بسم الله الرحمن الرحیم

Early Gastric Cancer

Diagnosis & Management

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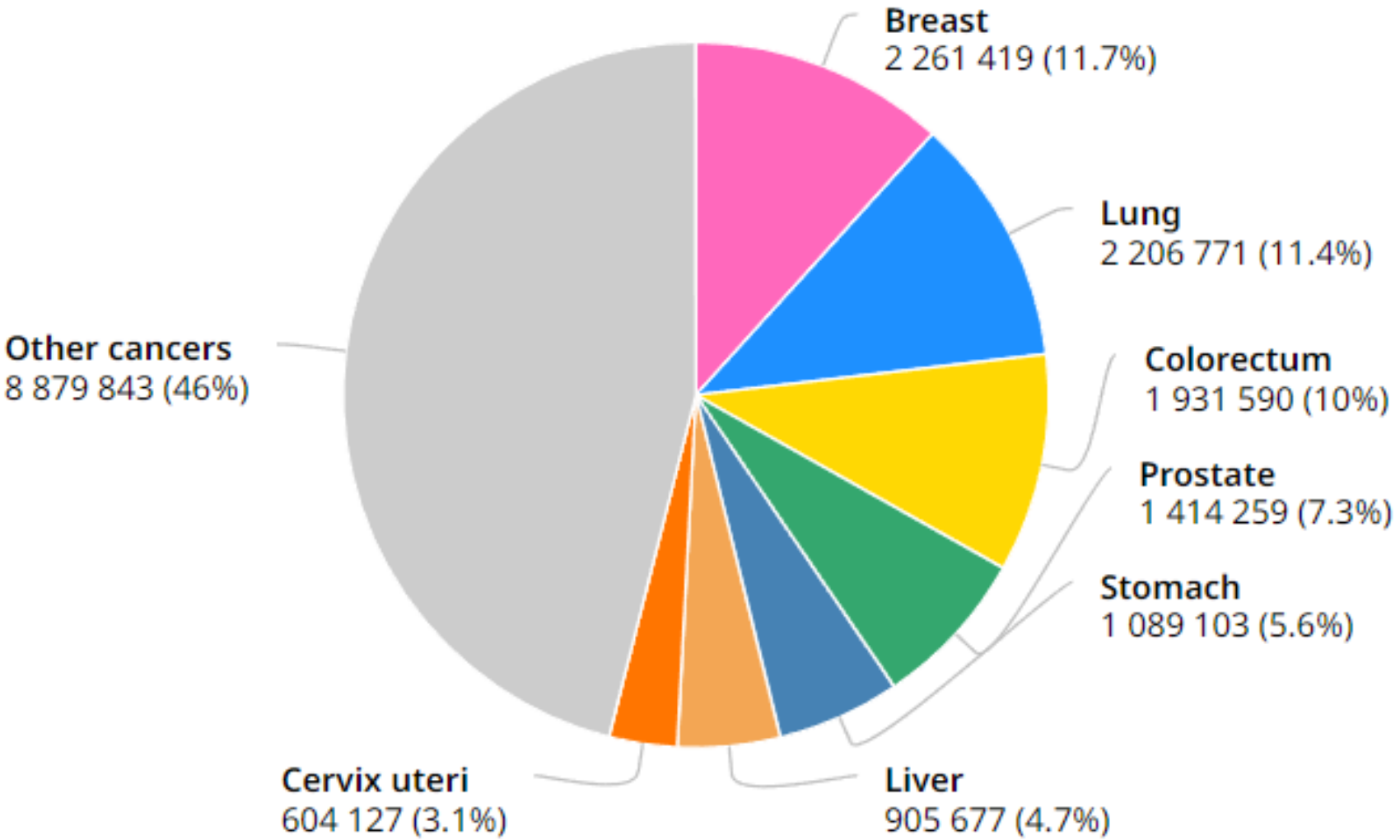
DISTINGUISHED PROFESSOR OF MEDICINE

SUMS

2024

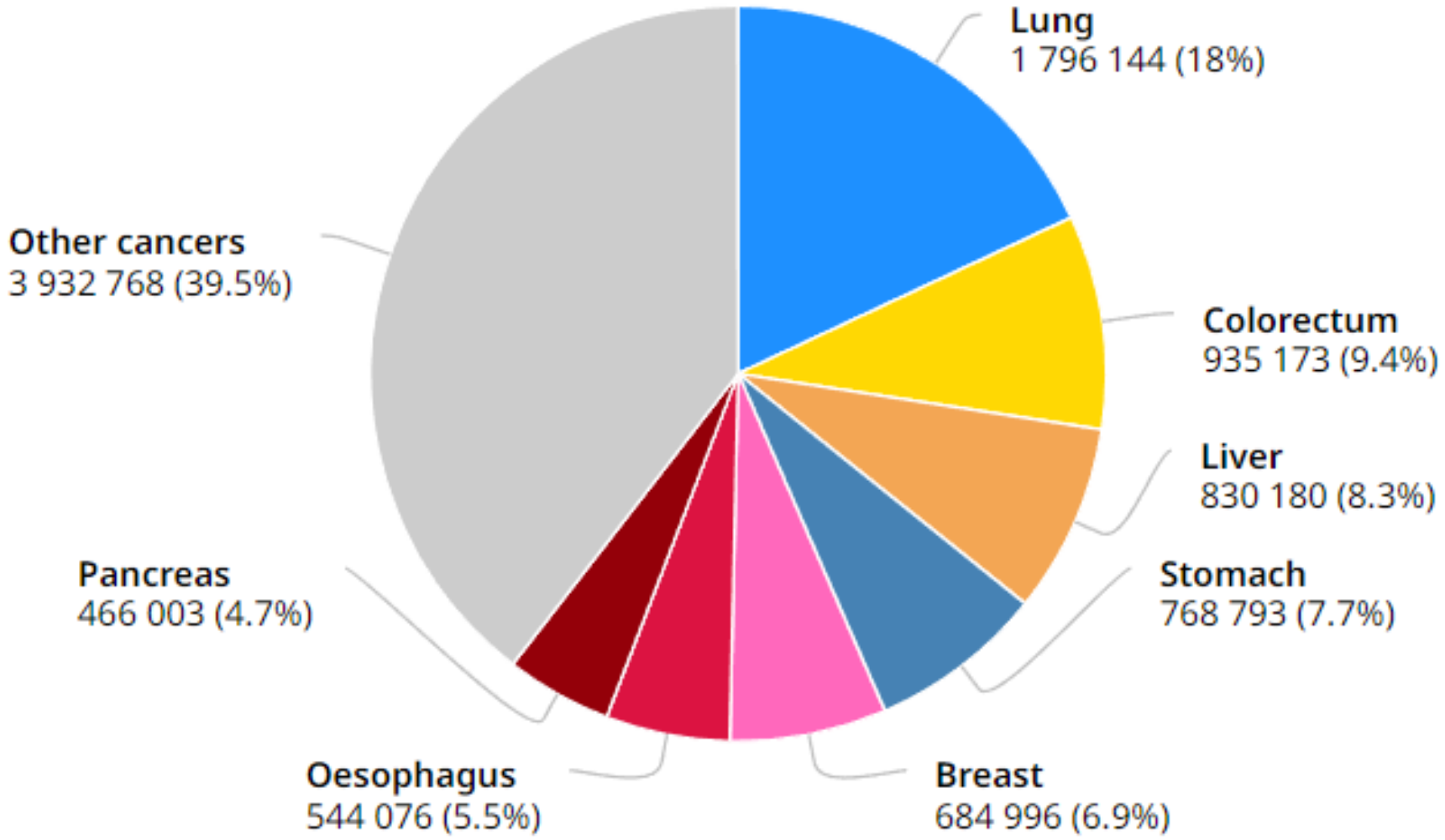
Last hospital in northern Gaza halts operation 6 Dec 2023

Estimated number of new cases in 2020, World, both sexes, all ages

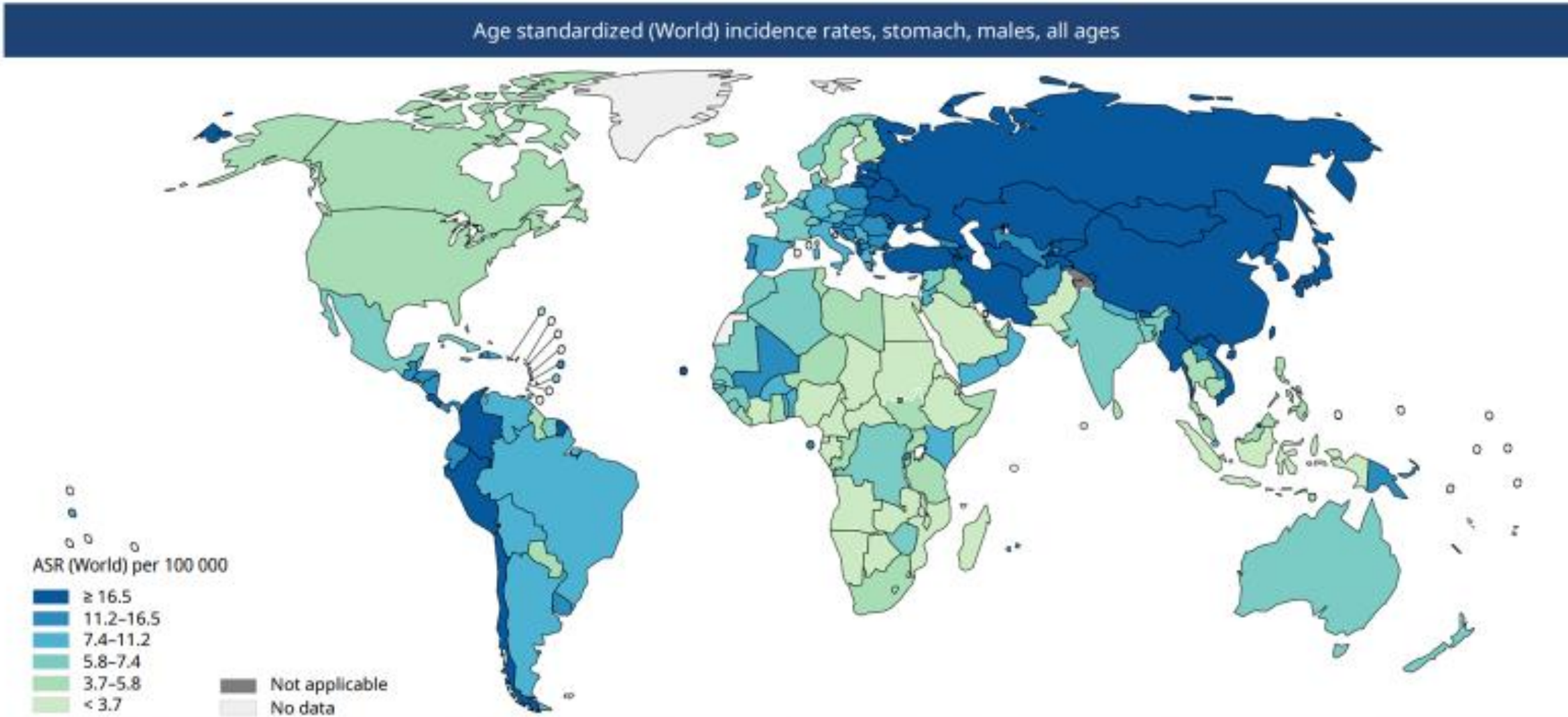


Total : 19 292 789

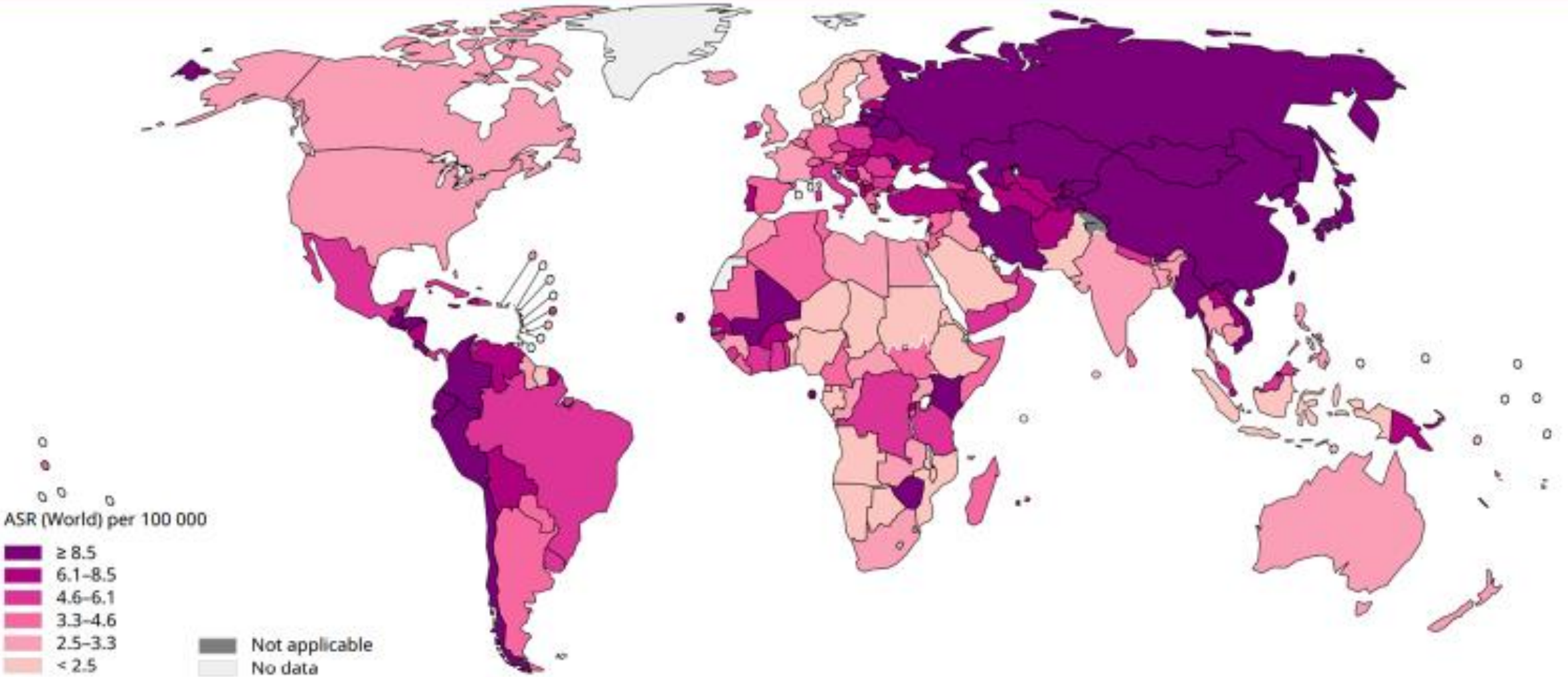
Estimated number of deaths in 2020, World, both sexes, all ages



Total : 9 958 133


Age standardized (World) incidence rates, stomach, males, all ages
ASR (World) per 100 000
≥ 16.5
11.2–16.5
7.4–11.2
5.8–7.4
3.7–5.8
< 3.7
Not applicable
No data

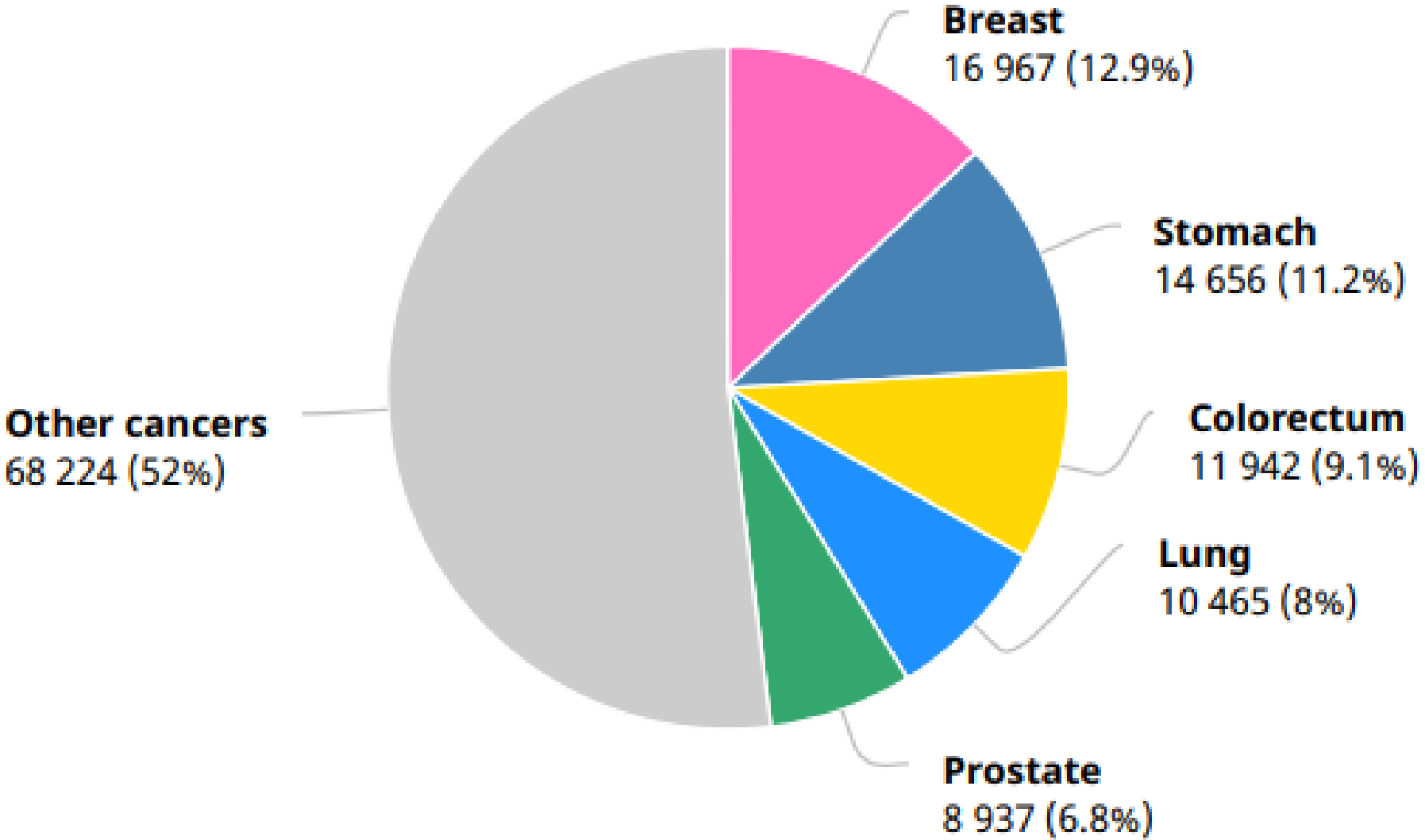
Age standardized (World) incidence rates, stomach, females, all ages



Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

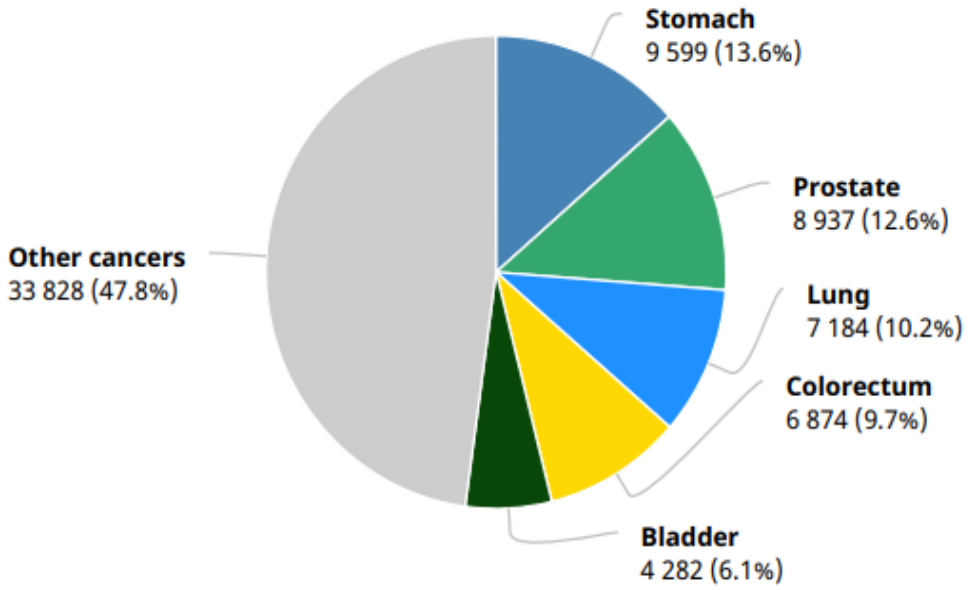
World Health Organization

Number of new cases in 2020, both sexes, all ages



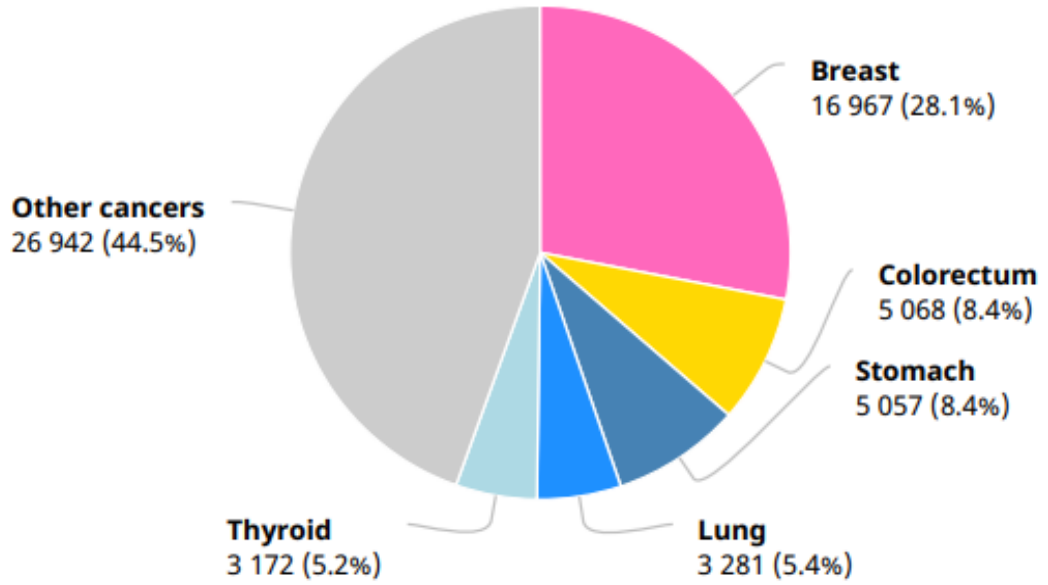
Total: 131 191

Number of new cases in 2020, males, all ages



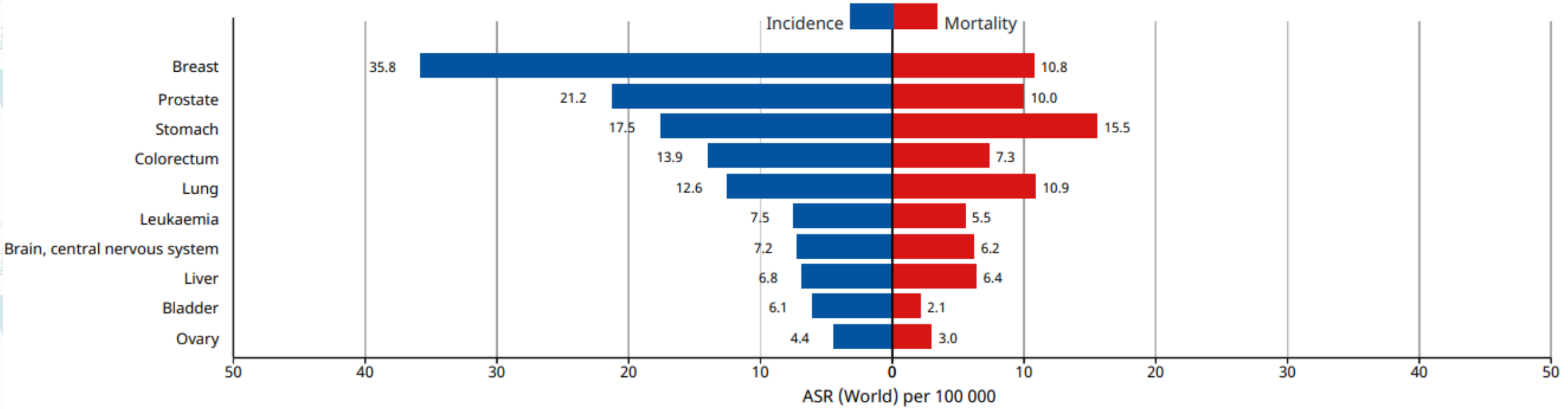
Total: 70 704

Number of new cases in 2020, females, all ages



Total: 60 487

Age-standardized (World) incidence and mortality rates, top 10 cancers



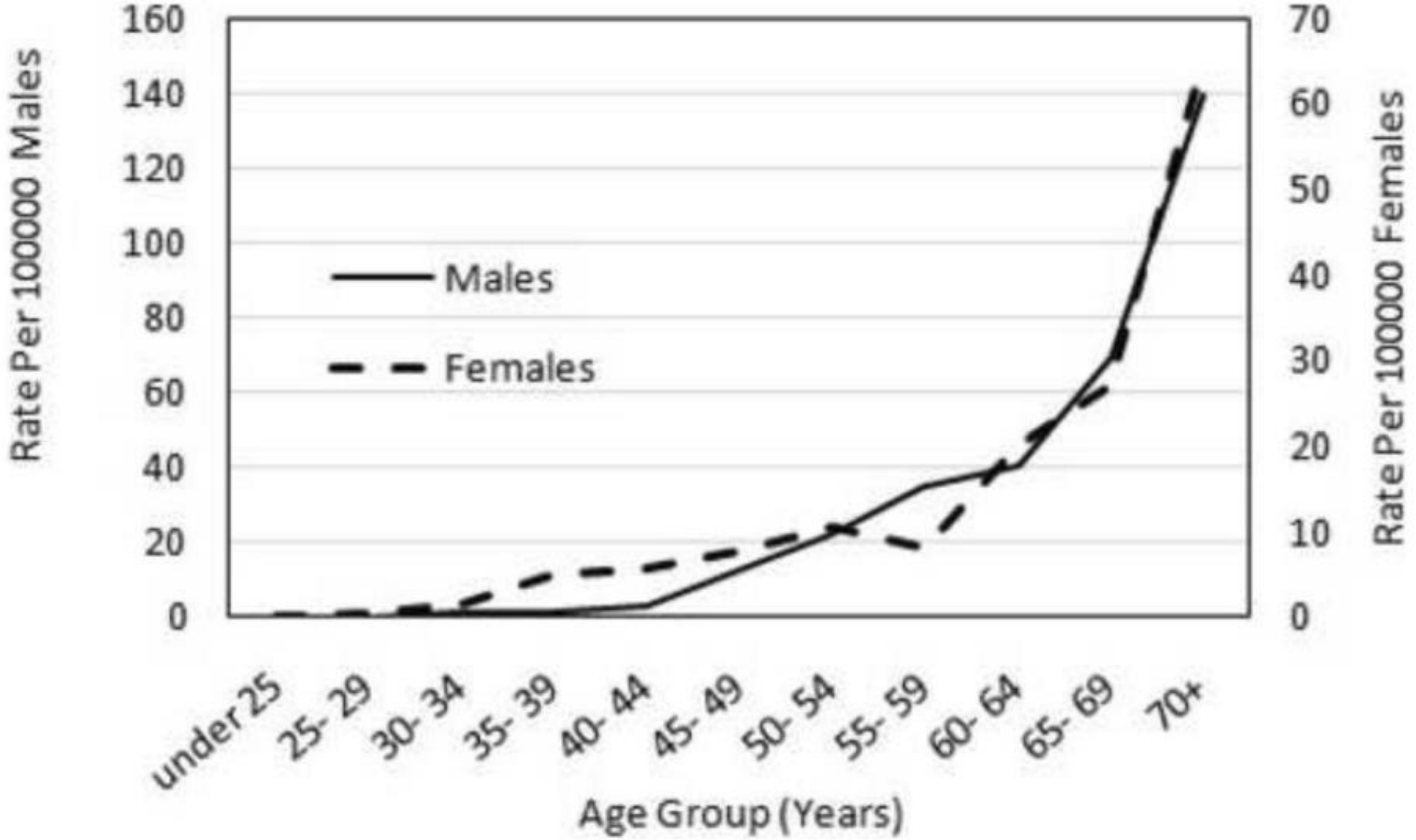
Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-021-00722-x

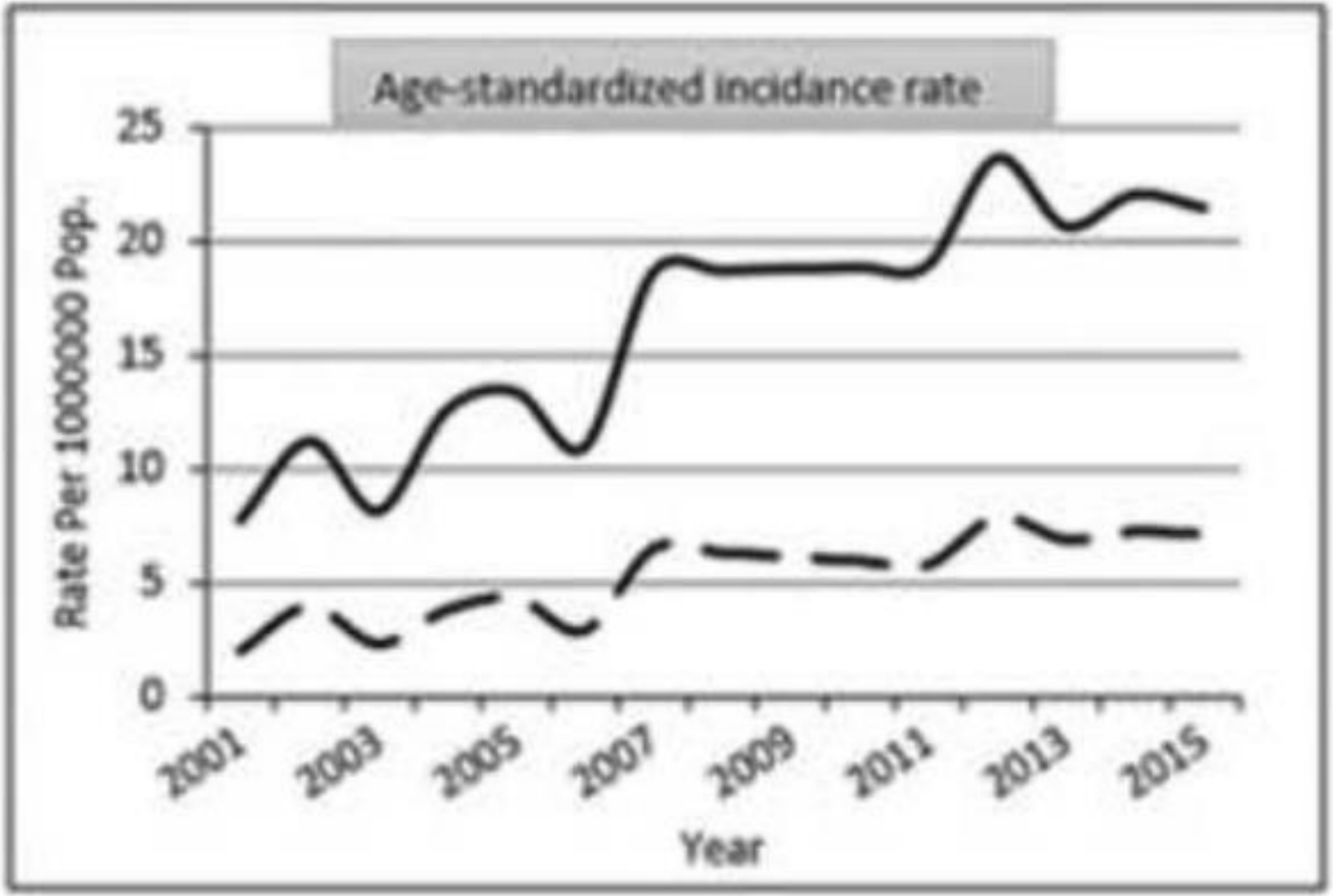
ORIGINAL RESEARCH

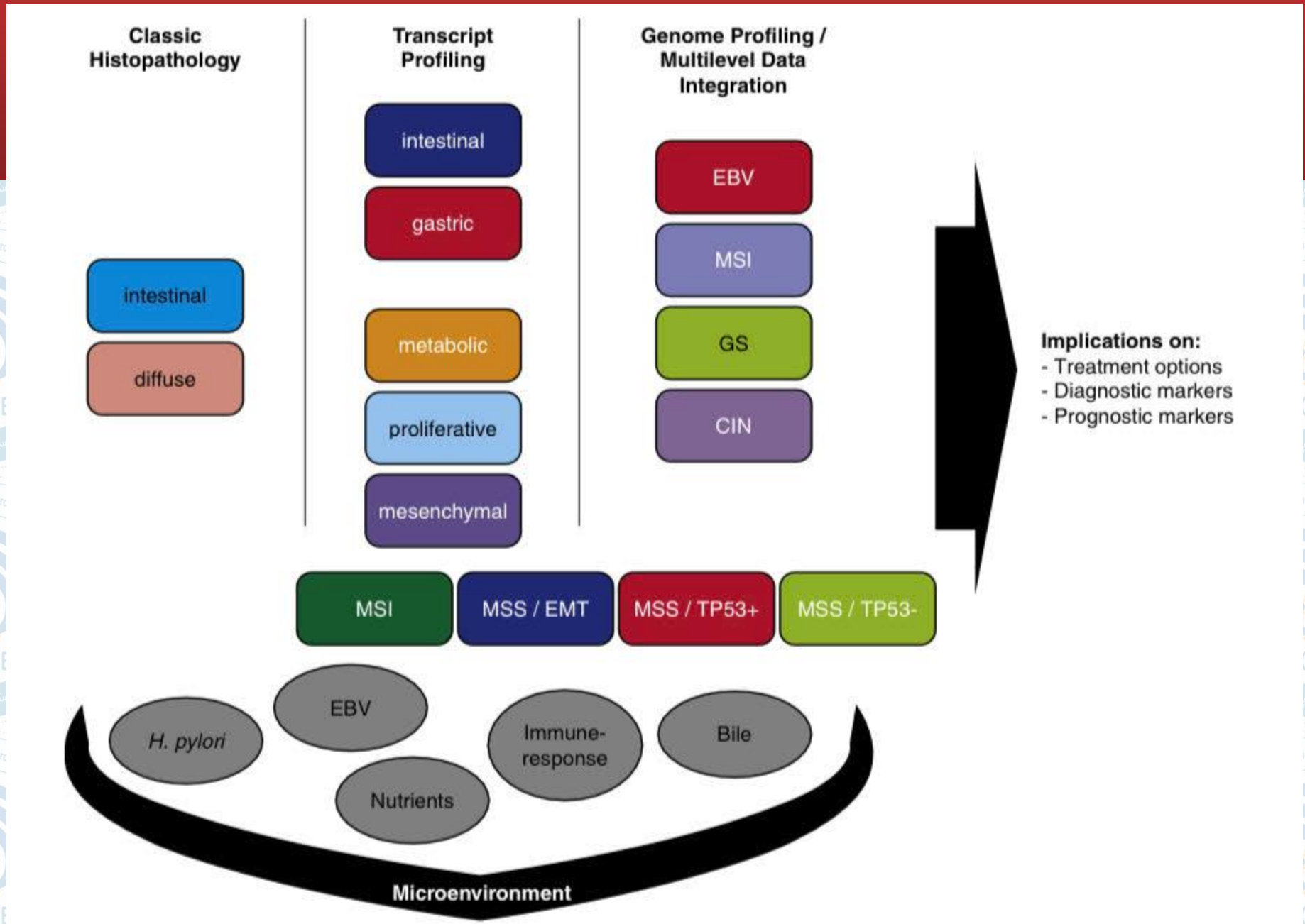
Incidence Trends of Gastric Cancer in Southern Iran: Adenocarcinoma and Non-cardia Gastric Cancer Are More Rising Among Younger Ages

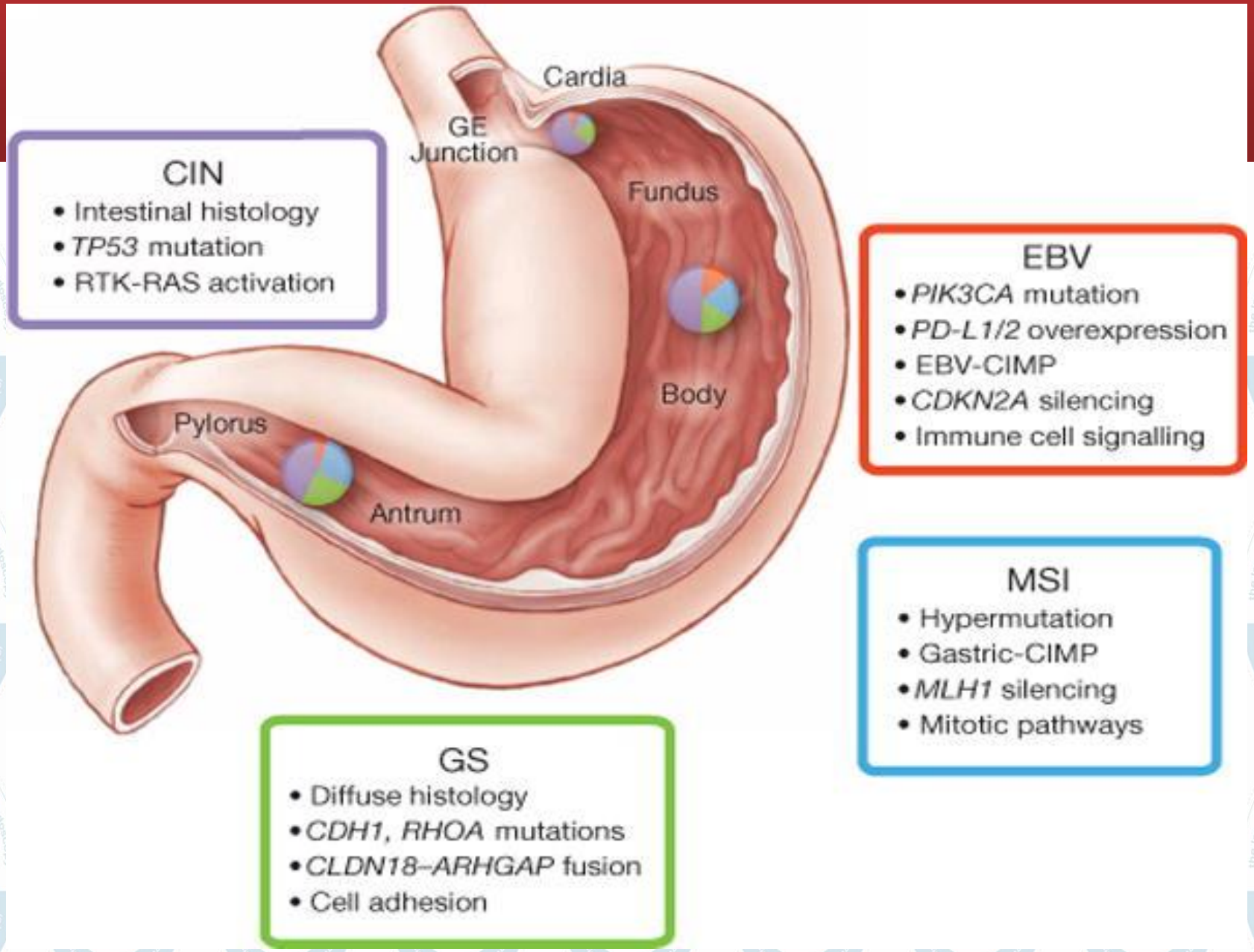
Mahanaz Hosseini-Bensenjan[1] · Hossein Molavi Vardanjani[2] · Zahra Khosravizadegan[3] · Kamran Bagheri-Lankarani[4]

Accepted: 26 September 2021

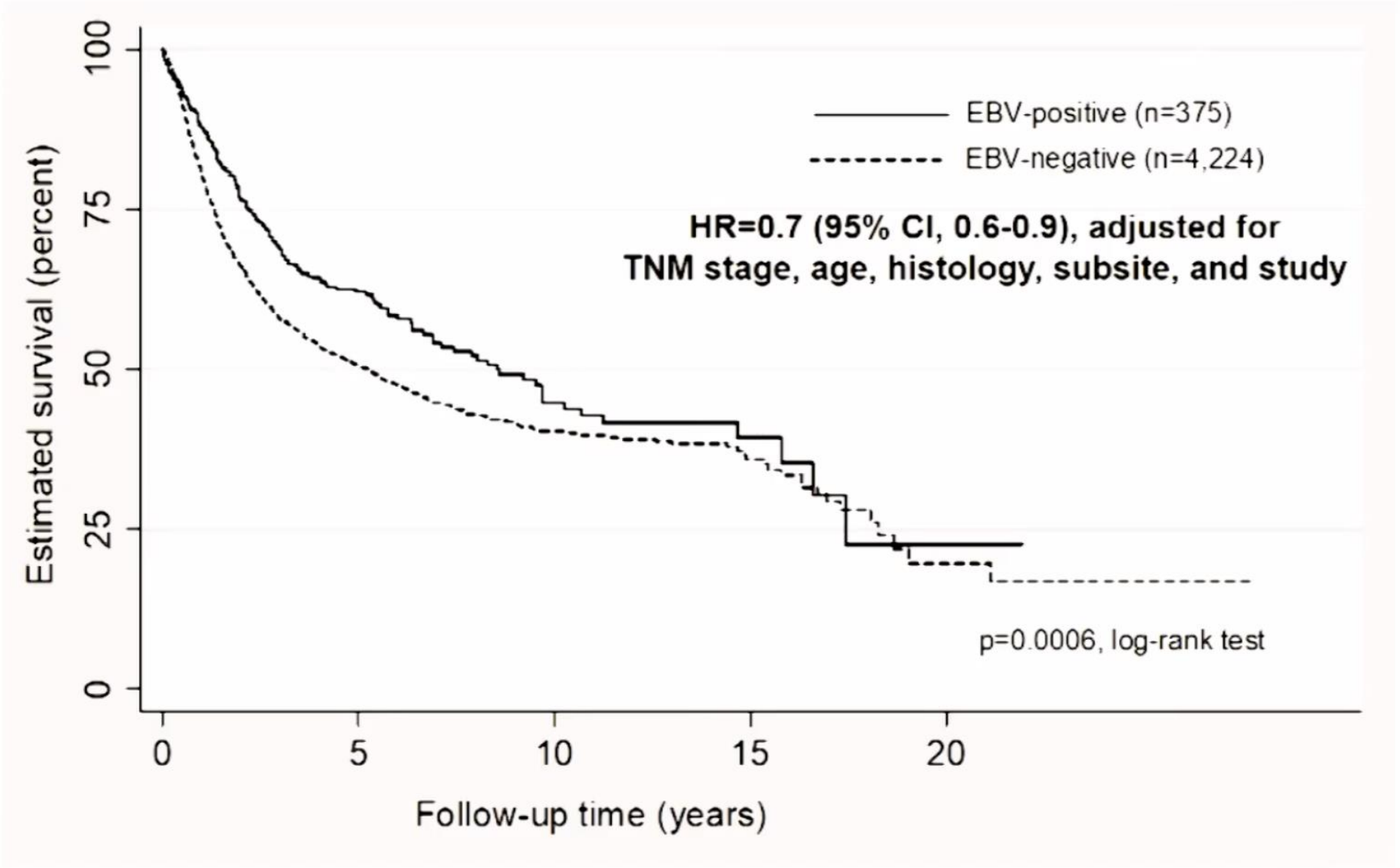

Rate Per 100000 Males
160
140
120
100
80
60
40
20
0
Males
Females
70
60
50
40
30
20
10
0
Rate Per 100000 Females
under 25
25- 29
30- 34
35- 39
40- 44
45- 49
50- 54
55- 59
60- 64
65- 69
70+
Age Group (Years)


Age-standardized incidance rate
Rate Per 10000000 Pop.
25
20
15
10
5
0
2001
2003
2005
2007
2009
2011
2013
2015
Year

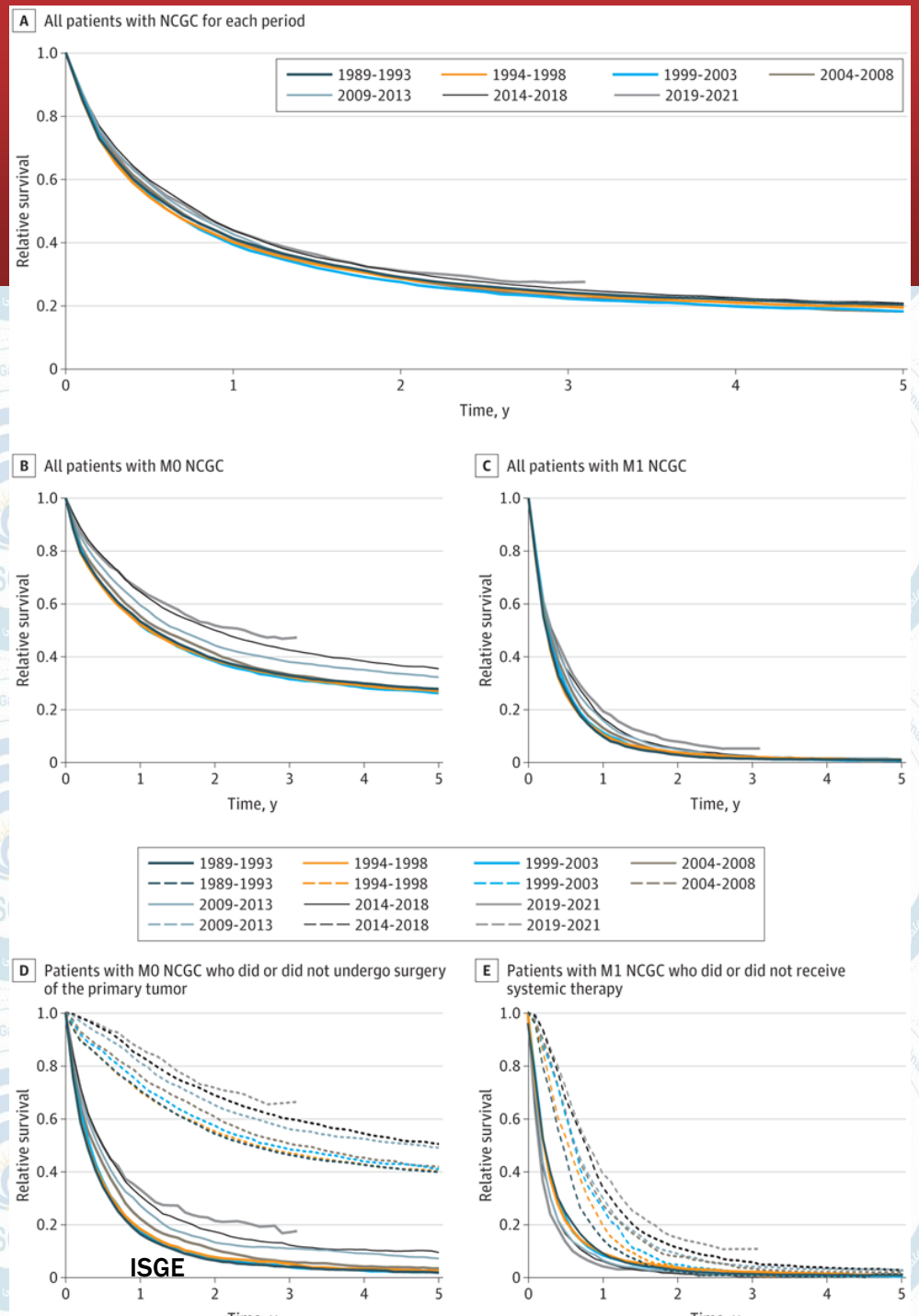

Classic Histopathology
intestinal
diffuse
Transcript Profiling
intestinal
gastric
metabolic
proliferative
mesenchymal
Genome Profiling / Multilevel Data Integration
EBV
MSI
GS
CIN
Implications on:
- Treatment options
- Diagnostic markers
- Prognostic markers
MSI
MSS / EMT
MSS / TP53+
MSS / TP53-
H. pylori
EBV
Nutrients
Immune-response
Bile
Microenvironment


CIN
• Intestinal histology
• *TP53* mutation
• RTK-RAS activation
Cardia
GE Junction
Fundus
Body
Pylorus
Antrum
EBV
• *PIK3CA* mutation
• *PD-L1/2* overexpression
• EBV-CIMP
• *CDKN2A* silencing
• Immune cell signalling
MSI
• Hypermutation
• Gastric-CIMP
• *MLH1* silencing
• Mitotic pathways
GS
• Diffuse histology
• *CDH1, RHOA* mutations
• *CLDN18–ARHGAP* fusion
• Cell adhesion

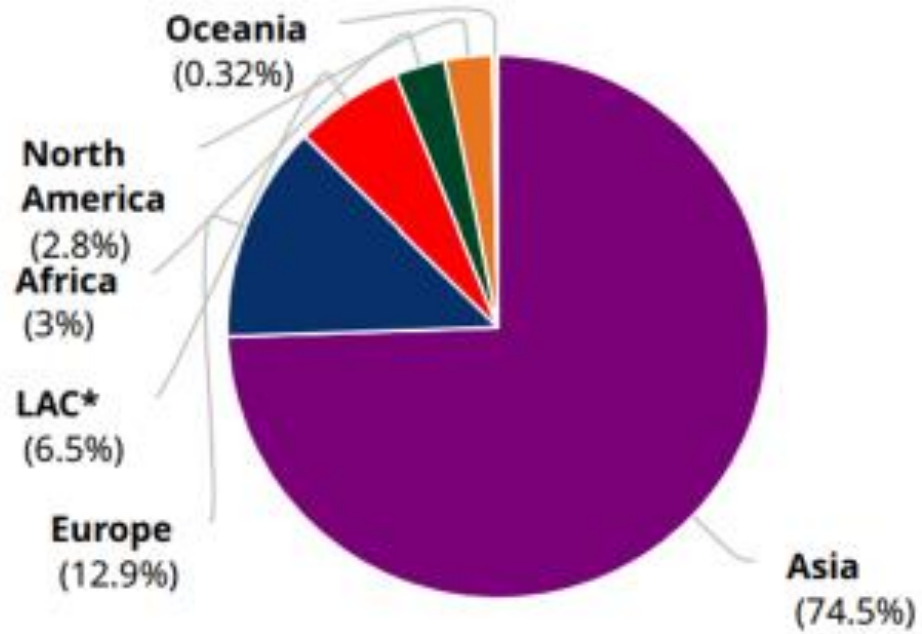
Overall Survival After Diagnosis
NCI International EBV-Gastric Cancer Consortium



Camargo *et al.*, *Gut* 2013

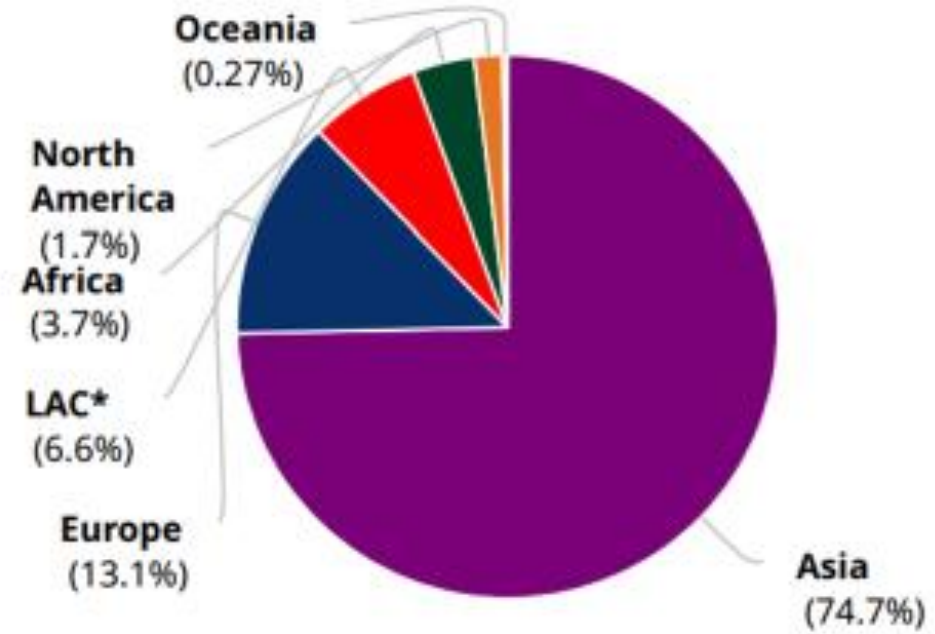

A All patients with NCGC for each period
1989-1993
1994-1998
1999-2003
2004-2008
2009-2013
2014-2018
2019-2021
Relative survival
Time, y
B All patients with M0 NCGC
C All patients with M1 NCGC
D Patients with M0 NCGC who did or did not undergo surgery of the primary tumor
E Patients with M1 NCGC who did or did not receive systemic therapy

Incidence, both sexes



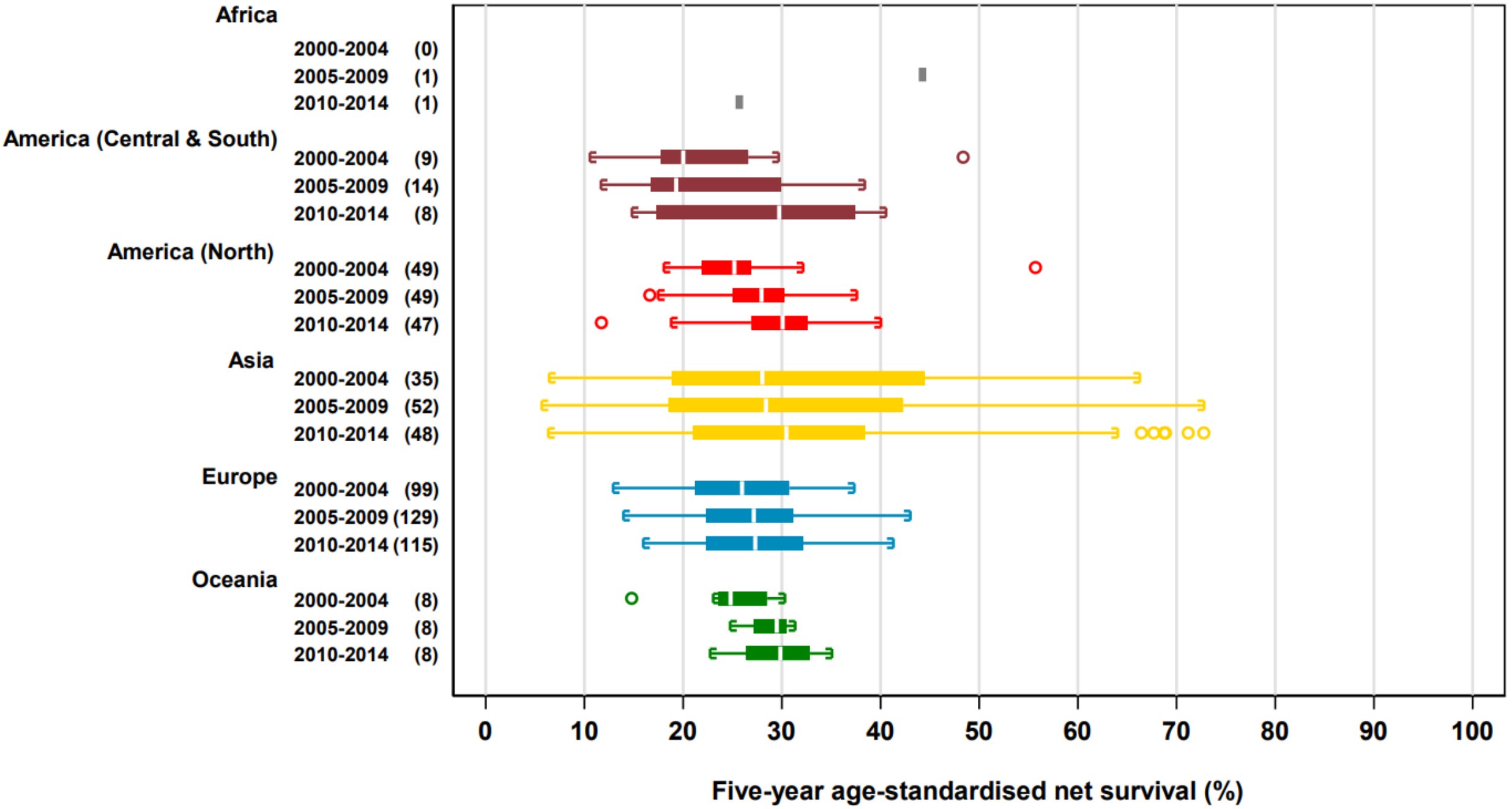
Population	Number
Asia	769 728
Europe	133 133
*Latin America and the Caribbean	67 058
Africa	31 148
North America	29 275
Oceania	3 359
Total	1 033 701

Mortality, both sexes



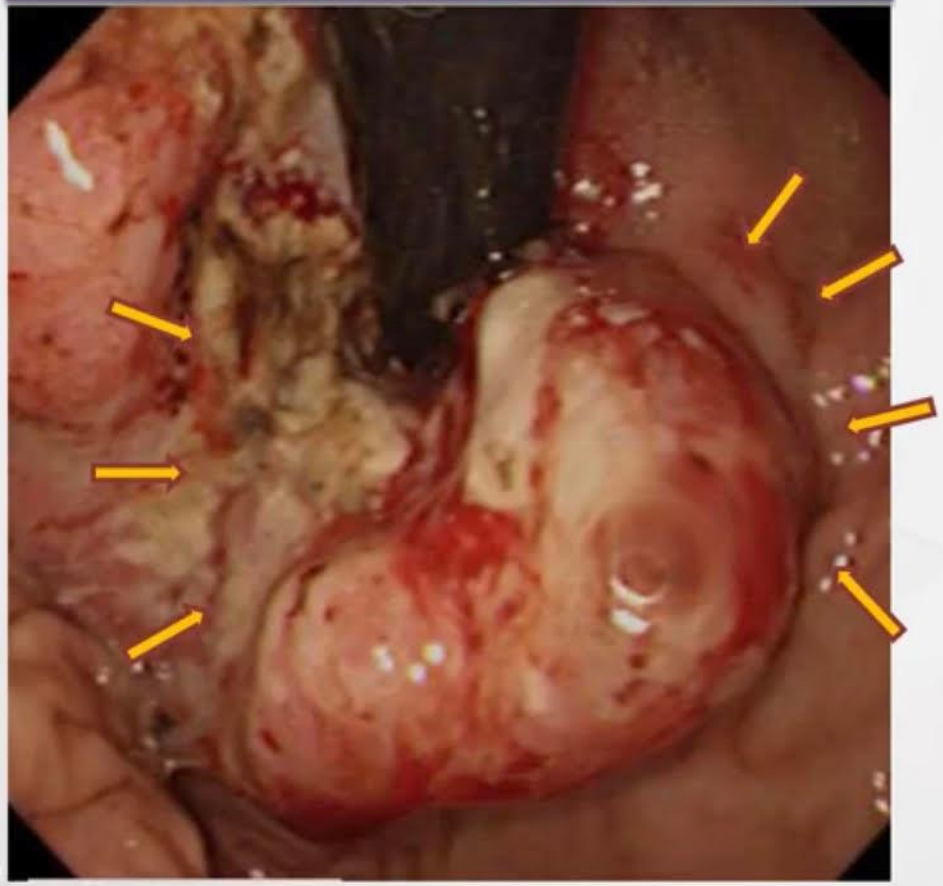
Population	Number
Asia	584 375
Europe	102 167
*Latin America and the Caribbean	51 914
Africa	28 707
North America	13 403
Oceania	2 119
Total	782 685

Back

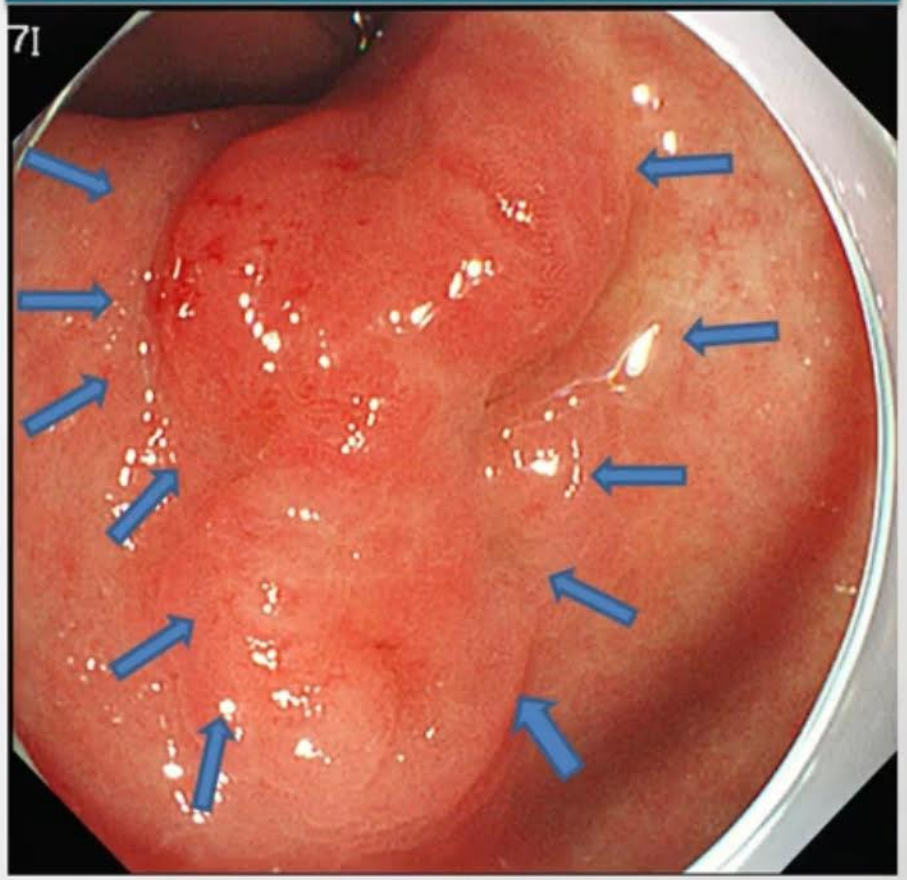

Africa
2000-2004 (0)
2005-2009 (1)
2010-2014 (1)
America (Central & South)
2000-2004 (9)
2005-2009 (14)
2010-2014 (8)
America (North)
2000-2004 (49)
2005-2009 (49)
2010-2014 (47)
Asia
2000-2004 (35)
2005-2009 (52)
2010-2014 (48)
Europe
2000-2004 (99)
2005-2009 (129)
2010-2014 (115)
Oceania
2000-2004 (8)
2005-2009 (8)
2010-2014 (8)
0
10
20
30
40
50
60
70
80
90
100
Five-year age-standardised net survival (%)

Prognosis of Gastric Cancer is related to stage of diagnosis!

ADVANCED CA STOMACH



EARLY GASTRIC CANCER



Importance of early Diagnosis of GC

- In localized distal gastric cancer>50% of patients can be cured.
- Early-stage disease accounts for only 10% to 20% of all cases
- Even with apparent localized disease, the 5-year survival rate of patients with proximal gastric cancer is only 10% to 15%.
- Although the treatment of patients with disseminated gastric cancer may result in palliation of symptoms and some prolongation of survival, long remissions are uncommon.

Diagnosis of EGC

Endoscopy

- Endoscopy & photofluorography
- Magnification chromoendoscopy
- Image-enhanced endoscopy technology
- Artificial intelligence

Serum

- Pepsinogen ,H. Pylori Ab
  - Low PG I:PG II ratio
- Circulating tumor cells
- Non coding RNA
  - microRNA
  - Circular RNA
- Exosomes
- Cell free DNA
- ....

Missed Lesions

- The rate of missed lesions as high as 10% in the 3 years
- Guidelines on the performance measures in upper GI endoscopy : at least total seven minutes and 3-4 minutes observation in stomach
- The reasons why lesions are missed:
  - Some stomach areas (blind areas) are difficult to observe by endoscopy (error in observation).
  - Although a lesion is observed, it is not recognized as a lesion (error in detection).
  - A lesion is recognized but wrongly diagnosed (error in characterization or diagnosis).

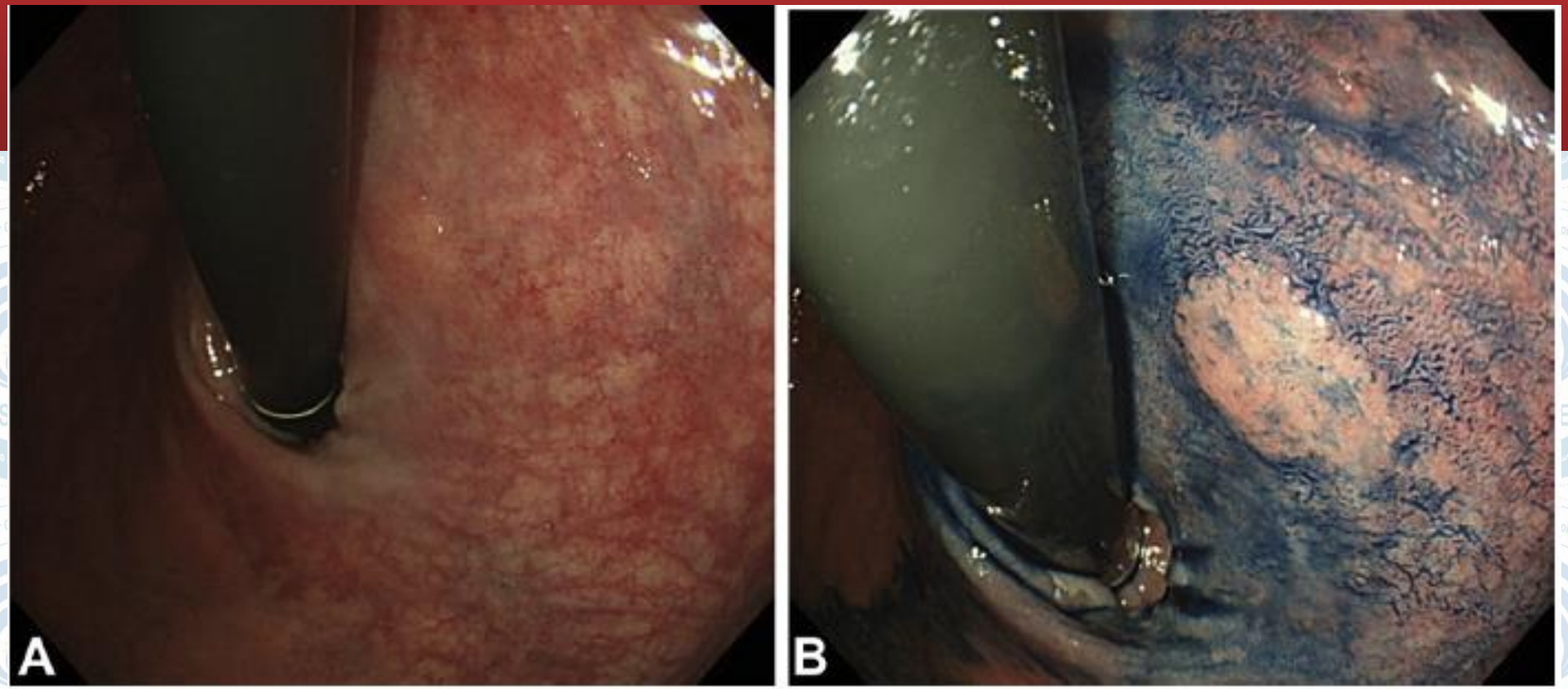


Figure 1. A, Slightly elevated lesion with redness can be seen at the curvature in the cardia. **B,** The elevated lesion can be observed clearly after indigo carmine dye spraying. The lesion was resected by endoscopic submucosal dissection. Histologically, the resected specimen showed a well-differentiated 9-mm adenocarcinoma.

How I inspect the stomach

Hisao Tajiri, MD,[1] Mário Dinis-Ribeiro, MD[2]

Tokyo, Japan; Porto, Portugal

GASTROINTESTINAL ENDOSCOPY Volume 89, No. 6 : 2019

How to eliminate blind areas

1. Gastric angle, posterior wall, and greater curvature of the gastric corpus.

- Frontal view, wherever possible, by adjusting the left and right angles and the amount of air.

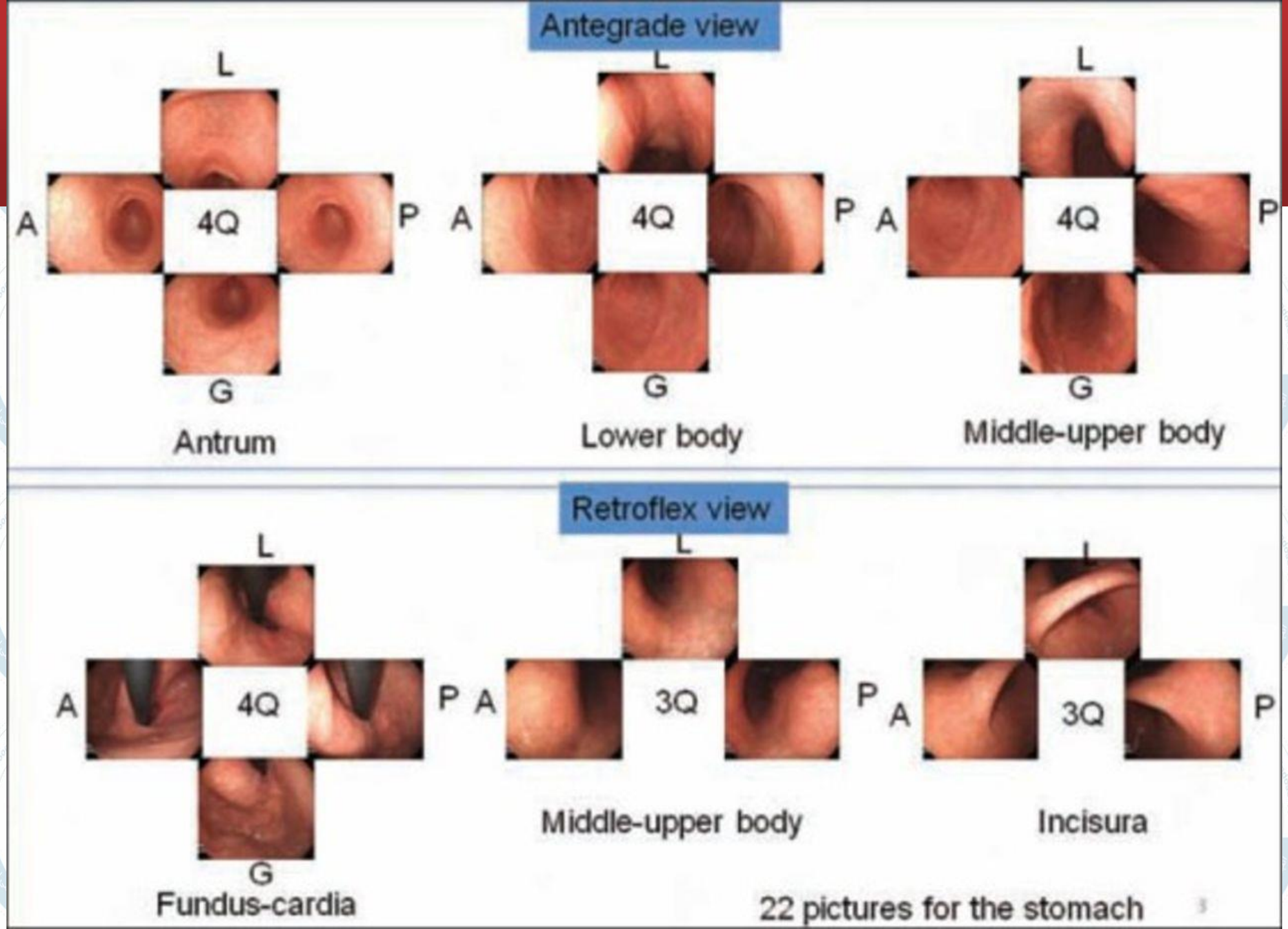
2. The lesser curvature in the cardia

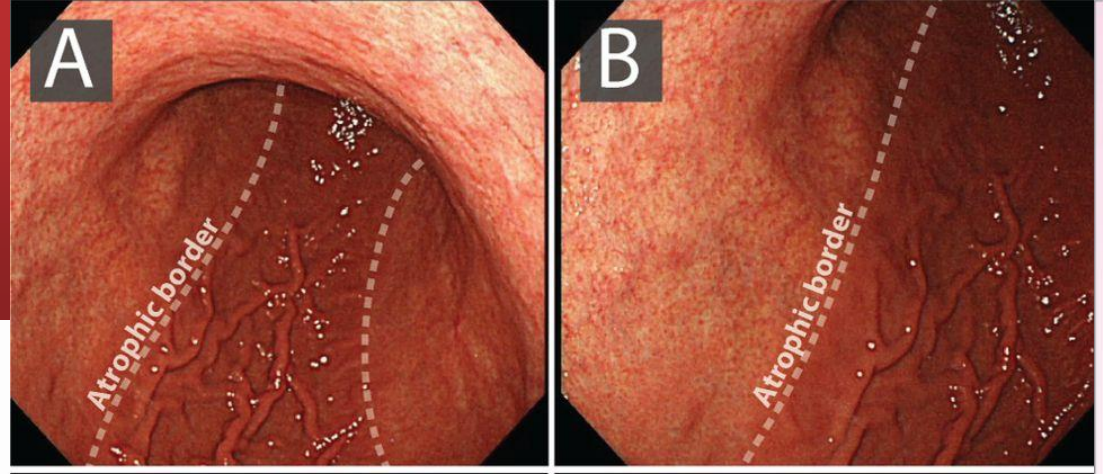
- up-angle and right-angle turns during retroflex examination

3. Avoid adherence of mucus to the gastric mucosa

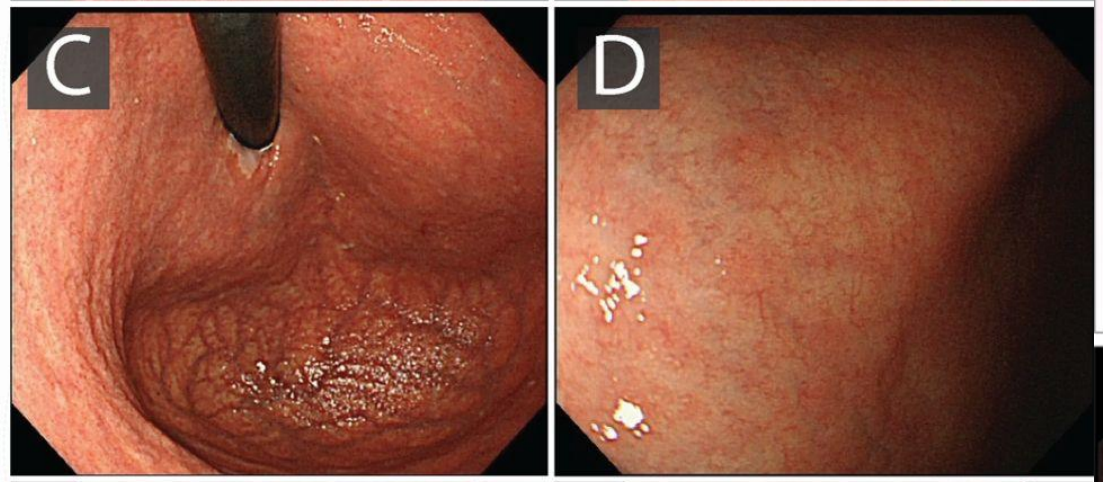
Images should be captured before specific areas, such as the greater curvature of the angularis and the pyloric ring, are passed, to avoid confounding by endoscope-induced abrasion/erythema.

The rugae of the greater curvature of the gastric corpus should be adequately stretched by insufflation to inspect between the rugae.

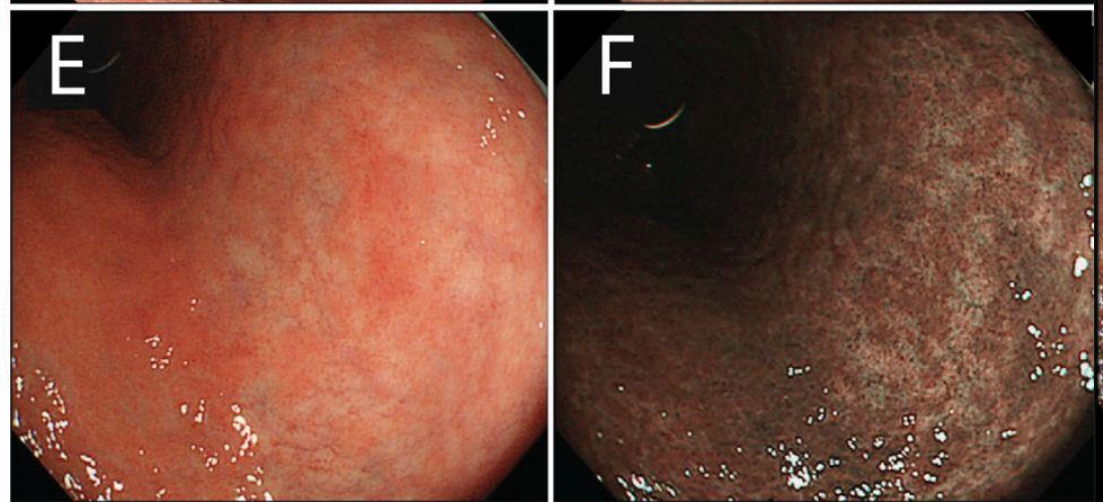

Antegrade view
L
A
4Q
P
G
Antrum
L
A
4Q
P
G
Lower body
L
A
4Q
P
G
Middle-upper body
Retroflex view
L
A
4Q
P
G
Fundus-cardia
L
A
3Q
P
Middle-upper body
L
A
3Q
P
Incisura
22 pictures for the stomach


A
Atrophic border

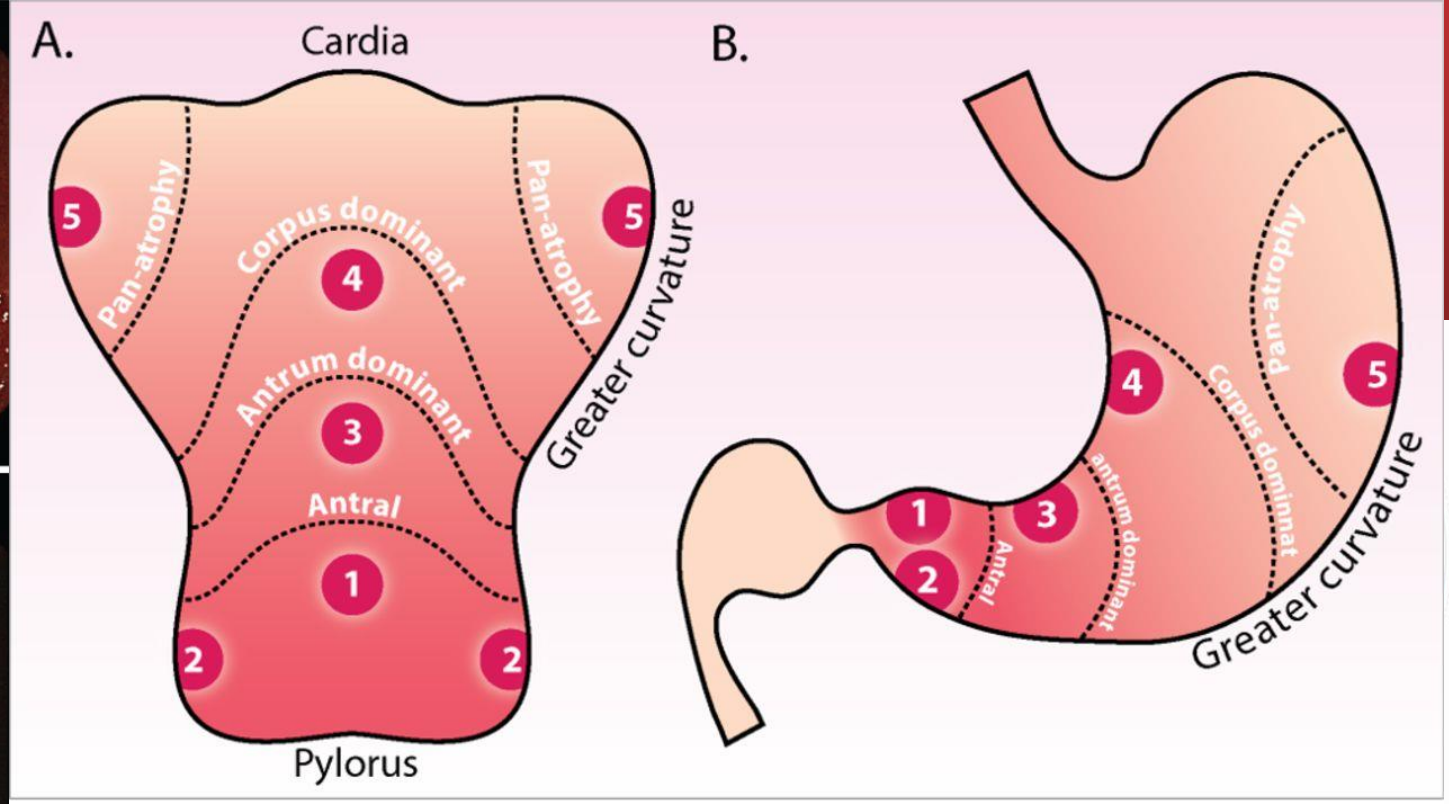
B
Atrophic border

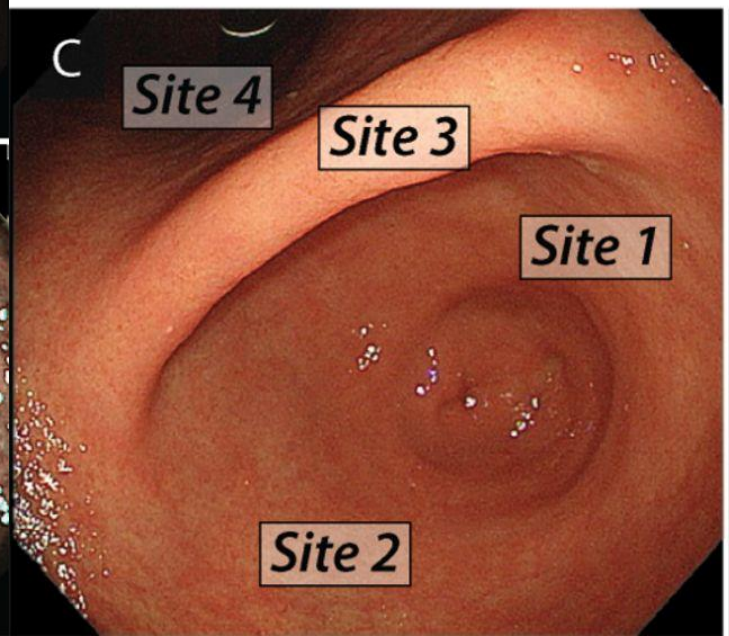

C

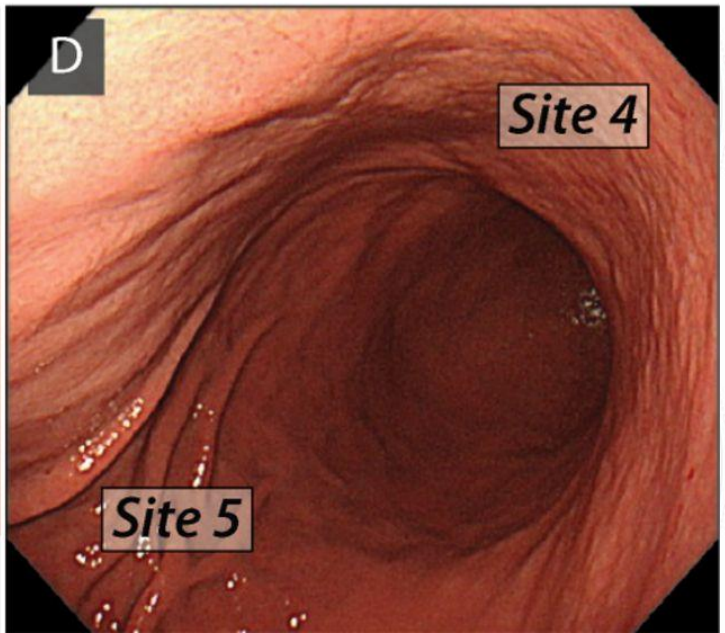
D

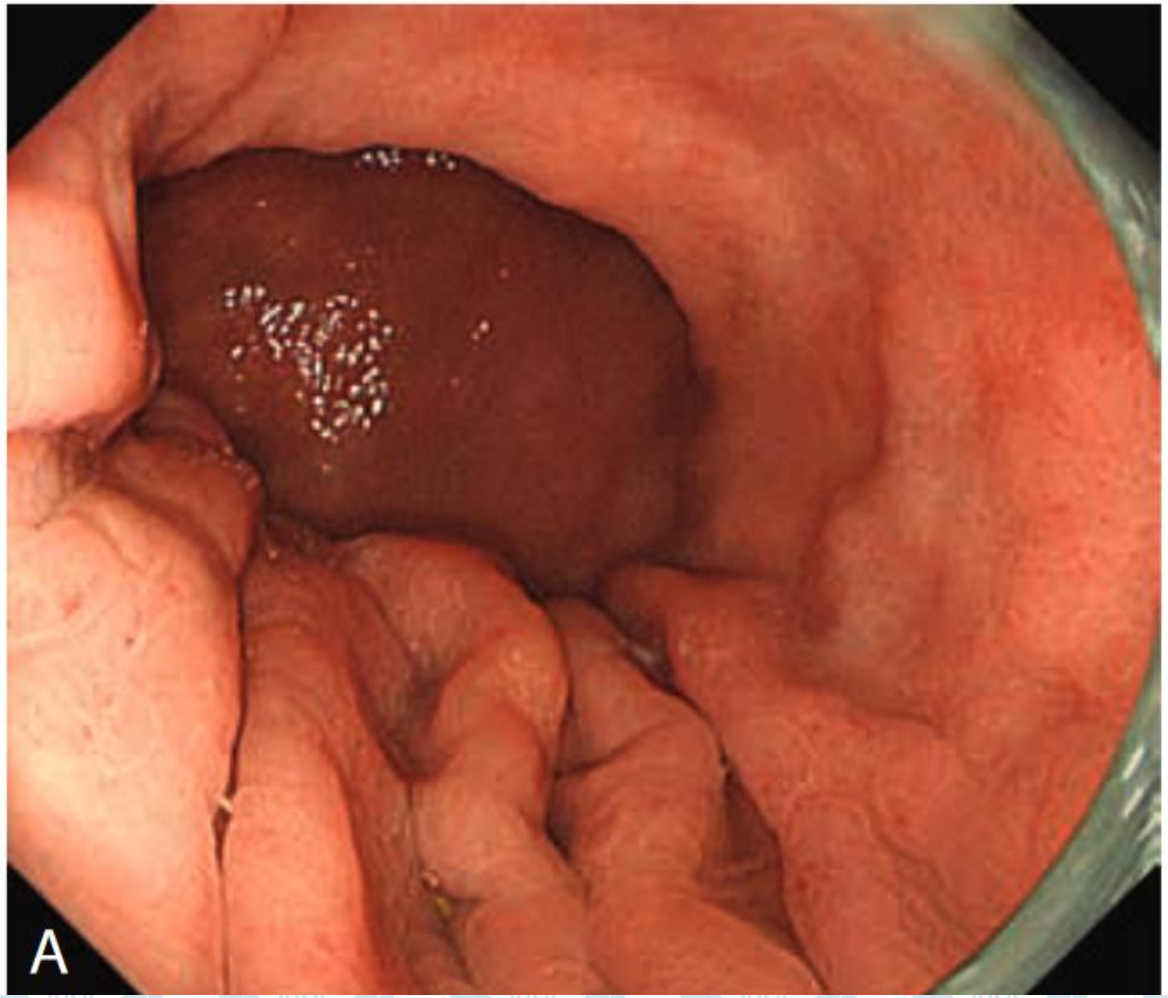

E

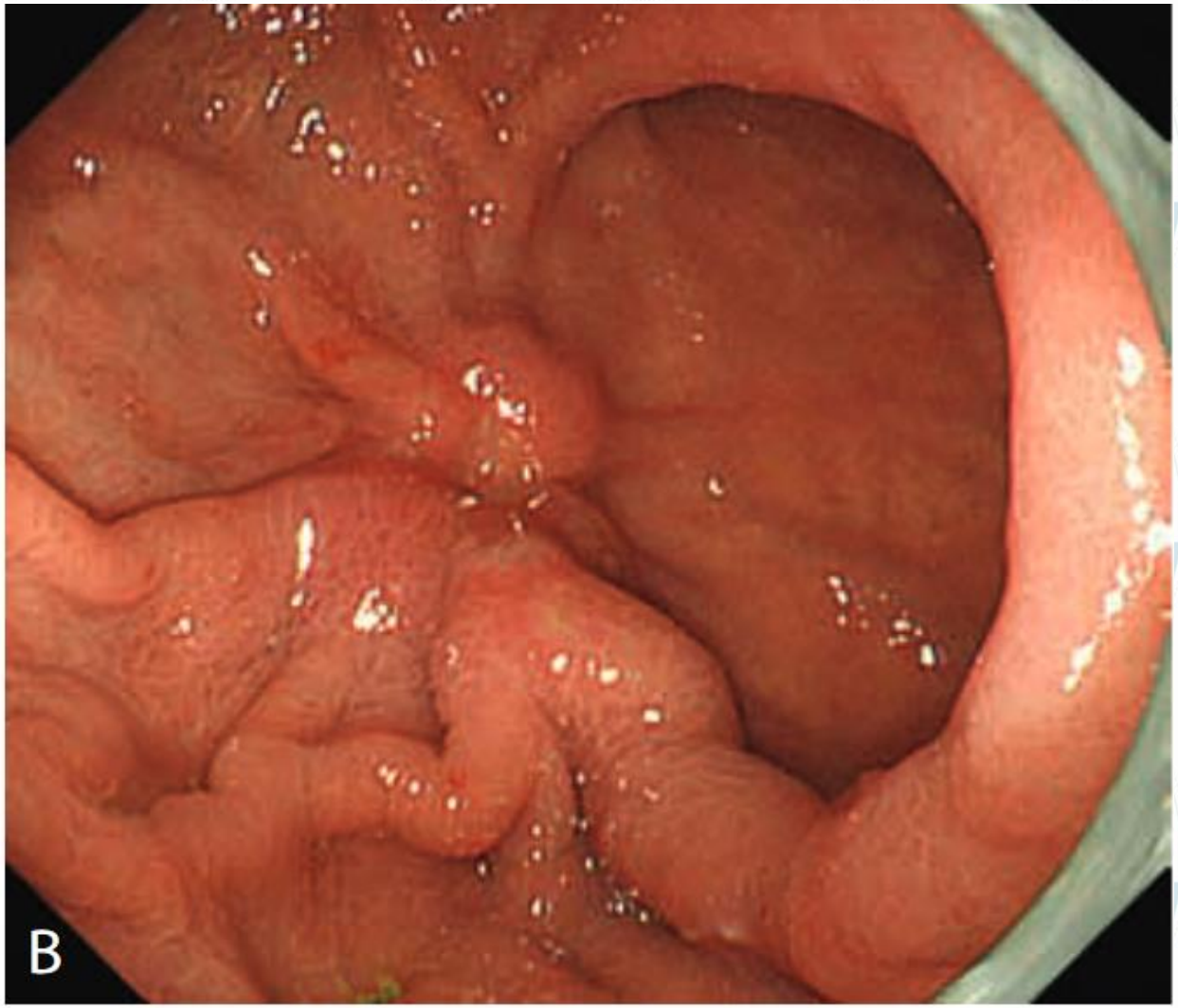
F

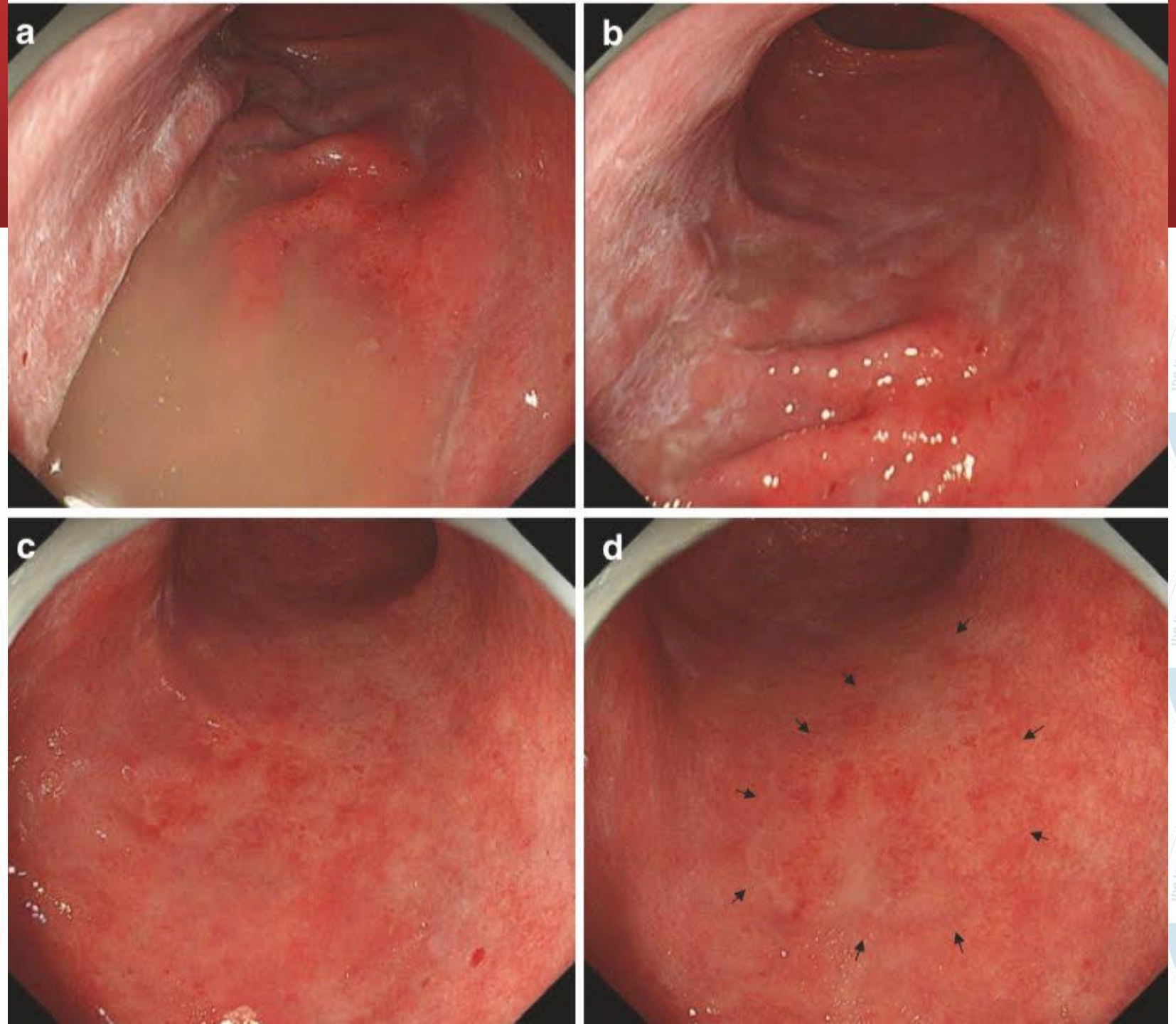

A.
Cardia
Pan-atrophy
Corpus dominant
Pan-atrophy
Antrum dominant
Greater curvature
Antral
Pylorus
B.
Pan-atrophy
Corpus dominant
antrum dominant
Antral
Greater curvature


C
Site 4
Site 3
Site 1
Site 2


D
Site 4
Site 5


A


B


a
b
c
d

How to eliminate detection errors

Factors affecting detection :

- The direction of endoscopy (front and tangential observations)
- The distance (distant and near views)
- The amount of insufflation (the degree of extension of the gastric wall)
- The light intensity.

The same site and the same lesion should be carefully observed in multiple ways

If focal lesion found still observe the entire stomach first to avoid missing any other lesions and then observe the lesion site.

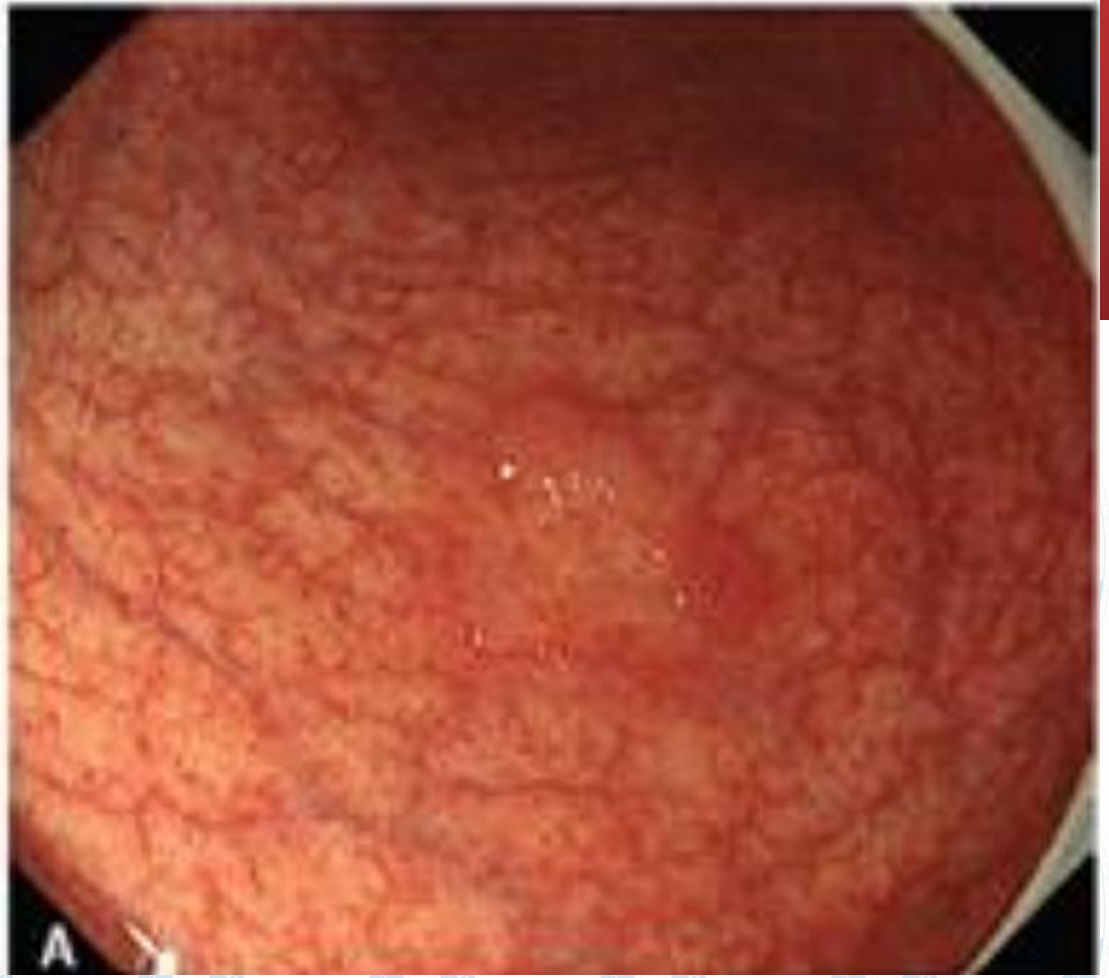
How to eliminate errors in diagnosis

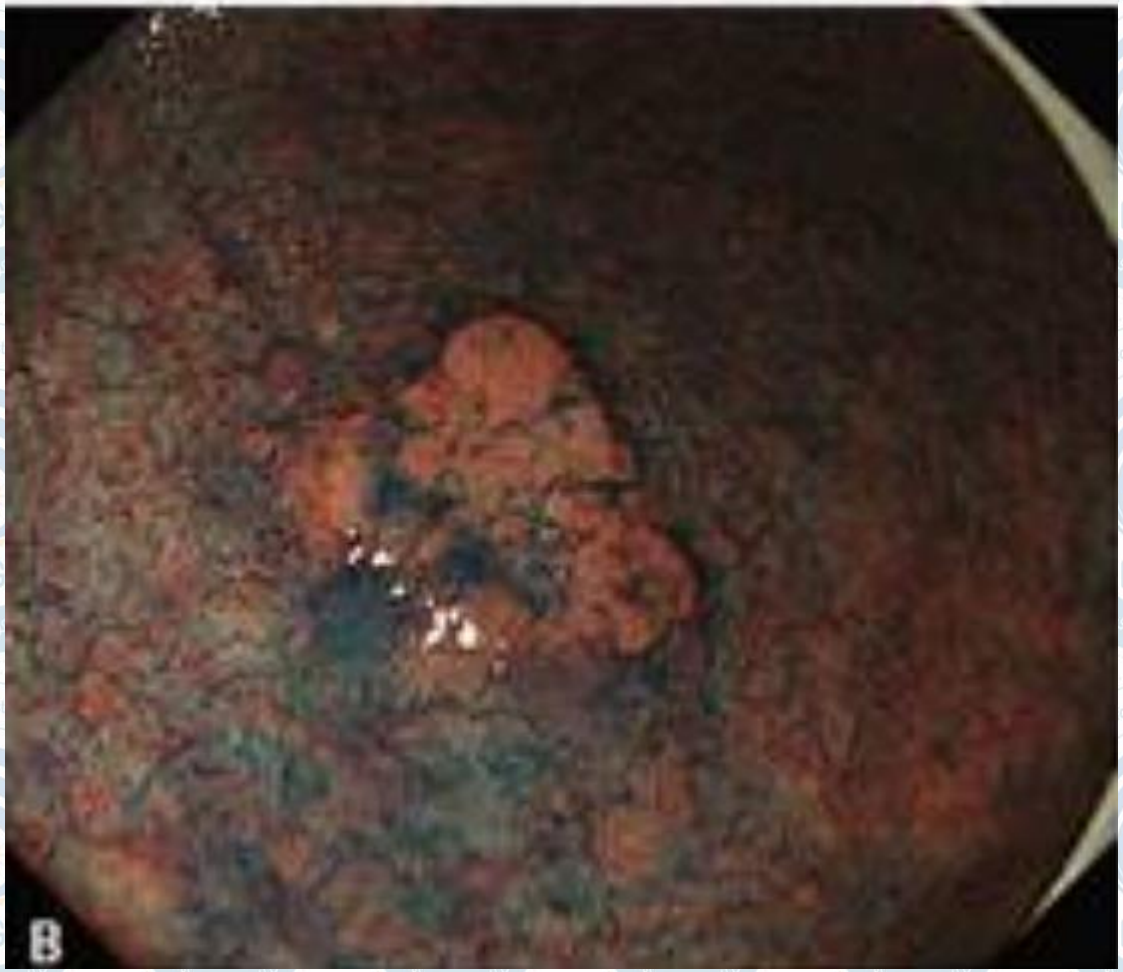
- It is necessary to enhance the ability of endoscopic diagnosis by observing many lesions to accumulate experience in diagnosis.
- Because normal endoscopy has a limitation in qualitative diagnosis, it is helpful to effectively use magnifying/near-focus endoscopy with virtual chromoendoscopy, making optical biopsy possible.

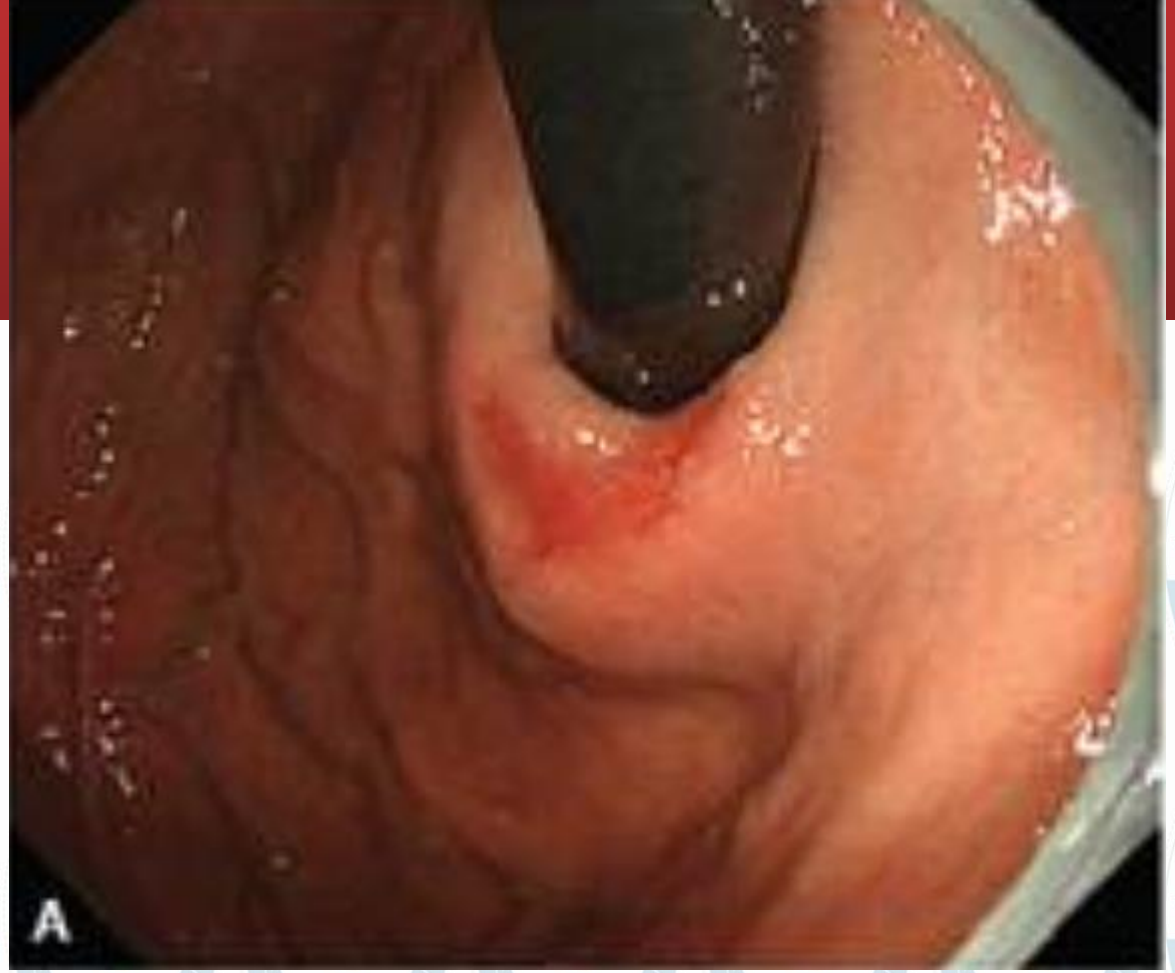
Pay attention to subtle changes of mucosal color and morphology.

Clues:

- Mucosal discoloration (erythema or pallor)
- Morphologic changes of the mucosal surface (protruding, elevated, or depressed)
- Tapered or interrupted mucosal folds
- Spontaneous bleeding
- Localized opacity of the mucosa (abrupt change in background vascular/ mucosal pattern)
- Loss of mucosal glossiness.


A


B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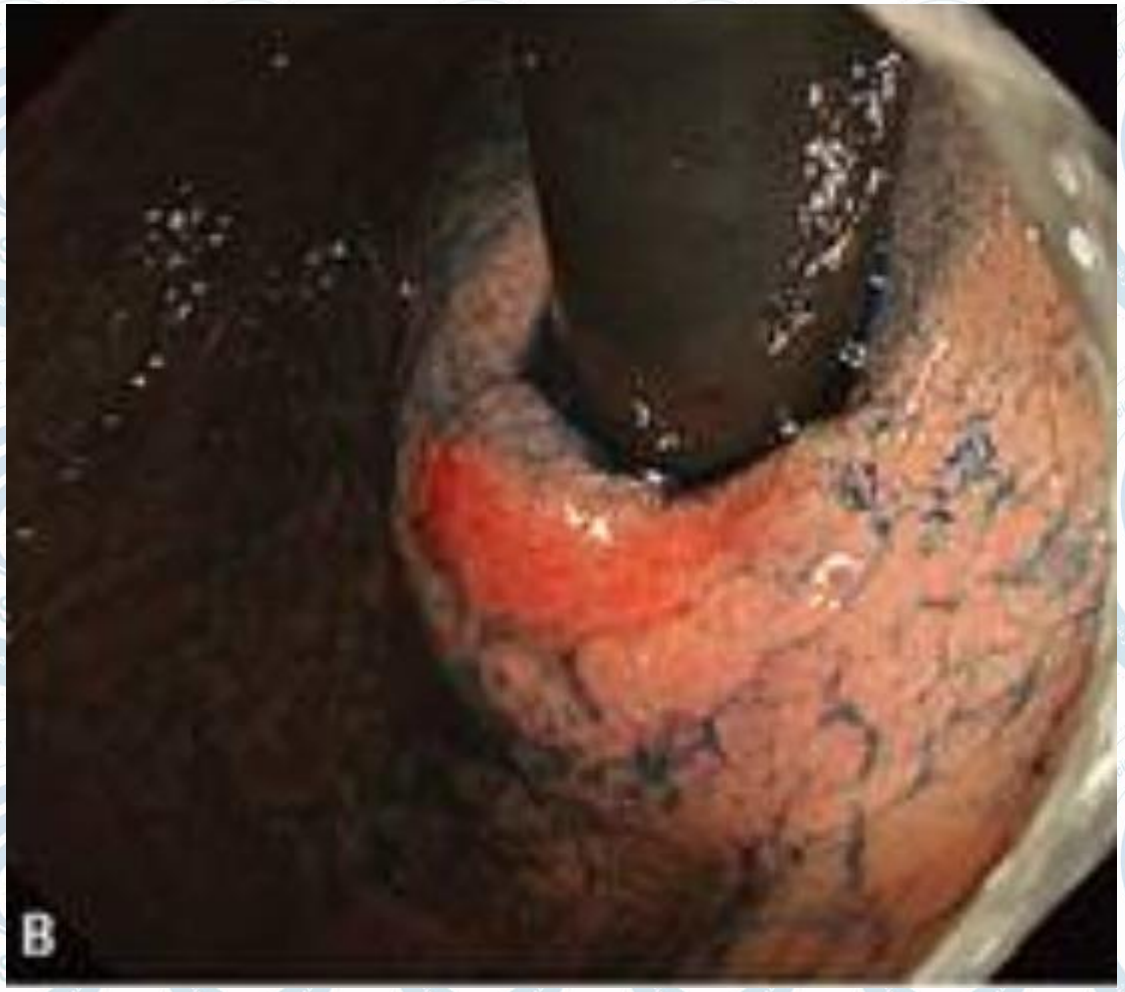
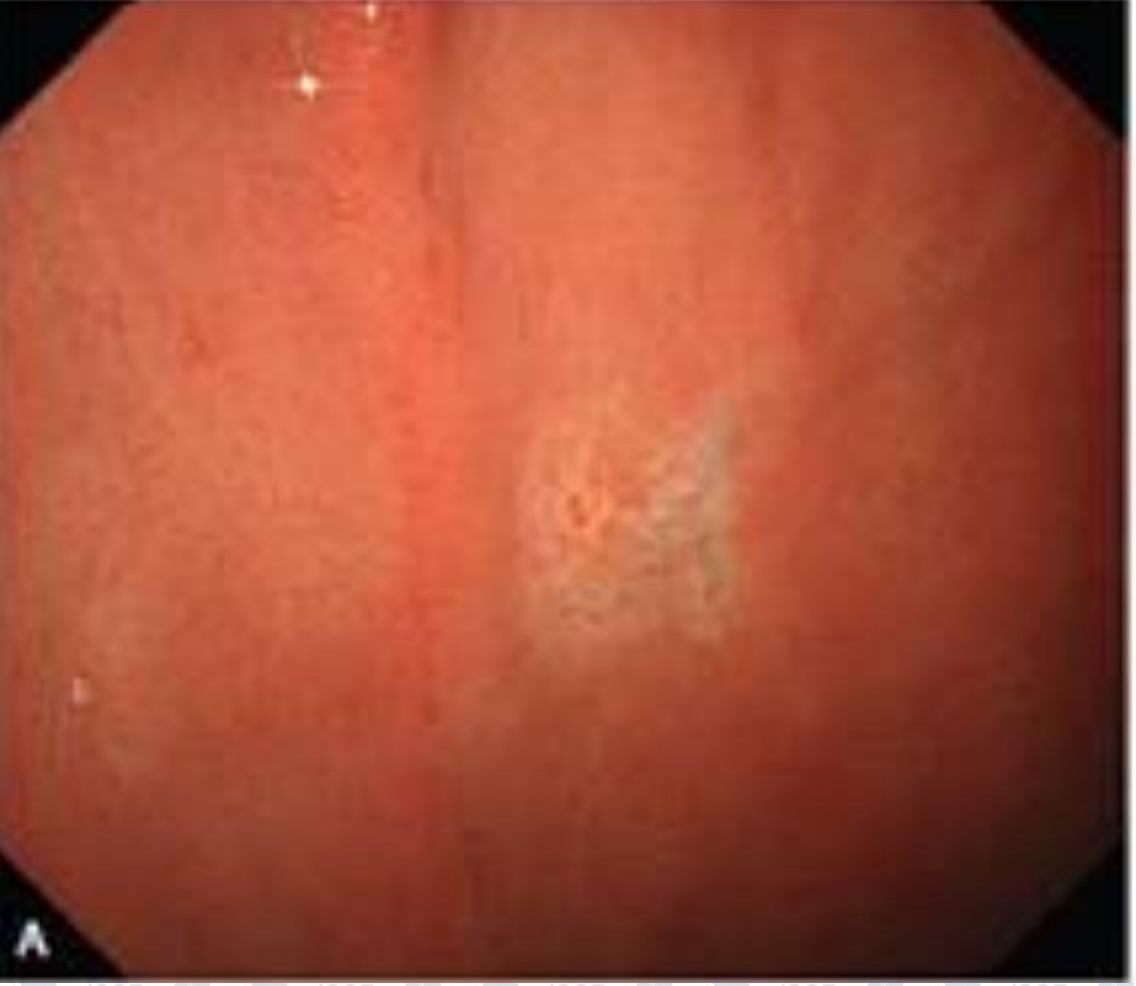
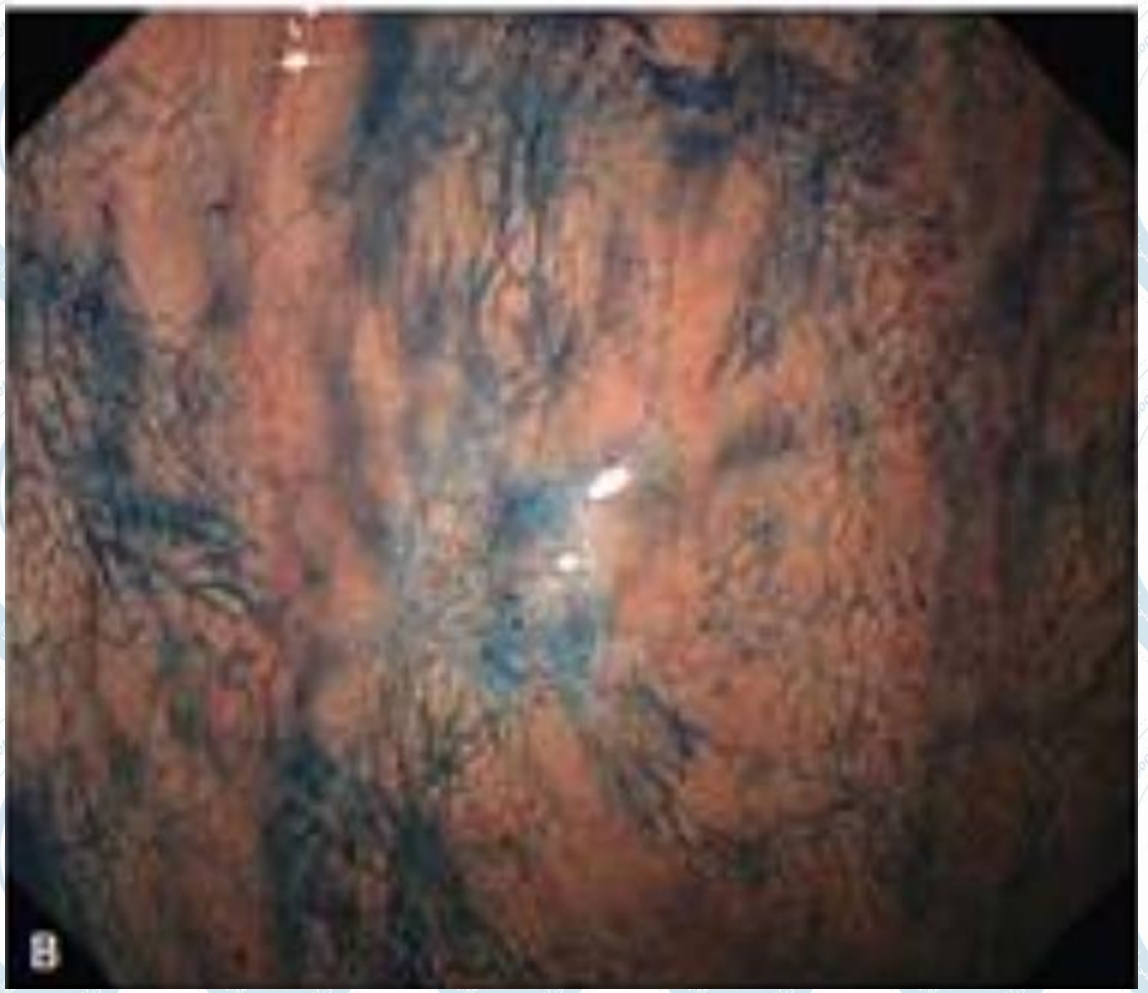

B


A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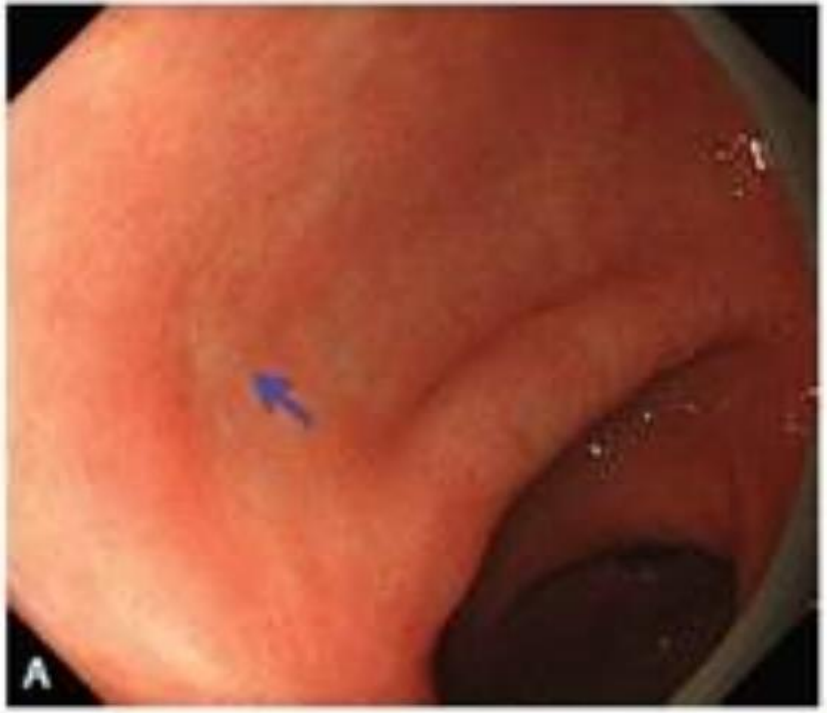
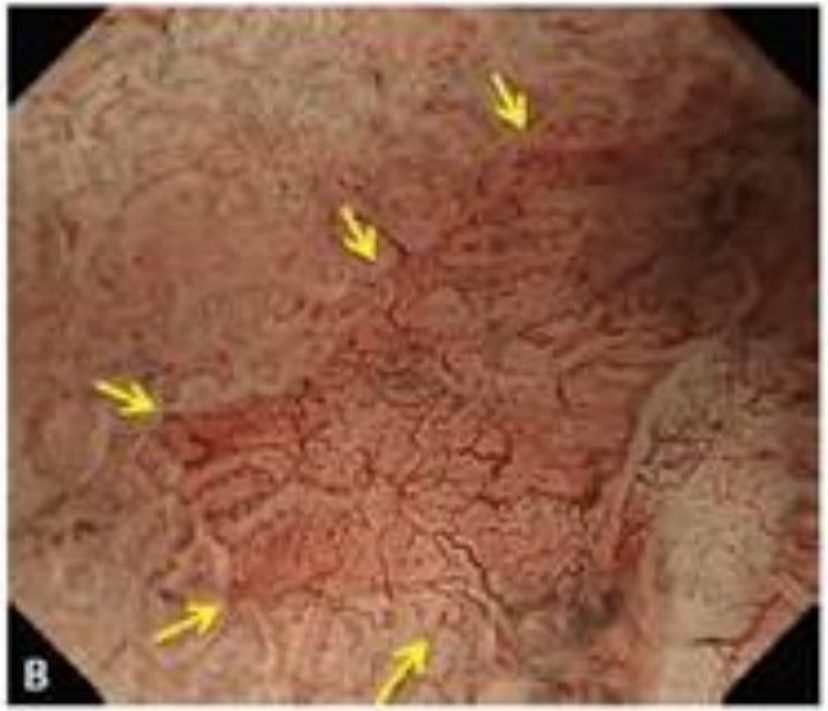

A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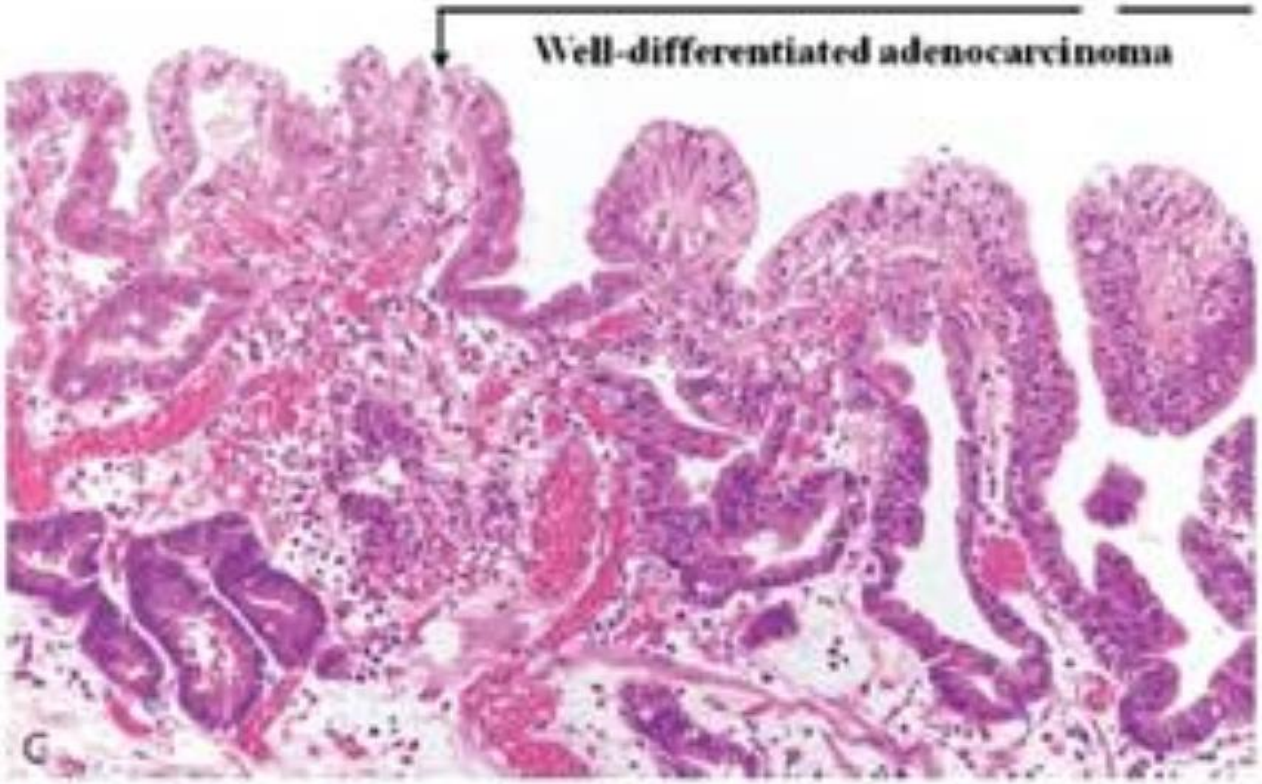
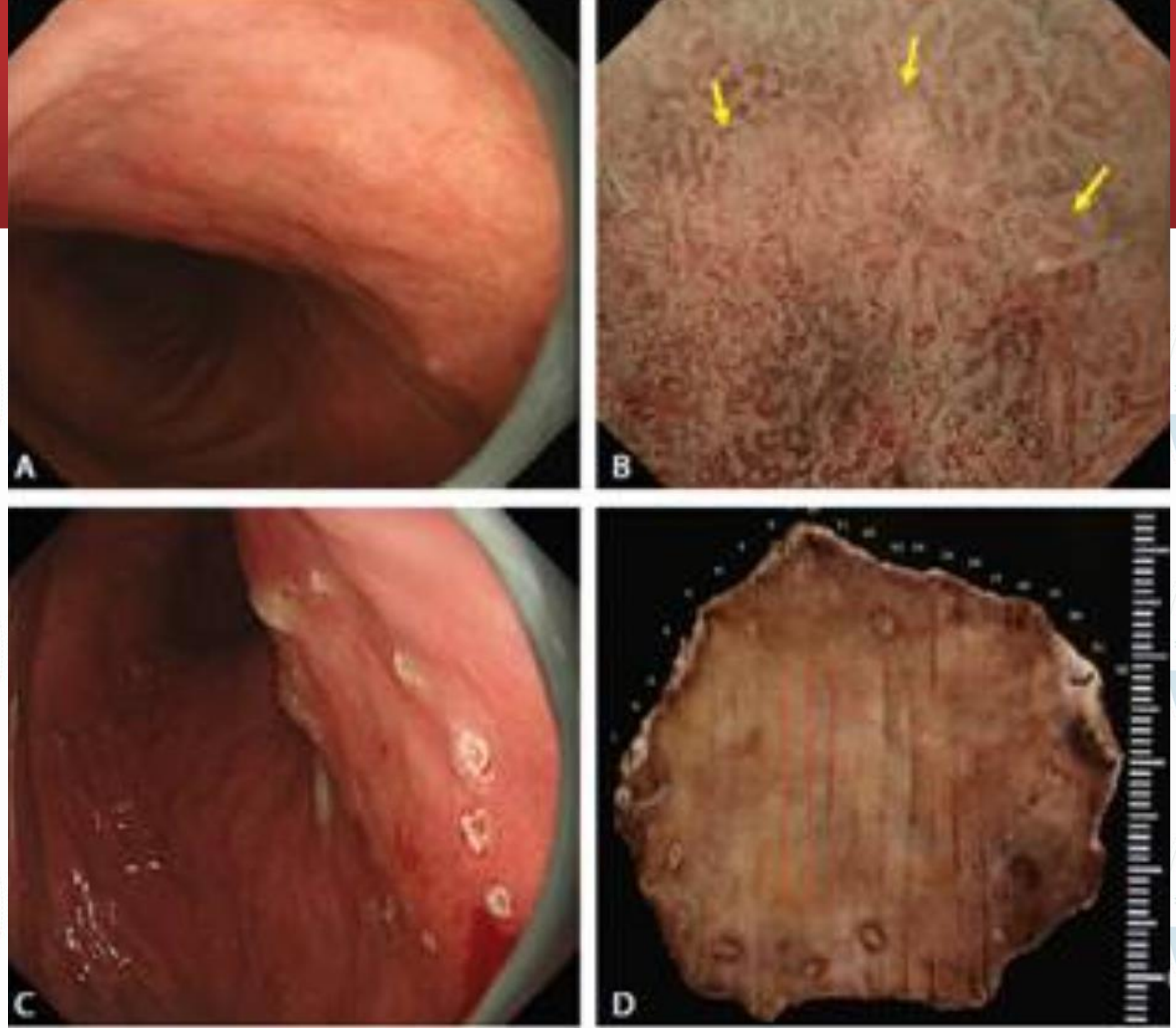

Well-differentiated adenocarcinoma
G


A
B
C
D

OPEN ACCESS

British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma

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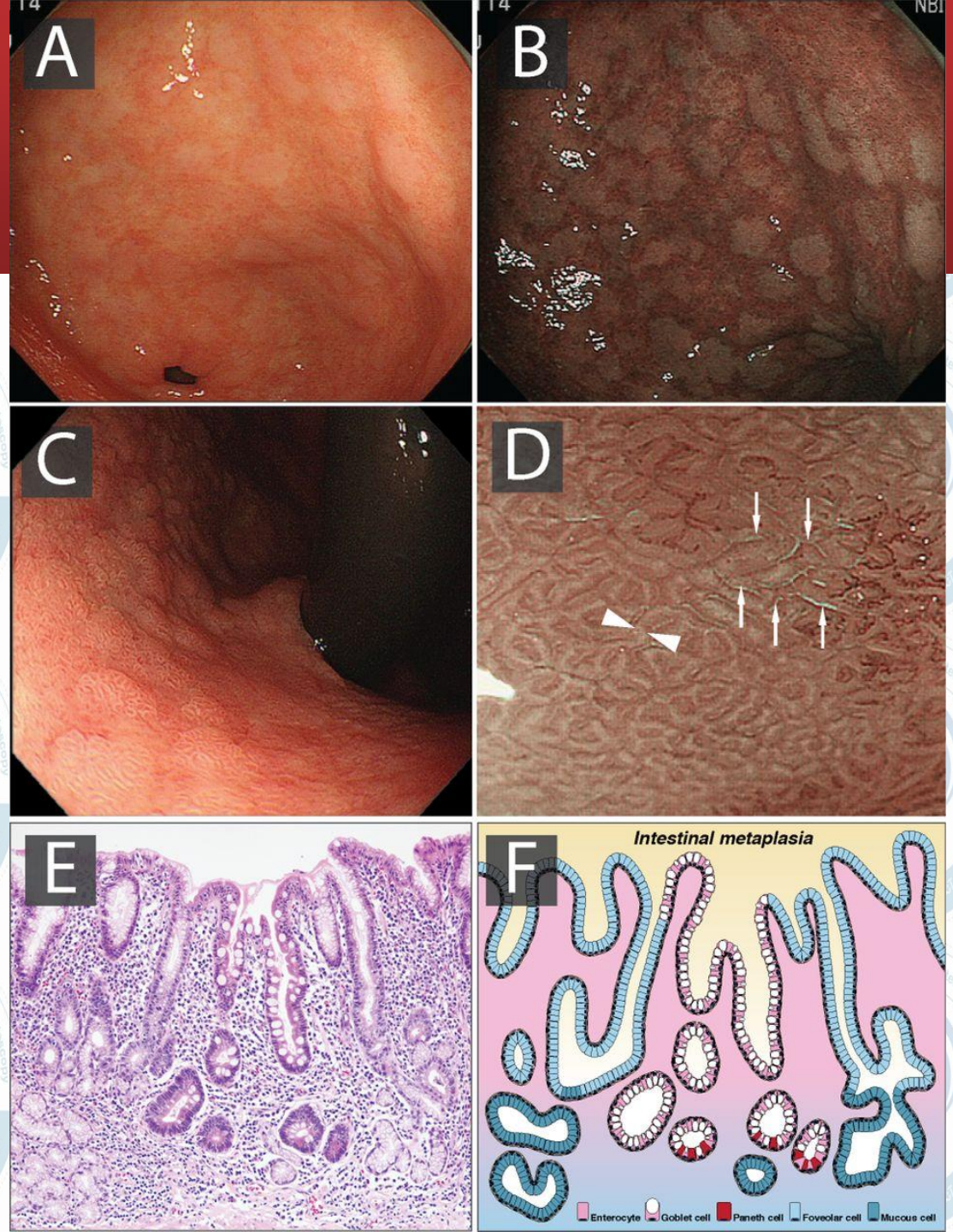
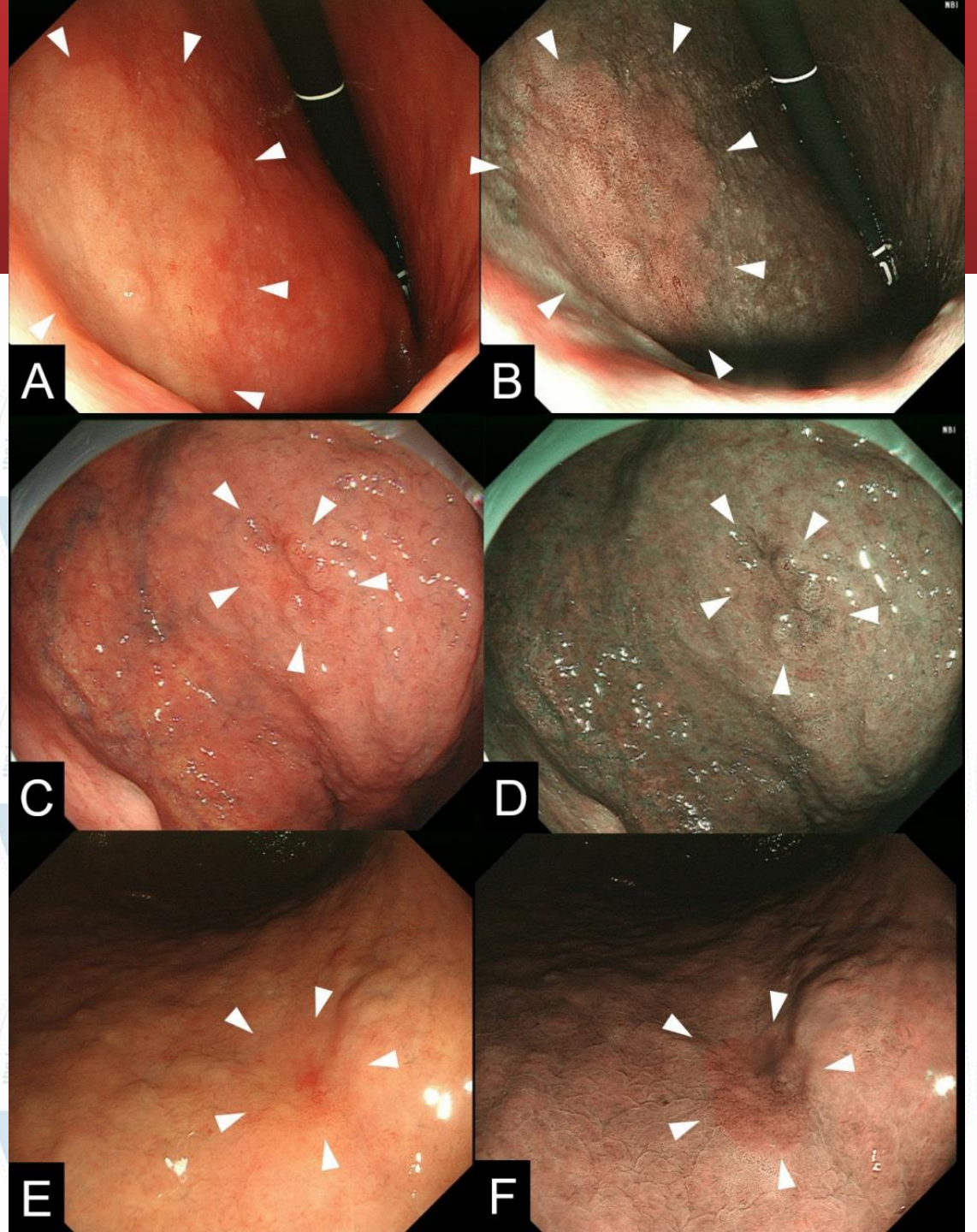
ABSTRACT

Gastric adenocarcinoma carries a poor prognosis, in part due to the late stage of diagnosis. Risk factors include *Helicobacter pylori* infection, family history of gastric cancer—in particular, hereditary diffuse gastric cancer and pernicious anaemia. The stages in the progression to cancer include chronic gastritis, gastric atrophy (GA), gastric intestinal metaplasia (GIM) and dysplasia. The key to early detection of cancer and improved survival is to non-invasively identify those at risk before endoscopy. However, although biomarkers may help in the detection of patients with chronic atrophic gastritis, there is insufficient evidence to support their use for population screening. High-quality endoscopy with full mucosal visualisation is an important part of improving early detection. Image-enhanced endoscopy combined greatest risk and intervene with recognised efficacious treatments, including endoscopic resection,before cancer is established. The British Society of Gastroenterology (BSG) endoscopy committee agreed to create a guideline to provide statements and recommendations on the prevalence, risks, diagnosis, treatment, surveillance and screening of gastric premalignant and early gastric malignant lesions. The principal patient group are those found to have GA, GIM, gastric epithelial dysplasia or early gastric adenocarcinoma limited to the mucosal or superficial submucosal layers. The target users include gastroenterologists, GI surgeons, pathologists, endoscopists and general practitioners. We followed the Appraisal of Guidelines for Research

- Endoscopic appearances on White Light Endoscopy of gastric dysplasia and early gastric cancer (differences in color, loss of vascularity, slight elevation or depression, nodularity, thickening, and abnormal convergence or flattening of folds) require escalation to Image Enhanced Endoscopy and, where available, magnification endoscopy (evidence level: low quality; grade of recommendation: strong; level of agreement: 100%).

- IEE as the best imaging modality to accurately diagnose and stage gastric dysplasia and early gastric cancer (evidence level: moderate quality; grade of recommendation: strong; level of agreement: 100%).


A
B
C
D
E
F
Intestinal metaplasia
Enterocyte
Goblet cell
Paneth cell
Foveolar cell
Mucous cell


A
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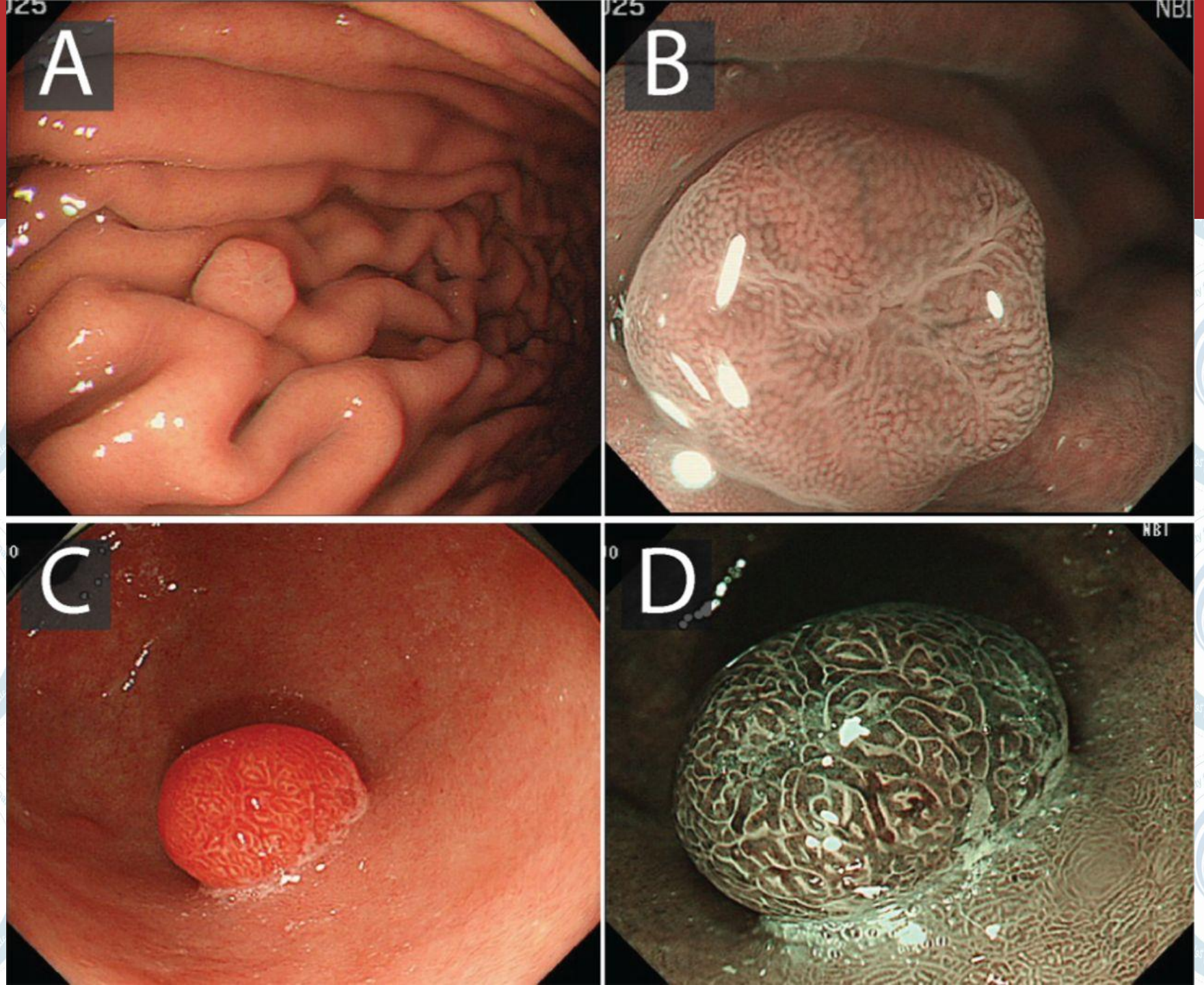
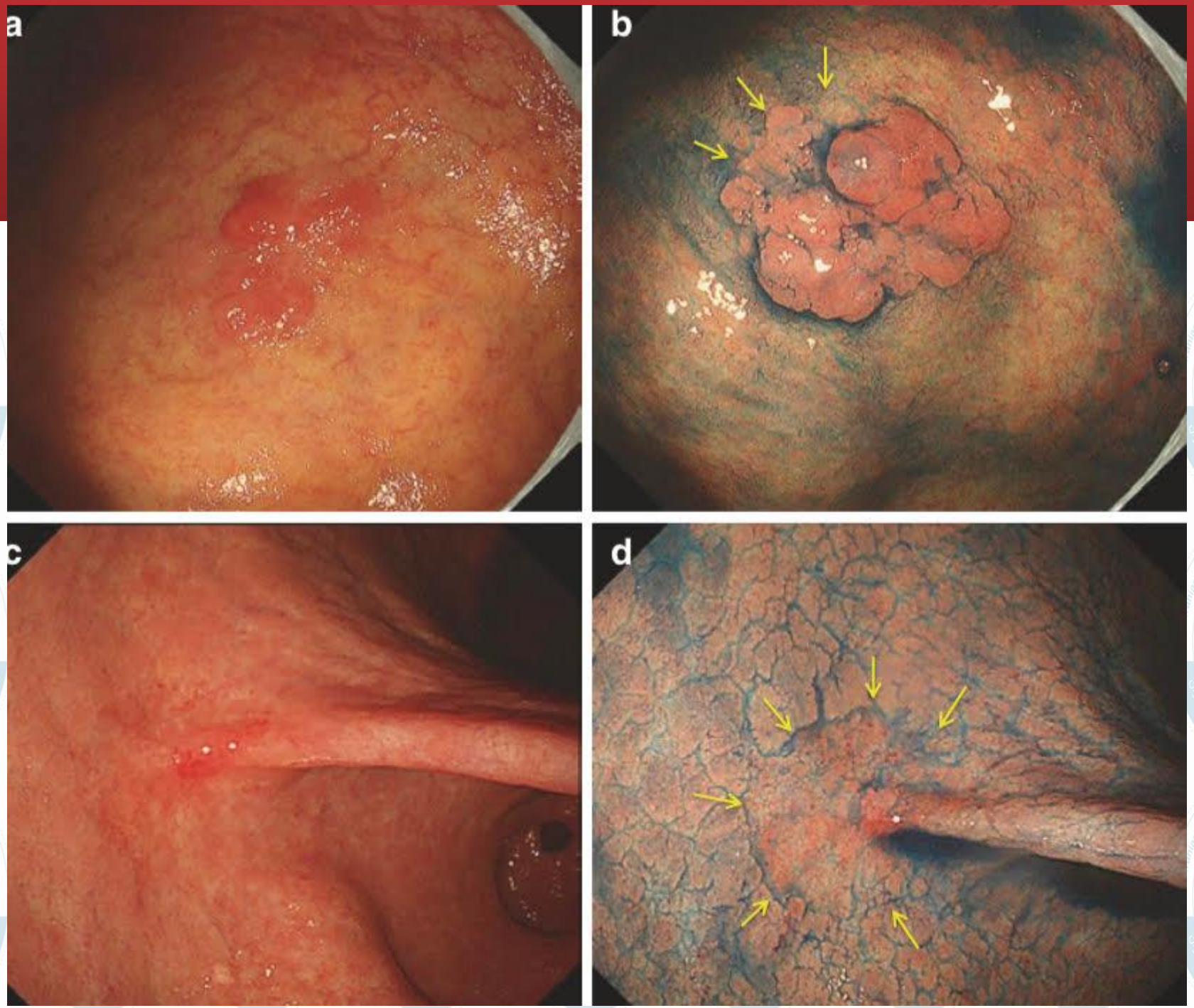
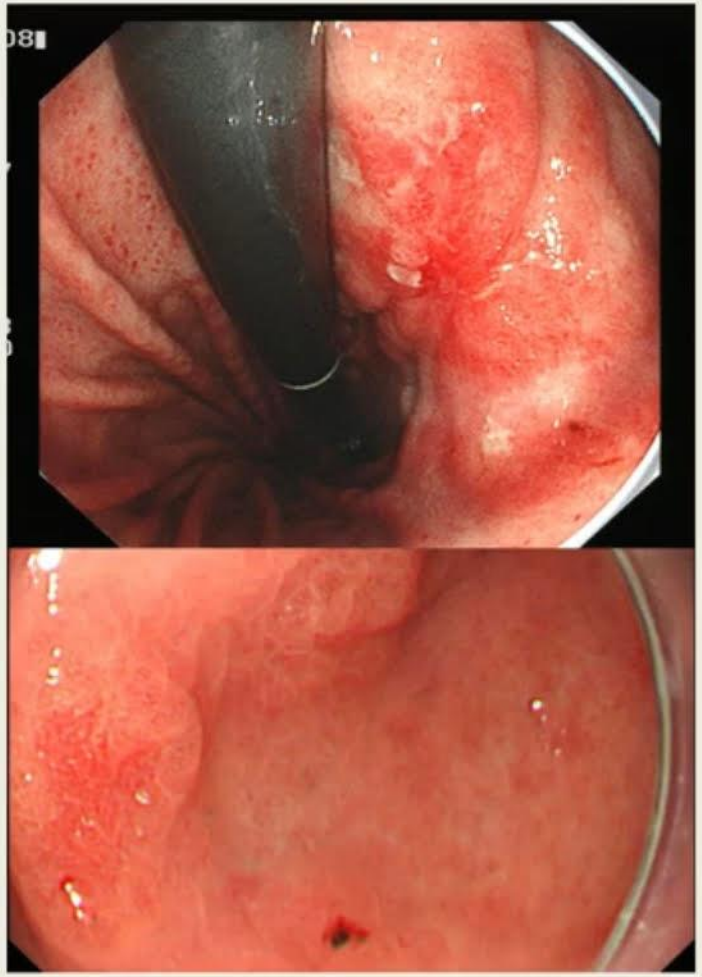

A
B
NBI
C
D
NBI


a
b
c
d

Diagnosis of early gastric cancer

- **Difficult to recognize upon ordinary endoscopy**
  - Subtle changes in microstructural and microvascular patterns
  - Uncommonly present as a polypoid growth (except in colon)

- **Developed from a background of premalignant changes (eg Gastric IM)**
  - Sometimes difficult to diagnose



Algorithm for the systematic examination of the upper gastrointestinal tract

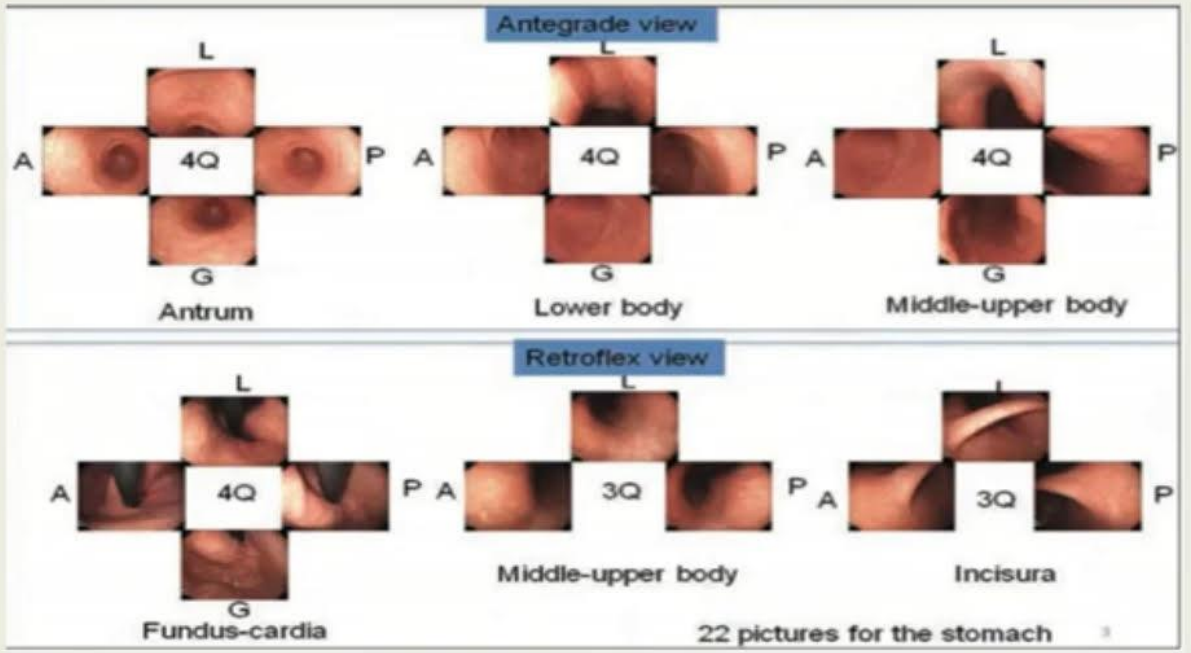
Evidence: Experts' opinion

INVITED REVIEW

Annals of Gastroenterology (2013) **26,** 11-22

The endoscopic diagnosis of early gastric cancer

Kenshi Yao
Fukuoka University Chikushi Hospital, Japan



Minimum total gastroscopy procedure time 8 min

2 min to 2nd part duodenum

Intubation
Cleaning, mucolytic, antifoam ± antispasmodic[41]

+

4 min with SSS protocol[37]

Stomach
Systematic examination, avoid miss at cardia[15]

+

2 min + 1 min/cm Barrett oesophagus[72]

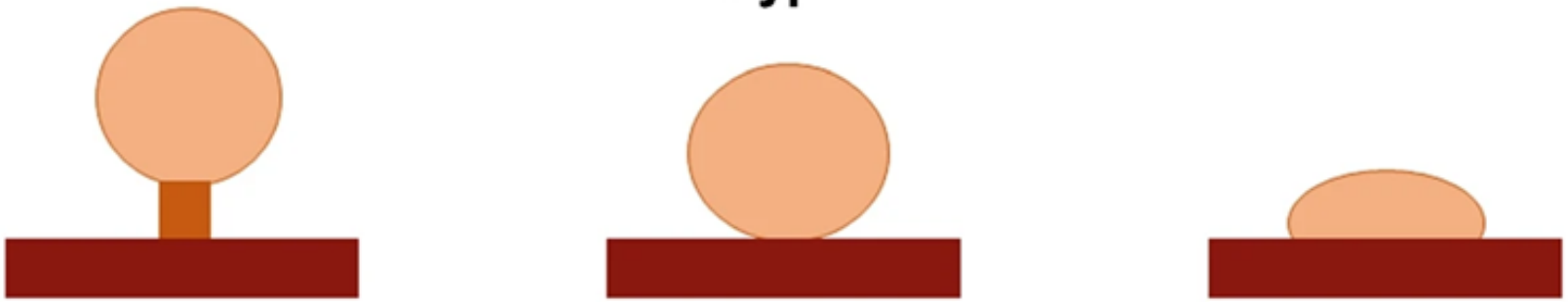
Oesophagus
Focus on 3 o'clock in Barrett oesophagus[52–54]

Higher Rates of EGC in SE Asia

- The longstanding screening programs
- EGC diagnostic expertise
- Quality of endoscopy
- Difference in the interpretation of gastric histology in Eastern versus non-Asian centers

Classification

Polypoid



Ip - Pedunculated

Isp - Semi-pedunculated

Is - Sessil

Non-Polypoid

IIa – Slightly elevated

IIb - Flat

IIc – Slightly depressed

III – Excavated

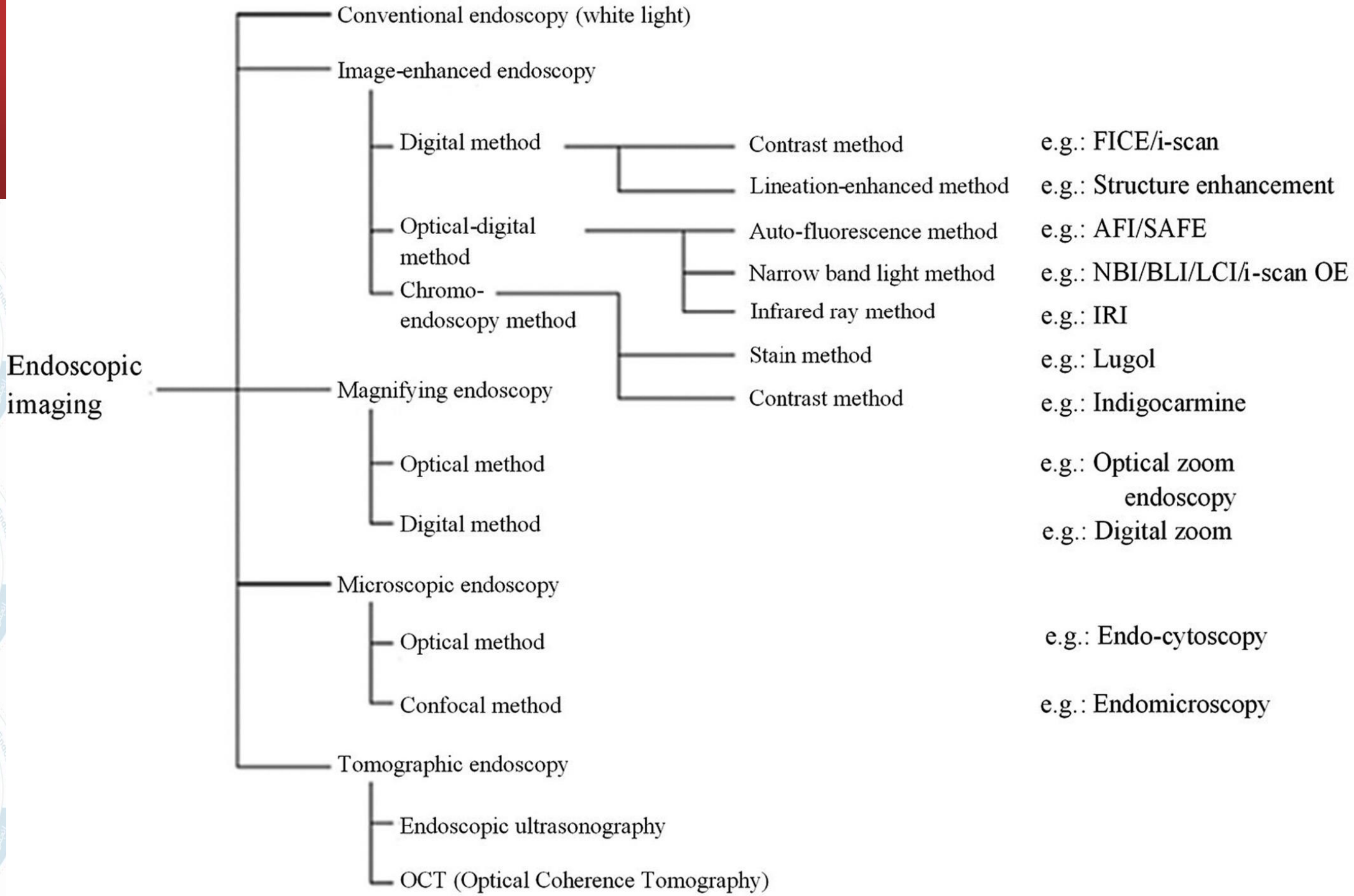
Paris Classification

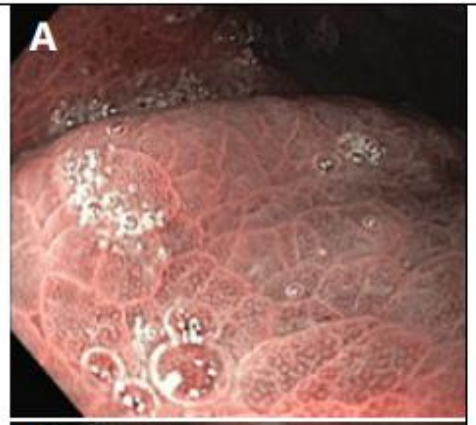
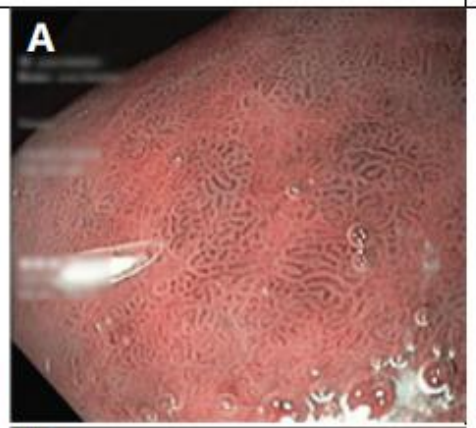
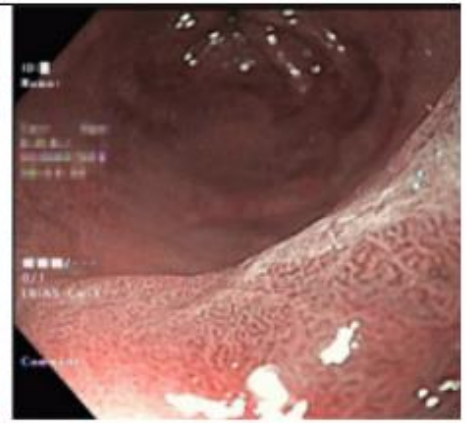
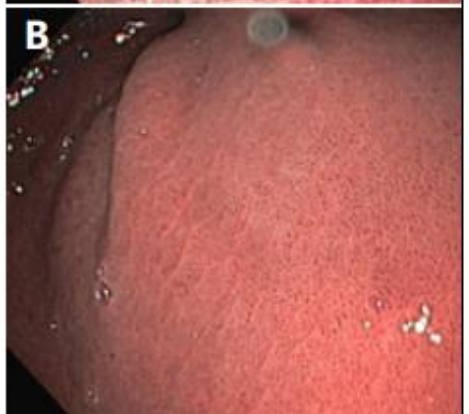
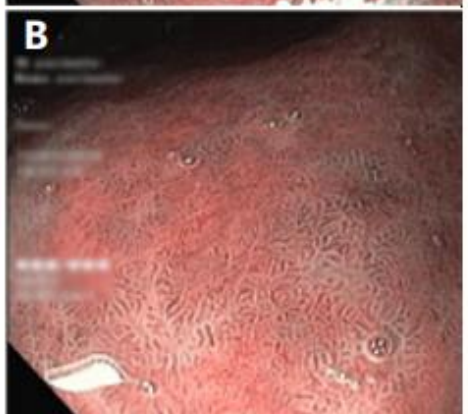
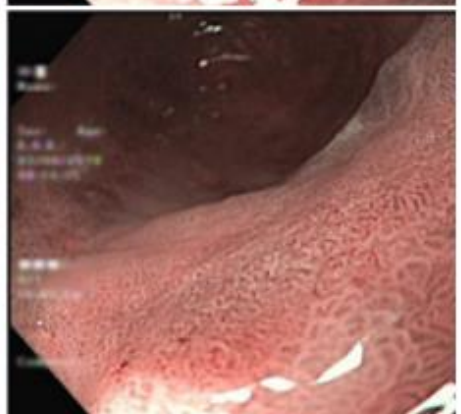
Type I vs Type II a

- Type I lesions extend above the mucosa more than 2.5 mm (the width of the closed cups of a biopsy forceps).
- Pathologically, the height of the lesion is more than double the thickness of the adjacent mucosa.

Type IIc and type III

- Type IIc lesions are slightly depressed with a normal epithelial layer or superficial erosions.
- Type III lesions are characterized by ulceration, with loss of the mucosa and possibly submucosa.


Endoscopic imaging
Conventional endoscopy (white light)
Image-enhanced endoscopy
Digital method
Contrast method
e.g.: FICE/i-scan
Lineation-enhanced method
e.g.: Structure enhancement
Optical-digital method
Auto-fluorescence method
e.g.: AFI/SAFE
Narrow band light method
e.g.: NBI/BLI/LCI/i-scan OE
Chromo-endoscopy method
Infrared ray method
e.g.: IRI
Stain method
e.g.: Lugol
Contrast method
e.g.: Indigocarmine
Magnifying endoscopy
Optical method
e.g.: Optical zoom endoscopy
Digital method
e.g.: Digital zoom
Microscopic endoscopy
Optical method
e.g.: Endo-cytoscopy
Confocal method
e.g.: Endomicroscopy
Tomographic endoscopy
Endoscopic ultrasonography
OCT (Optical Coherence Tomography)

	Normal	Intestinal metaplasia	Dysplasia
Mucosal pattern	Regular		Irregular/absent
	Circular	Ridge or tubulovillous Light-blue crest	
Vascular pattern	Regular (thin/peripheral vessels in gastric body and thick/central vessels in gastric antrum)		Irregular
			
			

NBI simplified classification for gastric pathology

GE Port J Gastroenterol 2022;29:299–310

A.

Atrophy score		Corpus			
		No atrophy (Score 0)	Mild atrophy (Score 1)	Moderate atrophy (Score 2)	Severe atrophy (Score 3)
Antrum (Including incisura angularis)	No atrophy (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

B.

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

*Operative link on gastritis assessment staging system **(A)** and operative link on gastric intestinal metaplasia assessment **(B)** staging system. IM, intestinal metaplasia; OLGA, Operative link on gastritis assessment system; OLGIM, Operative link on gastric intestinal metaplasia assessment.*

Adapted from Weng CY et al. (27)

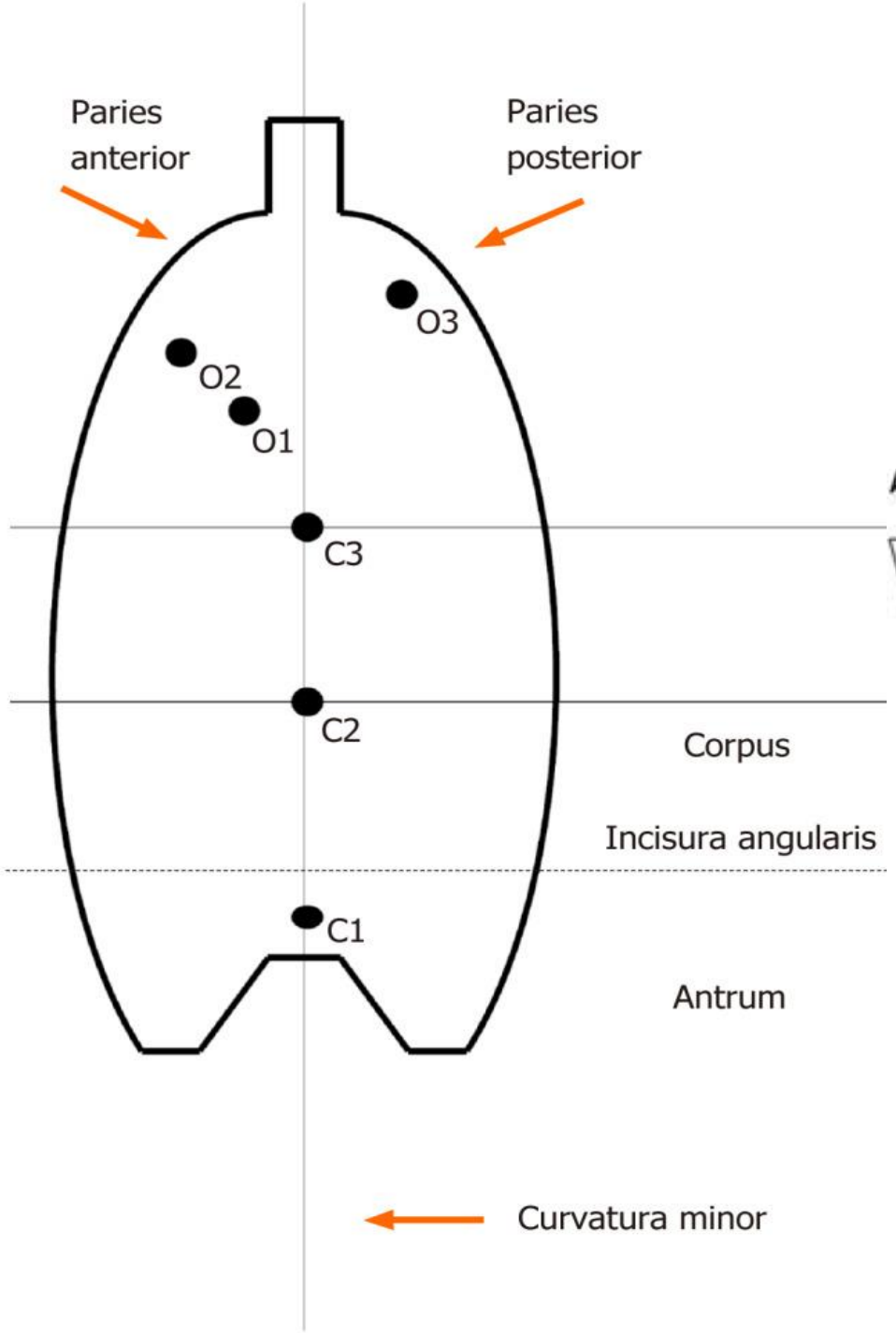
Higher intensity of colour means higher risk of Early Gastric Cancer.

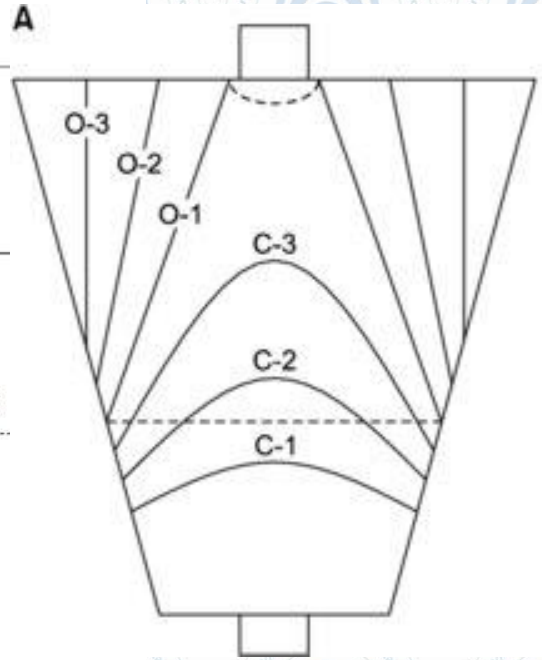
Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM) scale

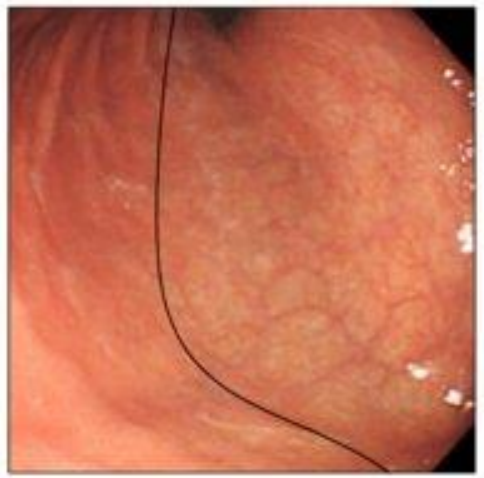
	Antrum		Incisura	Corpus	
	lesser curvature	greater curvature		lesser curvature	greater curvature
No intestinal metaplasia	0	0	0	0	0
Focal (≤30% intestinal metaplasia)	1	1	1	1	1
Diffuse (>30% intestinal metaplasia)	2	2	2	2	2
Intestinal metaplasia score for the area	0–4		0–2	0–4	
Total EGGIM score and management	0–10 No IM: 0 points – no surveillance Low-risk IM: 1–4 points – surveillance only if additional risk factors High-risk IM: ≥5 points – endoscopic surveillance				

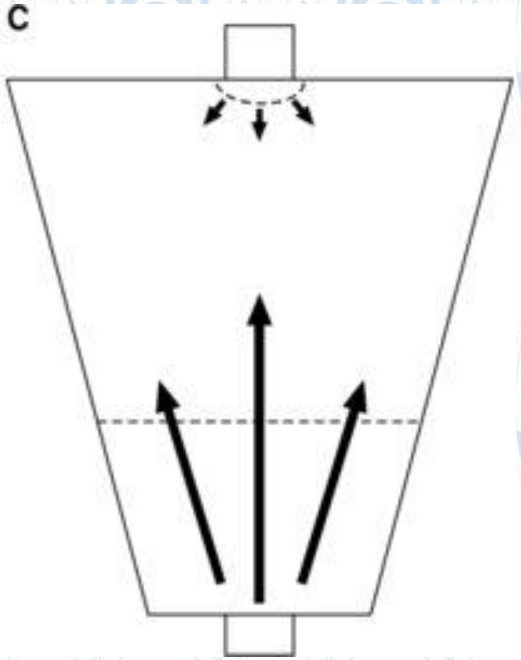
GE Port J Gastroenterol 2022;29:299–310

Kimura-Takemoto Classification of Endoscopic Gastric Mucosal Atrophy

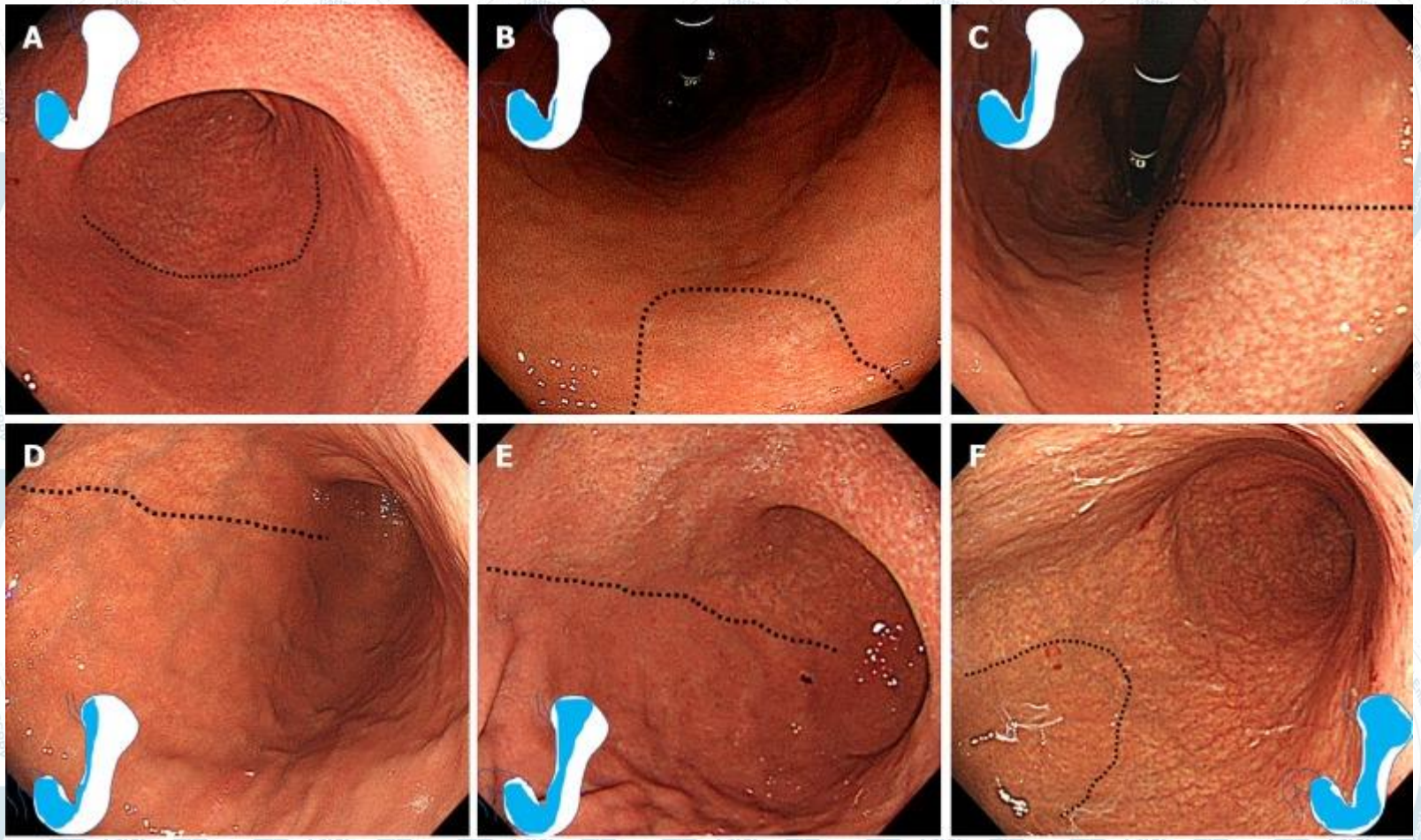


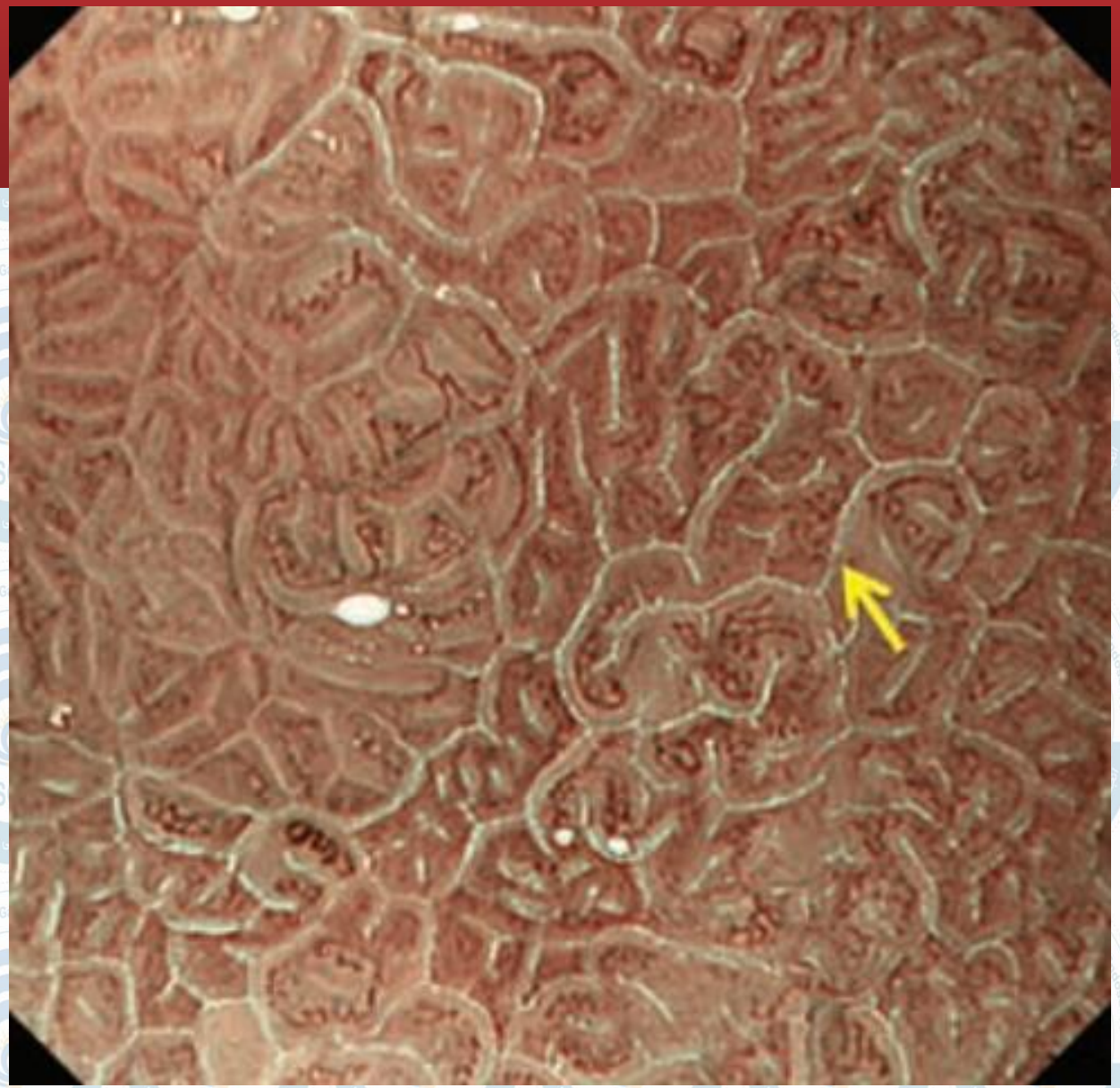






Kimura-Takemoto Classification of Endoscopic Gastric Mucosal Atrophy





M-NBI findings of IM

Light blue crest at the edge of mariginal crypt epithelium

Defined as fine, blue white line on the crest of the epithelial surface/gyri.

Highly predictive of histological intestinal metaplasia

Risk Stratification

- C1 :0%
- C2: 0.25%
- C3: 0.71%
- O1: 1.32%
- O2:3.70%
- O3: 5.33%

Digestion (2015) 91:30–6.

H.pylori eradication , no IM :

- Cumulative 5-year incidence of gastric cancer 1.5%

H.pylori eradication, antral IM:

- Cumulative 5-year incidence of gastric cancer 5.3%

H.pylori eradication, corpus IM:

- Cumulative 5-year incidence of gastric cancer 9.8%

Gastrointest Endosc. 2016,Oct;84(4):618-24

Risk Stratification

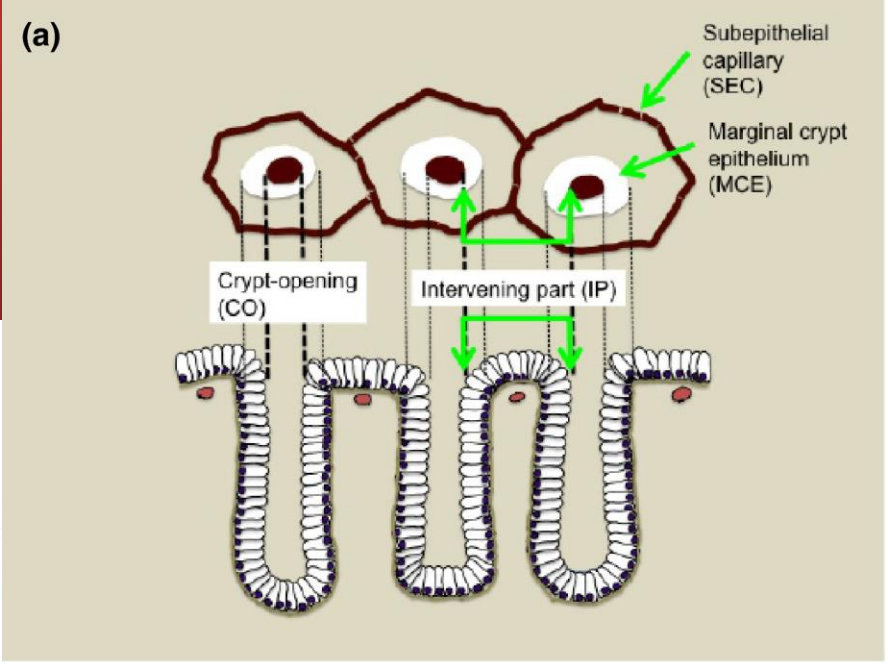
- IM at a single location has a higher risk of gastric cancer but because of prevalence of up to 33% surveillance is not justified.
- Advanced stages of atrophic gastritis and those with a family history of gastric cancer may benefit from a more intensive follow-up (e.g., every 1–2 years after diagnosis)
- Patients with advanced stages of atrophic gastritis (severe atrophic changes or intestinal metaplasia in both antrum and corpus, OLGA/OLGIM III/IV, EGGIM scores 5–10 have increased the risk of gastric cancer and should be followed up with a high quality endoscopy every 3 years

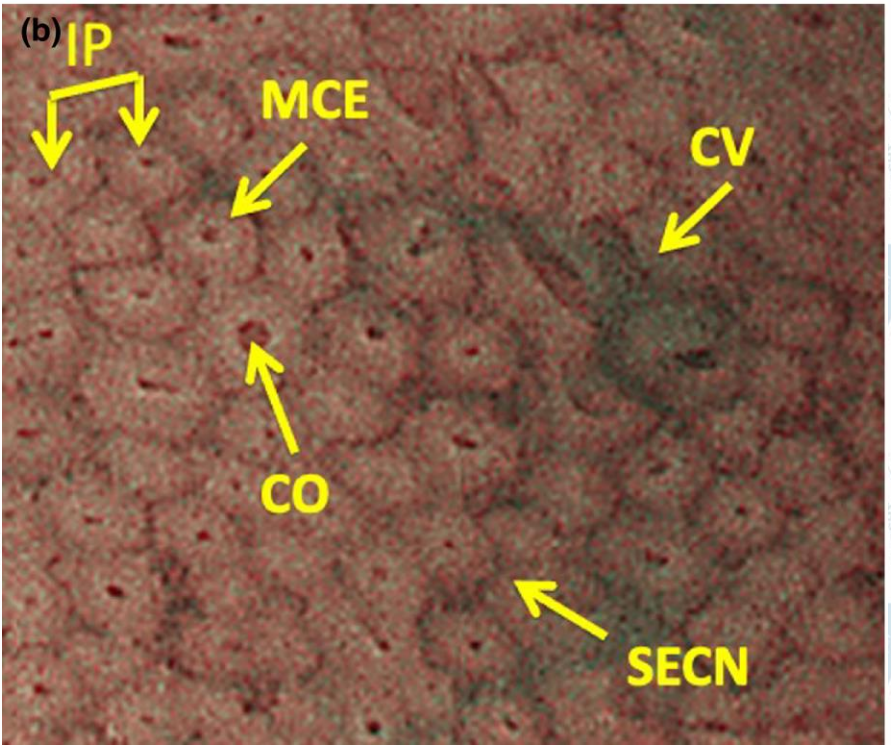
Kyoto classification score

Kyoto classification	Score
Atrophy	
None, C1	0
C2 and C3	1
O1-O3	2
Intestinal metaplasia	
None	0
Antrum	1
Corpus and antrum	2
Enlarged folds	
Absence	0
Presence	1
Nodularity	
Absence	0
Presence	1
Diffuse redness	
None	0
Mild (with RAC)	1
Severe	2
Kyoto score	0-8

Risk Stratification

- The Kyoto classification score in patients without a history of H. pylori eradication of 0, 1, and ≥2 was found to be associated with H. pylori infection rates of 1.5, 45, and 82%, respectively
- Kyoto classification scores of ≥4 may be associated with increased gastric cancer risk
- A modified Kyoto classification, which included open-type endoscopic atrophy, invisible regular arrangement of collecting venules at the incisura, virtual CE detecting intestinal metaplasia in >30% of the corpus and map-like redness in the corpus, performs better in determining EGC risk than the original Kyoto classification.





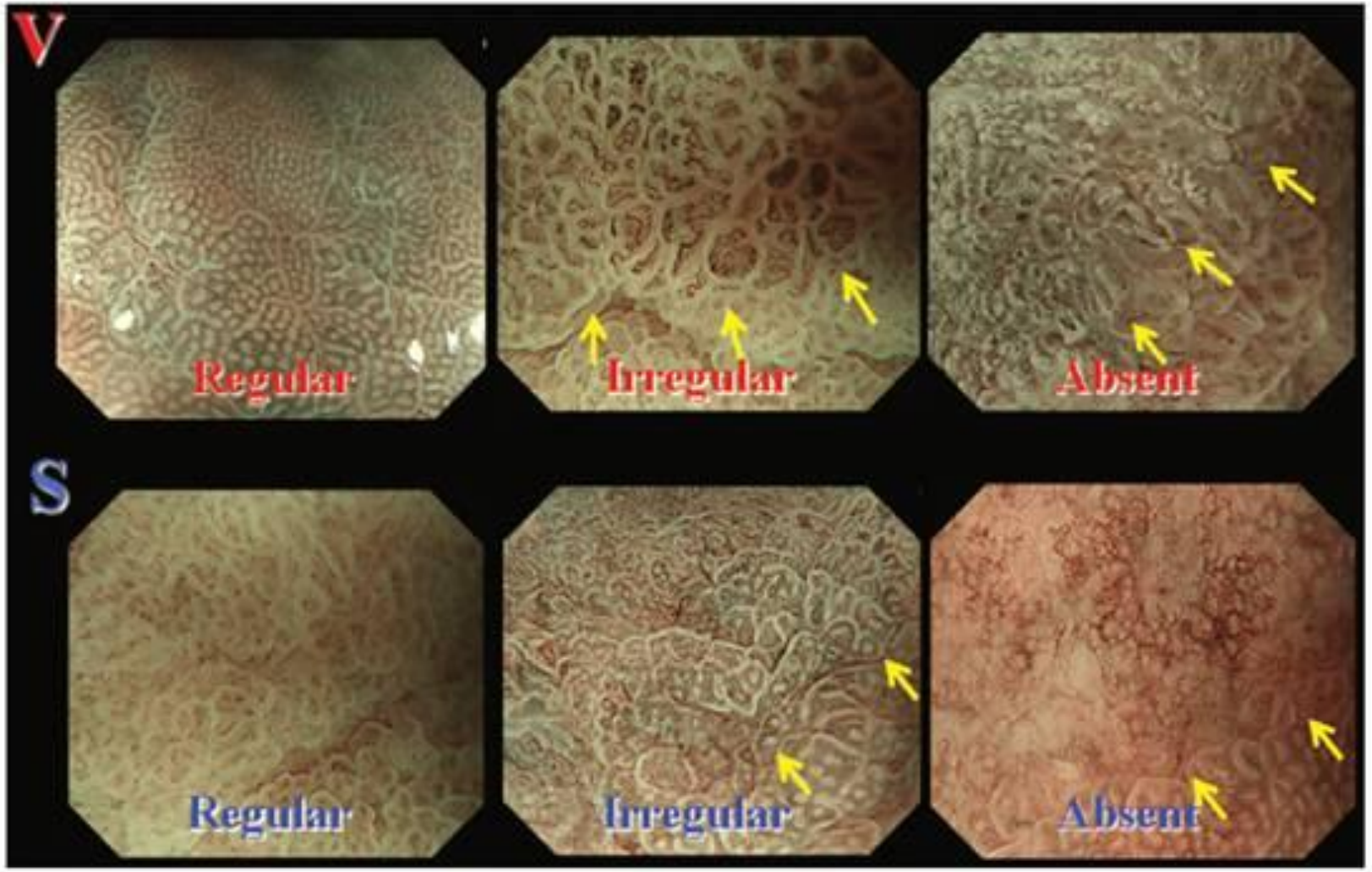
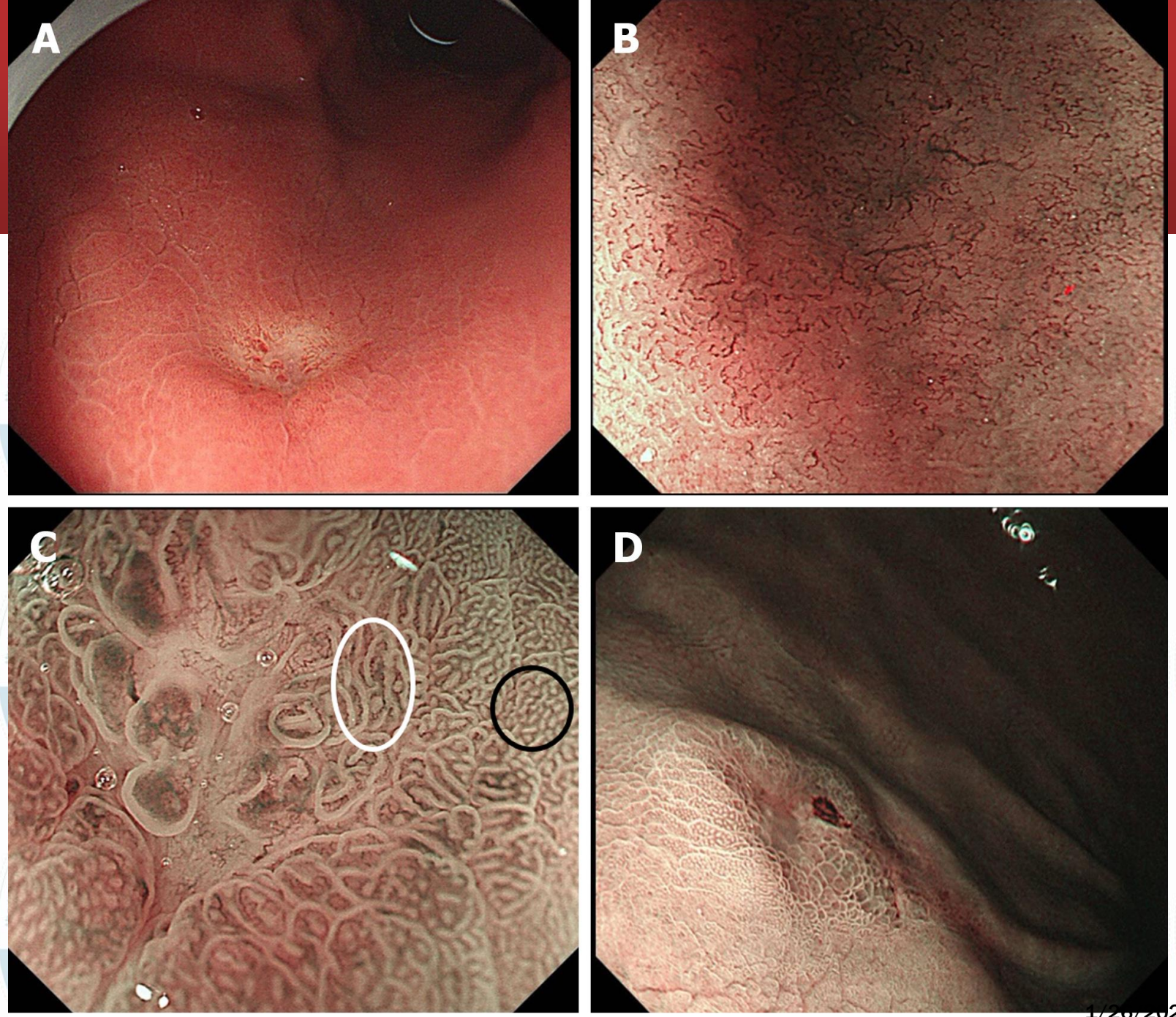


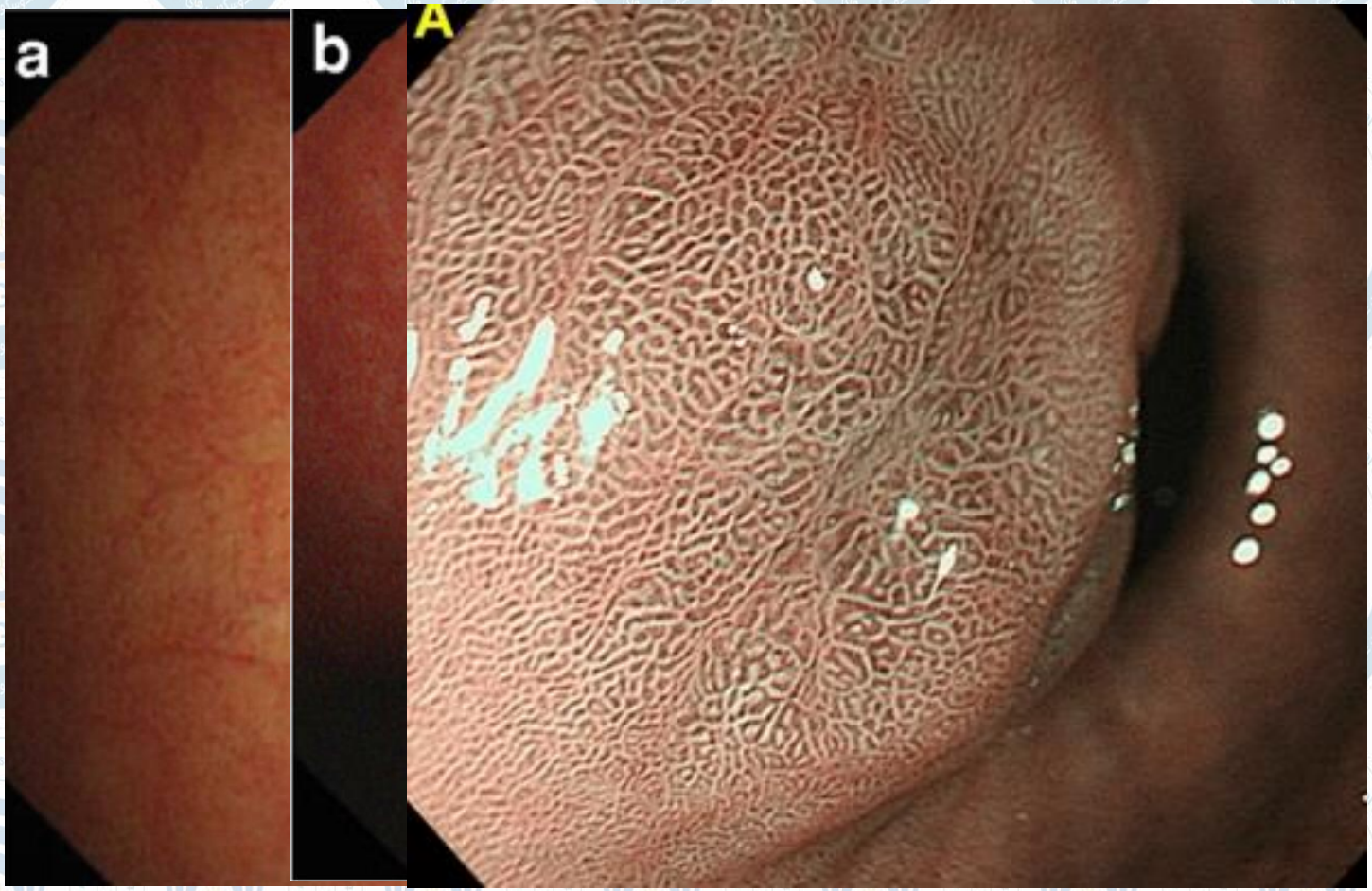
Figure 10 VS classification. Arrows show demarcation lines

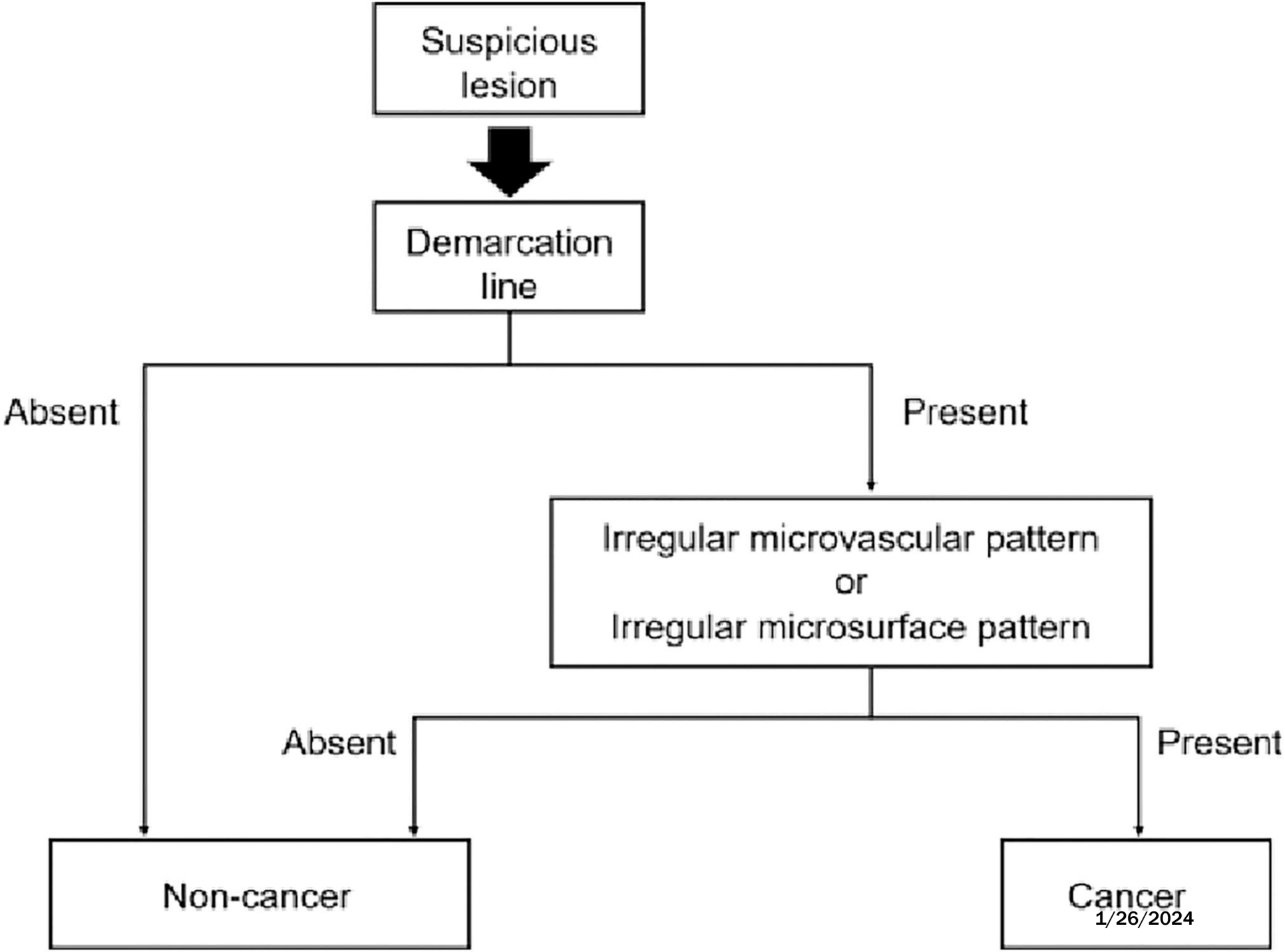


DOI: 10.4253/wjge.v15.i5.240

EGC on endoscopy

- Well-demarcated lesion
- Irregularity in color and surface

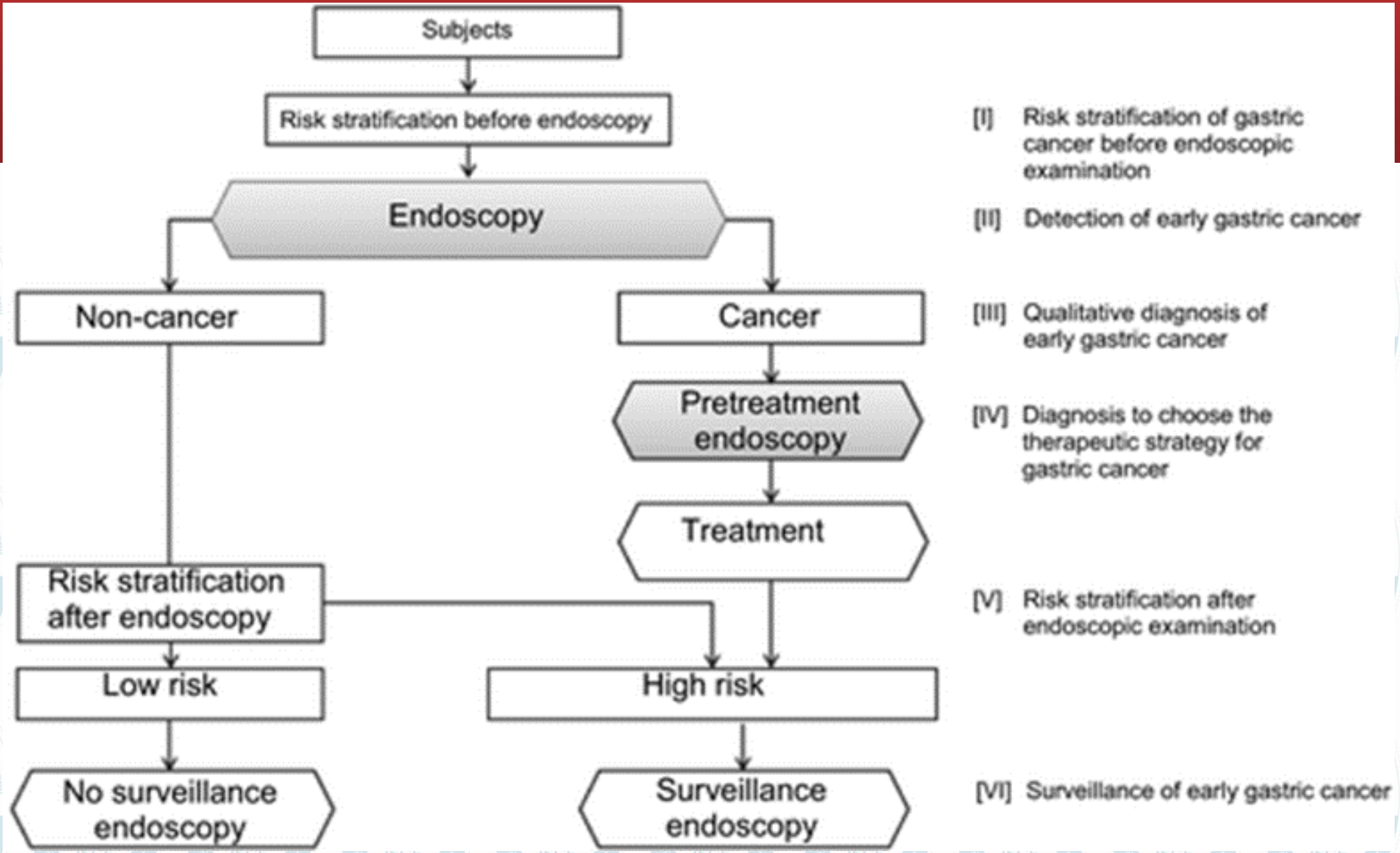



Suspicious lesion
Demarcation line
Absent
Present
Irregular microvascular pattern
or
Irregular microsurface pattern
Absent
Present
Non-cancer
Cancer

Risk Stratification

Atrophy, intestinal metaplasia, nodularity, enlarged fold, and gastric xanthoma are endoscopic findings related to the risk of gastric cancer.

Guidelines for endoscopic diagnosis of early gastric cancer. Digestive Endoscopy, 32: 663-698.

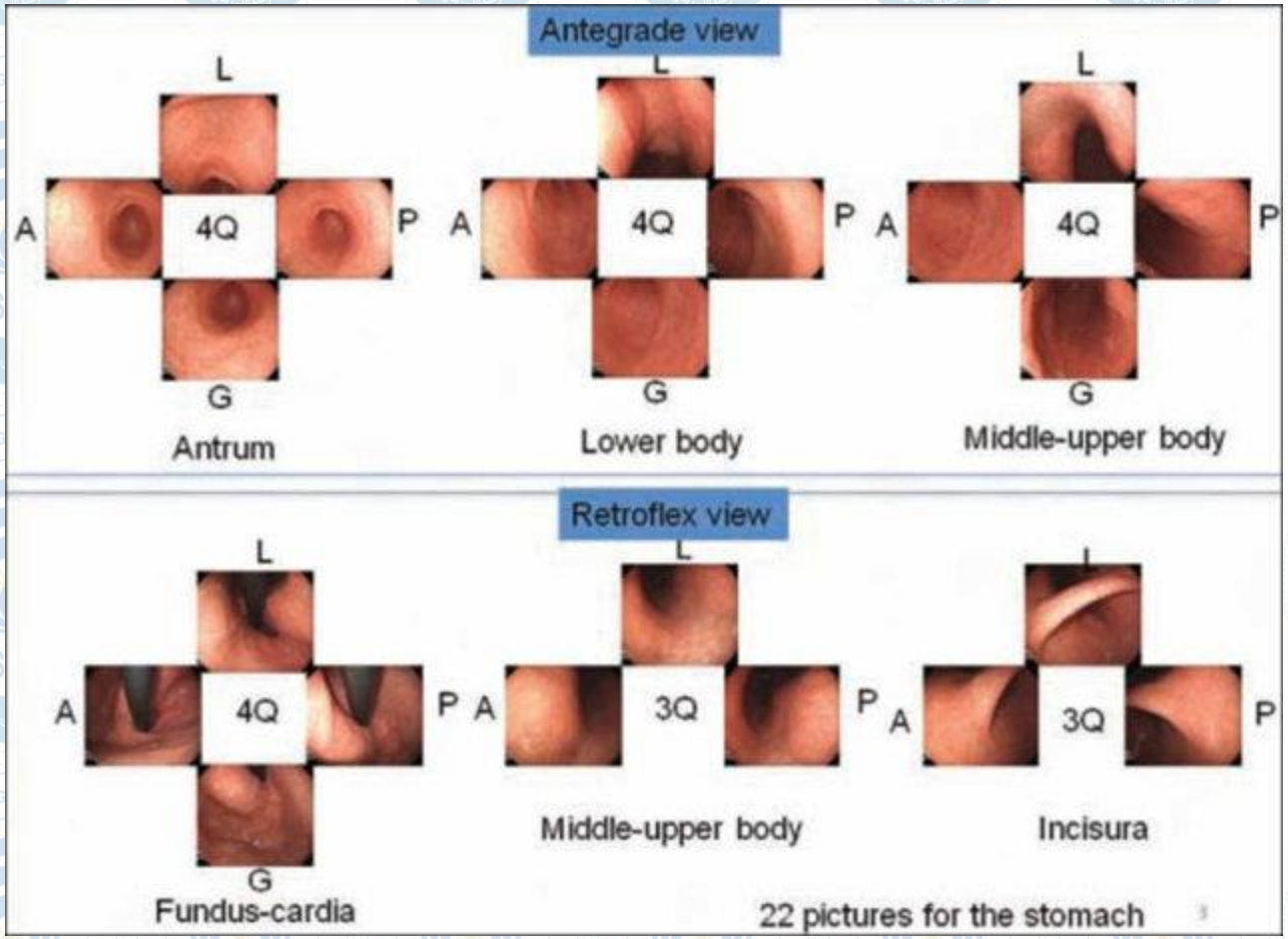

Subjects
Risk stratification before endoscopy
Endoscopy
Non-cancer
Cancer
Pretreatment endoscopy
Treatment
Risk stratification after endoscopy
Low risk
High risk
No surveillance endoscopy
Surveillance endoscopy
[I] Risk stratification of gastric cancer before endoscopic examination
[II] Detection of early gastric cancer
[III] Qualitative diagnosis of early gastric cancer
[IV] Diagnosis to choose the therapeutic strategy for gastric cancer
[V] Risk stratification after endoscopic examination
[VI] Surveillance of early gastric cancer

Endoscopy

- The GC endoscopy false negative rate can be as high as 25 percent
- Most centers 10% in three yrs

How to avoid ?

- A minimum duration of seven minutes
  - Minimal inspection time of the stomach 3 min
- Station-based protocols (with 22 pictures)
- Adequate gas insufflation
- Mucosal cleaning as needed
  - Use of mucolytic before endoscopy
- Image-enhanced endoscopy
- Sedation/anticholinergic/glucagon



Pre Endoscopy

a) 30 min before EGD, 100 mL of water mixed with 2 mL of acetylcysteine (200 mg/mL), and 0.5 mL activated dimethicone (40 mg/mL)

b) Just before EGD, 200 ml of water with 160 mg (4 drops) of simethicone .

Steps of high-quality upper endoscopy

Pre-procedure

- Patient' assessment
  - History review
  - Physical examination
  - UGI cancer risk factors
- Informed consent
- Premedication
  - Sedation
  - Defoaming agents
  - Antispasmodics

Intra-procedure

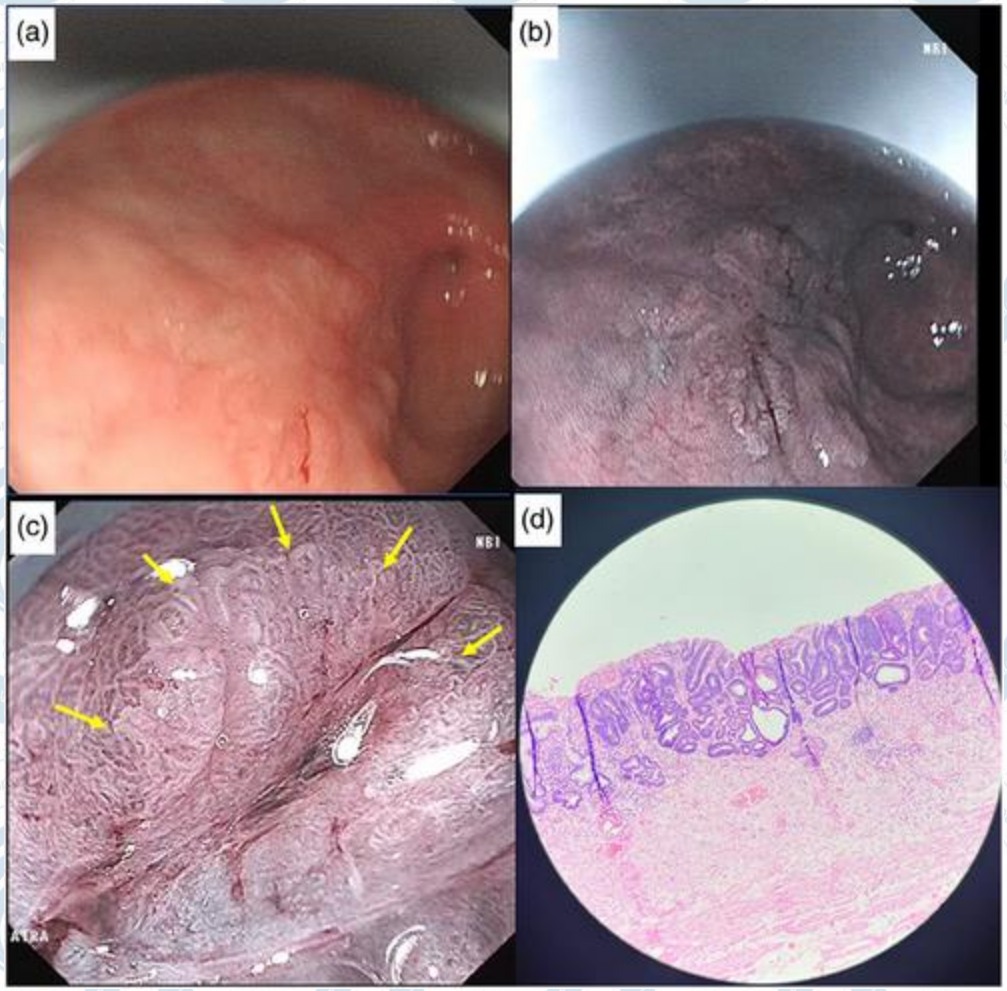
- Procedural time
  - Minimum 7 minutes*
- Photo-documentation
  - Minimum 10 images*
- Image-enhancing techniques
  - Lugol solution
  - Acetic acid
  - Narrow-spectrum imaging (NBI / BLI)
- Biopsy protocols
  - Eosinophilic esophagitis
  - Barrett's esophagus (Seattle protocol)
  - Atrophic gastritis (Sydney protocol)
  - Celiac disease

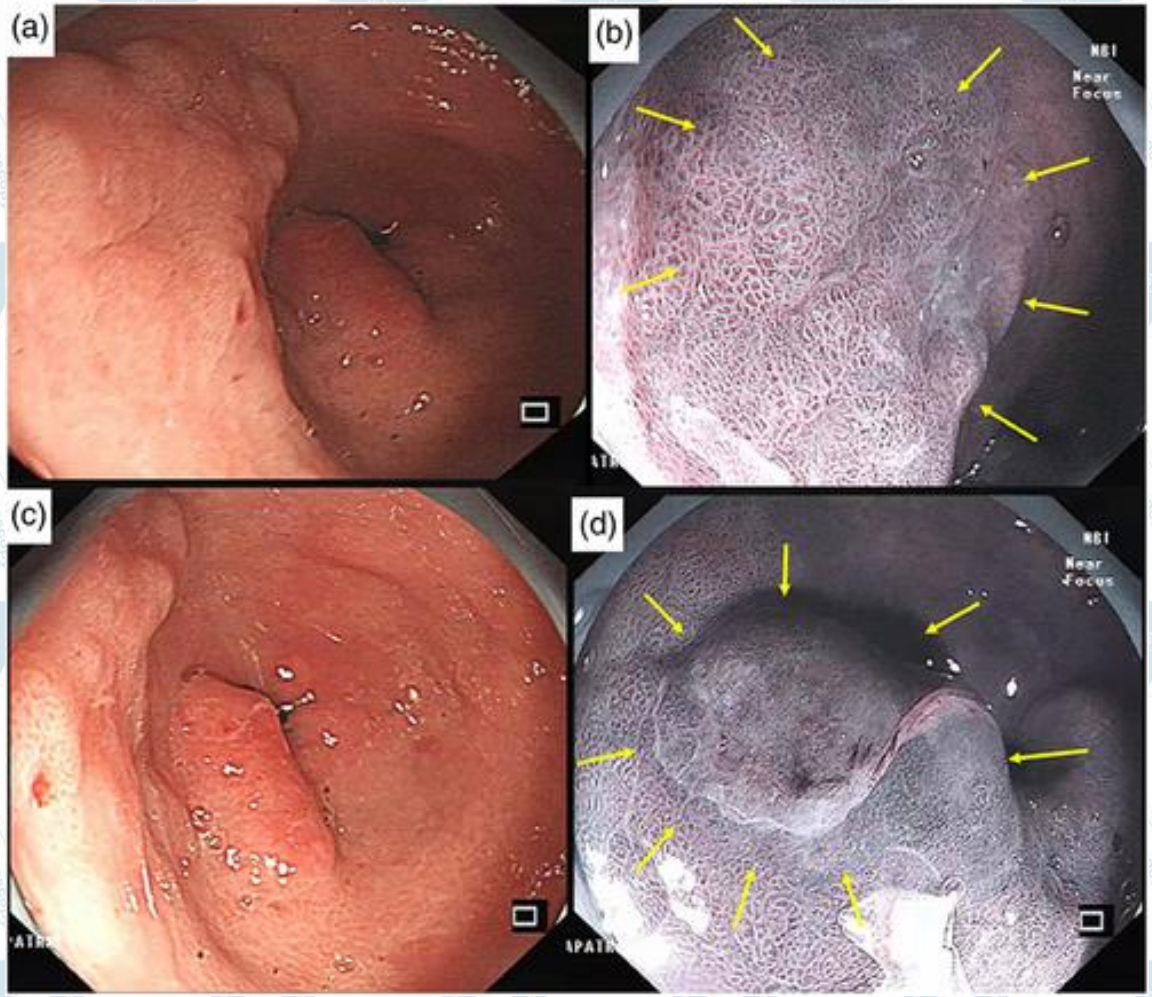
Post-procedure

- Registration of complications
- Patient satisfaction data
- Appropriate follow-up for high-risk conditions

*European Society of Gastrointestinal Endoscopy (ESGE) performance measures for upper gastrointestinal endoscopy (2016)

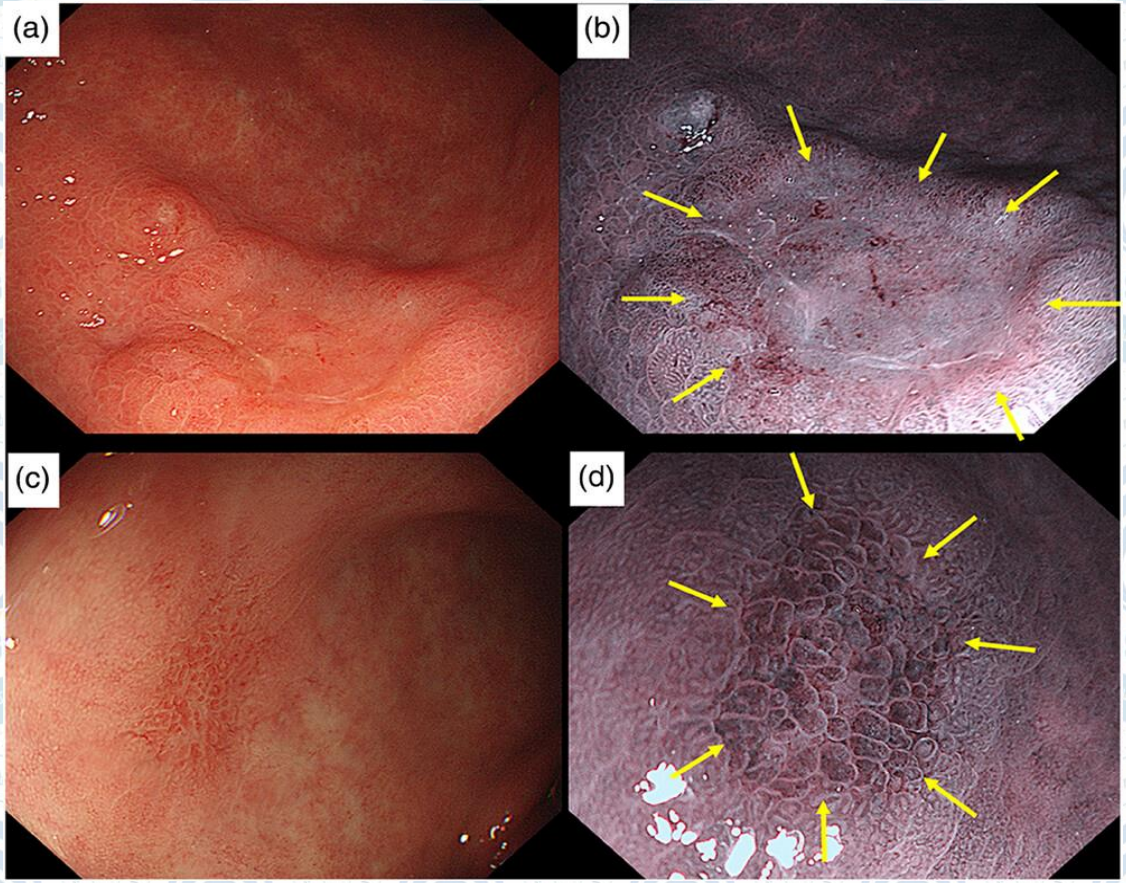
Endoscopic diagnosis of EGC

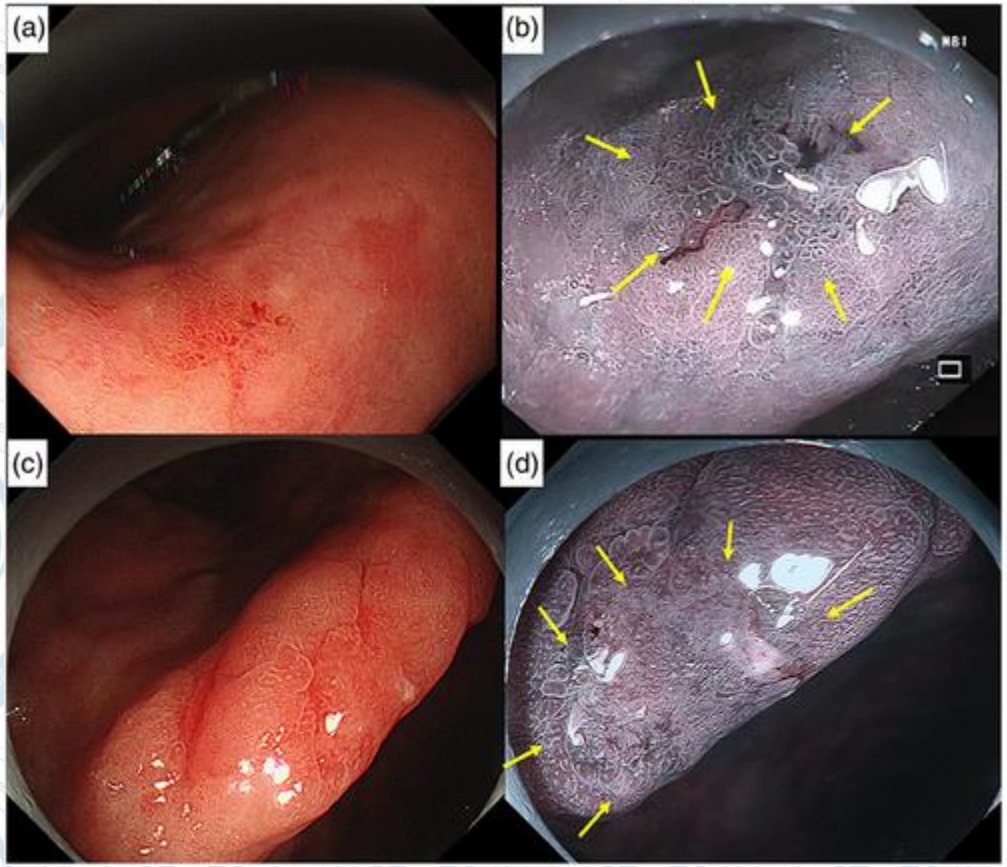




DEN Open, Volume: 4, Issue: 1, First published: 04 November 2023)

Endoscopic diagnosis of EGC





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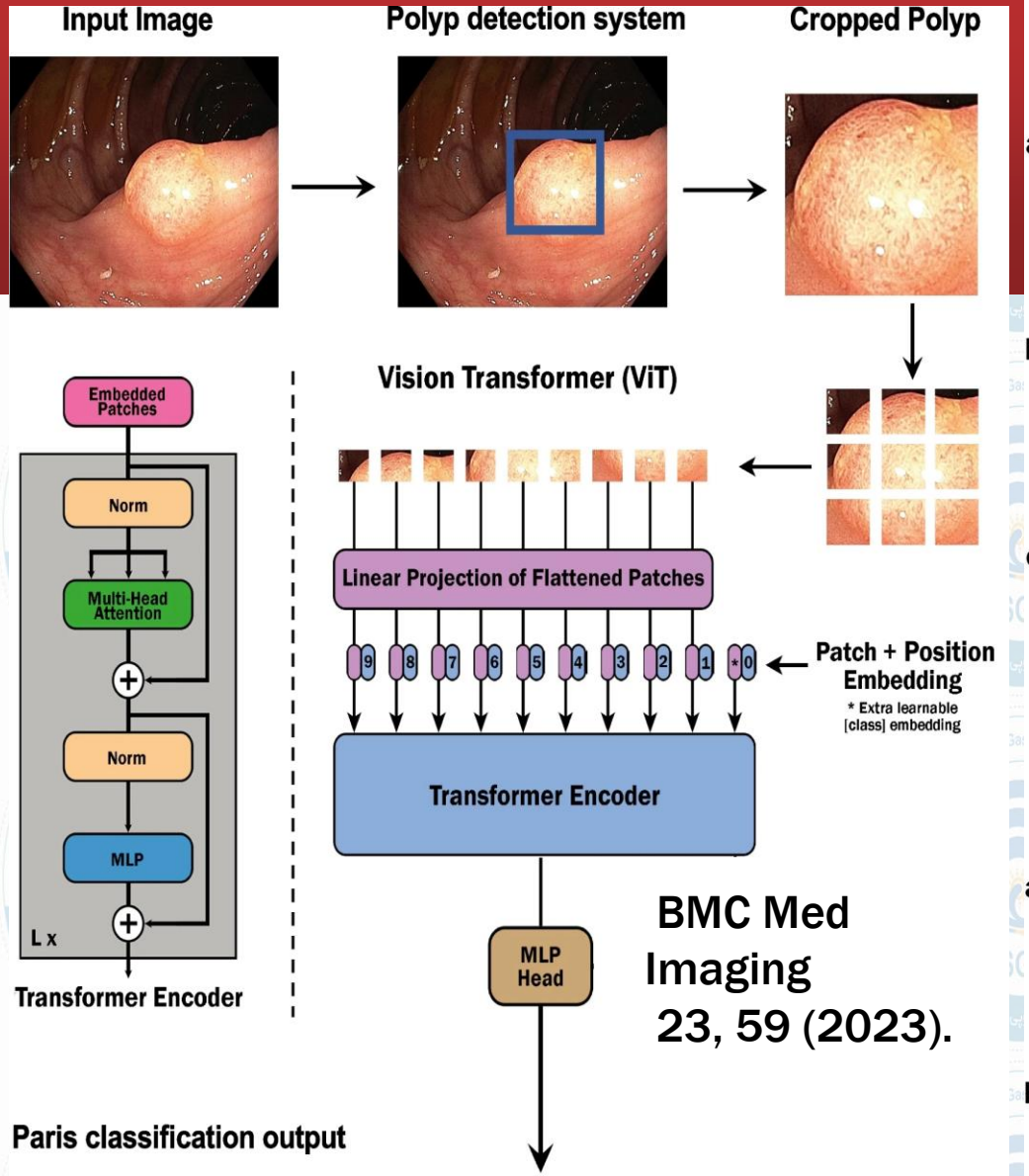
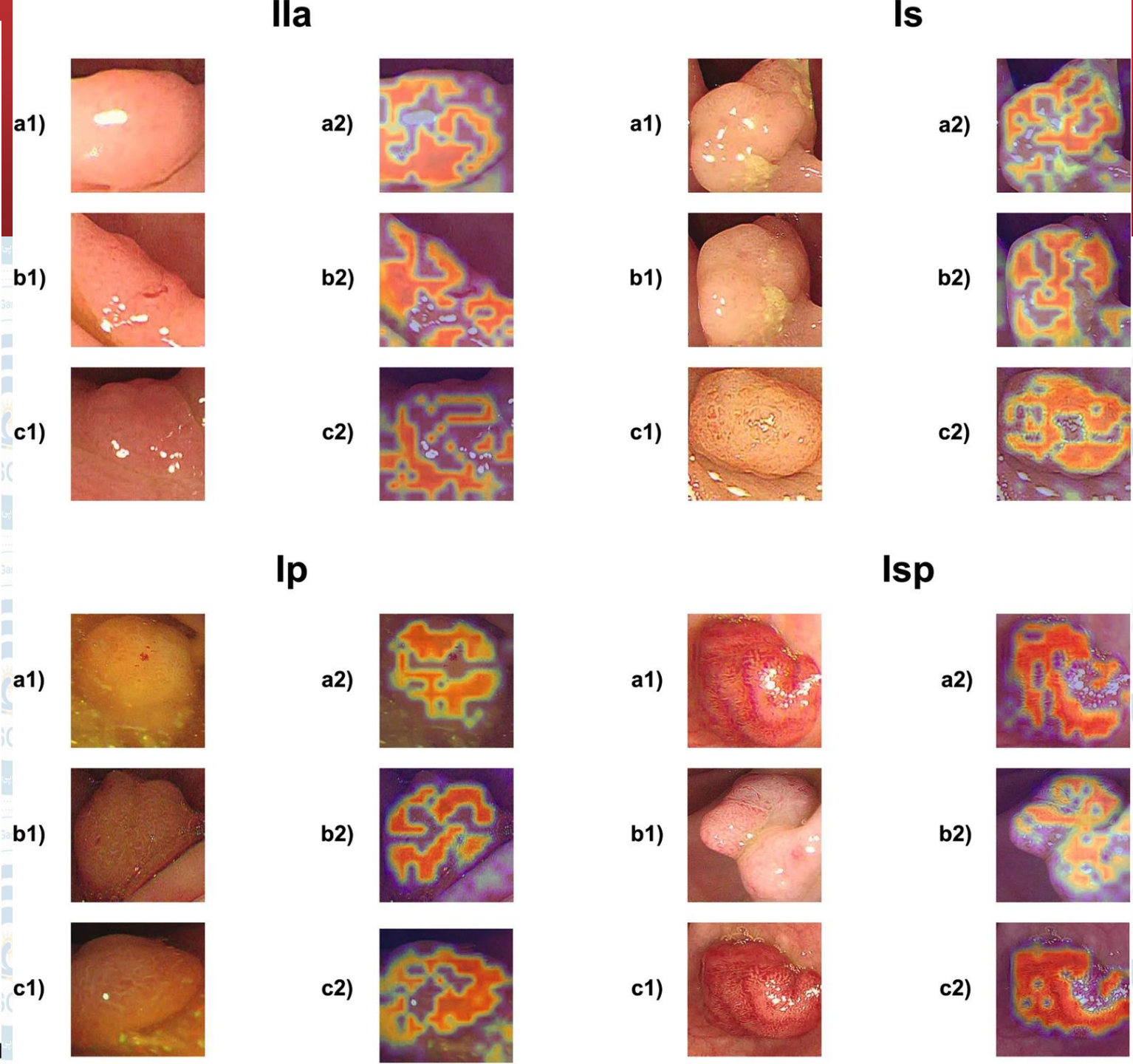
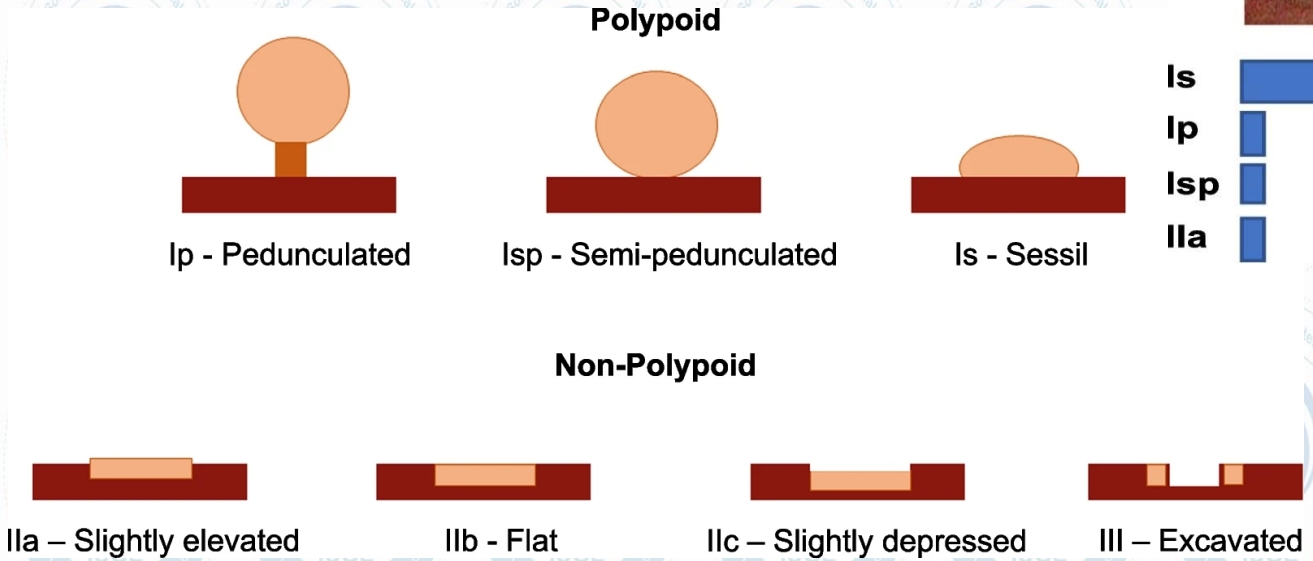
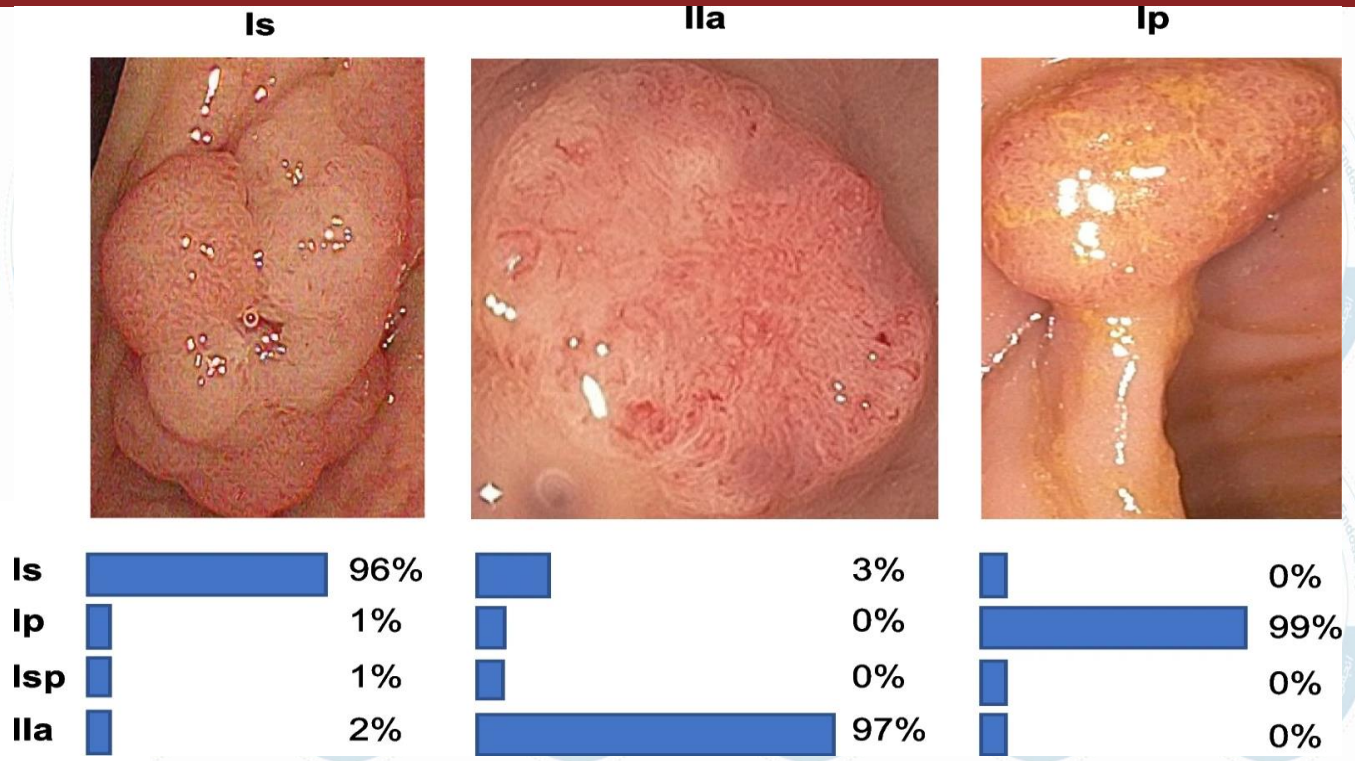


BMC Med Imaging 23, 59 (2023).



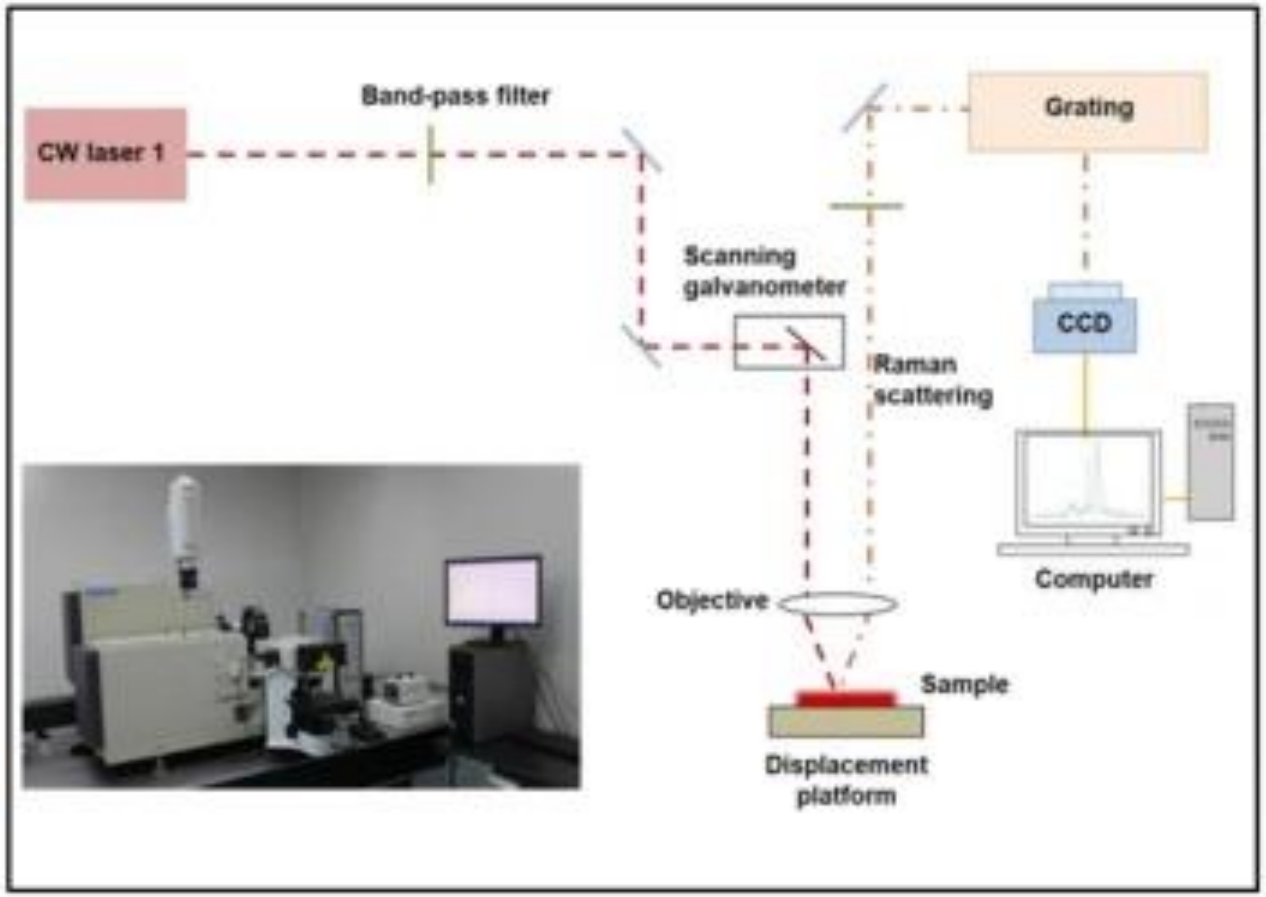
AI

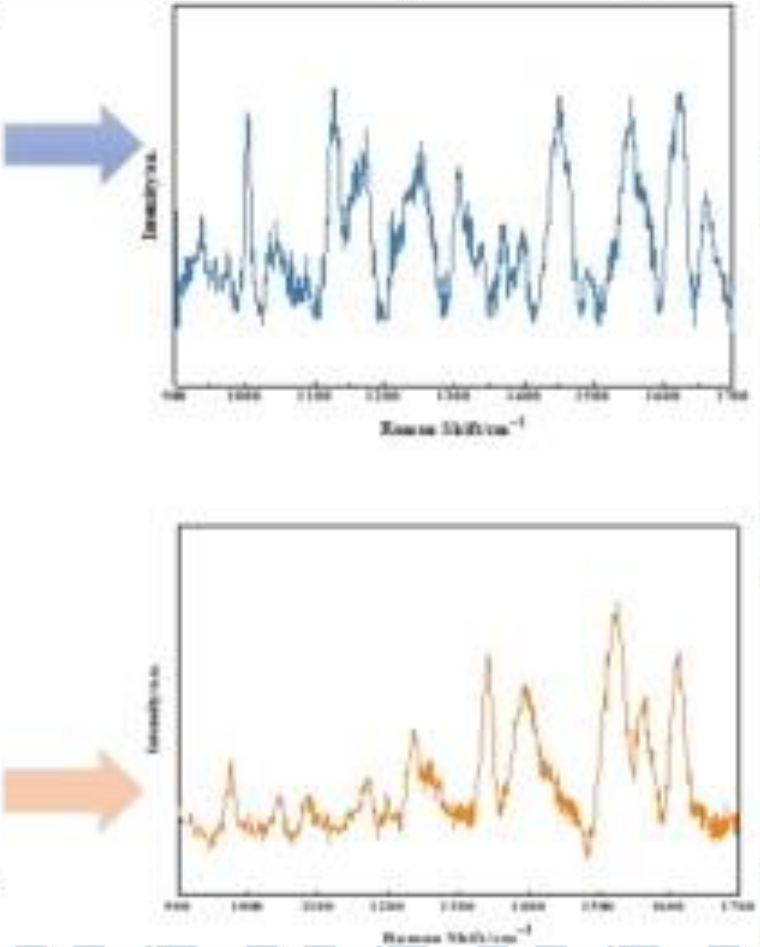




BMC Med Imaging 23, 59 (2023).

Spectroscopy

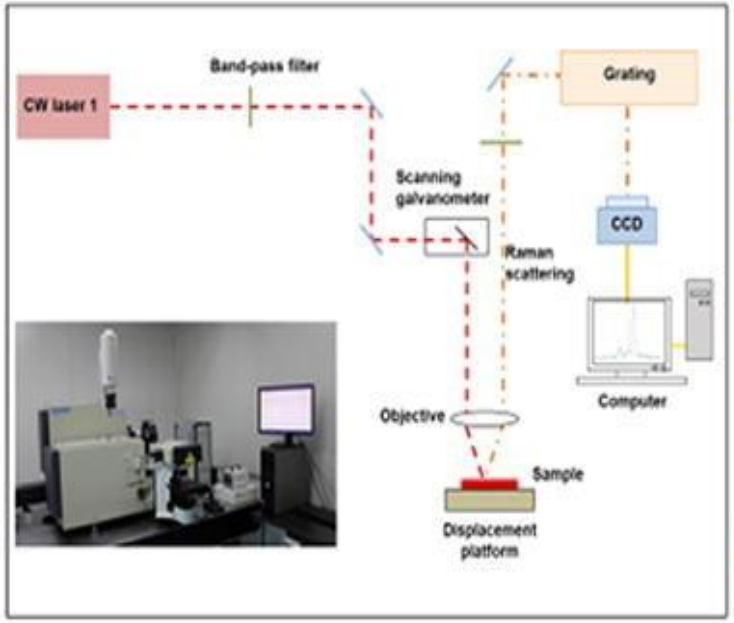




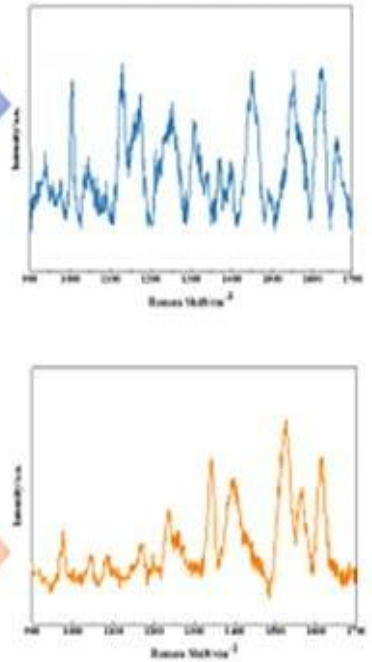
Spectroscopy

Endoscopic resected tissues and H&E stained slides

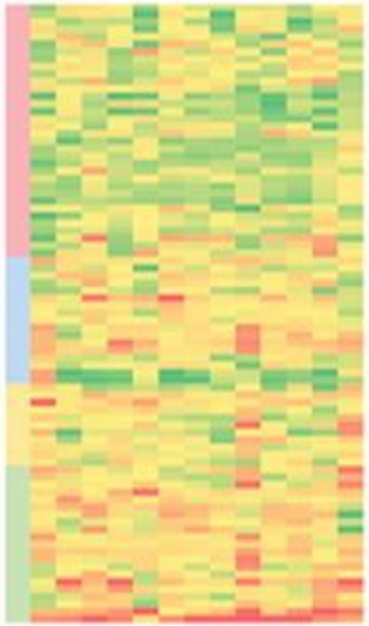
Raman measurement system



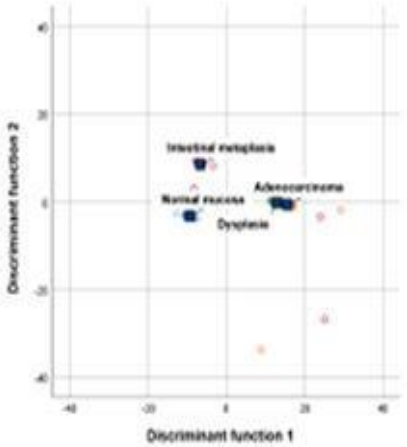
Feature extraction & characterization based on self-developed data-processing program



Biomolecular Analysis



Machine learning methods for diagnosis



Detection at the tissue and nuclei level

Provide mechanism insight!

Rapid, Objective, High-accuracy!

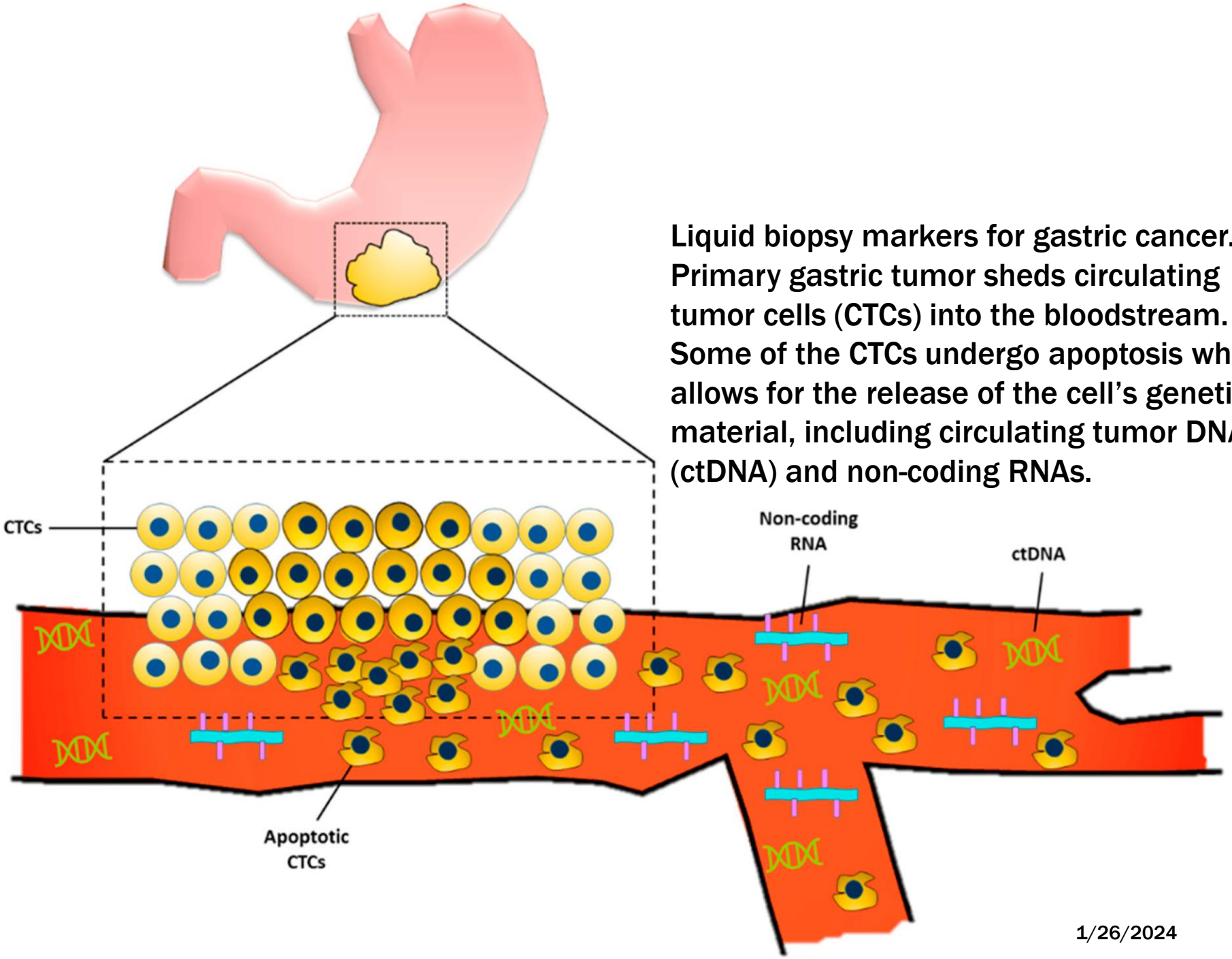
Diagnosis of EGC

Endoscopy

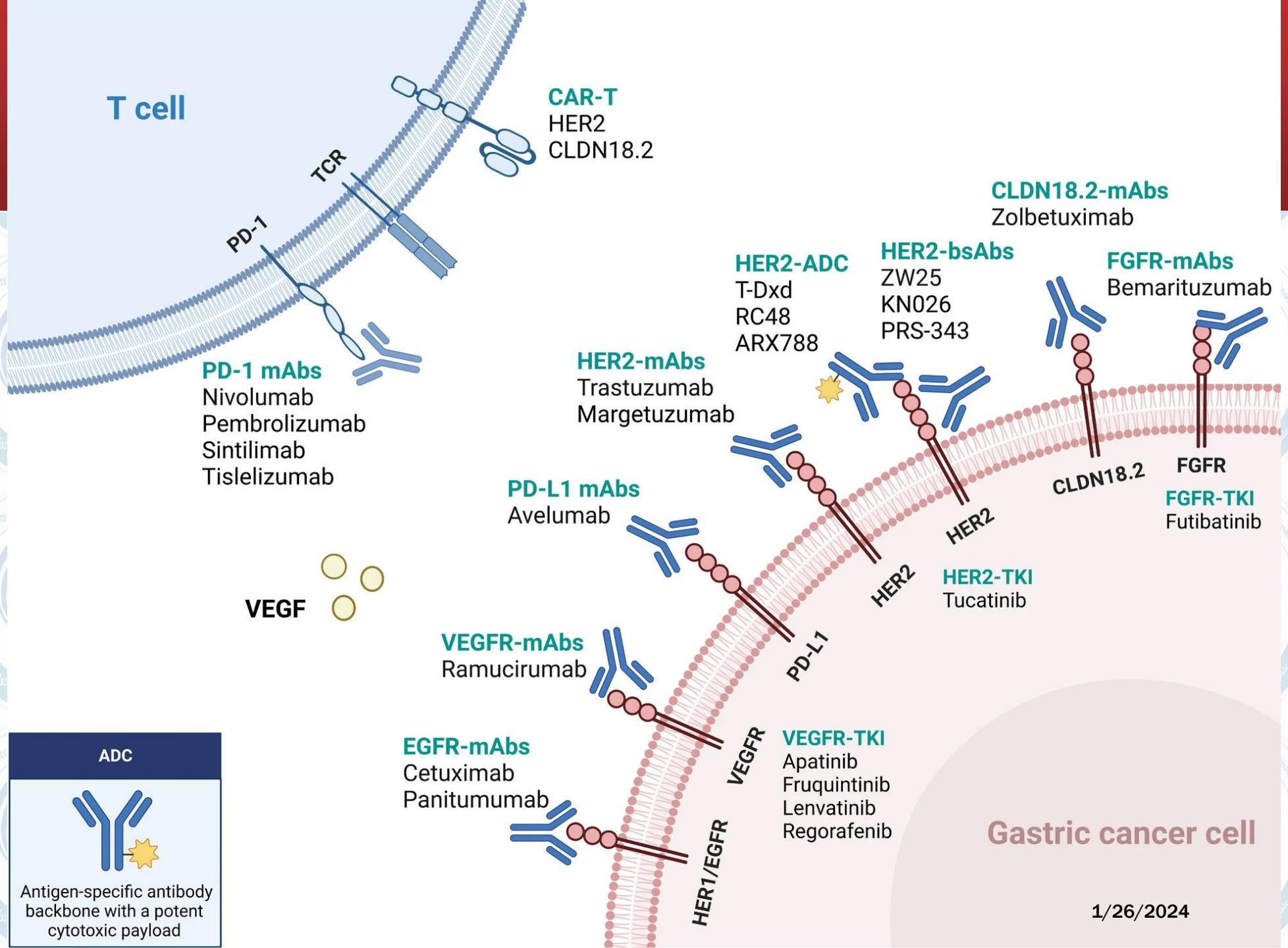
- Endoscopy & photofluorography
- Magnification chromoendoscopy
- Image-enhanced endoscopy technology
- Artificial intelligence

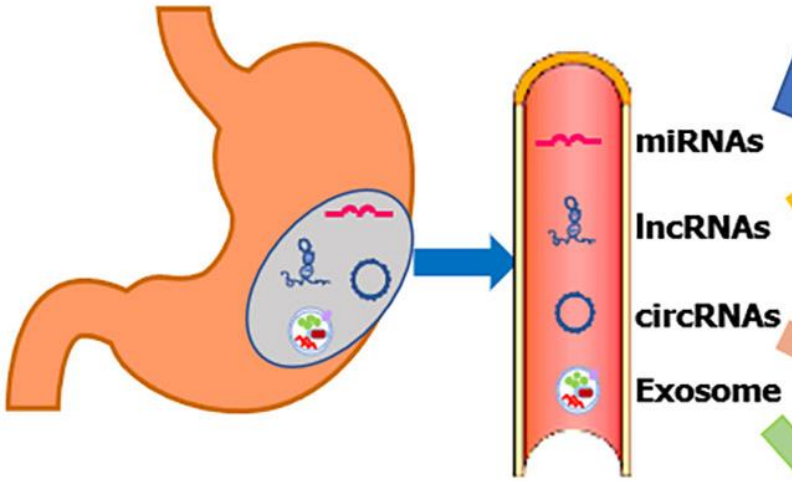
Serum

- Pepsinogen ,H. Pylori Ab
  - Low PG I:PG II ratio
- Circulating tumor cells
- Non coding RNA
  - microRNA
  - Circular RNA
- Exosomes
- Cell free DNA
- ....



Liquid biopsy markers for gastric cancer. Primary gastric tumor sheds circulating tumor cells (CTCs) into the bloodstream. Some of the CTCs undergo apoptosis which allows for the release of the cell's genetic material, including circulating tumor DNA (ctDNA) and non-coding RNAs.


T cell
CAR-T
HER2
CLDN18.2
TCR
PD-1
PD-1 mAbs
Nivolumab
Pembrolizumab
Sintilimab
Tislelizumab
CLDN18.2-mAbs
Zolbetuximab
HER2-ADC
T-Dxd
RC48
ARX788
HER2-bsAbs
ZW25
KN026
PRS-343
FGFR-mAbs
Bemarituzumab
HER2-mAbs
Trastuzumab
Margetuximab
PD-L1 mAbs
Avelumab
VEGF
HER2
CLDN18.2
FGFR
FGFR-TKI
Futibatinib
HER2
HER2-TKI
Tucatinib
PD-L1
VEGFR-mAbs
Ramucirumab
VEGFR
VEGFR-TKI
Apatinib
Fruquintinib
Lenvatinib
Regorafenib
EGFR-mAbs
Cetuximab
Panitumumab
HER1/EGFR
Gastric cancer cell
ADC
Antigen-specific antibody backbone with a potent cytotoxic payload



miRNAs

lncRNAs

circRNAs

Exosome

miRNAs expression analysis

Upregulated miRNAs
- miR-25 • miR-93 • miR-200c • miR376c
- miR-21, miR-93, miR-106a, and miR-196b
- miR-16, miR-25, miR-92a, miR-451, and miR-486-5p
- miR-4257, miR-6785-5p, miR-187-5p, and miR-5739
- miR-18a, miR-181b, and miR-335
- miRNA-3185, miRNA-6083, miRNA-6792-3p, and miRNA-659-3p

Downregulated miRNAs
- miR-214 • miR-381 • miR-551b-5p
- miR-425-5p • miR-1180-3p • miR-122-5p
- miR-24-3p and miR-4632-5p
- miRNA-936, and miRNA-1306-3p

lncRNAs expression analysis

Upregulated lnciRNAs
- ZNFX1-AS1 • LINC00978 • CTC-501O10.1
- AC100830.4 • RP11-210K20.5 • CTC-497E21.4.
- SNHG17 • PANDAR • FOXD2-AS1 • SMARCC2
- B3GALT5-AS1 • HCP5
- lnc-MB21D1-3:5, lnc-PSCA-4:2 and lnc-ABCC5-2:1

Downregulated lncRNAs
- ARHGAP27P1 • LINC00086
- C5orF66-AS1

circRNAs expression analysis

Upregulated circRNAs
- circPTPN22 • hsa_circ_0002874
- hsa_circ_0001020 • hsa_circ_0003195
- 8-circRNA biomarker panel

Down-regulated circRNAs
- hsa_circ_0000745 • hsa_circ_0001789

Exosome expression analysis

Upregulated
miRNAs; • miR-92b-3p, let-7g-5p, miR-146b-5p, and miR-9-5p
lncRNA; • HOTTIP • UEGC1 • Pcsk2-2:1 • RNA-GC1
piRNA; • piR-019308 • piR-004918 • piR-018569

Downregulated
miRNAs; • miR92a-3p • miR-590-5p
lncRNA; • GNAQ-6:1

DOI: 10.3748/wjg.v29.i17.2515

A

Chronic atrophic gastritis (CAG) suspected on white light endoscopy

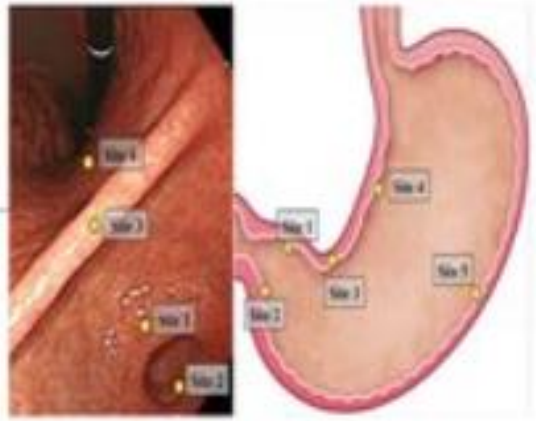
Eradicate H. pylori

Systematic endoscopy with image enhancement

Distal CAG Antrum Incisura	Low risk
Extensive CAG Corpus	High risk

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

Sydney protocol biopsies



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

CAG with dysplasia
(See guidance)

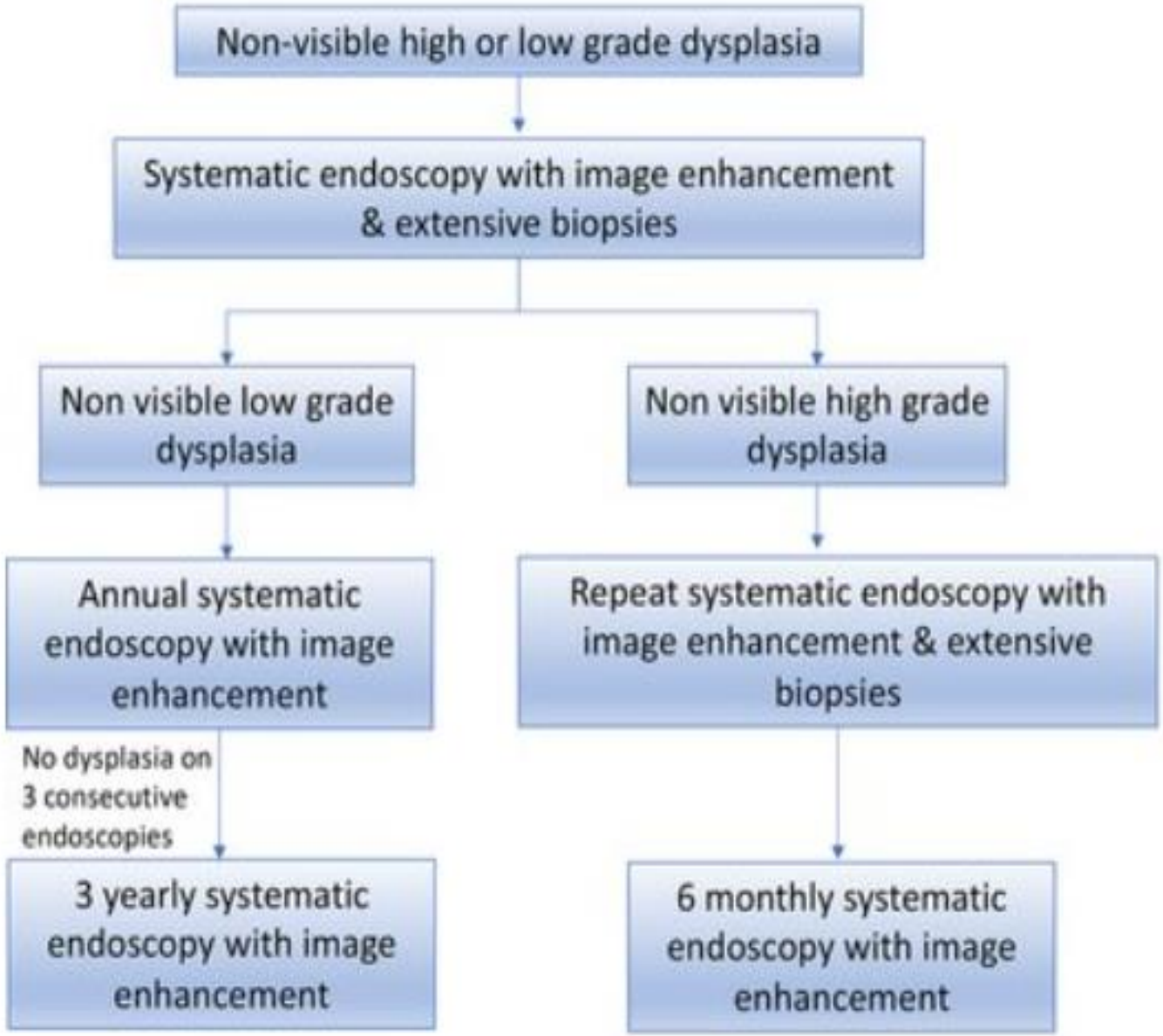
High risk CAG

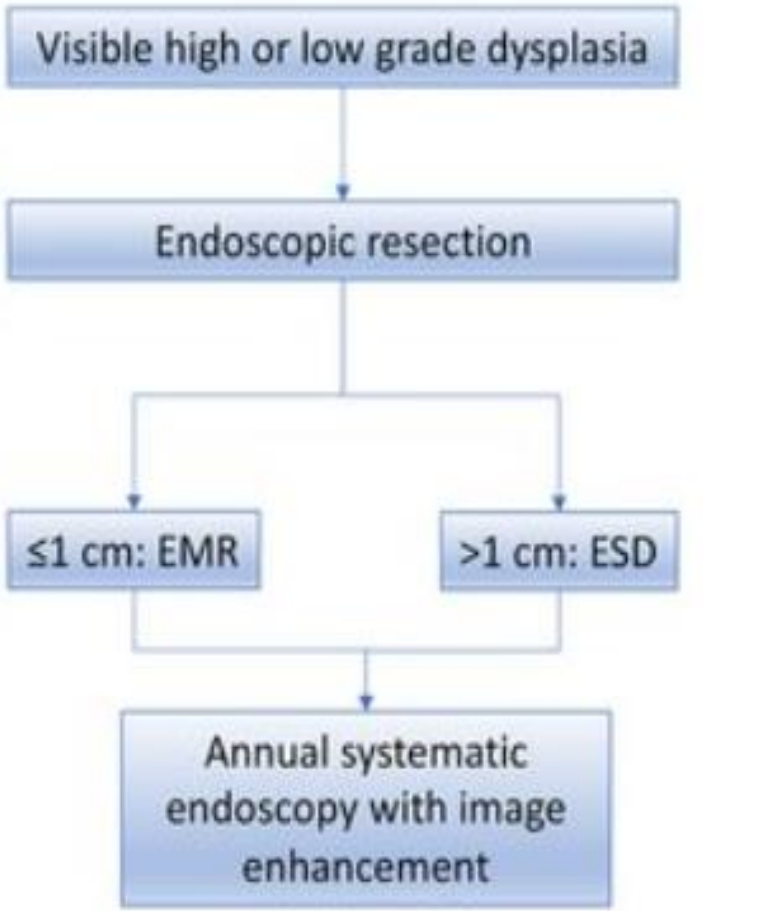
Low risk CAG

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

3 yearly endoscopic surveillance
(with image enhancement)

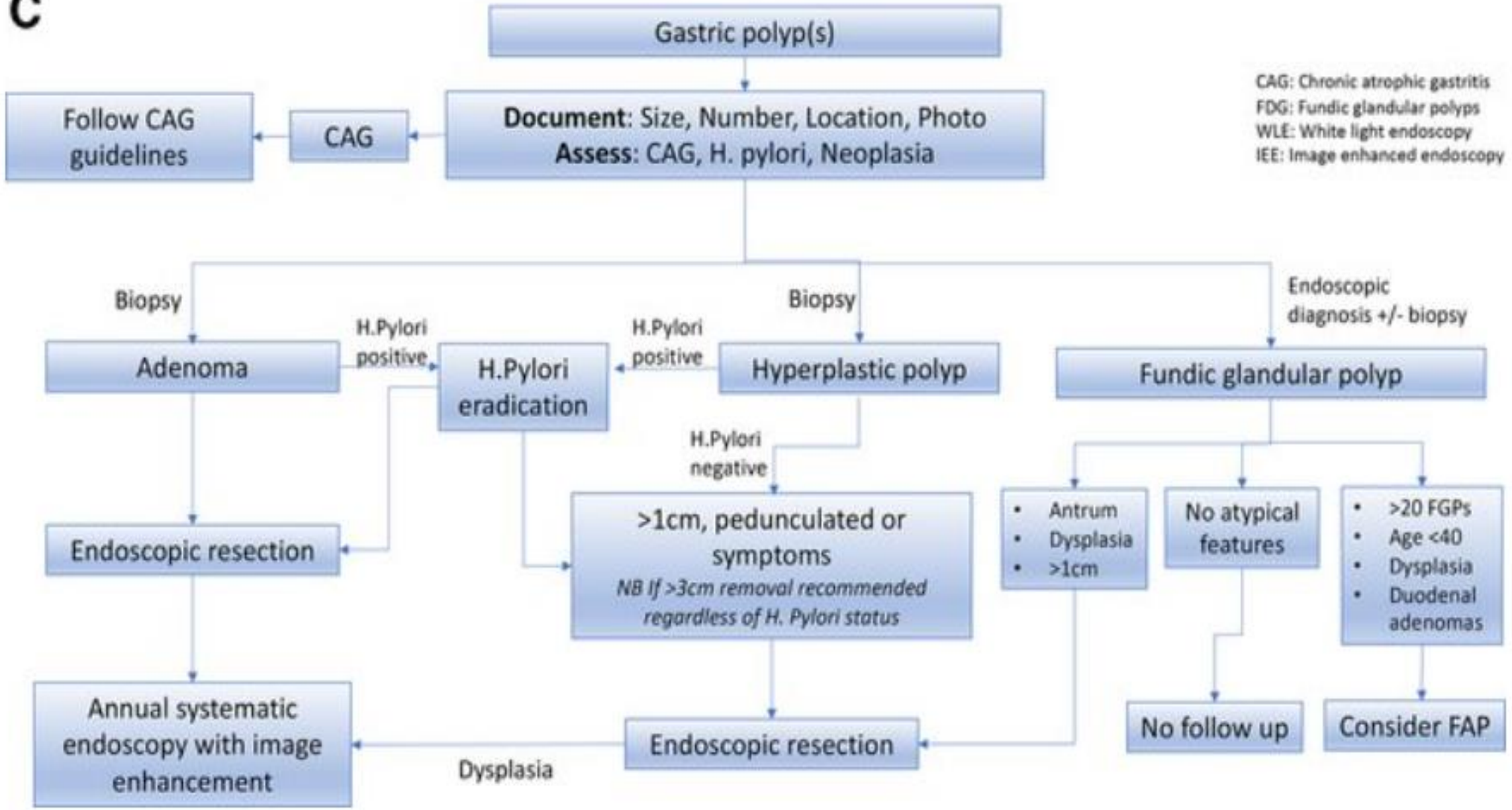
No surveillance

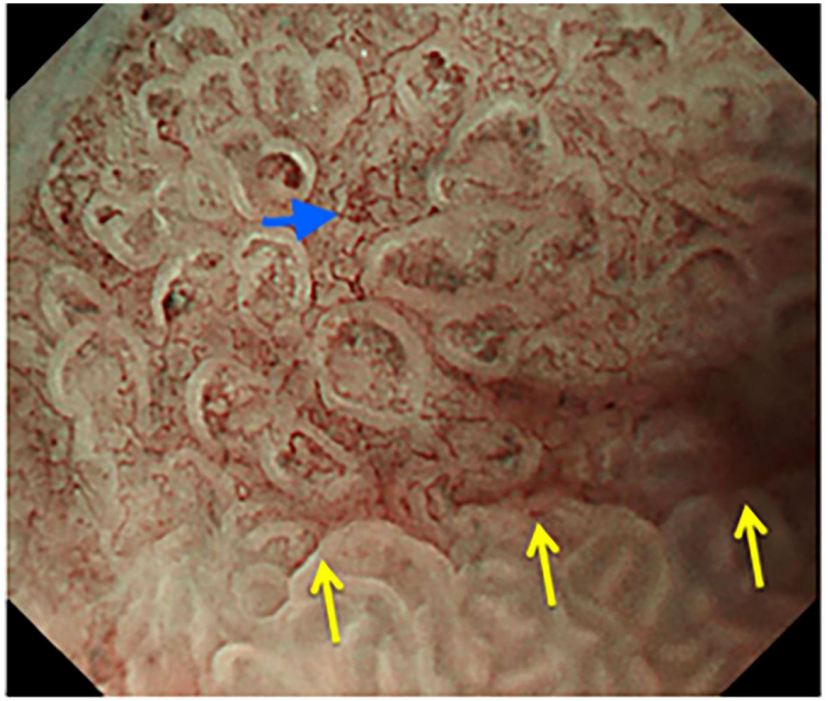


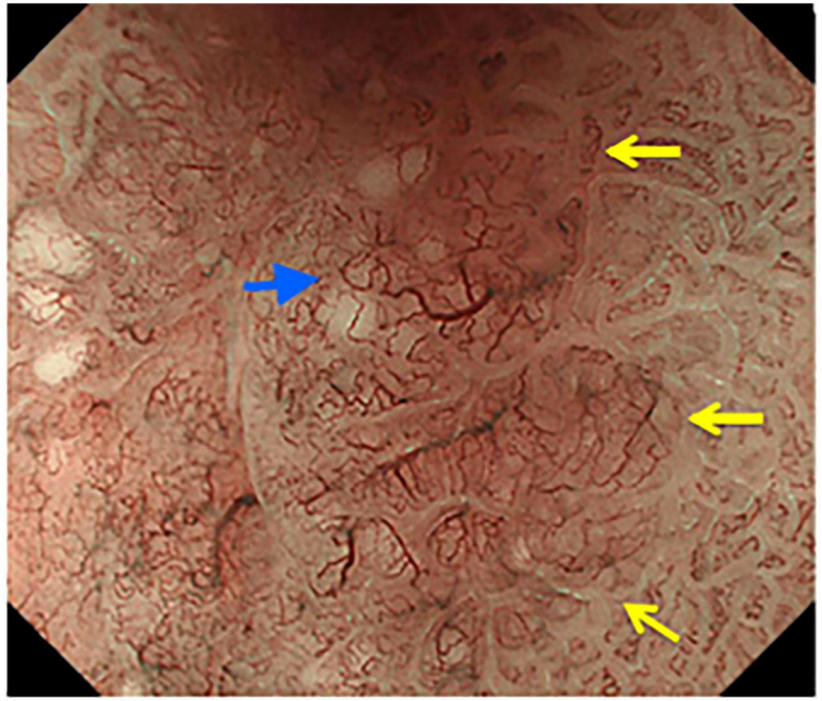


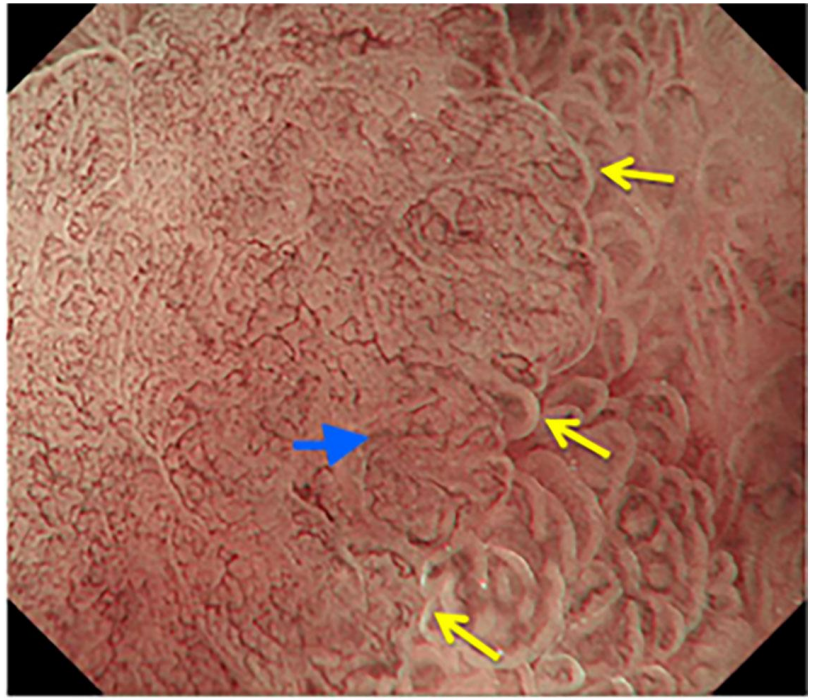
EMR: endoscopic mucosal resection
ESD: endoscopic submucosal dissection
NVLGD: non-visible low grade dysplasia
NVHGD: non-visible high grade dysplasia

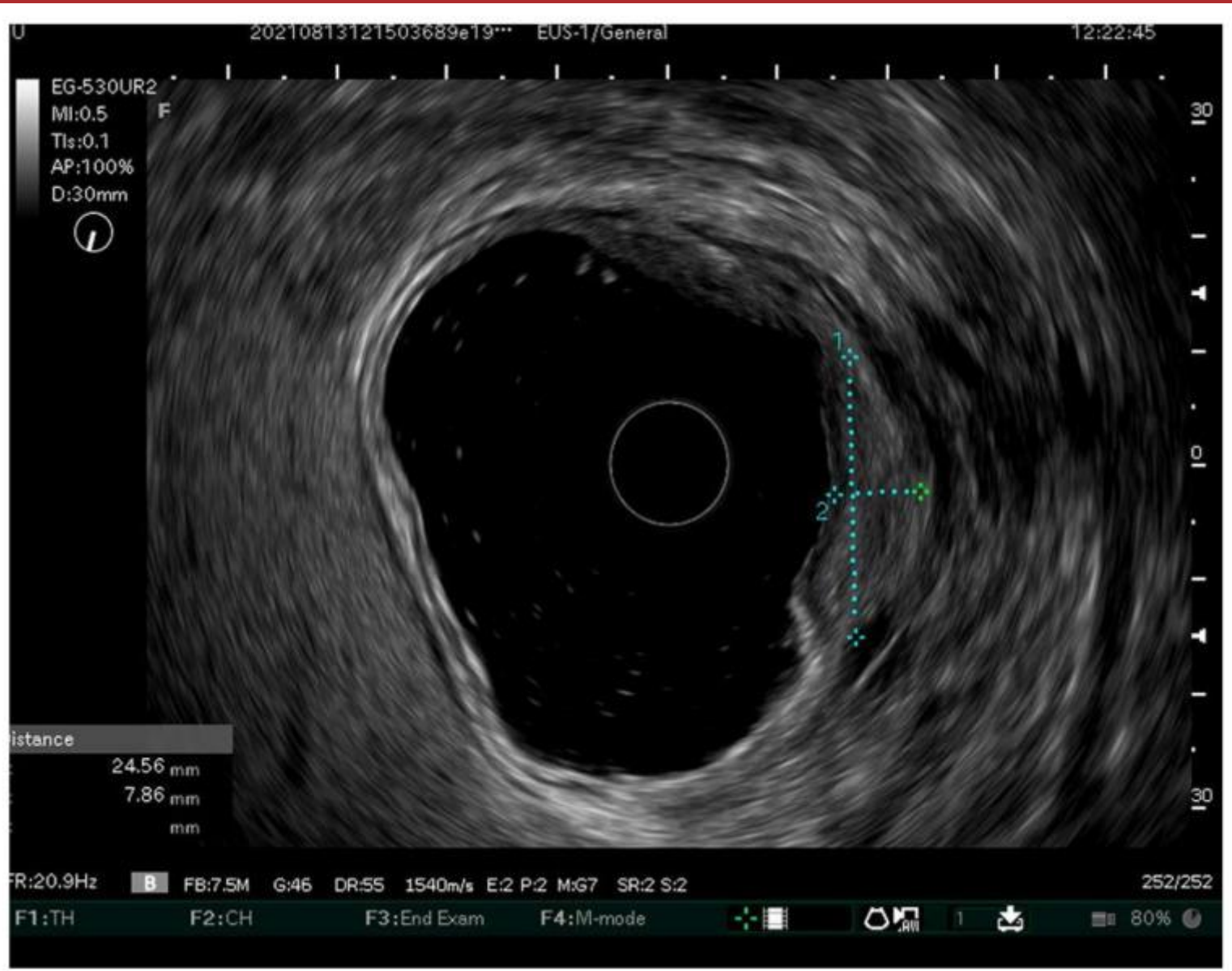
C

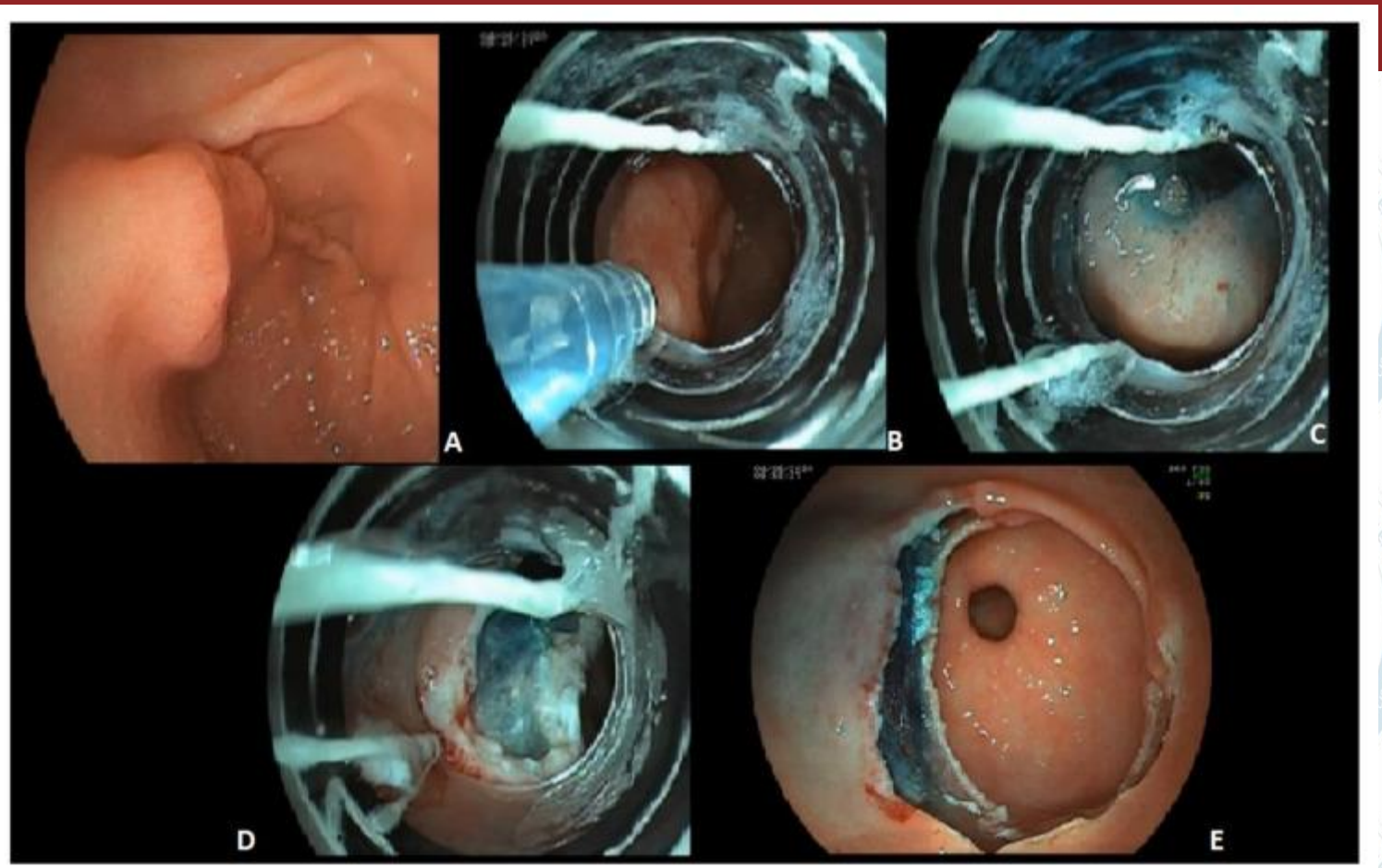

Gastric polyp(s)
Document: Size, Number, Location, Photo
Assess: CAG, H. pylori, Neoplasia
CAG
Follow CAG guidelines
CAG: Chronic atrophic gastritis
FDG: Fundic glandular polyps
WLE: White light endoscopy
IEE: Image enhanced endoscopy
Biopsy
Biopsy
Endoscopic diagnosis +/- biopsy
Adenoma
H.Pylori positive
H.Pylori eradication
H.Pylori positive
Hyperplastic polyp
Fundic glandular polyp
H.Pylori negative
Endoscopic resection
>1cm, pedunculated or symptoms
NB If >3cm removal recommended regardless of H. Pylori status
Antrum
Dysplasia
>1cm
No atypical features
>20 FGPs
Age <40
Dysplasia
Duodenal adenomas
Annual systematic endoscopy with image enhancement
Dysplasia
Endoscopic resection
No follow up
Consider FAP

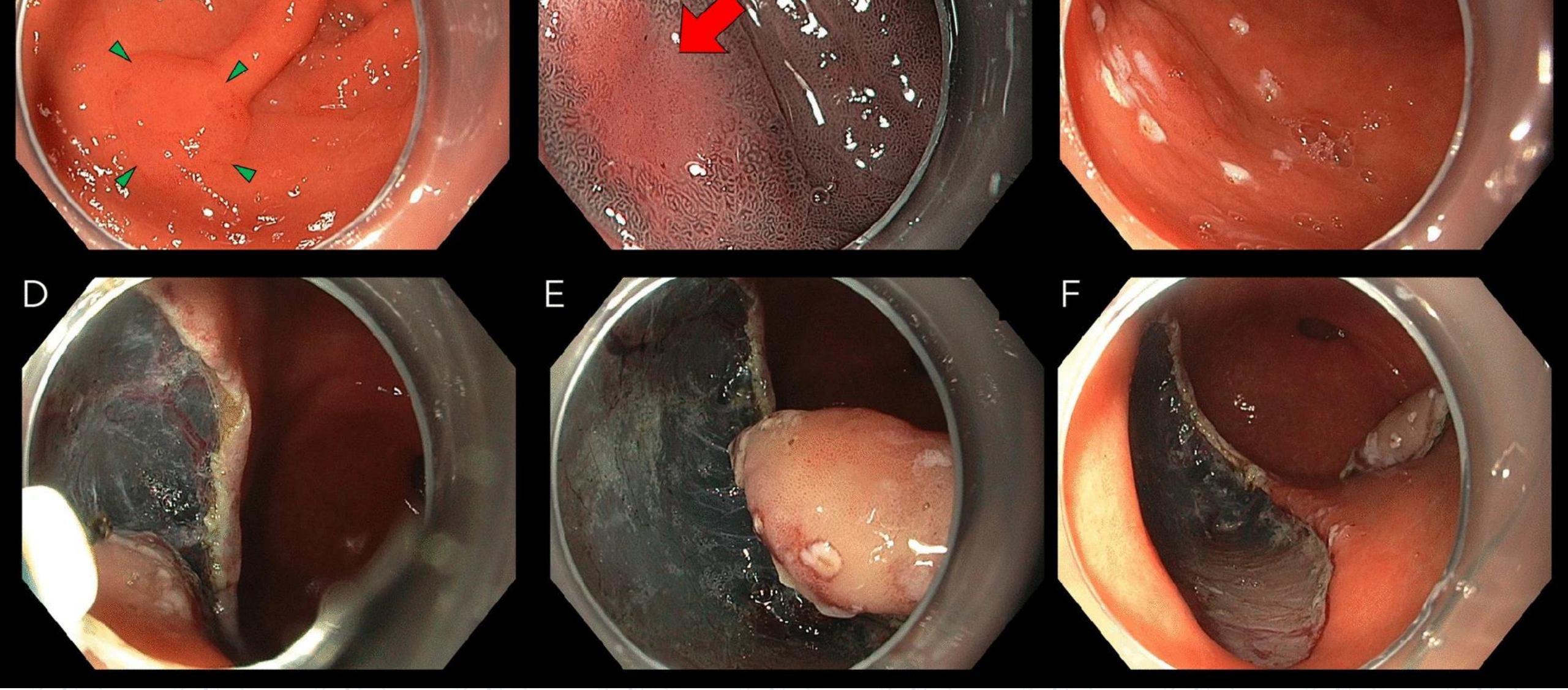


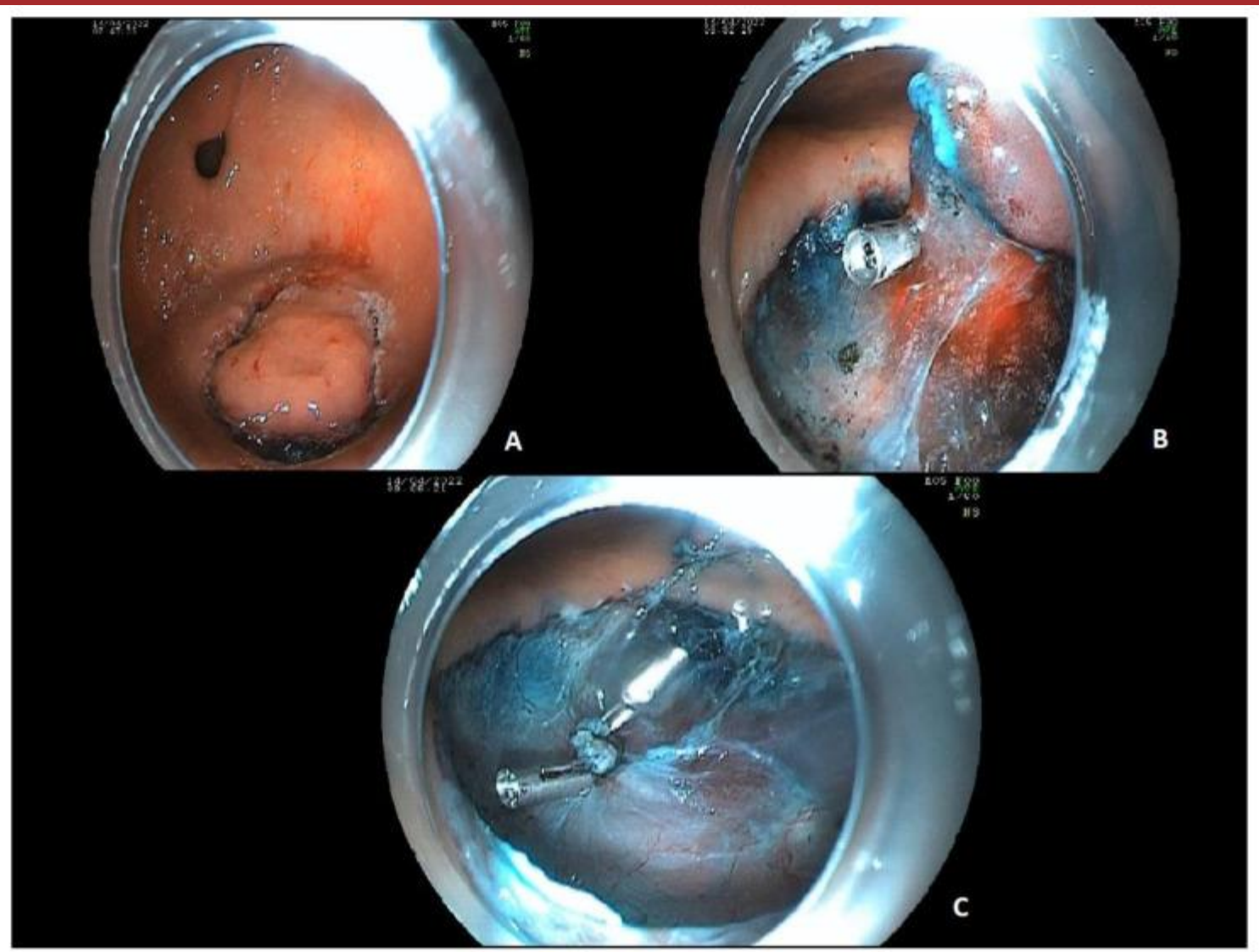





EUS-1/General
12:22:45
EG-530UR2
MI:0.5
TIs:0.1
AP:100%
D:30mm
F
30
0
30
1
2
istance
24.56 mm
7.86 mm
mm
FR:20.9Hz
B
FB:7.5M
G:46
DR:55
1540m/s
E:2 P:2 M:G7
SR:2 S:2
252/252
F1:TH
F2:CH
F3:End Exam
F4:M-mode
80%


A
B
C
D
E


D
E
F


A
B
C

Risk factors	OR	95% CI
Clinical variables		
Male sex	1.25	1.03–1.52
Cardiopathy	1.54	1.05–2.25
Antithrombotics	1.63	1.30–2.03
Cirrhosis	1.76	1.14–2.73
Chronic kidney disease	3.38	2.31–4.97
Lesion characteristics		
Flat/depressed morphology	1.43	1.12–1.84
Carcinoma (vs. dysplasia)	1.46	1.12–1.91
Ulceration	1.64	1.21–2.21
Localization in the lesser curvature	1.74	1.10–2.73
Tumour size >20 mm	2.70	1.44–5.06
Procedural/pharmacological variables		
Procedure duration >60 min	2.05	1.19–3.55
H_2RA (vs. PPI)	2.13	1.21–3.74
Resected size >30 mm	2.85	1.40–5.77

Risk Factors for Post Procedural Bleeding After ESD

5.1% risk PPB

Second look endoscopy was not associated with lower PPB (ORbleeding 1.34, 95% CI 0.85–2.12)

>50% of bleeding occur before second-look endoscopy

Prophylactic hemostasis on second-look endoscopy is not capable of significantly reducing PPB.

Gastro intest Endosc. 2016 Oct;84(4):572–86.

- 20% of the lesions ESD resected do not meet curative criteria
- EUS did not improve the selection criteria

EUS for staging of EGC

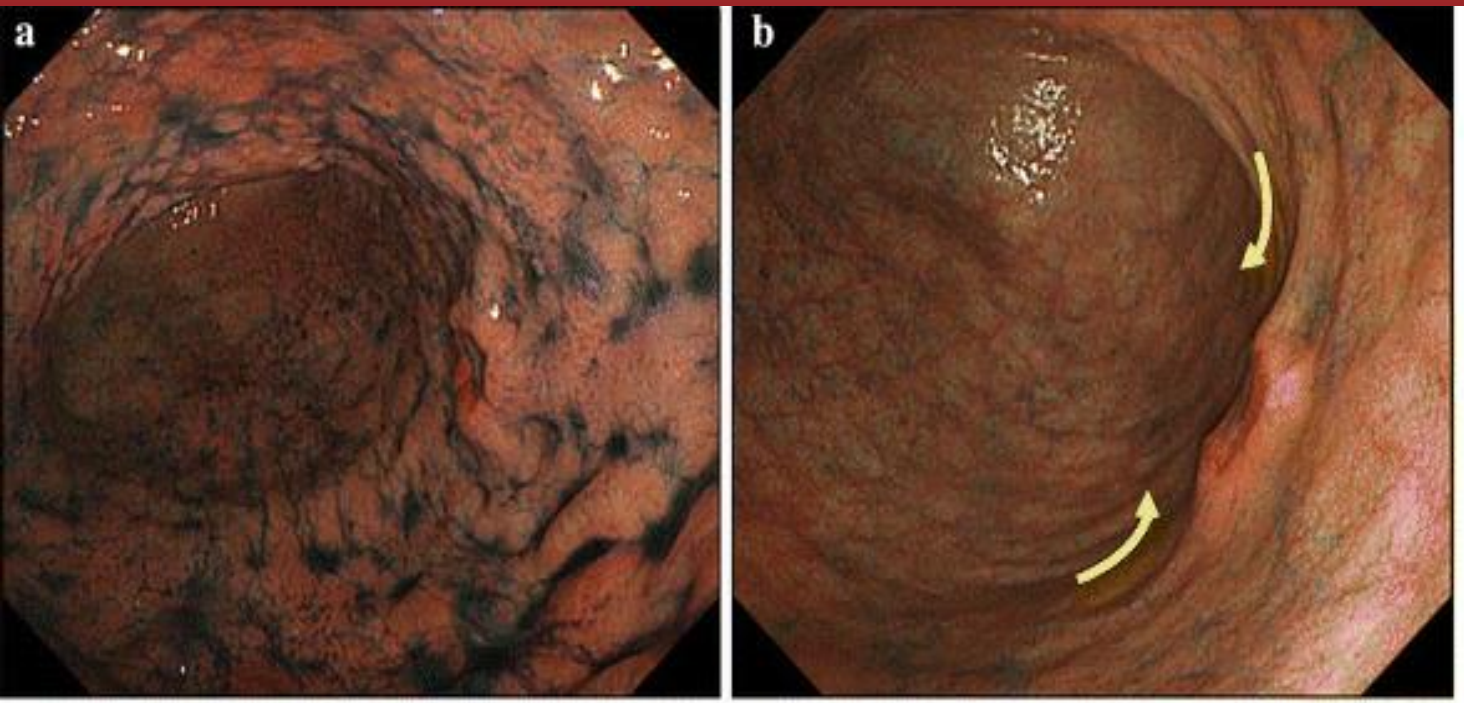
The overall accuracy of staging

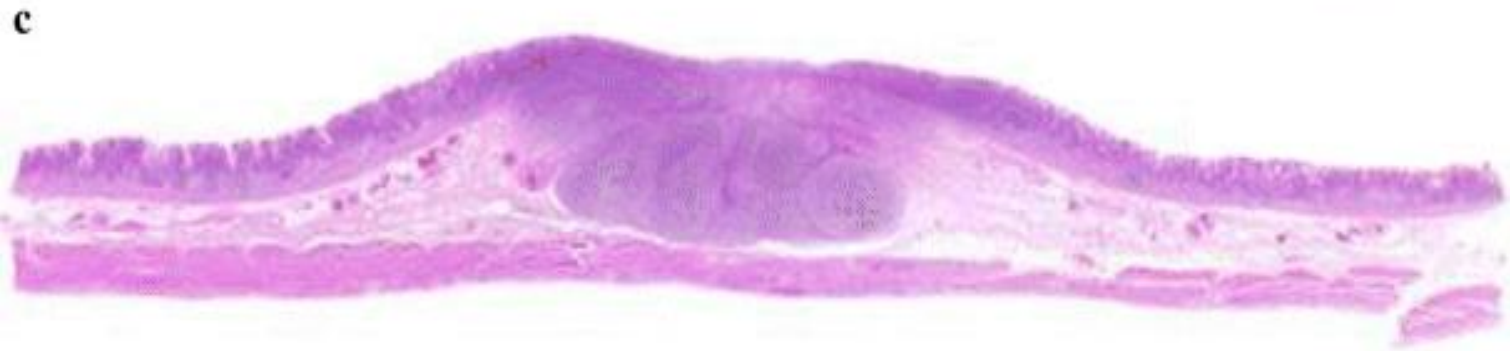
- EUS : 67.4 % (644 / 955)
- Conventional endoscopy : 73.7 % (704 / 955) (P < 0.001).
- Miniprobe EUS vs radial EUS : (79.5 % vs. 59.6 %, P < 0.001), but did not differ significantly from that of conventional endoscopy (79.0 %).

Endoscopy . 2010 Sep;42(9):705-13

Conventional white-light endoscopy should be used for determining the depth of invasion of early gastric cancer. If this is difficult, EUS may be a useful adjunctive diagnostic tool.

Guidelines for endoscopic diagnosis of early gastric cancer. Digestive Endoscopy, 32: 663-698.





The “non-extension sign”

Localized increase in thickness and rigidity due to deep submucosal invasion.

Highly useful diagnostic marker, with 92 % sensitivity and 97.7 % specificity for diagnosing gastric SM-d (depth of 500 μm or more) cancer.

Can only be seen when the gastric wall is strongly distended

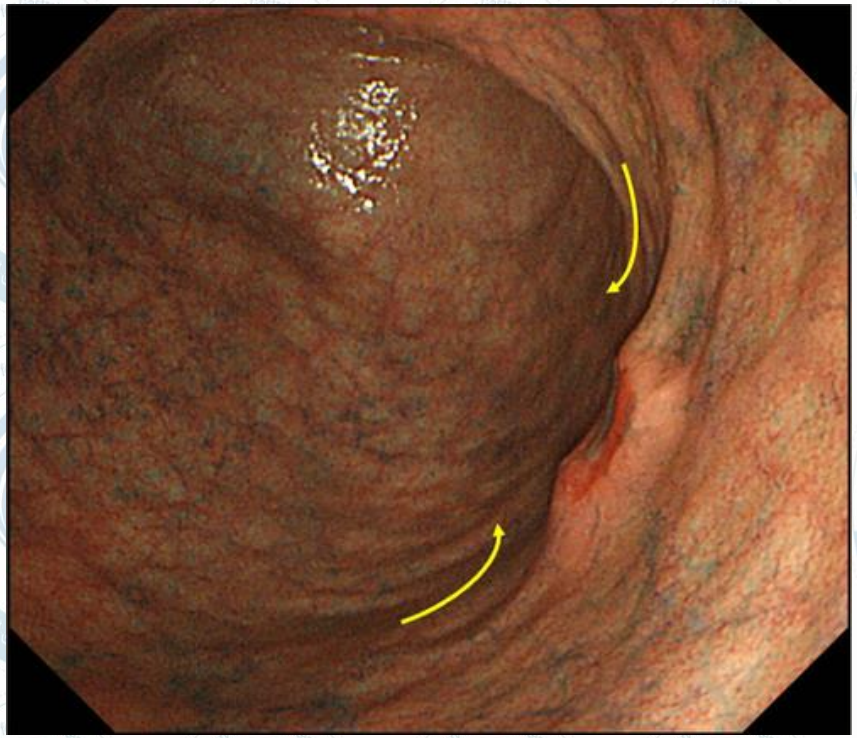
The area with invasion to the deep SM can be seen as a trapezoid elevation with elevation of the surrounding mucosa.

Gastric Cancer . 2017 Mar;20(2):304-313

Is this pt candidate for endoscopy Rx

T1a/ T1b , depth of invasion of cancers at least 0.5 mm

- **Hypertrophy or fusion of concentrated folds**
- **Tumor size at least 30 mm**
- **Marked redness**
- **Irregular surface**
- **Marginal elevation Submucosal tumor-like raised margins**
- **Non-extension sign**



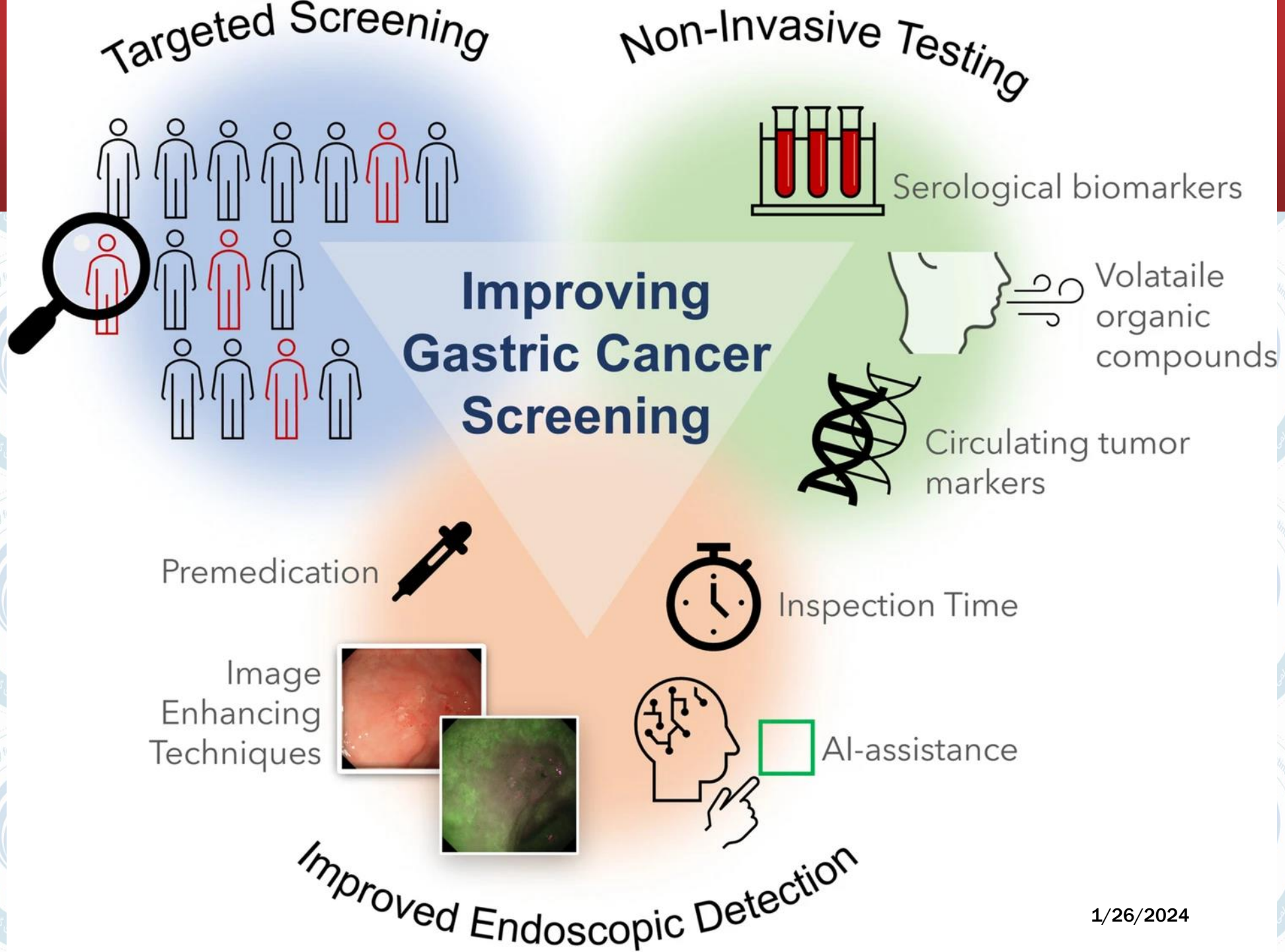
Conventional endoscopy may be superior to EUS (73.7% vs. 67.4%, P < 0.001) in detecting deep invasion

Endoscopy . 2010 Sep;42(9):705-13.

Dig Dis . 2019;37(3):201-207

Main features	Low risk (curative)	High risk (noncurative)
R0, intramucosal, well to moderately differentiated	– any size without ulceration, or – ≤30 mm with ulceration	– >30 mm with ulceration
R0, SM1, well to moderately differentiated	– ≤30 mm and – no lymphovascular invasion and – no ulcers	– >30 mm or – lymphovascular invasion or – with ulceration
R0, intramucosal, poorly differentiated	– ≤ 20 mm and – no lymphovascular invasion and – no ulcers	– >20 mm or – lymphovascular invasion or – with ulceration

Ulceration
Size>30 mm
Poorly differentiated


Targeted Screening
Non-Invasive Testing
Serological biomarkers
Volataile organic compounds
Circulating tumor markers
Improving Gastric Cancer Screening
Premedication
Inspection Time
Image Enhancing Techniques
AI-assistance
Improved Endoscopic Detection

Digestive Endoscopy 2020; **32**: 663–698 doi: 10.1111/den.13684

Guidelines

Guidelines for endoscopic diagnosis of early gastric cancer

Kenshi Yao, Noriya Uedo, Tomoari Kamada, Toshiaki Hirasawa, Takashi Nagahama, Shigetaka Yoshinaga, Masashi Oka, Kazuhiko Inoue, Katsuhiro Mabe, Takashi Yao, Masahiro Yoshida, Isao Miyashiro, Kazuma Fujimoto and Hisao Tajiri

Japan Gastroenterological Endoscopy Society, Tokyo, Japan

Gastric Cancer (2017) 20 (Suppl 1):S28–S38
DOI 10.1007/s10120-016-0680-7

CrossMark

REVIEW ARTICLE

Development of an e-learning system for teaching endoscopists how to diagnose early gastric cancer: basic principles for improving early detection

Kenshi Yao[1] · Noriya Uedo[2] · Manabu Muto[3] · Hideki Ishikawa[4]

Conclusion

- GC would be a growing problem in future both in younger and elderly
- Risk stratification for FU of precancerous lesions could guide need and frequency of surveillance
- High quality endoscopy can diagnose EGC
- EGC can be treated endoscopically but there is need to avoid futile treatments