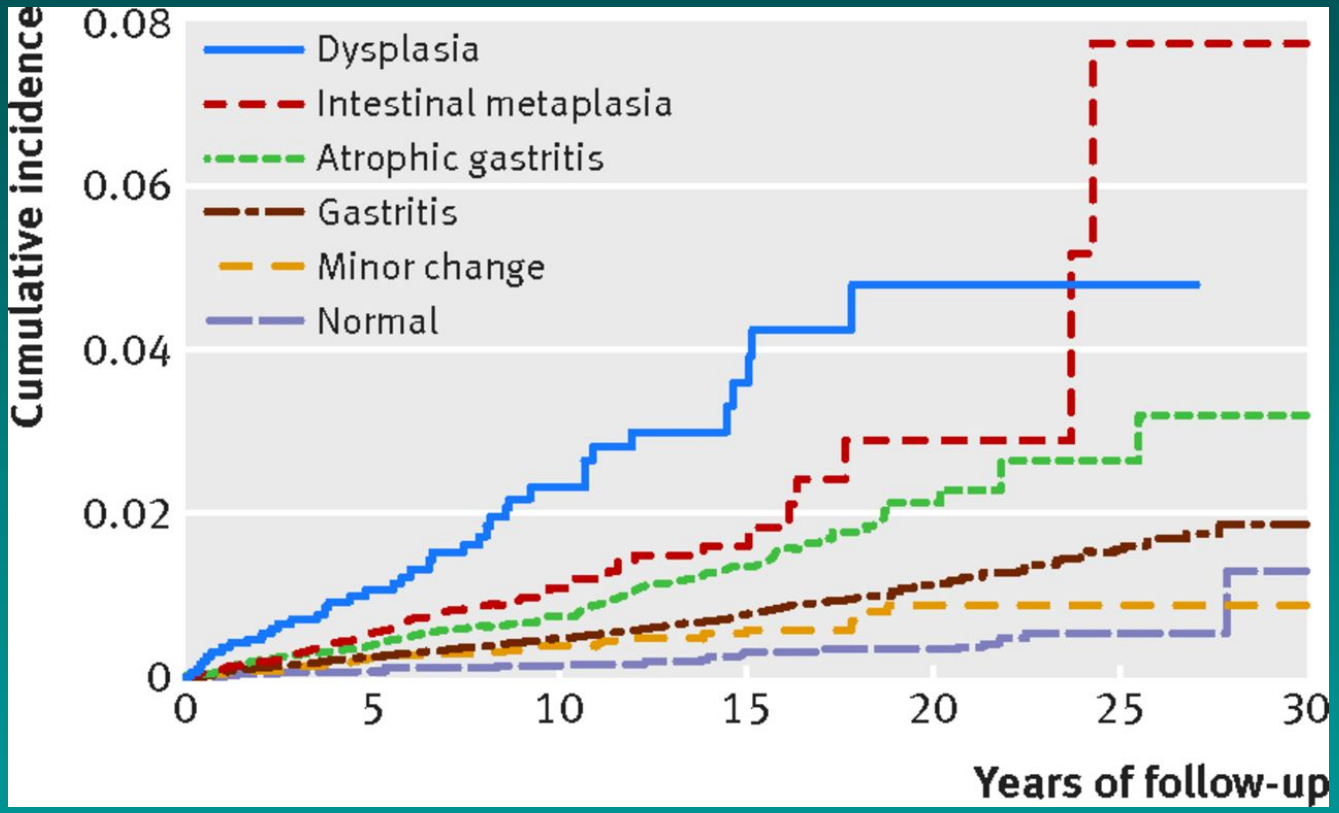
de Vries et al, GE 2008;134:945-52

Proportion of patients with premalignant gastric lesions receiving follow-up endoscopy in the Netherlands



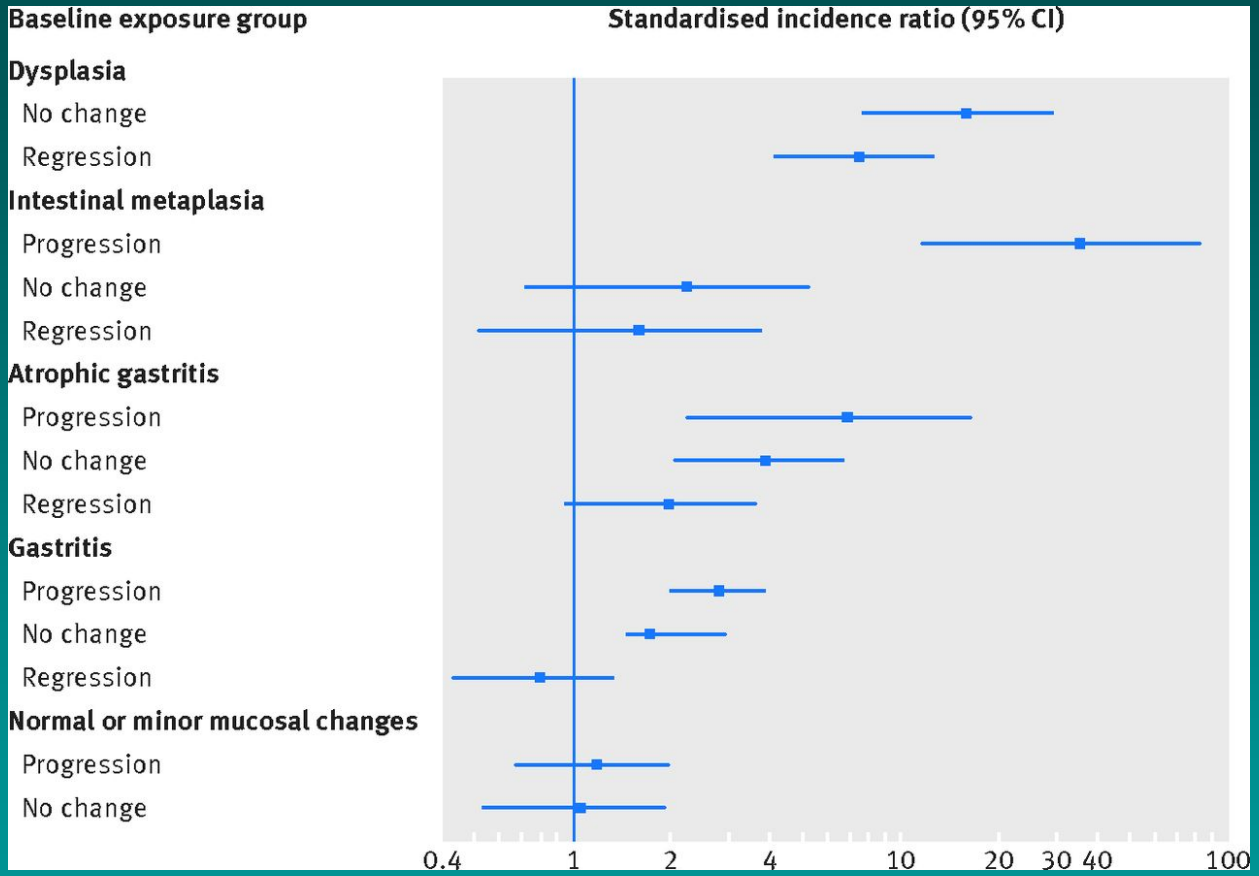
de Vries AC et al. Gastroenterology 2008

Cumulative Incidence of GC among patients (n=55621) with different baseline diagnosis



Song et al, BMJ 2015;351:h3867

Standardized Incidence ratio for non-cardia GC in patients (n=55621) with F/U biopsies



Song et al, BMJ 2015;351:h3867

Both European Society of Gastroenterology (MAPS guidelines) and Kyoto Global Consensus on *Hp* gastritis recommend that:

Patients with more extensive and severe intestinal metaplasia should be offered endoscopic and histological surveillance

AGA Technical review

- Recommends against routine use of surveillance in patients with gastric intestinal metaplasia

GE 2020;158:693-702

AGA Technical review

- Recommends use of surveillance is reasonable in patients with gastric intestinal metaplasia and higher risk
  - Extensive IM
  - Family history gastric cancer
  - Populations at higher risk

- Gastroscopy every 3-5 years ?

GE 2020;158:693-702

Population Screening

- Not realistic in Canada

- In other countries (Korea, Japan) has resulted in higher rates detection of early GC and lower mortality rates

AGA Technical review

- 22 studies, 3 RCTs, 7 cohort studies
- *Hp* cure *with or without IM* resulted in 32% reduction in incident gastric cancer cases compared to placebo and 33% decrease in GC mortality

GE 2020;158:705-731

AGA Technical review

In patients with Intestinal metaplasia

- 0.16% annual risk of gastric cancer
- 1.6% 10 year risk of gastric cancer
- *No effect special populations*

- Pooled prevalence IM 4.8% (N=897,371)

Gastric Cancer in Canada

Special populations

- First Nation's people
- Immigrants from South East Asia and Central and South America

- Lower (age) threshold for gastroscopy

Gastric Cancer in Northern Populations of North America

- 4th most frequently diagnosed cancer in NWT males in contrast to 10th for males across Canada
- age-adjusted incidence rate for NWT males twice Canadian rate (higher for regions with predominantly Aboriginal populations)

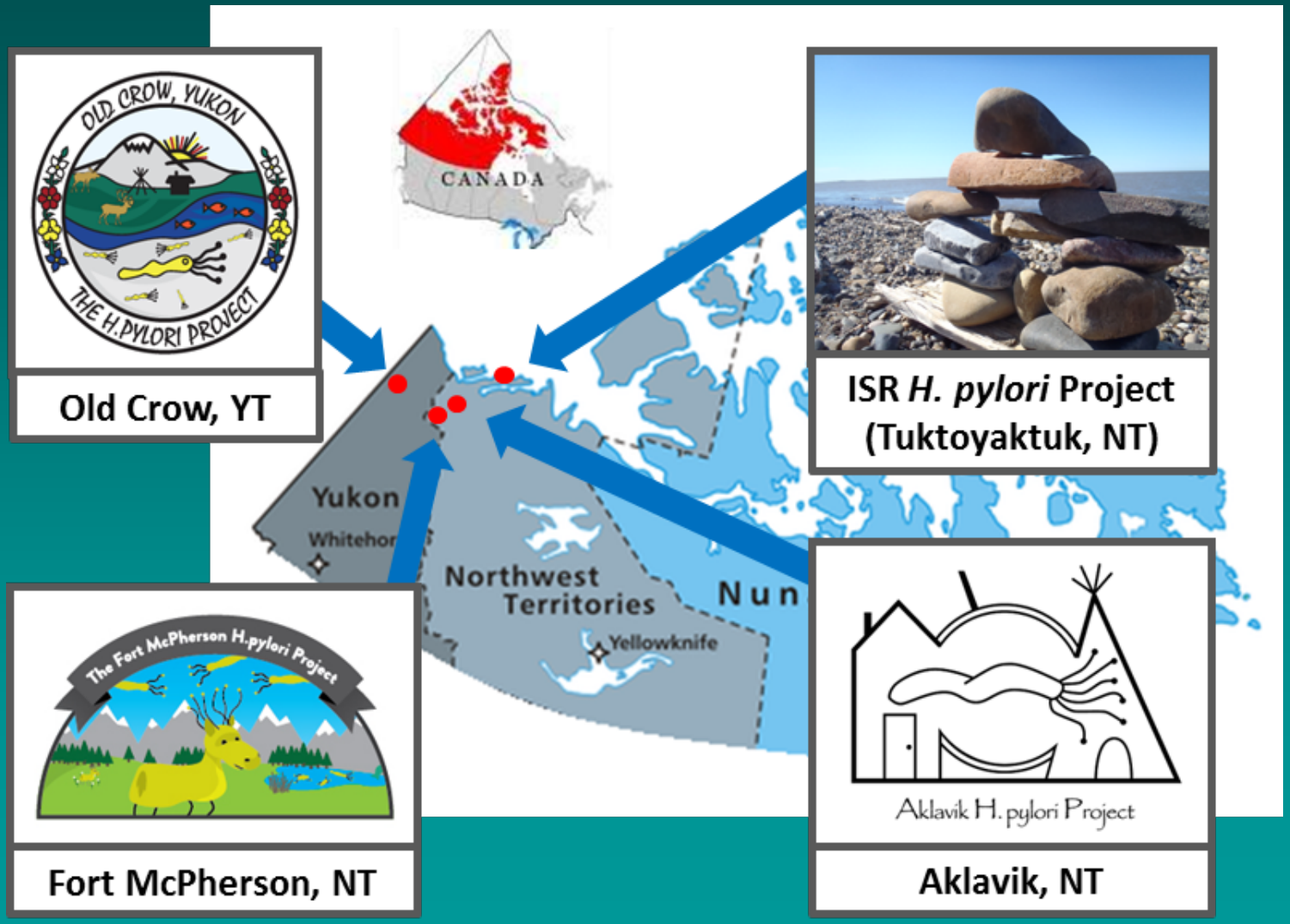
People of Northern Canada

- 2011 Census Population

Nunavut	38,854
NorthWest Territories	44,958
Yukon	41,352


Ross River
AKLAVIK
Old Crow
Tuktoyaktuk
Teslin
Fort McPherson
Yukon Territory
Whitehorse
Northwest Territories
Yellowknife
Nunavut
Iqaluit
British Columbia
Victoria
Alberta
Edmonton
Saskatchewan
Regina
Manitoba
Winnipeg
Ontario
Ottawa
Toronto
Quebec
Québec
Newfoundland and Labrador
Charlottetown
Fredericton
Halifax
New Brunswick
Nova Scotia
CANADA – Political
International boundary
Provincial/territorial boundary
Alberta Province/territory
Ottawa National capital
Regina Provincial/territorial capital
Scale
0 250 500 750 1 000 km

Community *H. pylori* Projects



Hamlet of Aklavik, Northwest Territories

- 2019 population: 690
  - 90% Inuvialuit (Inuit) or Gwich'in Dene (First Nation)
- Access
  - Reached only by air, water, or winter ice-road


NORCAN
SALES

Health Center


CYST0 4
009233016
BIG SHEX
01/12/2008
10:31:53
Colon
SONY
OLYMPUS
OLYMPUS

Findings

- Very high prevalence *Hp* >60%
- Severe gastritis with atrophic gastritis and IM
- Gastric ulcers> duodenal ulcers
- High prevalence smoking

Family History Gastric cancer

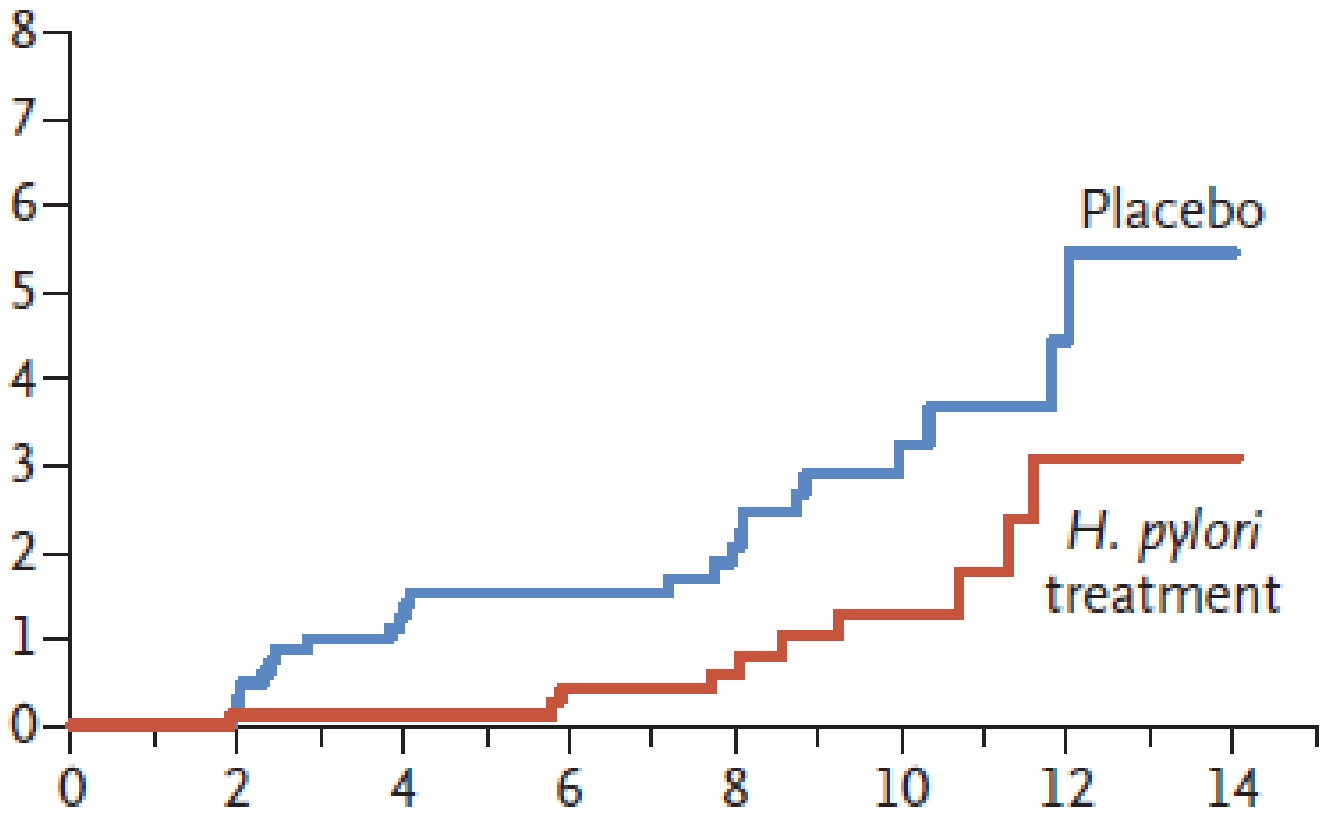
1st Degree Relatives

Hp-Rx in patients with 1 st degree relative with gastric cancer

- RCT, N=1838, Korea
- Age 40-65 years
- Hp Rx: Lanso-Clari-Amox x 7 days
  - Efficacy 71%
- Gastroscopy q 2 years
- Median F/U 9.2 years

Choi et al, NEJM 2020;382:427-36

Cumulative Incidence Gastric Cancer



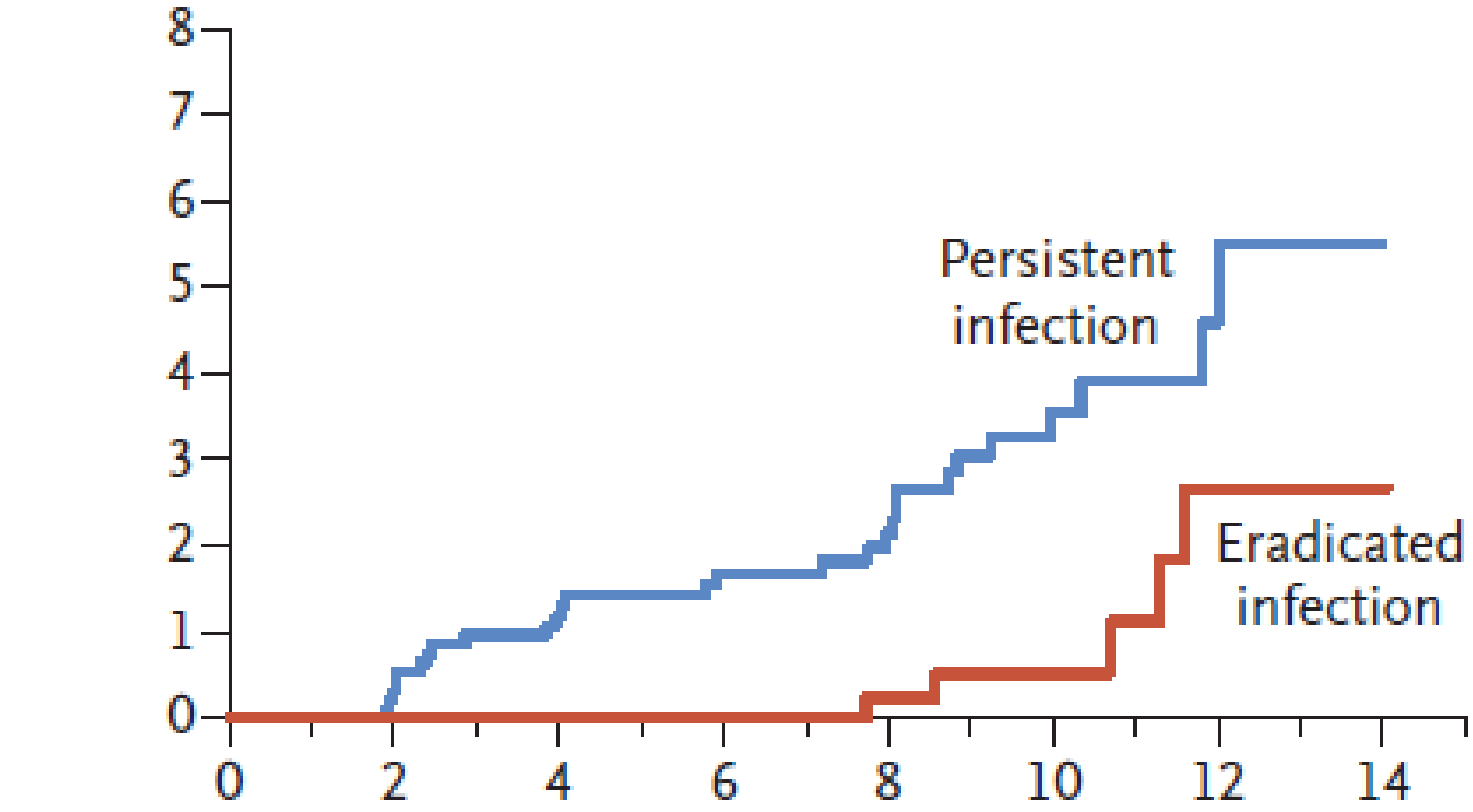
Hazard ratio, 0.45 (95% CI, 0.21–0.94)
P=0.03 by log-rank test

Placebo 2.7%

Hp–Rx 1.2%

Choi et al, NEJM 2020;382:427-36

Cumulative Incidence Gastric Cancer by *Hp* status



***Hp* persist 2.9%**

***Hp* cured 0.8%**

Choi et al, NEJM 2020;382:427-36

Case 45 Year old male

- Healthy
- Father died Gastric cancer age 53

- What would you advise ?

Management

- Check for *Helicobacter* (non-invasively)
- Treat *Hp* if positive
- Gastroscopy with biopsies
  - Separate: antrum and body
  - *Helicobacter*
  - Intestinal metaplasia
  - Atrophic gastritis

Follow-up gastroscopy ?

- Non-evidence based
- If index gastric cancer < 60 years of age ⟶ gastroscopy every 5 years, starting 10 years before diagnosis in index case
- Especially, if intestinal metaplasia and atrophic gastritis are present

Intestinal metaplasia F/U

- look both at antrum and body
- any location > mild
- Both antrum and body mild IM (?)

→ Do F/U gastroscopy

Conclusions

- *Hp* is a definite and modifiable risk factor for gastric cancer
- Outcome *Hp* infection depends on gastritis pattern
- Strong evidence to test and treat for *Hp* in patients with family history of gastric cancer

Conclusions

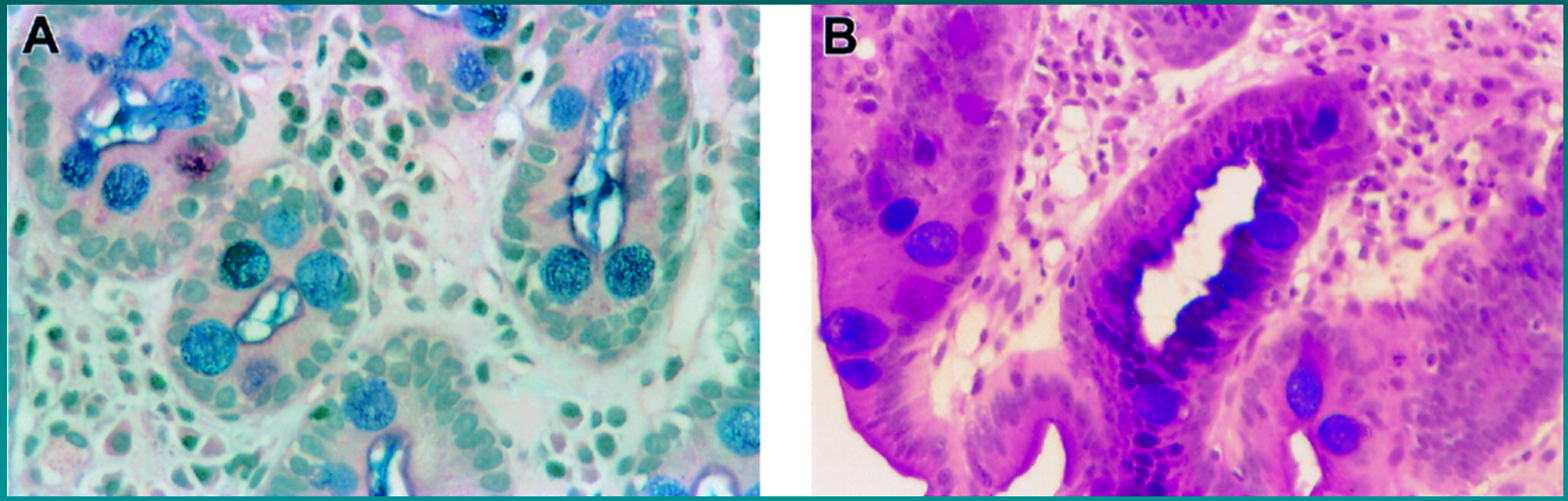
- Testing and treating for *Hp* should be considered in patients who undergo gastroscopy for dyspepsia
- Lower thresholds apply for populations at increased risk for gastric cancer
- Follow-up gastroscopies are indicated for patients with more extensive intestinal metaplasia

- Goblet cells **without** acidic Alcian blue staining

- Interspersed goblet cells and mucus cells, **Alcian blue positive**
- No brush border

Complete IM

Incomplete IM



Voutilainen et al, Gut 1999;45:644-648

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Concomitant Therapy (CLAMET)

- All drugs given for 14 days

- PPI bid
- Clarithromycin 500mg bid
- Amoxicillin 1g bid
- Metronidazole 500mg bid

Bismuth Based Quadruple therapy

PPI-BMT

PPI	bid
Bismuth (PeptoBismol)	2 tabs qid
Metronidazole 500 mg	tid or qid
Tetracycline 500mg	qid

APT 2002;16:1047-1057

Levofloxacin based Triple Therapy

- PPI bid
- Amoxicillin 1 g bid
- Levofloxacin 250 (500) mg bid

Fourth Line Rifabutin Therapy

- Only regimen were duration is 10 days
  - PPI bid
  - Amoxicillin 1g bid
  - Rifabutin 150mg bid
- Success rate 62%

Can J GE 2010;24:303-6