Endoscopy in gastric cancer: New imaging techinques, new treatment modalities (EMR, ESD)

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

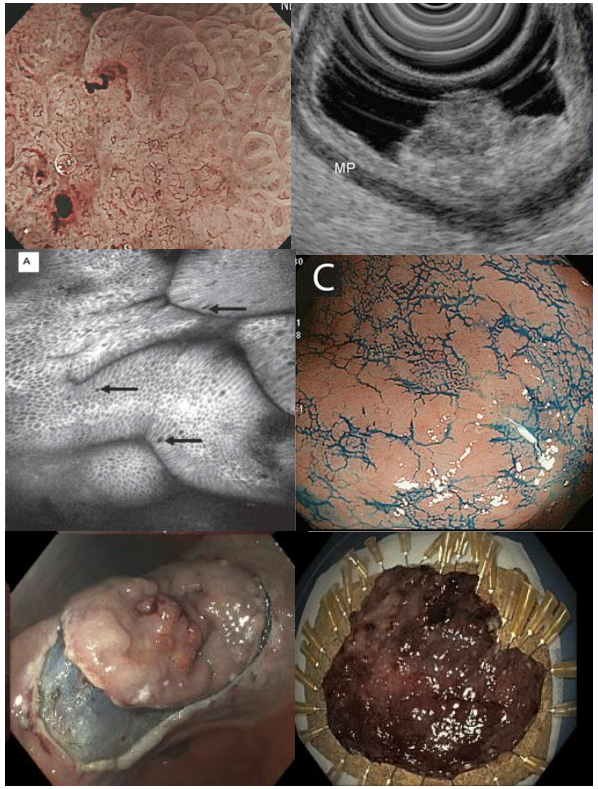
Disclosure of interest

“No conflict of interests”

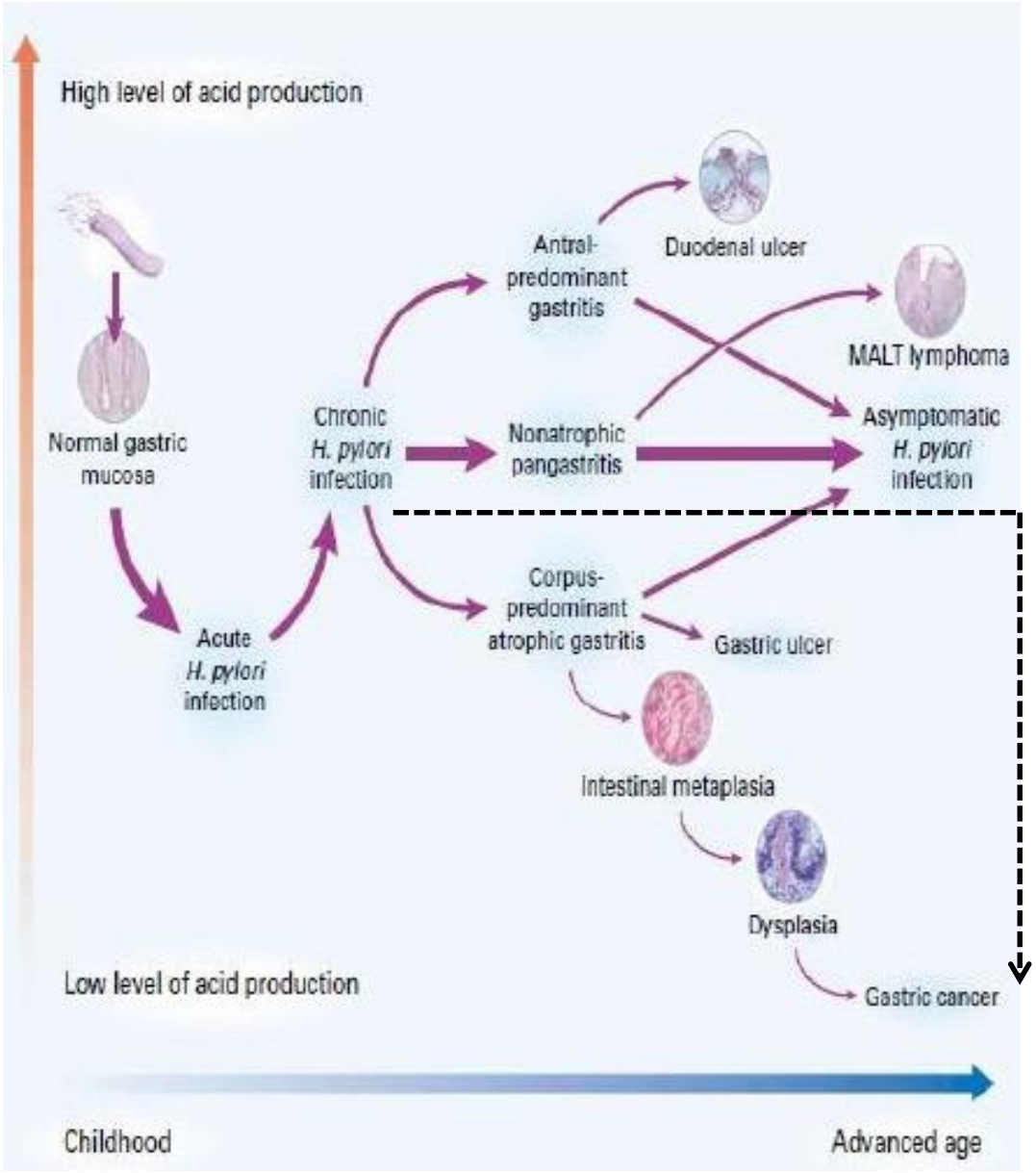
Role of endoscopy in gastric cancer:

1. **SCREENING**
2. **DIAGNOSIS**
3. **STAGING**
4. **TREATMENT**

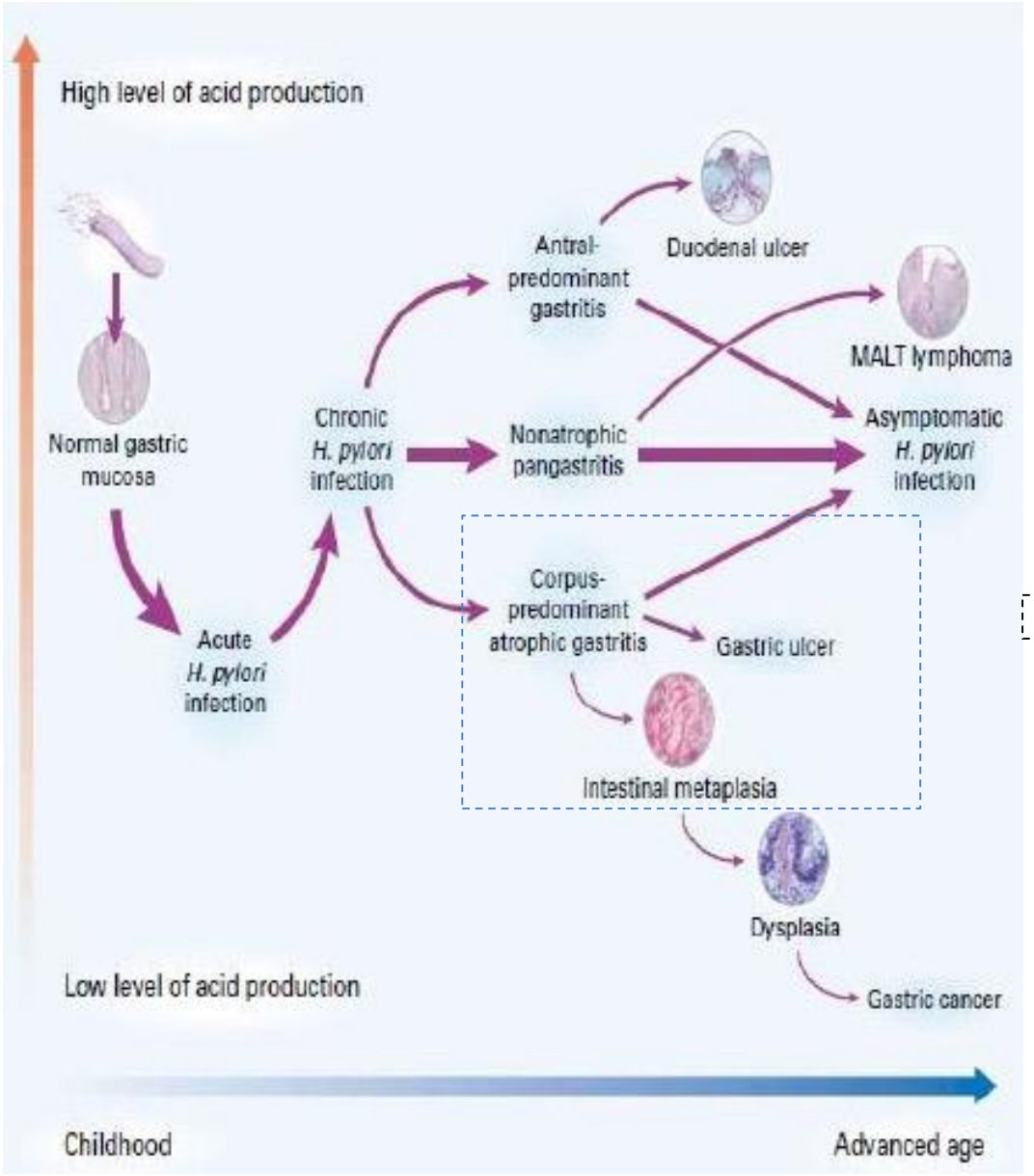
New imaging techinques



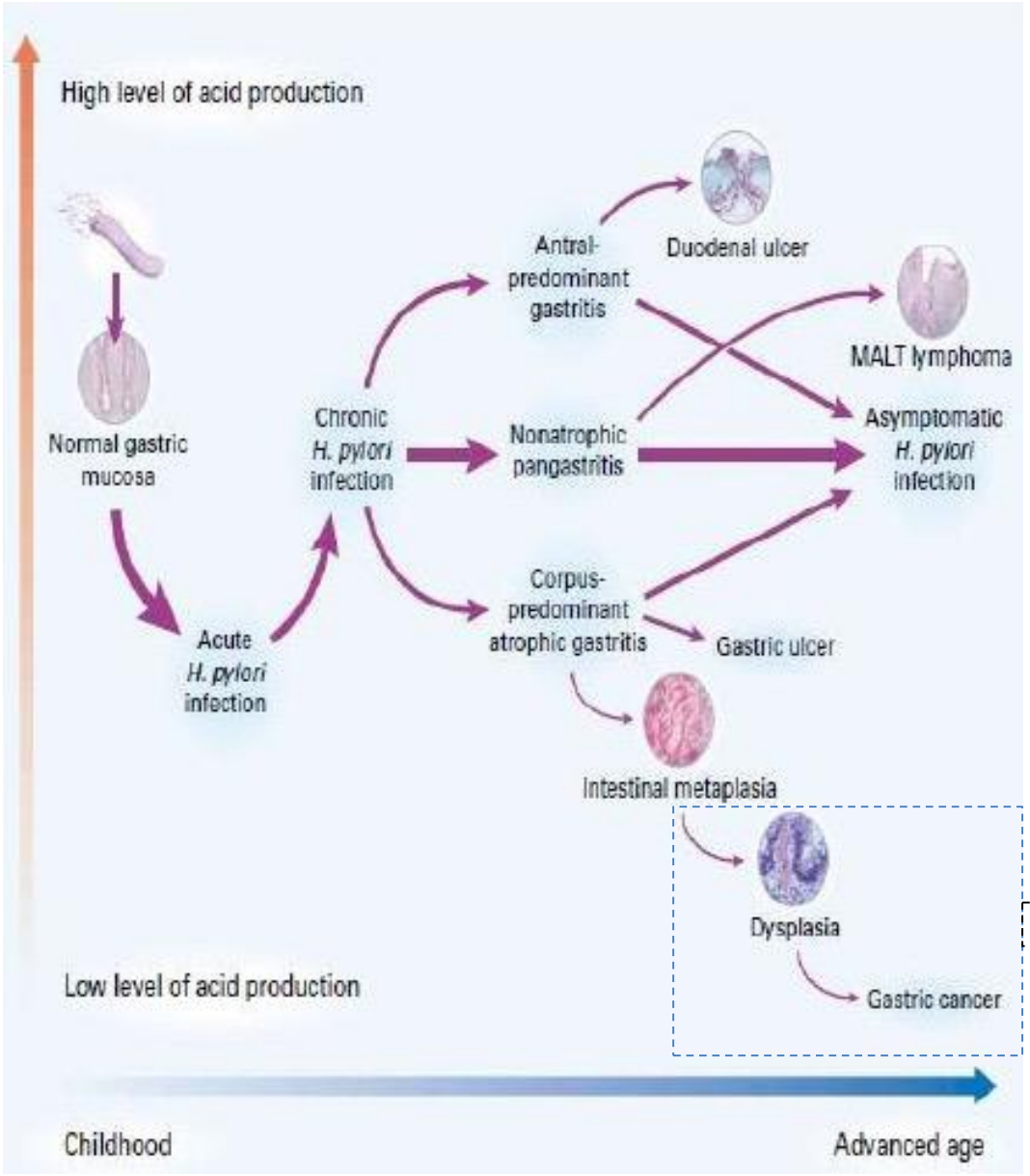
1.Screening



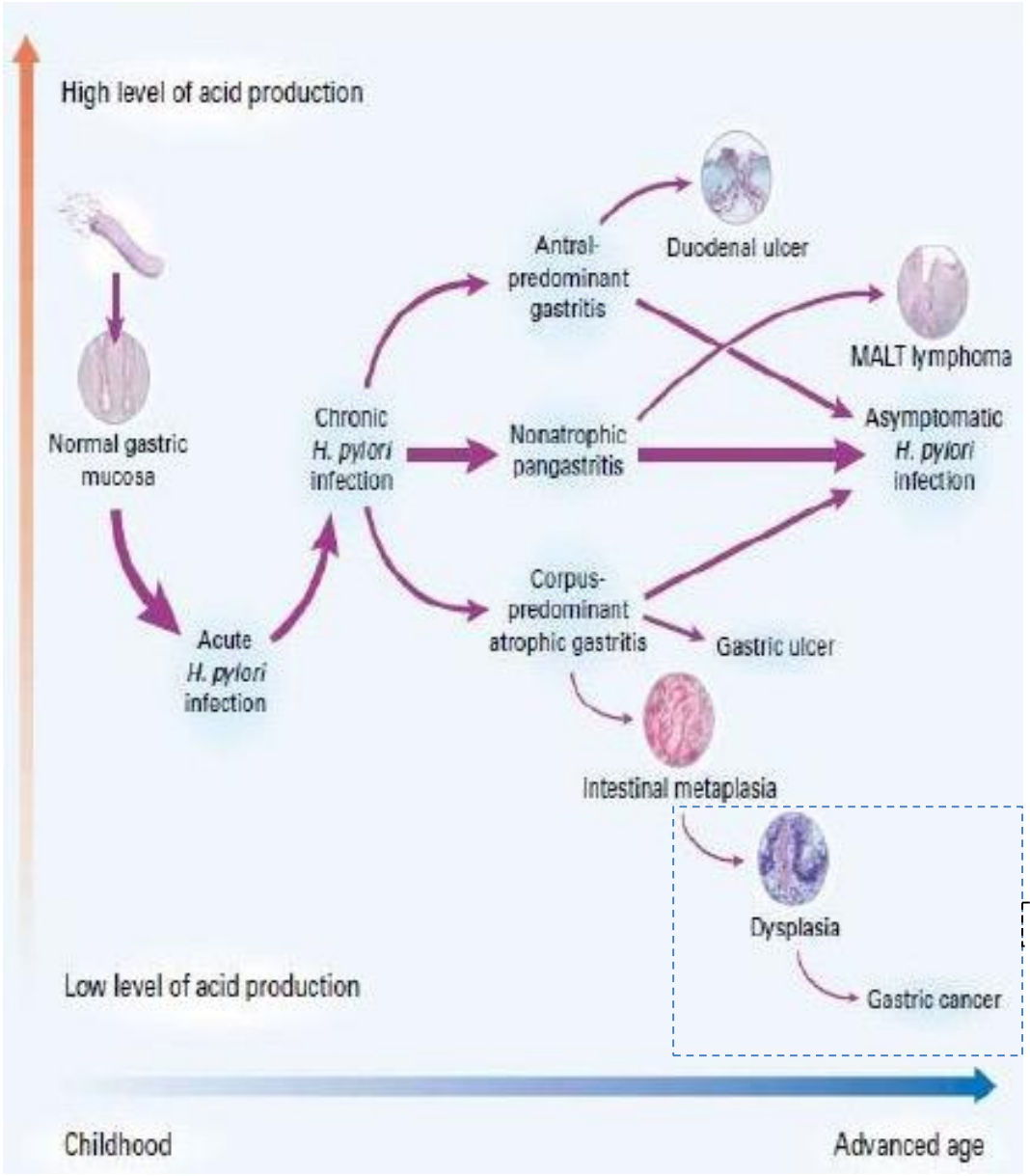
Correa Model of carcinogenesis



Preneoplastic conditions

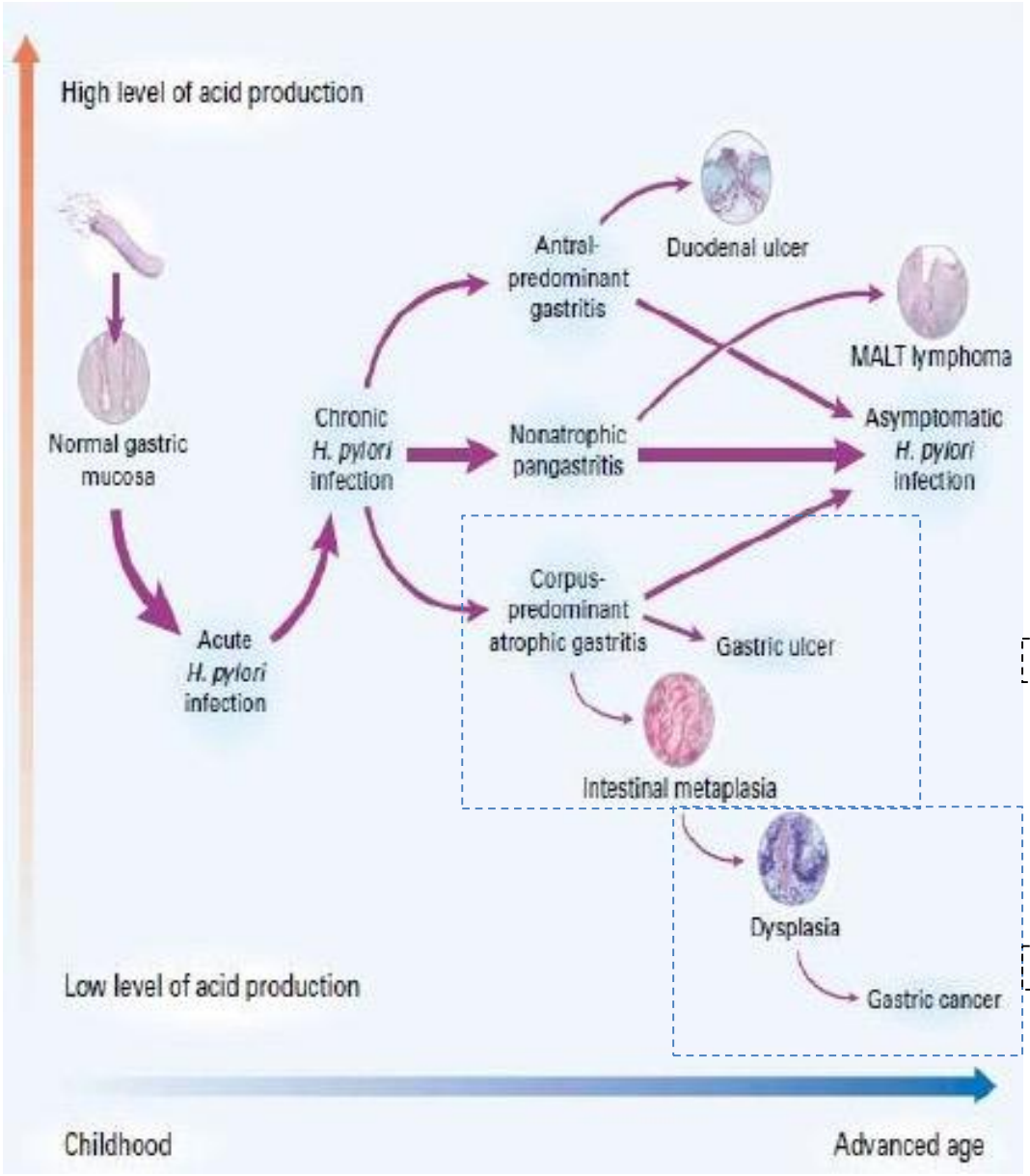


Neoplastic lesions



"Early detection and tratment is the only way to reduce mortality"

Importance of endoscopy



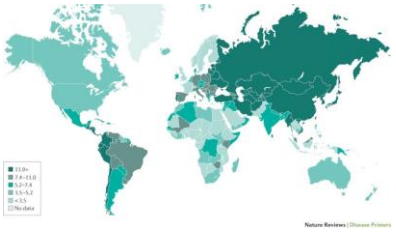
screening

Preneoplastic conditions

surveillance

Neoplastic lesions

"Early stages"



SCREENING POPULATION?

1º *screening*

PRENEOPLASTIC CONDITIONS?

2nd *surveillance*

NEOPLASTIC LESIONS?

Screening and surveillance for gastric cancer in the United States: Is it needed? Kim. GH. GIE 2016

SCREENING POPULATION

Inmigrants (high risk regions) Familiy History

"Oportunistic screening" (EGD endoscopies)

1º

screening

PRENEOPLASTIC CONDITIONS

Chronic Atrophic Gastritis (CAG) Gastrointestinal metaplasia (GIM)

2nd

surveillance

NEOPLASTIC LESIONS

Displasia (Intraepithelial neoplasia) Adenocarcinoma

Detection of EGC will improve the survival rate of this cancer.

Screening and surveillance for gastric cancer in the United States: Is it needed? Kim. GH. GIE 2016

SCREENING POPULATION

PRENEOPLASTIC CONDITIONS

NEOPLASTIC LESIONS

Eastern Countries (Japan, Korea): 60% of gastric cancers are EGC (early gastric cancer)

Western Countries: Only less than 10%.

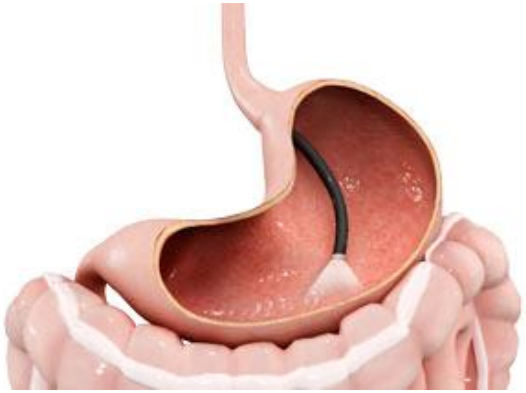
1º

2nd

Is time for new imaging techinques?

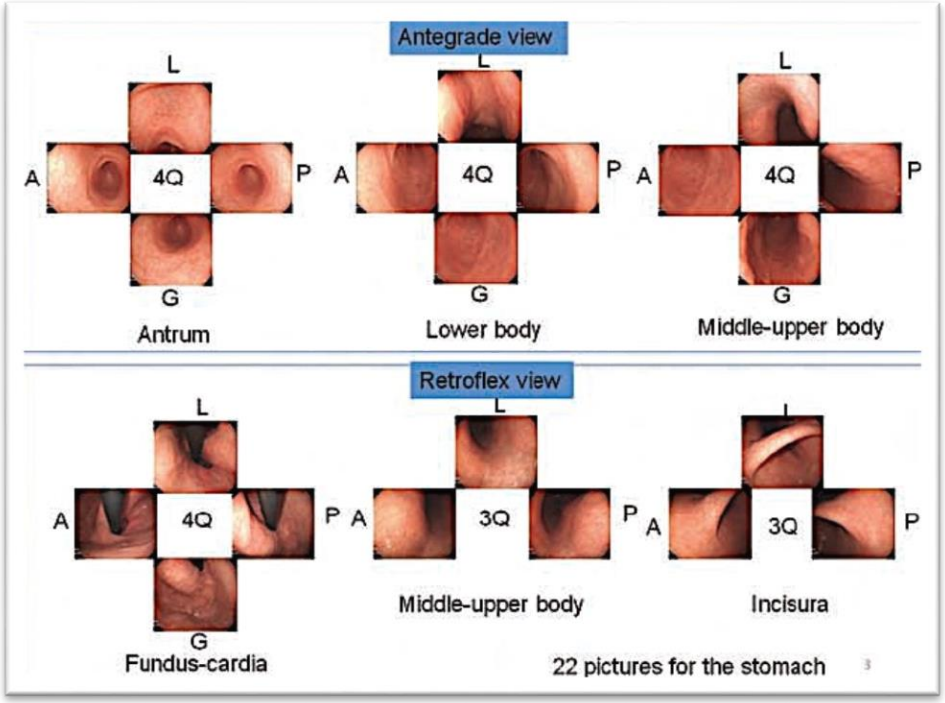
Screening and surveillance for gastric cancer in the United States: Is it needed? Kim. GH. GIE 2016

first step: is high-quality endoscopy: Rutine Conventional With Light Endoscopy (WLE)



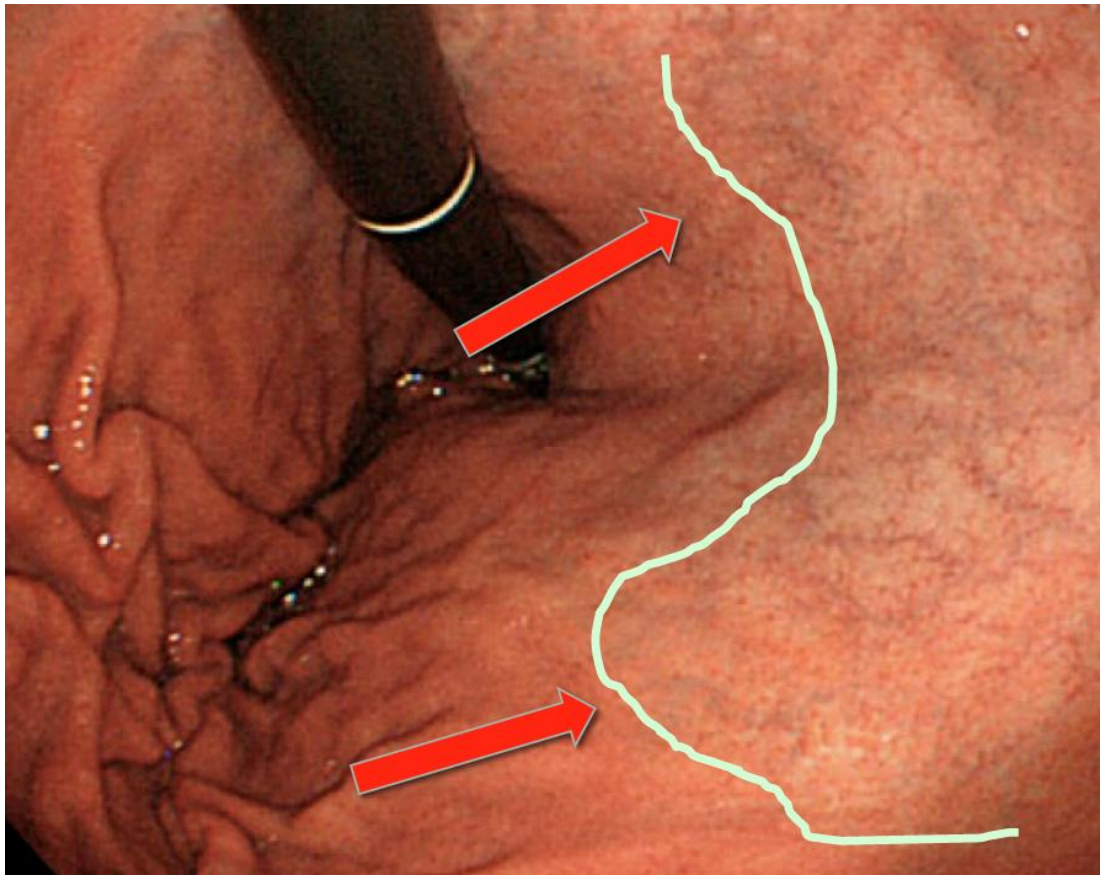
- 7 minutes
- Adequate preparation
- Insuflation
- Image documentation
- Avoid Blind Areas (SSS protocol)

SSS protocol



Performance measures for upper gastrointestinal endoscopy: A European Society of Gastrointestinal Endoscopy quality improvement initiative. Bisschops et al.2016

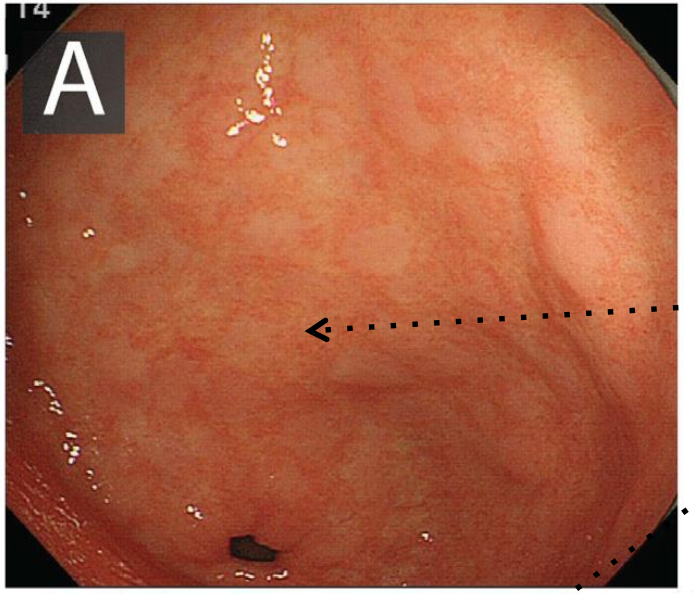
WHITE LIGHT ENDOSCOPY (WLE): Chronic atrophic gastritis



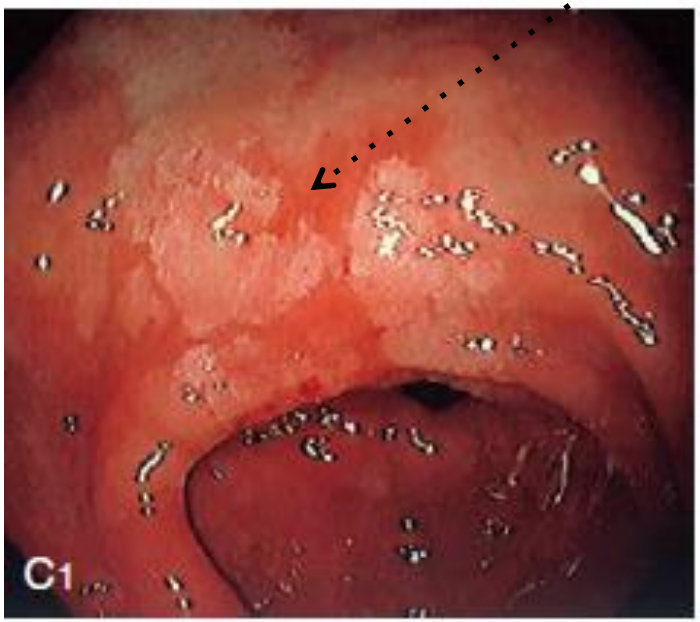
- **Loss of gastric folds**
- **Mucosal pallor**
- **Increase visibility of mucosal vessels**

ATLAS OF CLINICAL GASTROINTESTINAL ENDOSCOPY Third edition C. Mel Wilcox

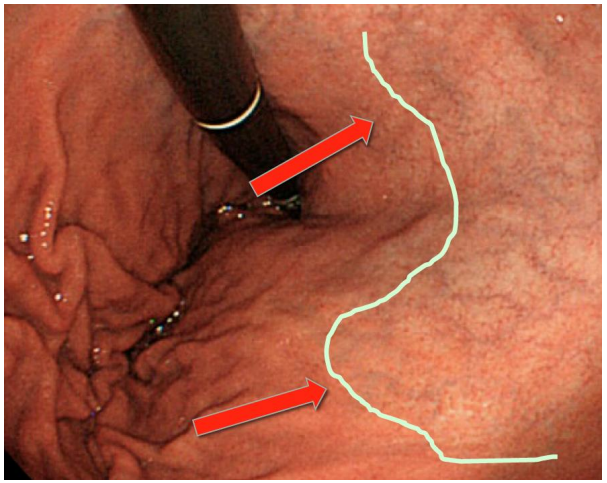
WITHE LIGHT ENDOSCOPY (WLE): GASTRIC INTESTINAL METAPLASIA (GIM)



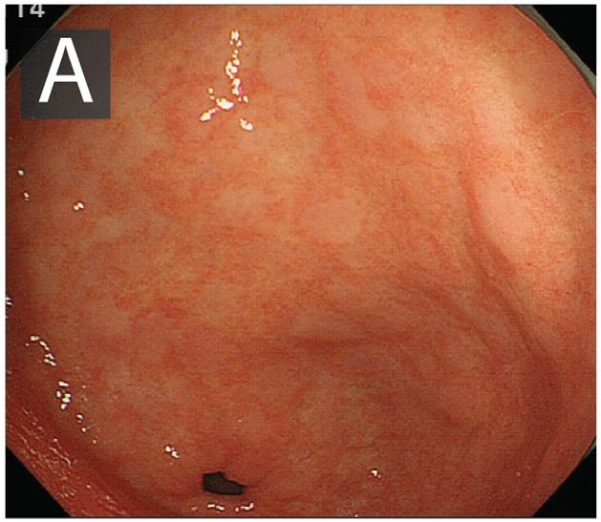
- white plaquelike lesions with a verrucous appearance



White light endoscopy in the diagnosis of Chronic atrophic gastitis and intestinal metaplasia



Crhonic atrophic gastritis



Intestinal metaplasia

- ❑ Poor sensitivity and specificity
- ❑ Poor interobserver agreement
- ❑ Poor correlation with histology

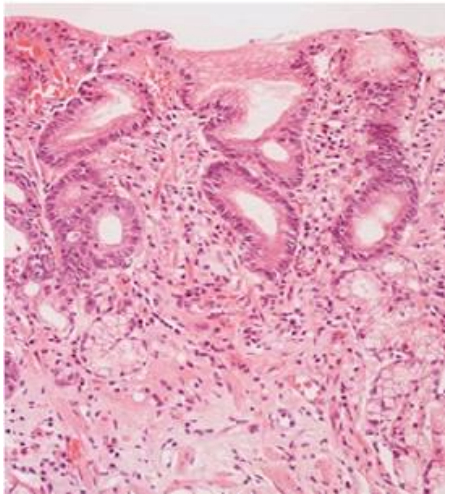
Diagnosis and staging

Endoscopy

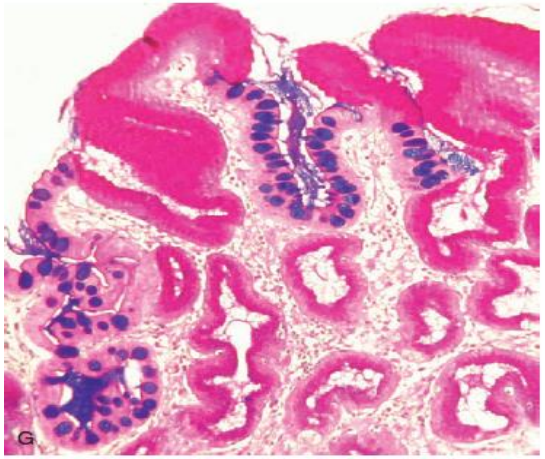
4. Conventional white light endoscopy cannot accurately differentiate and diagnose preneoplastic gastric conditions (evidence level2++, recommendation grade B) [agree 94% (vote: a, 46%; b, 24%; c, 24%; d, 4%; e, 2%)].

Waddinham W. F1000Research 2018; Dinis-Ribeiro M, Endoscopy 2012

White light endoscopy in the diagnosis of Chronic atrophic gastirtis and intestinal metaplasia



Crhonic atrophic gastritis

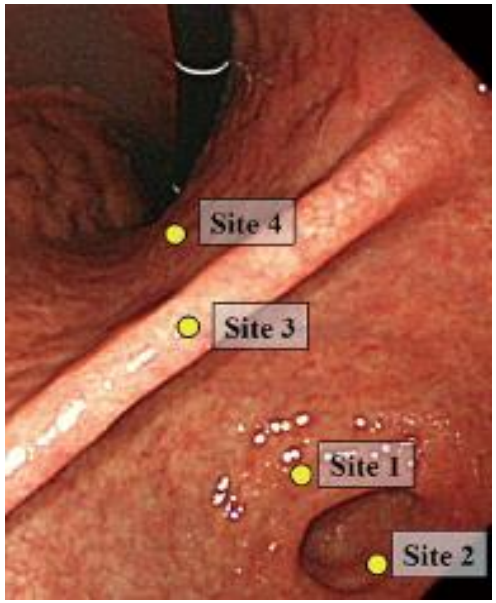


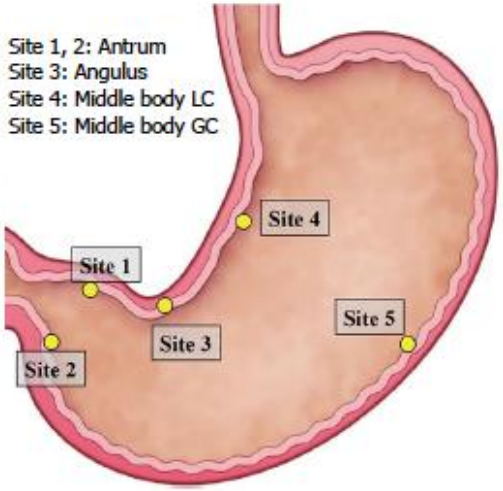
Intestinal metaplasia

The ***diagnosis and risk stratification of premalignant changes*** in the stomach, such as chronic atrophic gastritis (CAG) and gastric intestinal metaplasia (GIM), ***are reliant on histopathology***

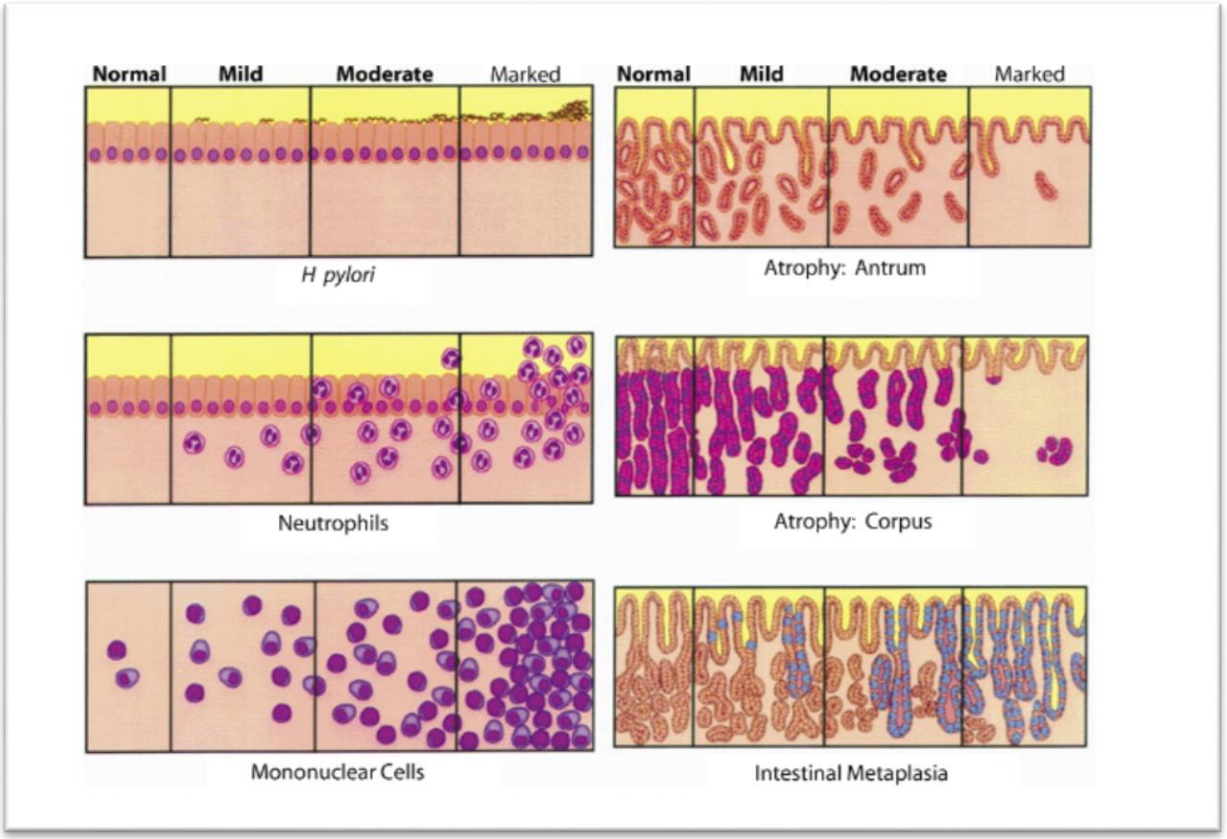
Waddinham W. F1000Research 2018; Dinis-Ribeiro M, Endoscopy 2012

"Non-targeted biopsies"





Update Sidney System



Dixon MF, Am J Surg Pathol 1996

Staging CAG and GIM: OLGA and OLGIM system

TABLE 1. The OLGA staging system[6]

		Corpus			
	Atrophy score	**Not fat: 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

OLGA, Operative link on gastritis assessment.

TABLE 2. Proposal for the OLGIM staging system

		Corpus			
	IM score	**Not fat: 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

IM, Intestinal metaplasia; *OLGIM*, operative link on gastric intestinal metaplasia assessment.

Capelle LG, de Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, van Dekken H, Meijer J, van Grieken NC, Kuipers EJ. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. Gastrointest Endosc. 2010;71(7):1150–8.

Gastric Cancer (2018) 21:579–587
https://doi.org/10.1007/s10120-018-0812-3

REVIEW ARTICLE

The significance of OLGA and OLGIM staging systems in the risk assessment of gastric cancer: a systematic review and meta-analysis

Hu Yue[1,2] · Liu Shan[1] · Lv Bin[1,2]

- six case–control studies and two cohort studies,
- 2700 subjects

RELATIVE RISK: OLGIM,OLGA LOW STAGES (I/II) VS HIGH STAGES (III/IV)

OLGIM III/IV: RR=3.99

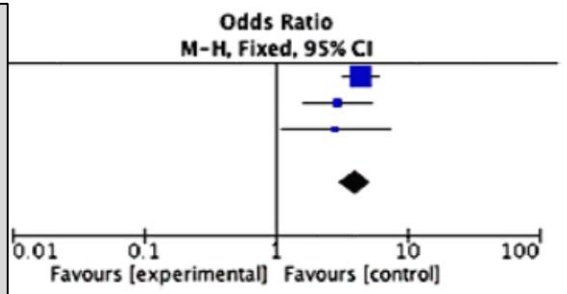


Fig. 3 Forest plot of odds ratio (OR) for gastric cancer (GC) of high stage of OLGIM versus low stage in case–control studies. The cumulative GC risk among patients with OLGIM stage III/IV was 3.99 (95% CI 3.05–5.21; $I^2 = 0\%$; $n = 3$)

OLGA III/IV: RR=27,70

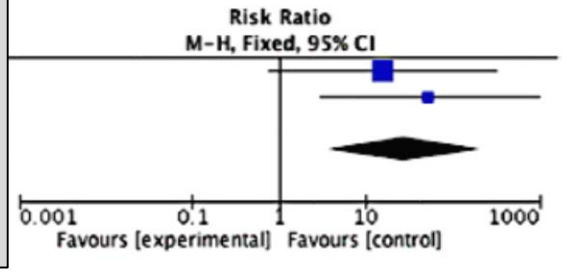
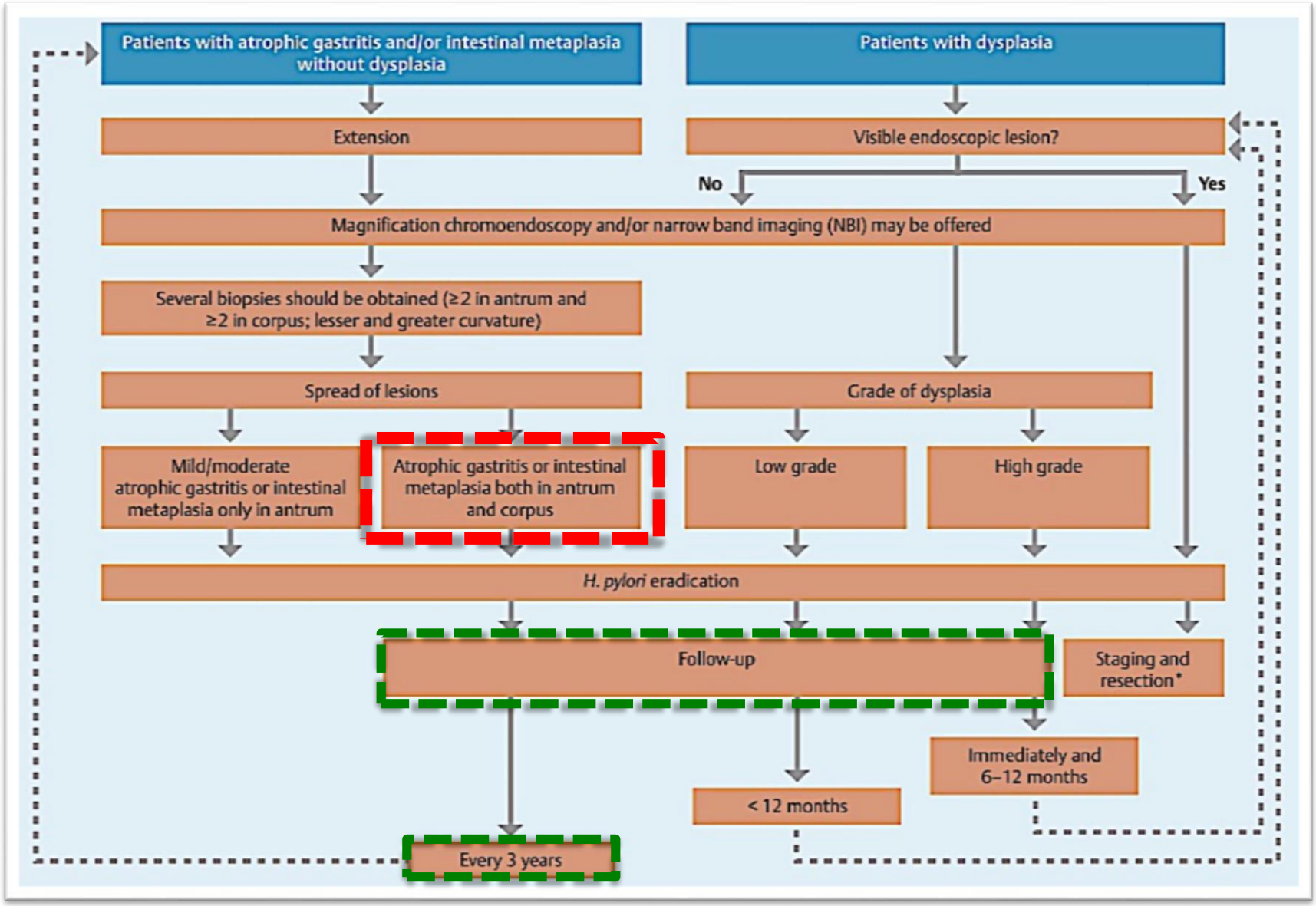


Fig. 4 Forest plot of risk ratio (RR) for gastric cancer (GC) of high stage of OLGA versus low stage in cohort studies. The cumulative GC risk among patients with OLGA stage III/IV was 27.70 (95% CI 3.75–204.87; $I^2 = 0\%$; $n = 2$)



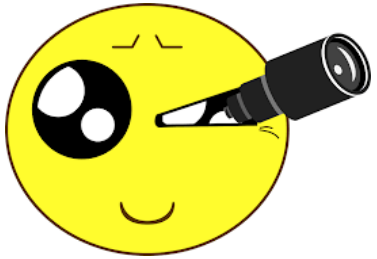
Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED) Dinis-Ribeiro M, Endoscopy 2012

Update Sidney System

Limitations……..

- Low acurracy in WLE detection of CAG and GIM
- “Non -targeted biopsies (blind)
- Poor correlation endoscopy and biopsies
- Poor interoberver agreement in histology (OLGA/OLGIM)

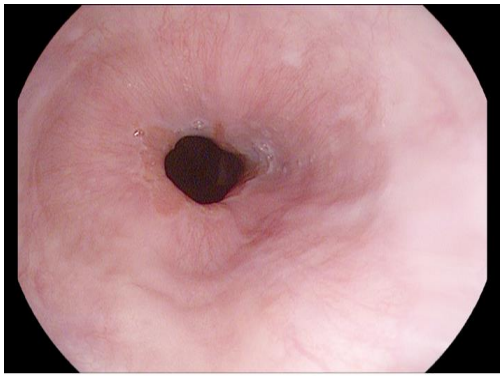
Is it possible to improve the diagnosis of CAG and GIM?
New advanced techiques???? The era of “optic diagnosis”

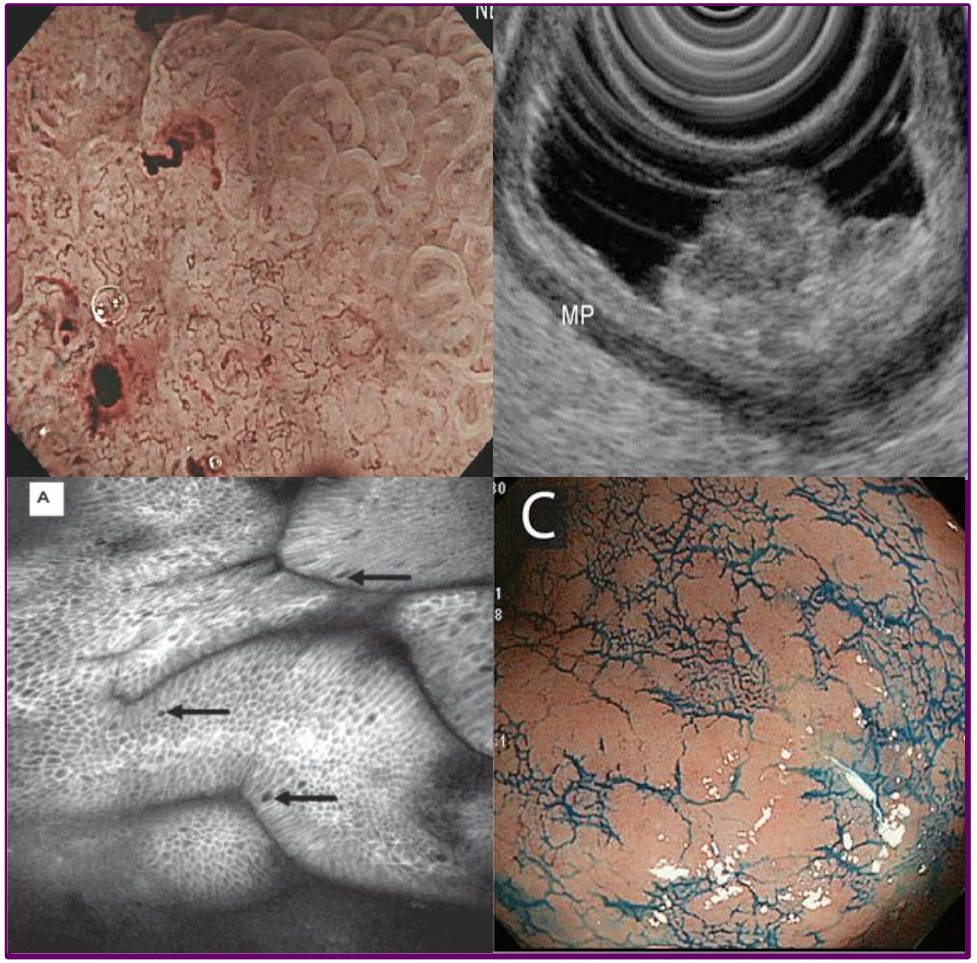


Conventional endoscopy

New advanced imaging tecnniques

White light endoscopy (WLE)





Conventional endoscopy

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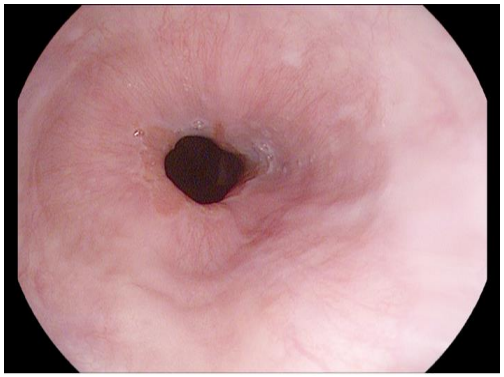
White light endoscopy (WLE)



- Dye-Based Image-Enhanced Endoscopy **(Chromoendoscopy)**

- image-enhancing endoscopy techniques (virtual Chromoendoscopy):
  Narrow Band Imaging (NBI)
  Others (FICE, iScan…)

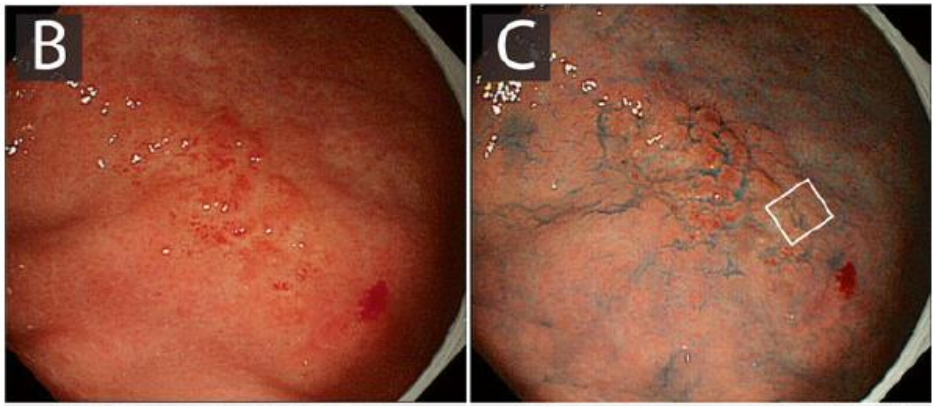
- **Magnifying Endoscopy**:
  -Magnifying Endoscopy + Chromoendoscopy
  -Magnifying Endoscopy + NBI

- **Confocal Laser endomicroscopy (CLE)**

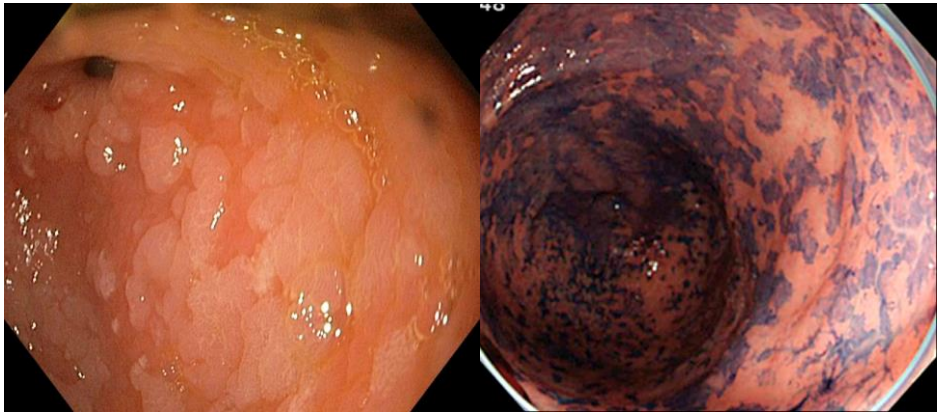
- **Endoscopic ultrasound (EUS)**

Dye-Based Image-Enhanced Endoscopy (Chromoendoscopy)

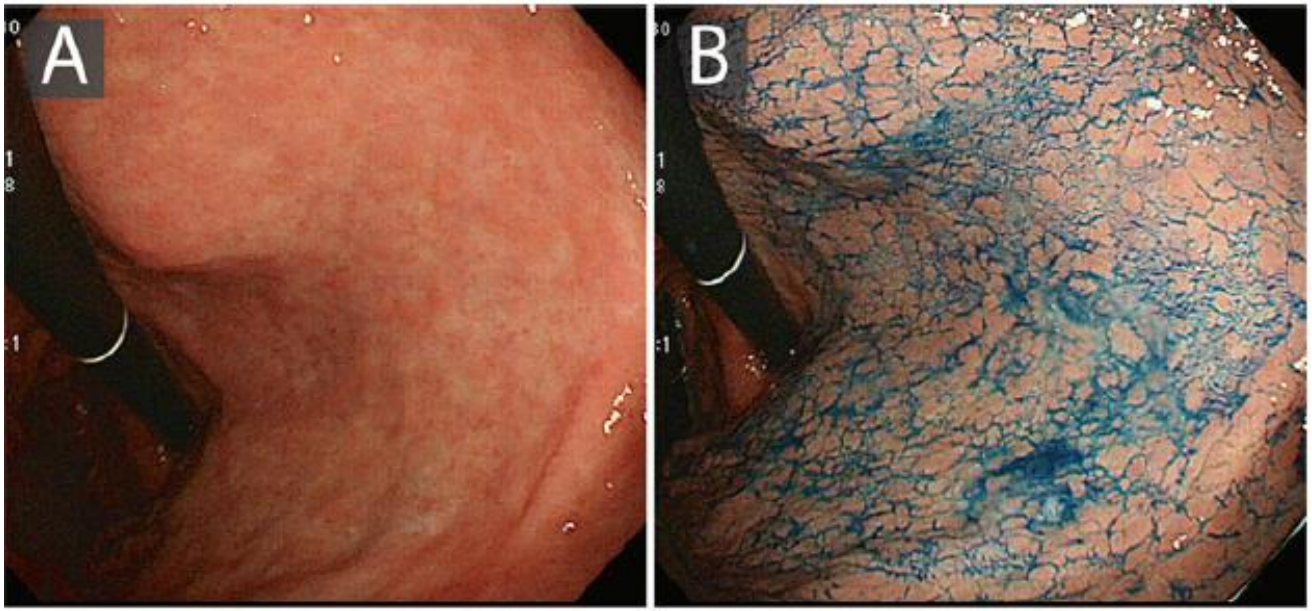
INDIGO CARMINE: morphological characteristics of the *surface mucosa*

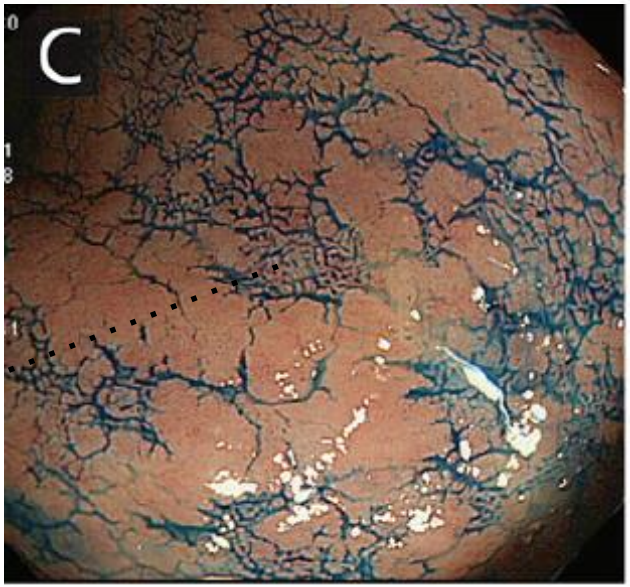


METHYLENE BLUE: Stains *gastric intestinal metaplasia*



Dye-Based Image-Enhanced Endoscopy (Chromoendoscopy) with WLE

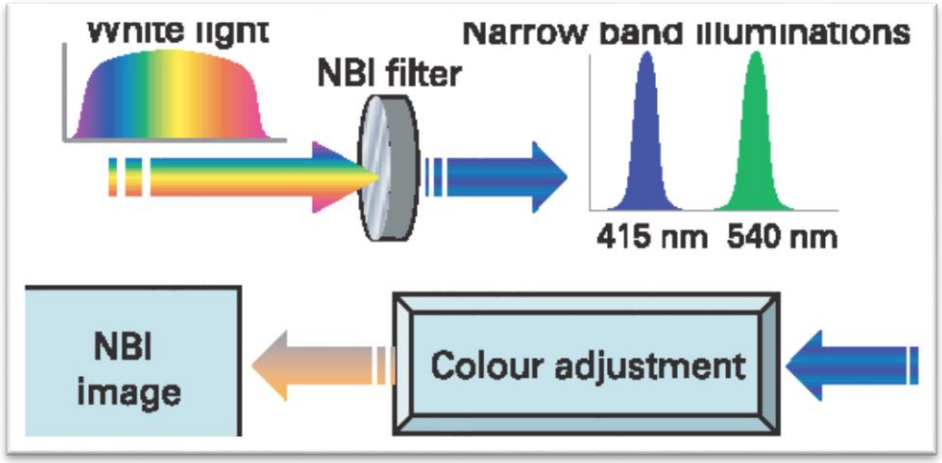




Atrophic areas

CHRONIC ATROPHIC GASTRITIS (Indigo carmine)

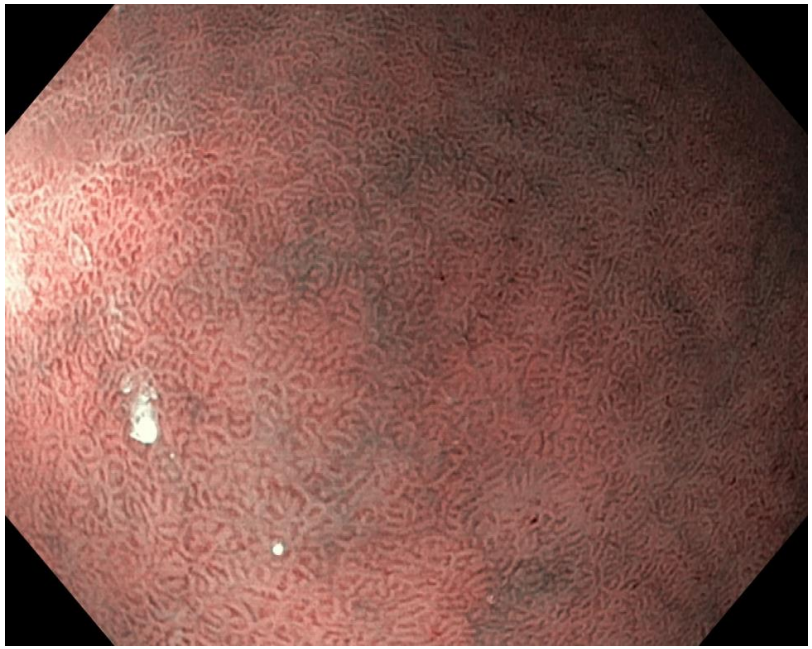
image-enhancing endoscopy techniques (“virtual chromoendoscopy”): NARROW BAND IMAGING (NBI)



blue and green narrowband lights
(absorbed by hemoglobin)

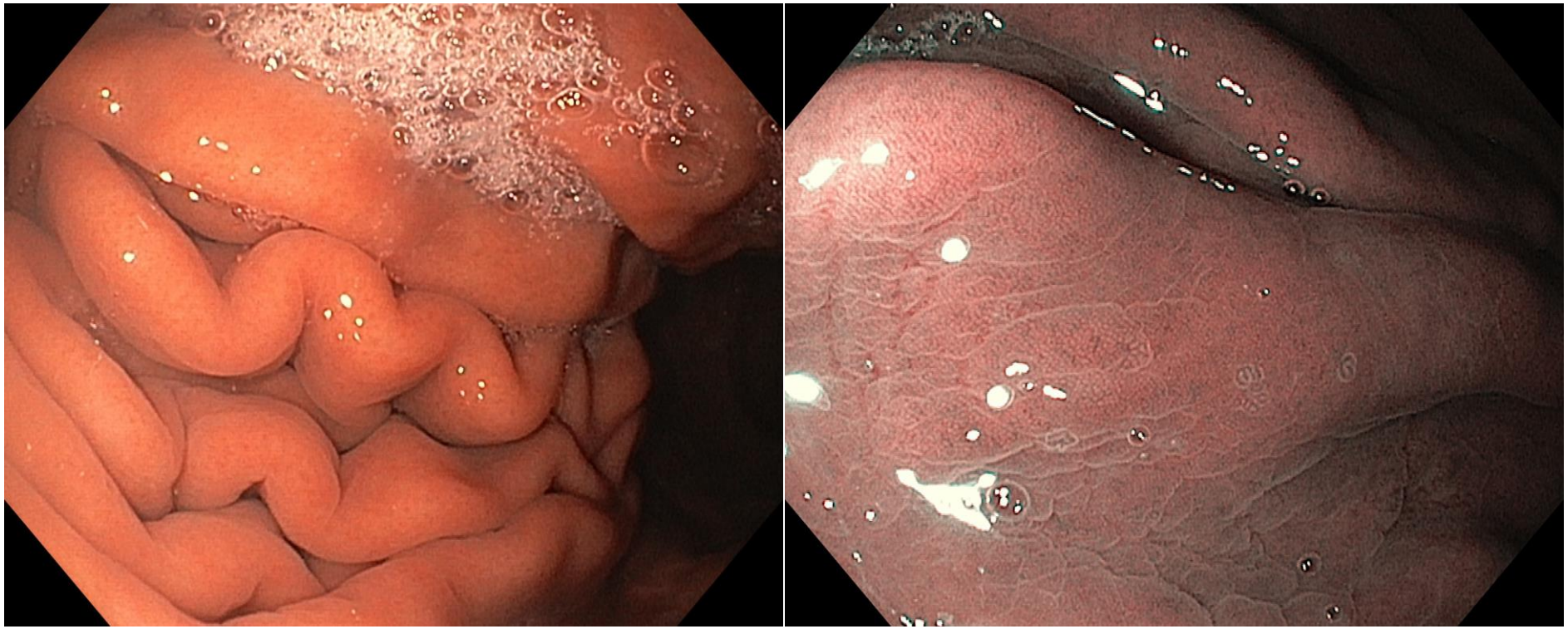
Vascular and surface architecture

- superficial capillary network
- Depht collecting vessels



NARROW BAND IMAGING (NBI)

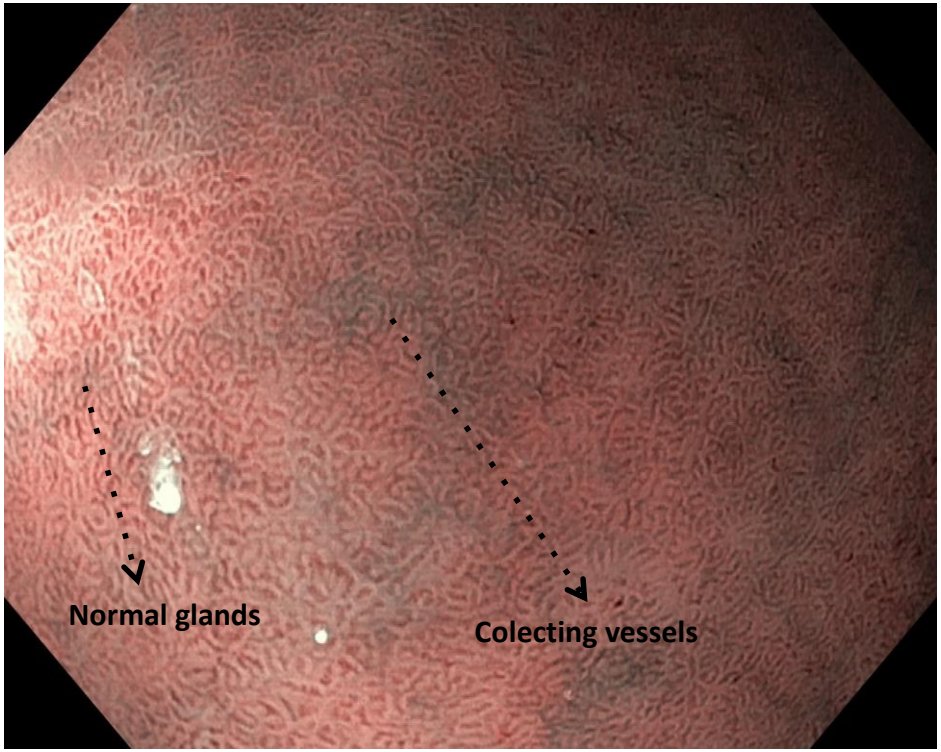
WLE **NBI**



"Normal gastric Body"

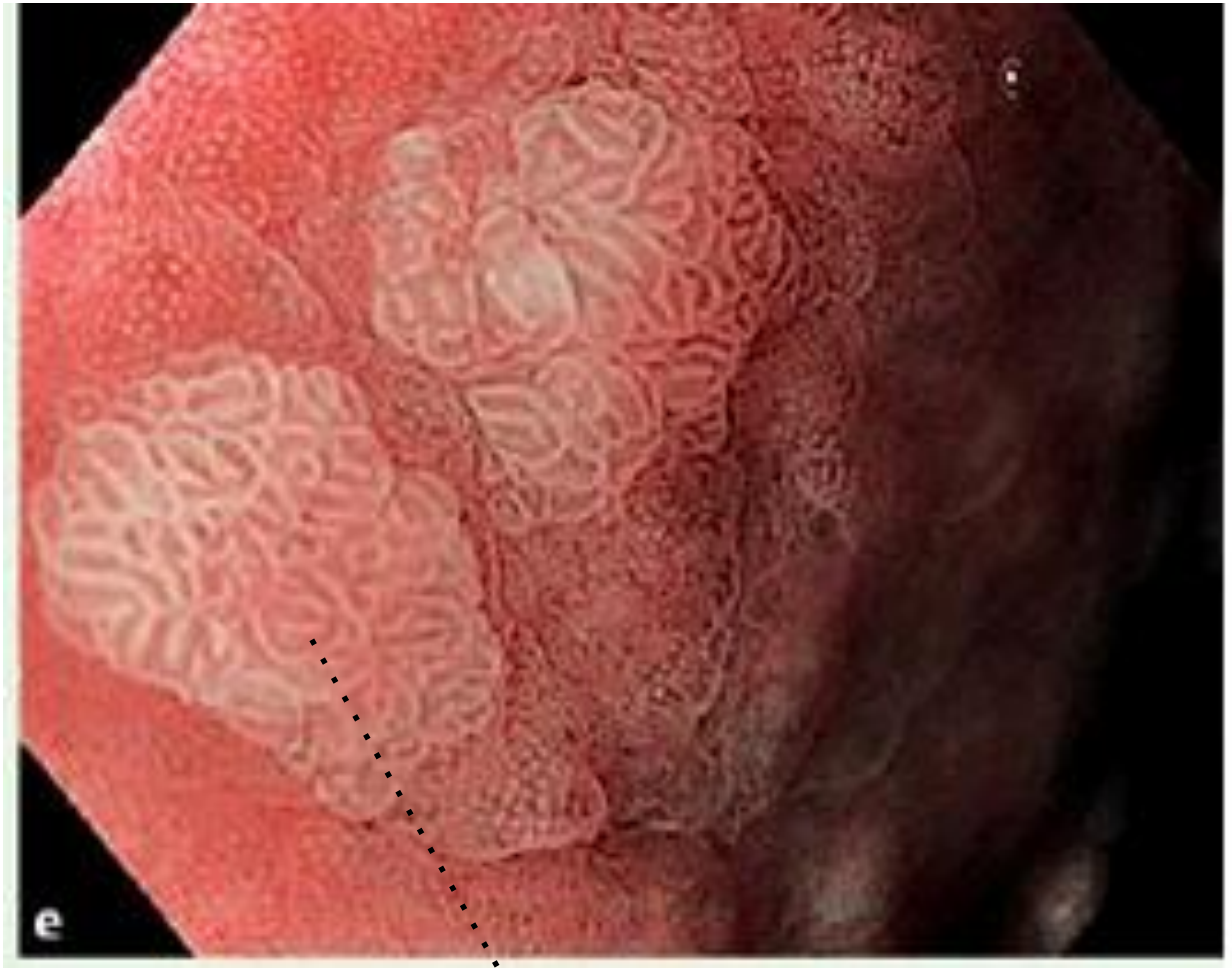
NARROW BAND IMAGING (NBI)

WLE **NBI**



"Normal antrum"

NARROW BAND IMAGING (NBI)

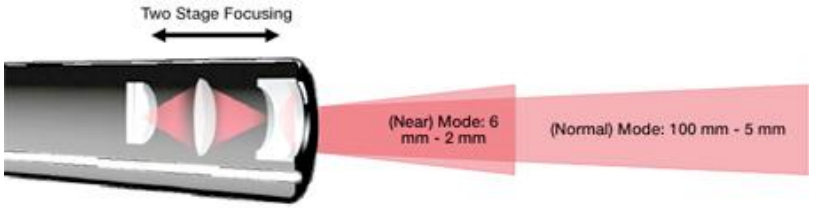


“intestinal metaplasia”

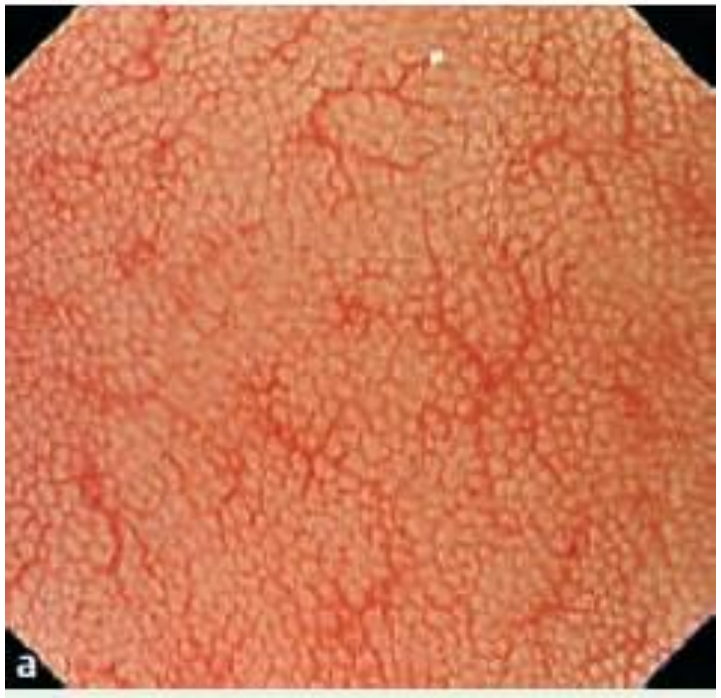
Magnifying Endoscopy (ME)

OPTIC ZOOM (x80)

“Real-time Optic diagnostic”

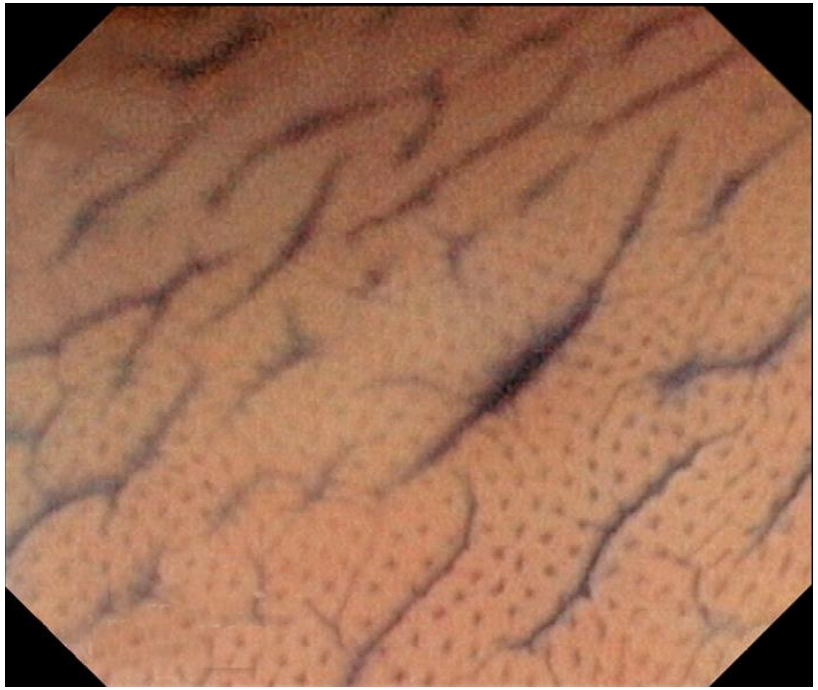


M-WLE

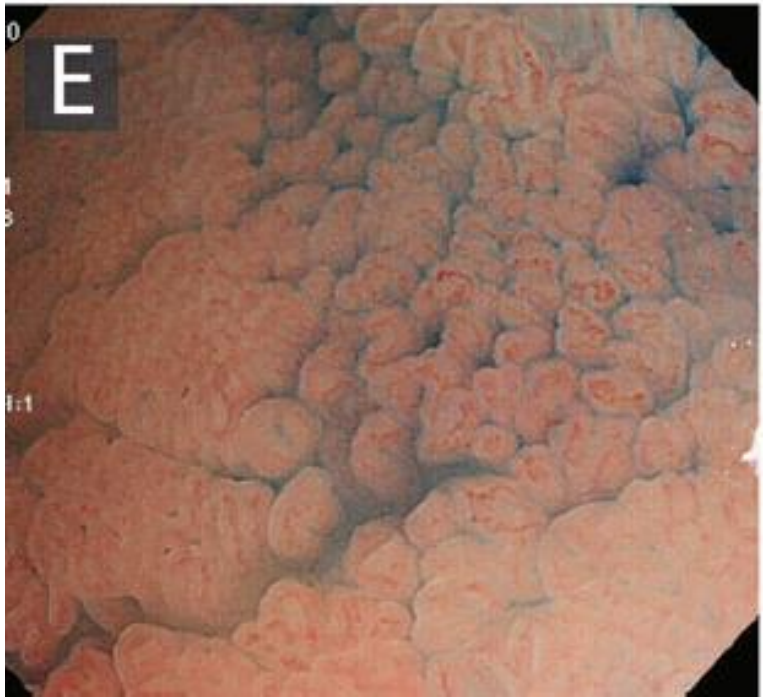


ME + CHROMOENDOSCOPY ***Microsurface* mucosa structure**
ME + Narrow Band iImaging (NBI) **Mucosal *microvascular* architectura**

Magnifying Endoscopy (ME)
+ Chromoendoscopy (indigo carmine)

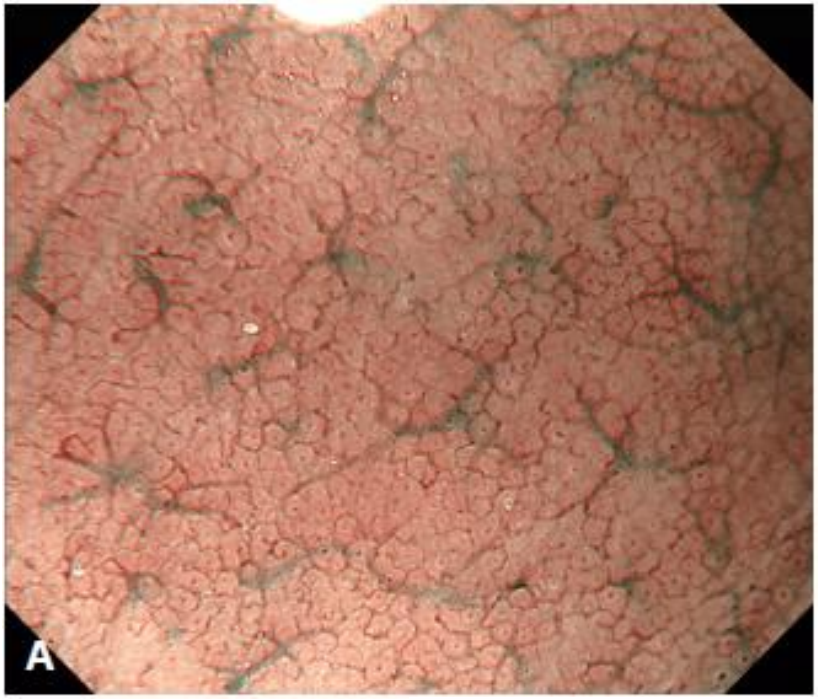


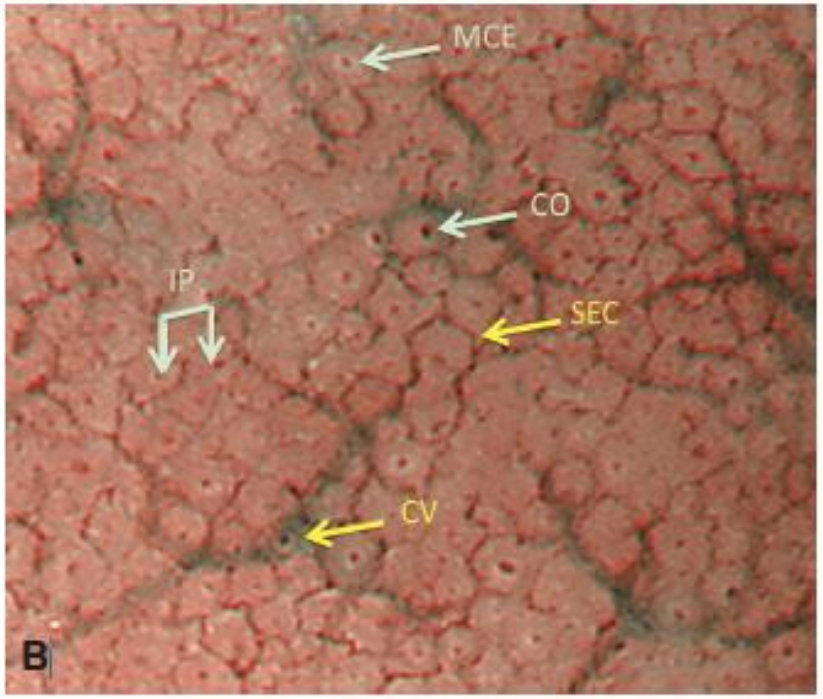
NORMAL BODY

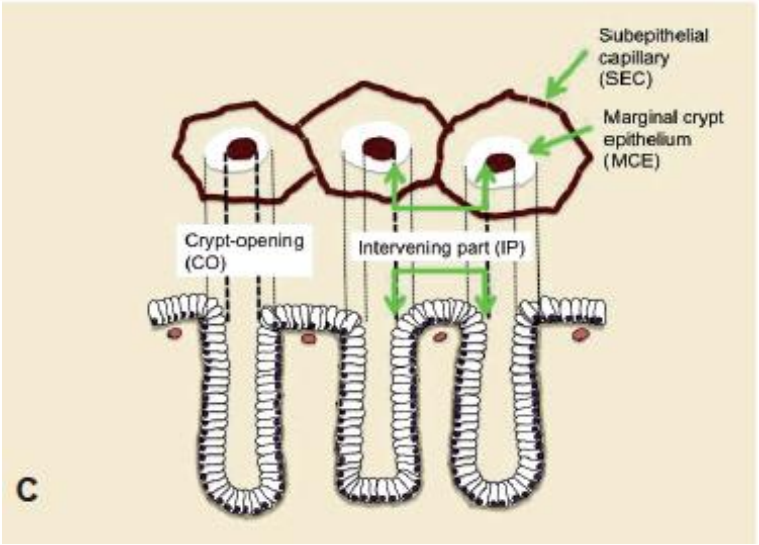


INTESTINAL METAPLASIA

Magnifying Endoscopy + NBI (M-NBI)

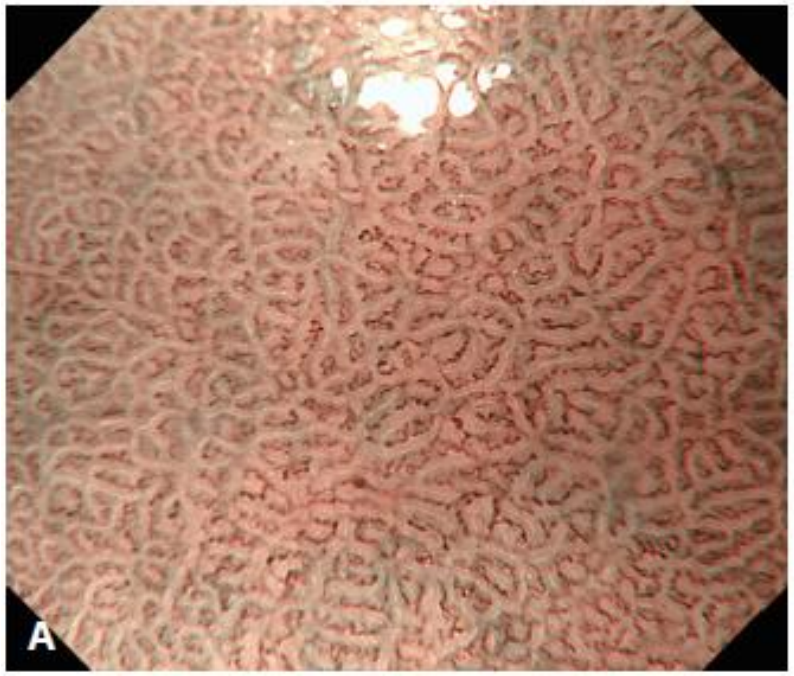


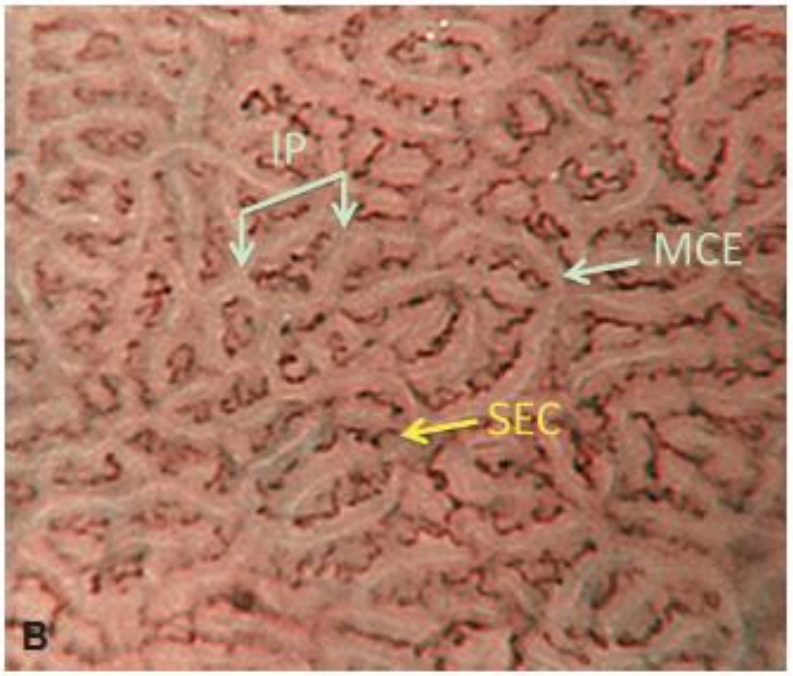


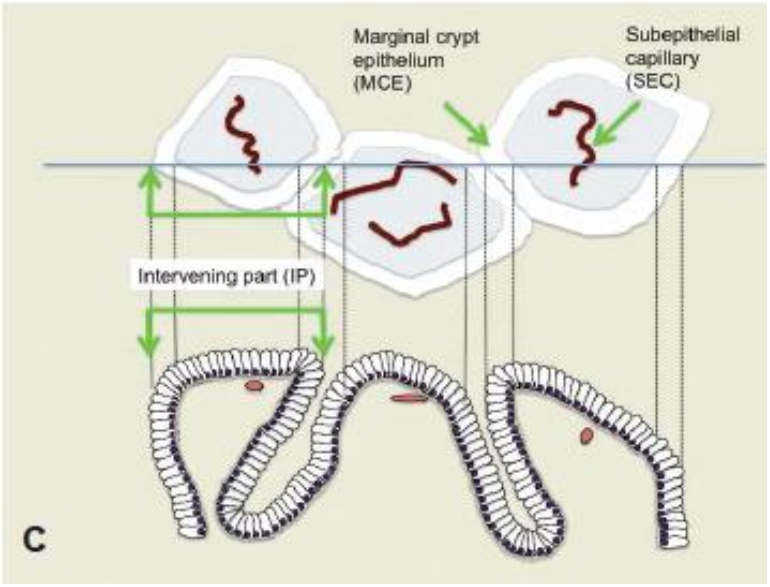


Normal corpus-fundus mucosa

Magnifying Endoscopy + NBI (M-NBI)

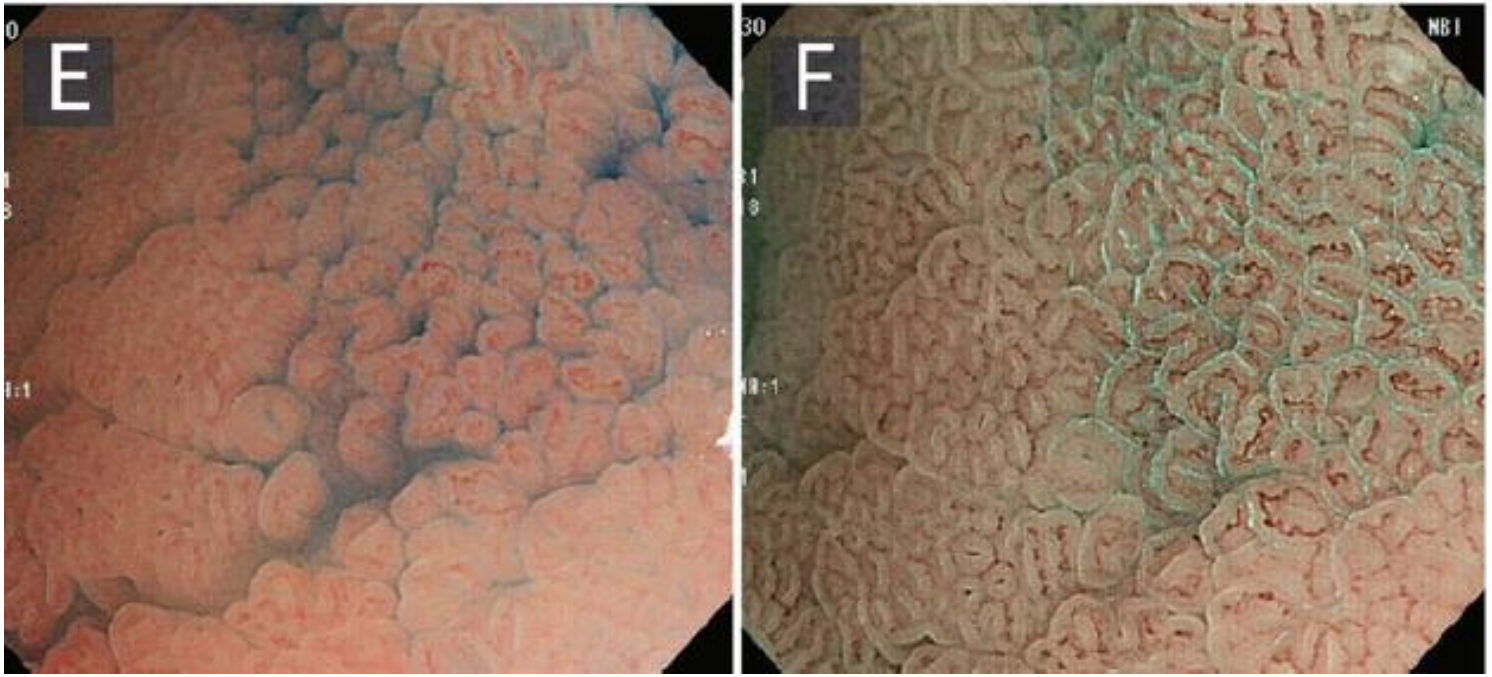


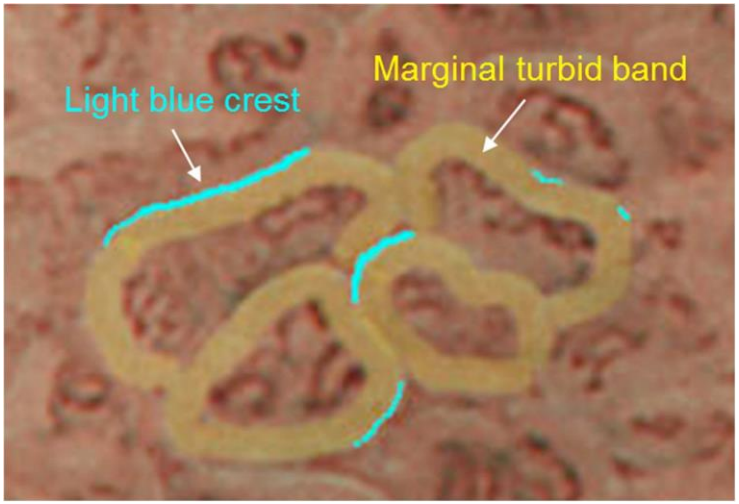




Normal antral mucosa

Magnifying Endoscopy + NBI (M-NBI)





GASTRIC INTESTINAL METAPLASIA

Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED)

Virchows Arch (2012) 460:19–46

M. Dinis-Ribeiro · M. Areia · A. C. de Vries · R. Marcos-Pinto · M. Monteiro-Soares · A. O'Connor · C. Pereira · P. Pimentel-Nunes · R. Correia · A. Ensari · J. M. Dumonceau · J. C. Machado · G. Macedo · P. Malfertheiner · T. Matysiak-Budnik · F. Megraud · K. Miki · C. O'Morain · R. M. Peek · T. Ponchon · A. Ristimaki · B. Rembacken · F. Carneiro · E. J. Kuipers · on behalf of MAPS Participants

Diagnosis and staging

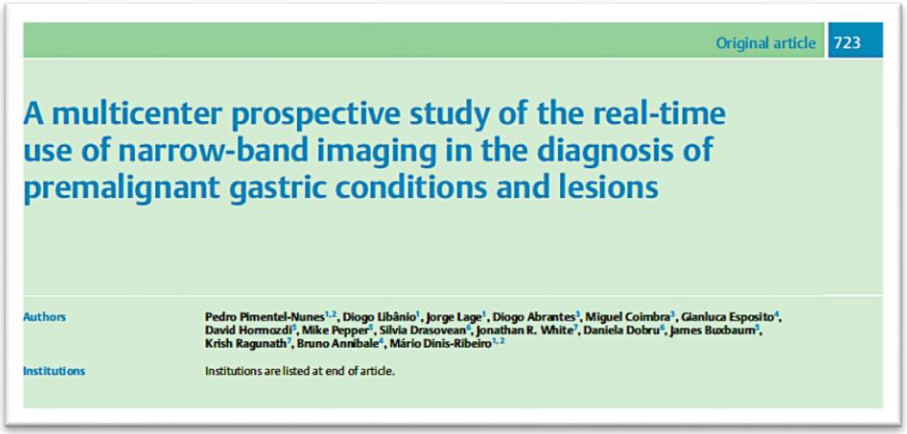
Endoscopy

4. Conventional white light endoscopy cannot accurately differentiate and diagnose preneoplastic gastric conditions (evidence level2++, recommendation grade B) [agree 94% (vote: a, 46%; b, 24%; c, 24%; d, 4%; e, 2%)].
5. Magnification chromoendoscopy and NBI, with or without magnification, improve the diagnosis of gastric preneoplastic conditions/lesions (evidence level 2++, recommendation grade B) [agree 98% (vote: a, 47%; b, 27%; c, 24%; d, 2%); 83% of voters stated that they would apply this statement; 67% of those representing national societies mentioned that it would also be applicable (63%) or widely applicable (4%) in their countries].
6. Within this context, diagnostic upper gastrointestinal endoscopy should include gastric biopsies sampling (evidence level 4, recommendation grade D) [agree 93% (vote: a, 66%; b, 18%; c, 9%; d, 7%)].

NO WLE

ME-CHROMOENDOSCOPY OR NBI

Biopsies should be taken



Original article 723

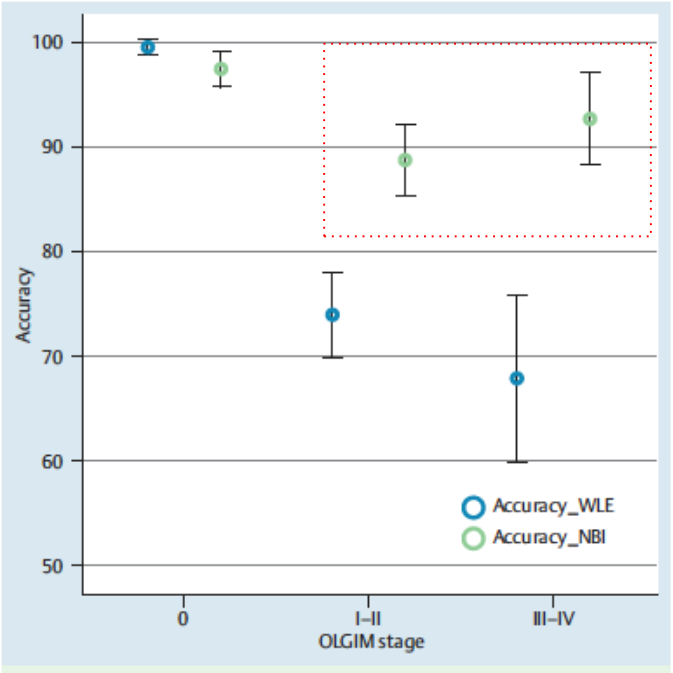
A multicenter prospective study of the real-time use of narrow-band imaging in the diagnosis of premalignant gastric conditions and lesions

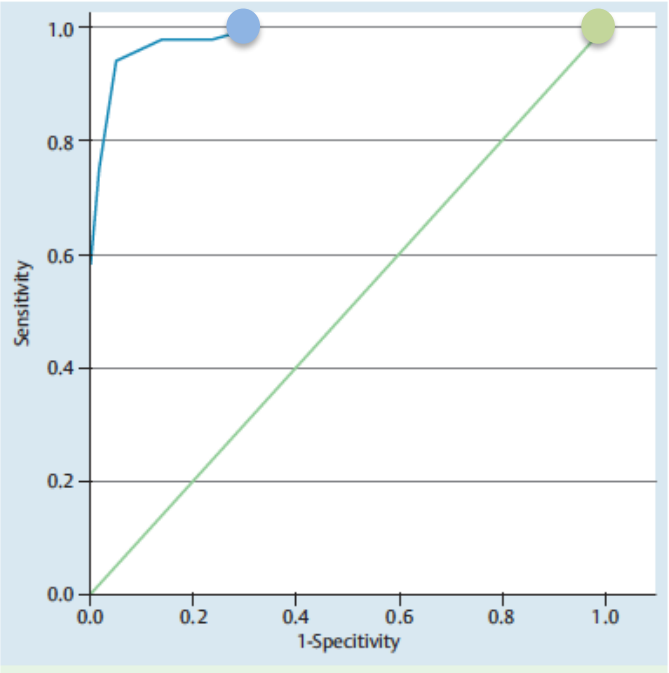
Authors Pedro Pimentel-Nunes[1,2], Diogo Libânio[1], Jorge Lage[1], Diogo Abrantes[3], Miguel Coimbra[3], Gianluca Esposito[4], David Hormozdi[5], Mike Pepper[5], Silvia Drasovean[6], Jonathan R. White[7], Daniela Dobru[6], James Buxbaum[5], Krish Ragunath[7], Bruno Annibale[4], Mário Dinis-Ribeiro[1,2]

Institutions Institutions are listed at end of article.

White Light Endoscopy- biopsies
Vs
NBI-Targeted biopsies

Accuracy, Sen, Spe NBI-targeted biopsies > WLE-biopsies





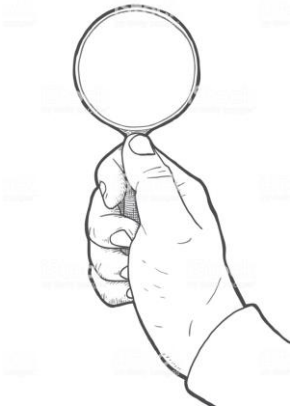
Pimentel-Nunes Pedro et al. NBI for the diagnosis of gastric lesions… Endoscopy 2016; 48: 723–730

*Take home message

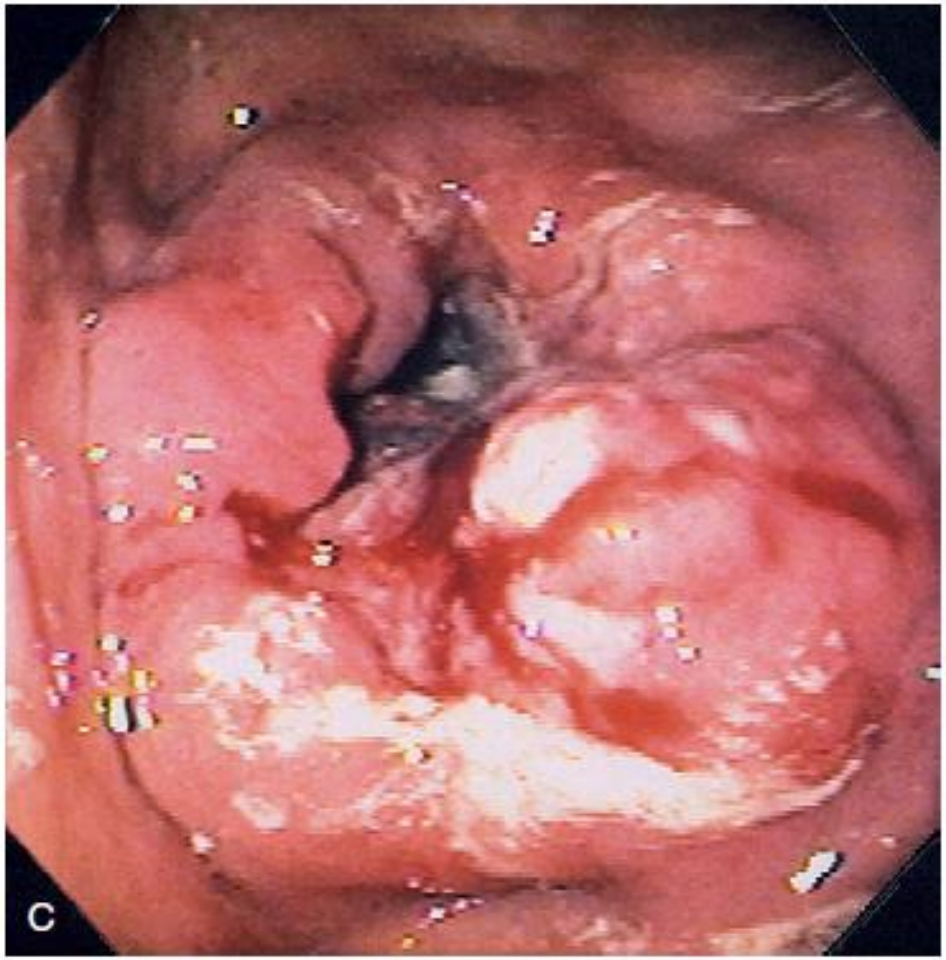
- Importance of the "**oportunistic screening** in our "scenario" (low risk population) with a high quality endoscopy

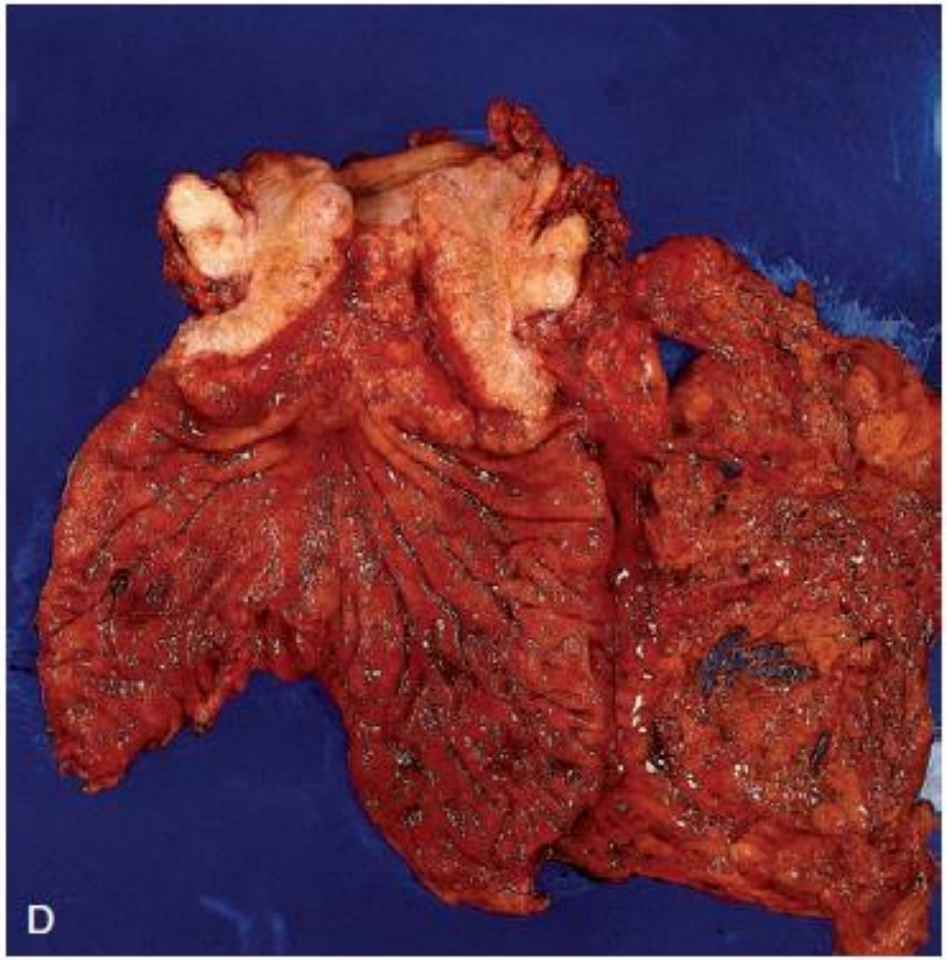
- **New advanced imaging endoscopy** (Magnification endoscopy with chromoendoscopy or Narrow Band Imaging with or without magnification**) sholud be offered** to improve the detection of precancerous conditions (CAG and GIM)

2.Diagnosis

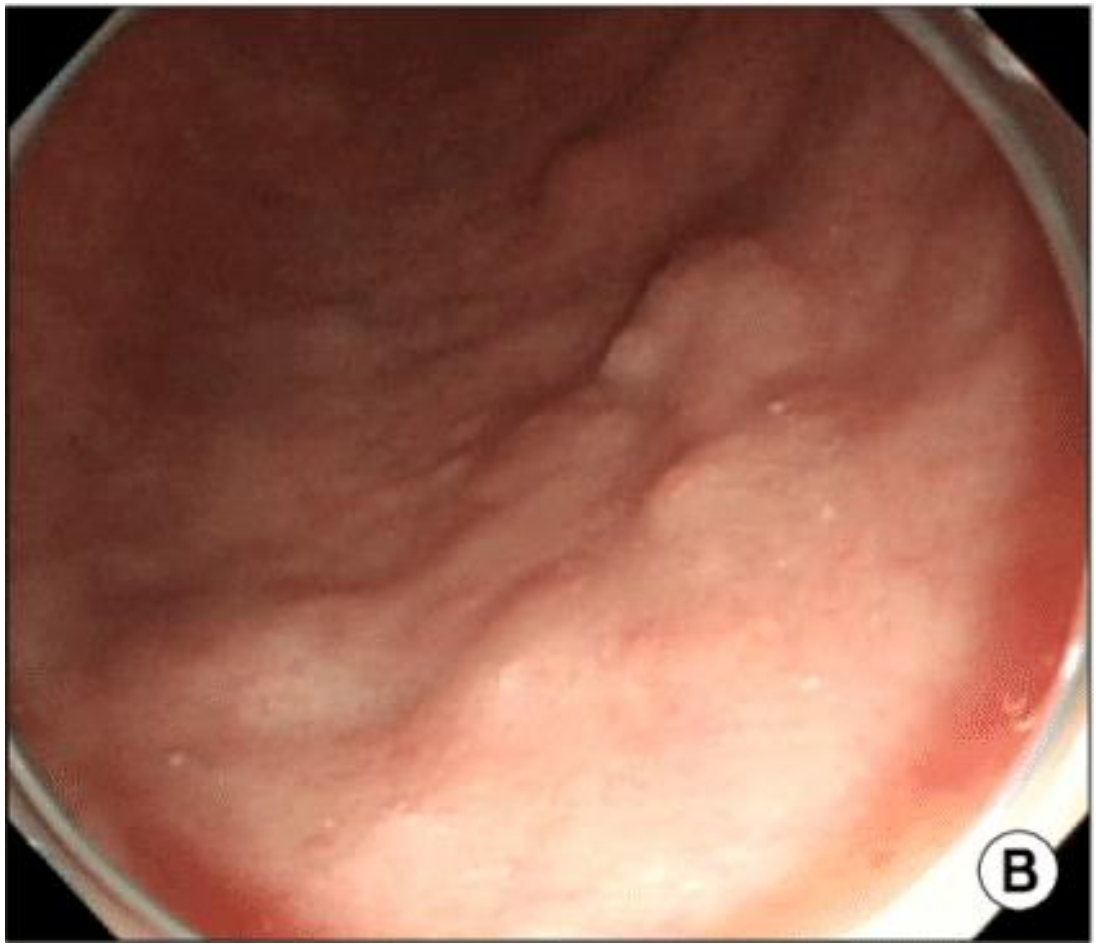


Advanced gastric cancer

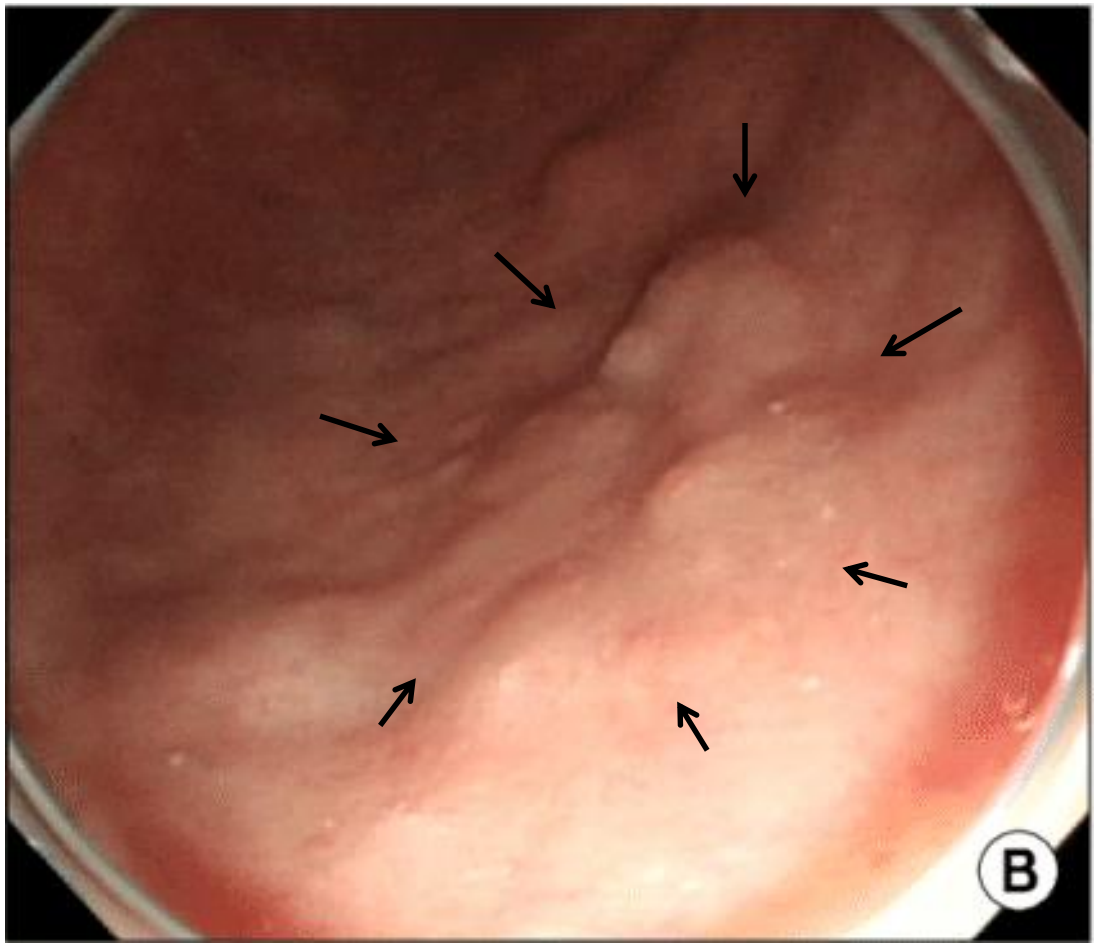




Atlas of Clinical Gastrointestinal Endoscopy . Third edition C. Mel Wilcox, MD, MSPH. Elsevier


B

early gastric cancer



SCREENING POPULATION

Inmigrants (high risk regions) Familiy History

"Oportunistic screening" (EGD endoscopies)

1º

screening

PRENEOPLASTIC CONDITIONS

Chronic Atrophic Gastritis (CAG) Gastrointestinal metaplasia (GIM)

surveillance

2nd

NEOPLASTIC LESIONS

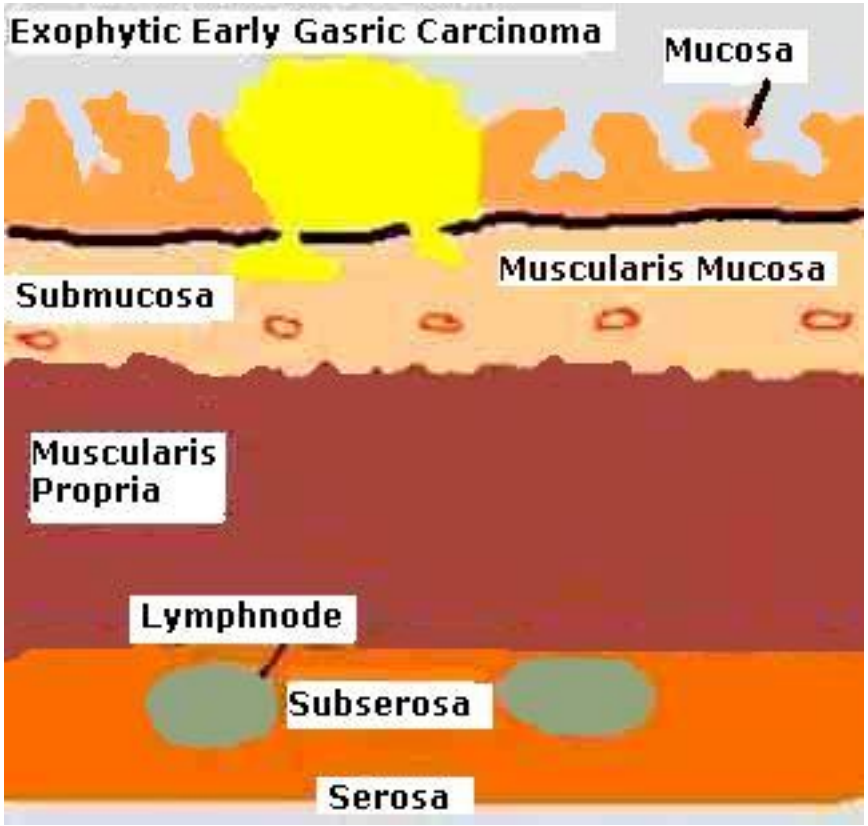
Displasia (Intraepithelial neoplasia) Adenocarcinoma

Detection of EGC will improve the survival rate of this cancer.

Screening and surveillance for gastric cancer in the United States: Is it needed? Kim. GH. GIE 2016

EARLY GASTRIC CANCER (EGC) DEFINITION

"EGC is a cancer in which tumor invasion is confined to the mucosa or submucosa (T1) regardless of the presence of lymph node metastasis".

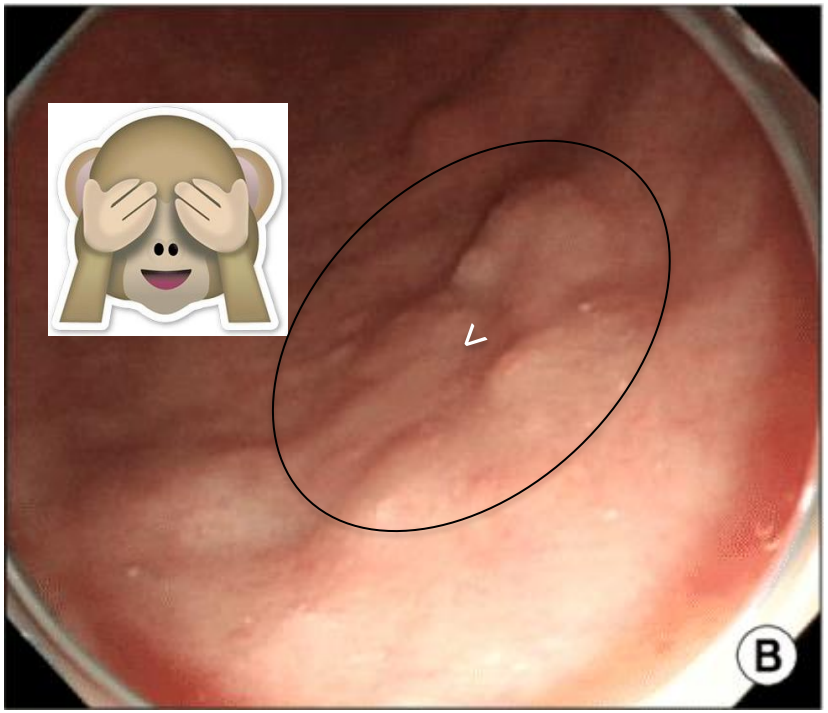


IMPORTANCE OF EARLY DETECTION

- Good prognosis
- Can be cured by minimally invasive approaches.

Japanese Gastric Cancer Association, "Japanese classification of gastric carcinoma—2nd English edition," Gastric Cancer, vol. 1, no. 1, pp. 10–24, 1998

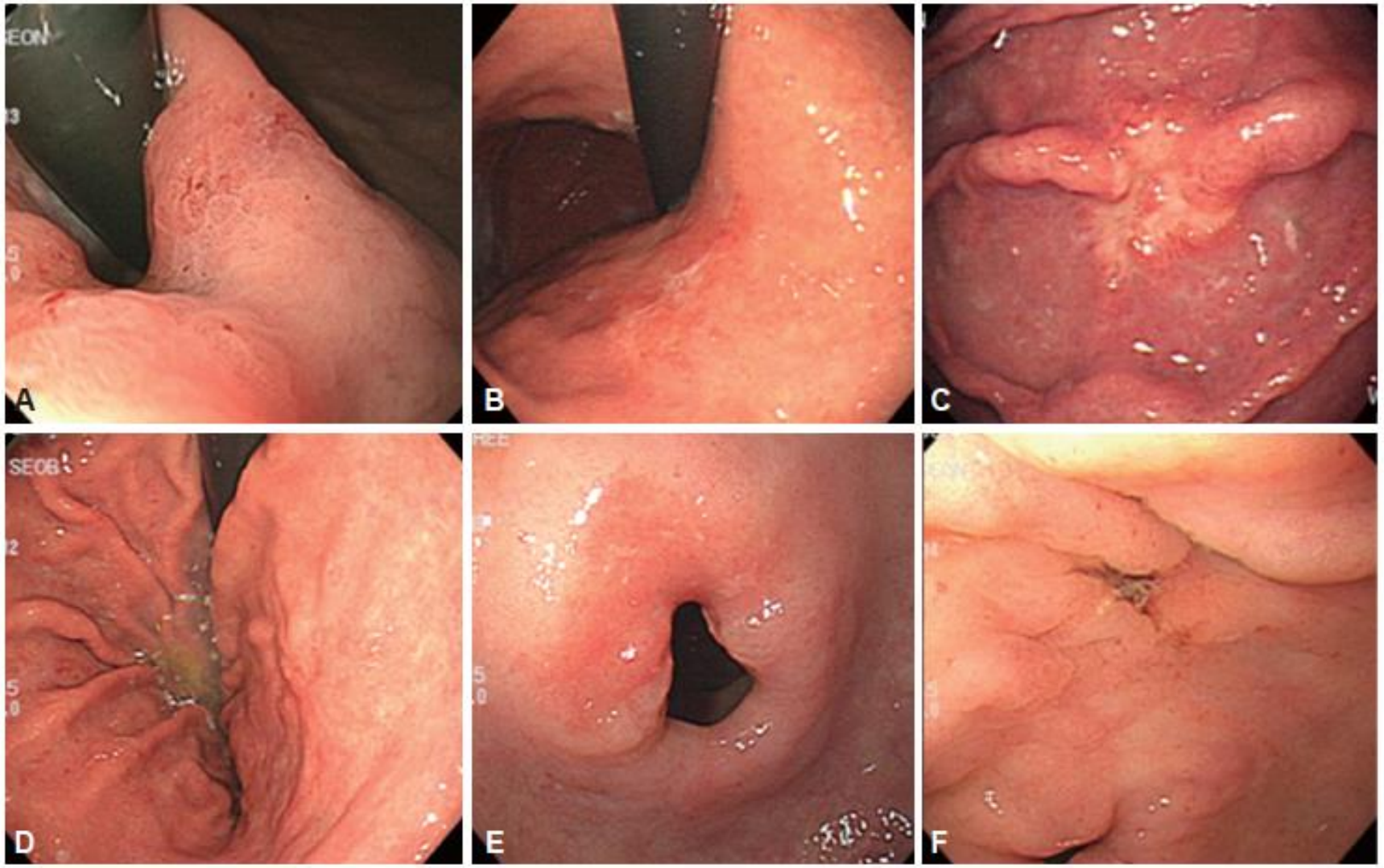
- ✓ 9,4% of EGC are missed during Upper gastrointestinal endoscopy



Is time for new advanced imaging technology?

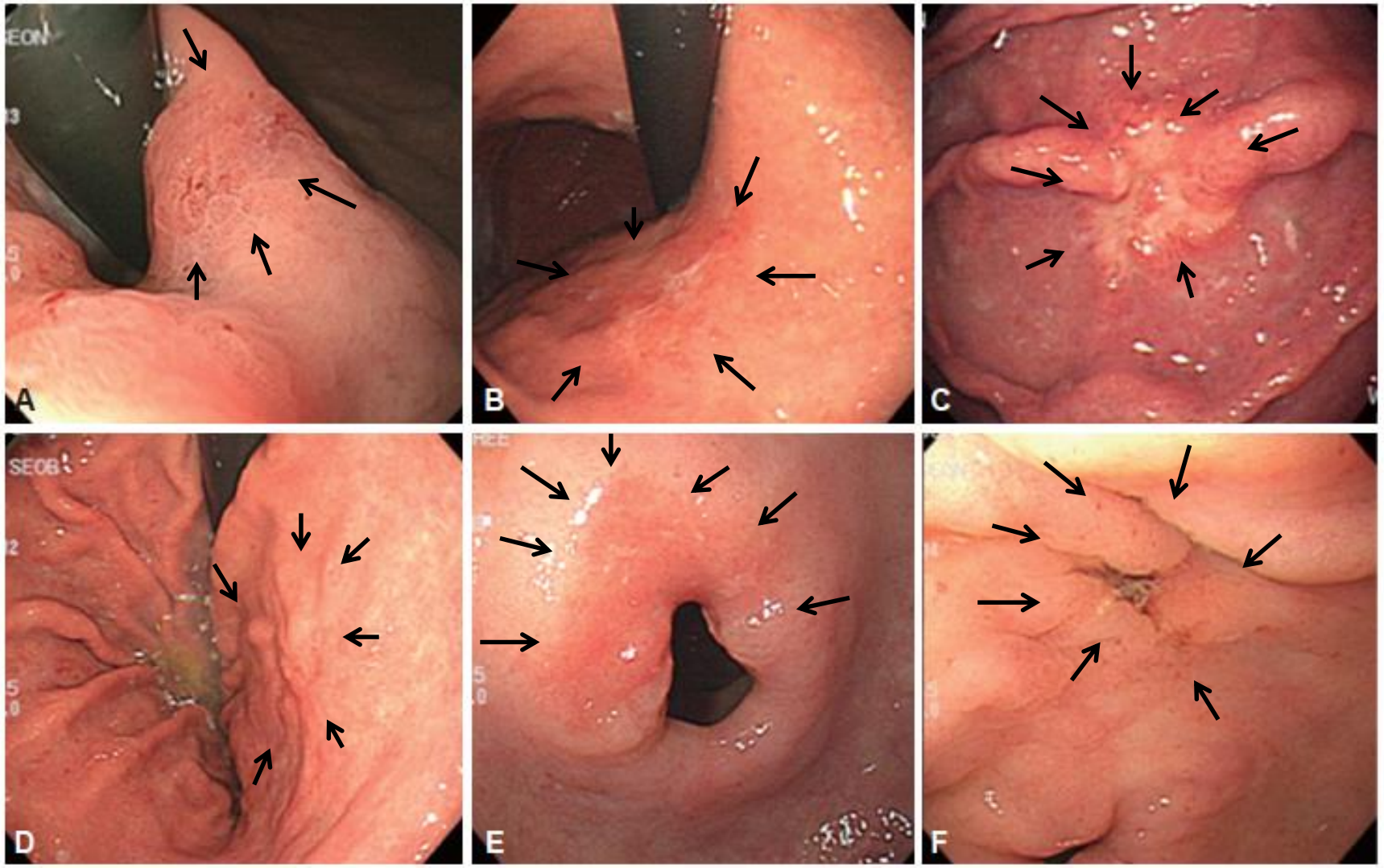
Pimenta-Melo et al. Missing ratefor gastric cancer during upper gastrointestinal endoscopy: A systematic review and teta-analysis. Eur J Gastroenterol Hepatol 2016

EARLY GASTRIC CANCER (EGC) :WHITE LIGHT ENDOSCOPY



Improving the Endoscopic Detection Rate in Patients with Early Gastric Cancer . Moon HS. 2015

EARLY GASTRIC CANCER (EGC) :WHITE LIGHT ENDOSCOPY

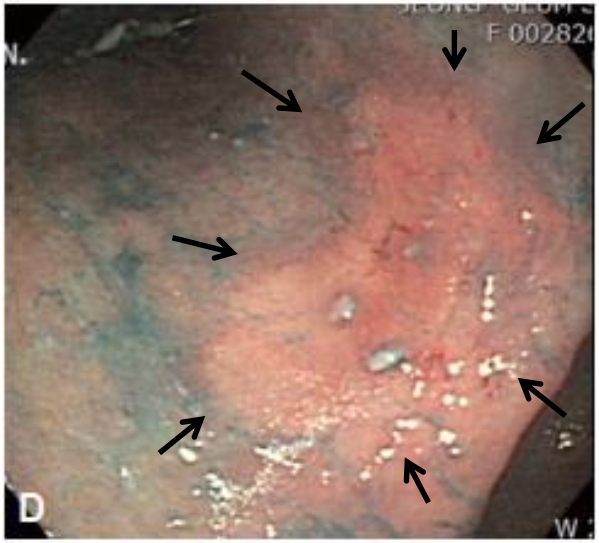


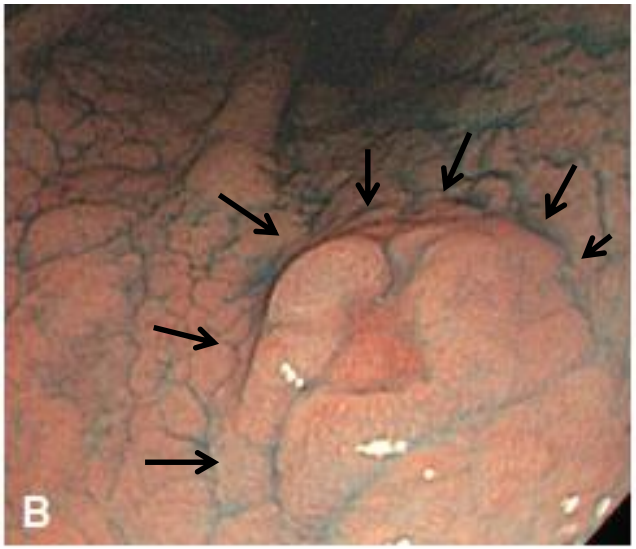
Improving the Endoscopic Detection Rate in Patients with Early Gastric Cancer . Moon HS. 2015

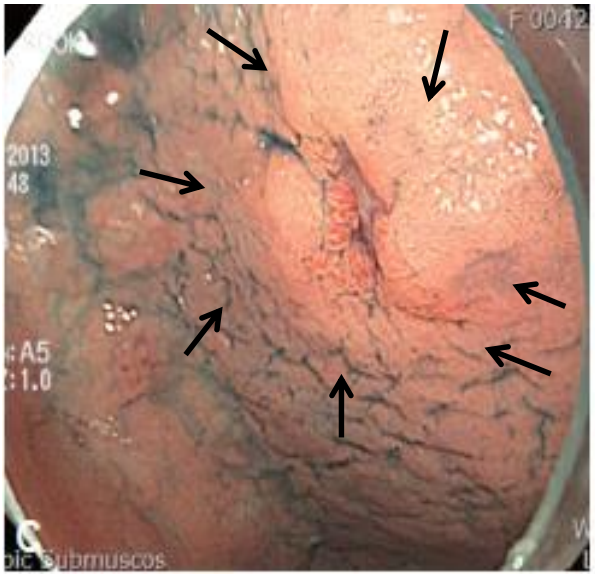
EARLY GASTRIC CANCER (EGC) :Dye-based image endoscopy

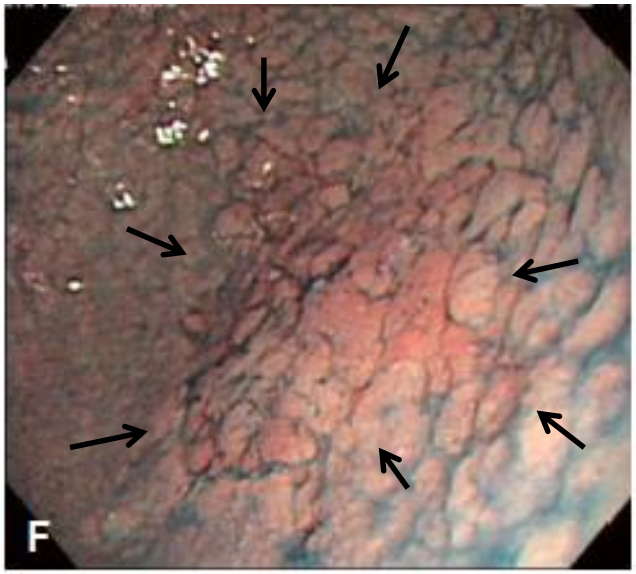
INDIGO CARMINE
(0,2-0,4%):
morphological characteristics of the *surface mucosa*

“Demarcation line”

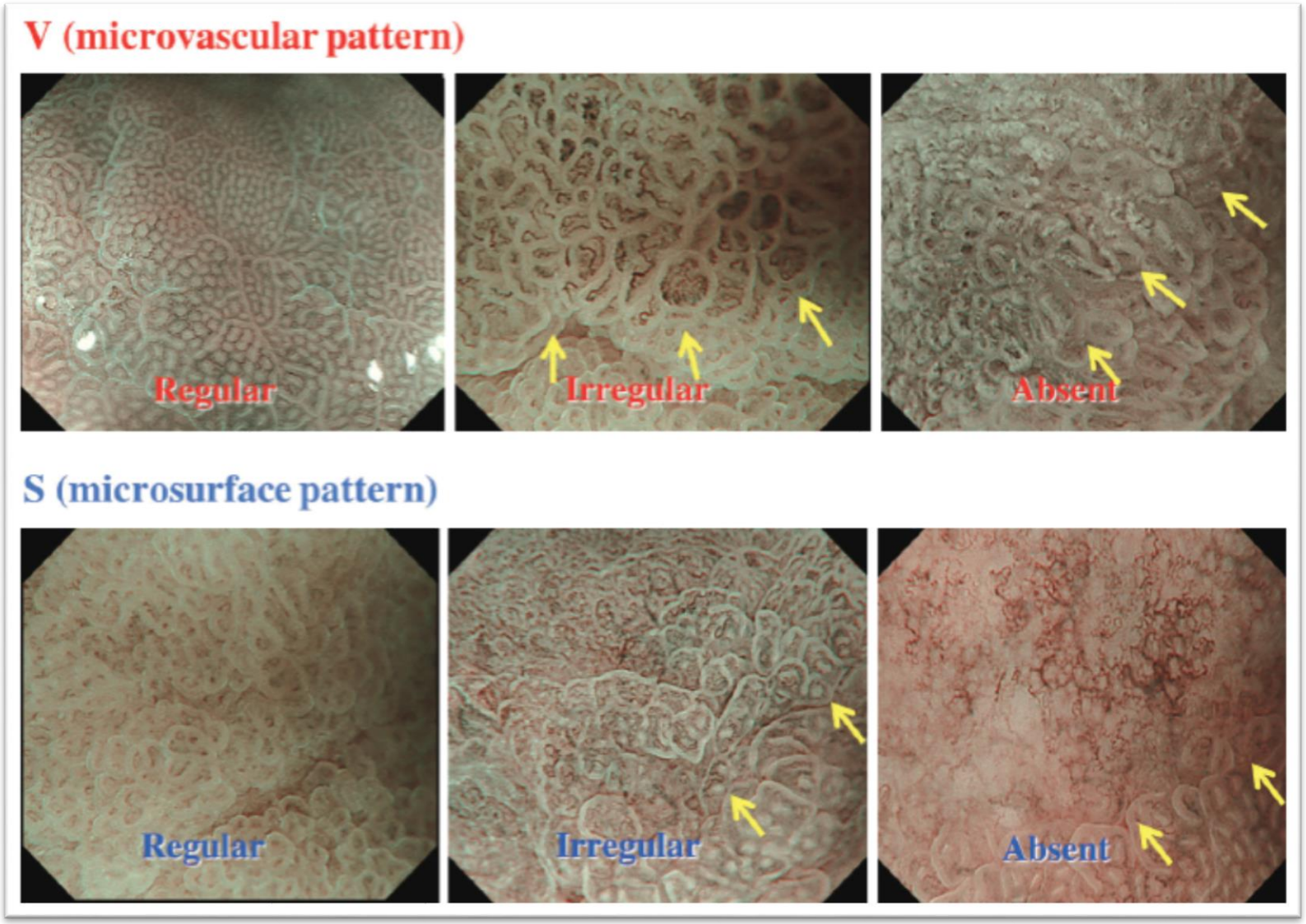






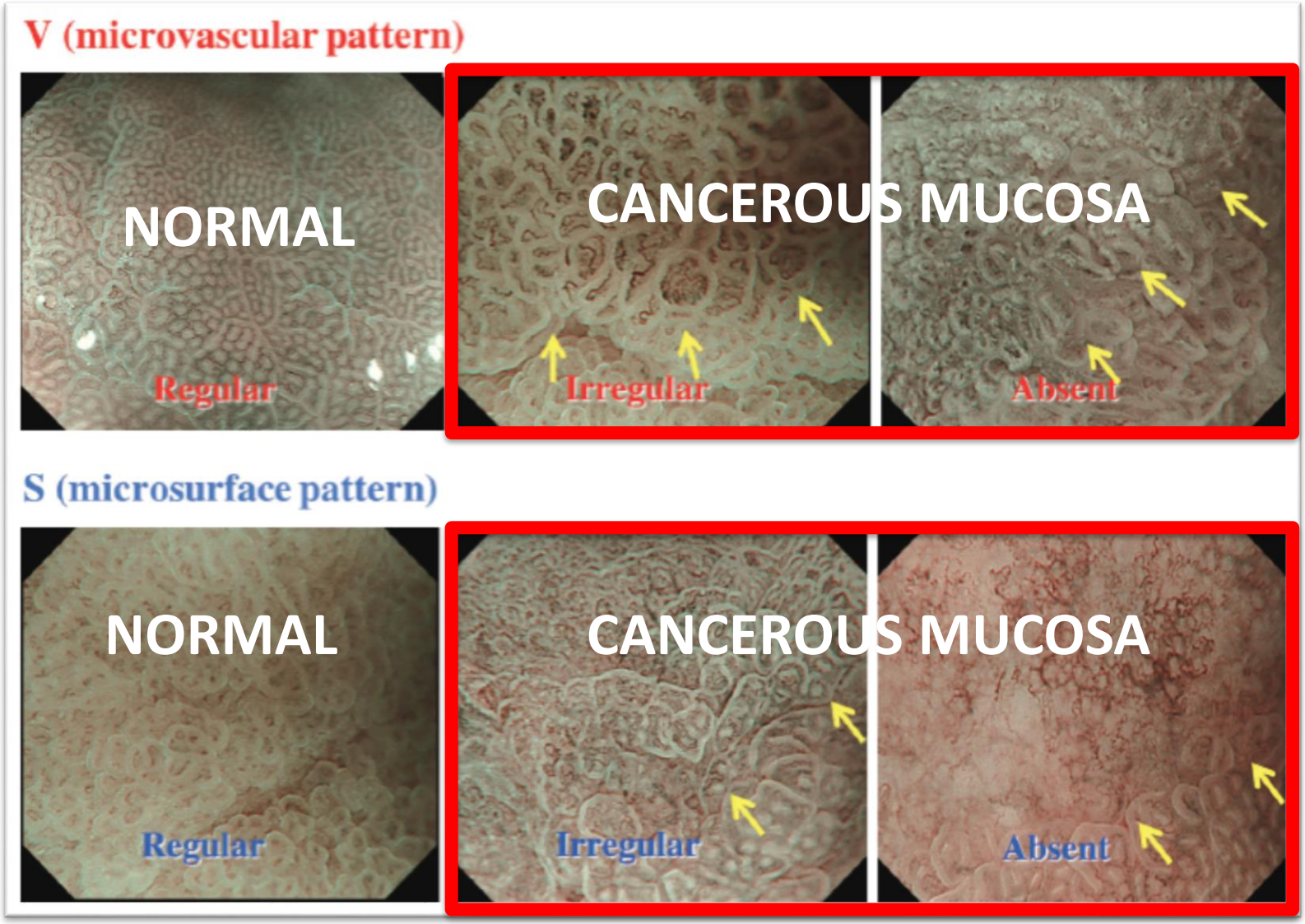


EARLY GASTRIC CANCER (EGC) :ME- NBI



Clinical Application of Magnifying Endoscopy with Narrow-Band Imaging in the Stomach. Kenshi Yao Clin Endosc 2015;48:481-490

EARLY GASTRIC CANCER (EGC) :ME- NBI



Clinical Application of Magnifying Endoscopy with Narrow-Band Imaging in the Stomach. Kenshi Yao Clin Endosc 2015;48:481-490

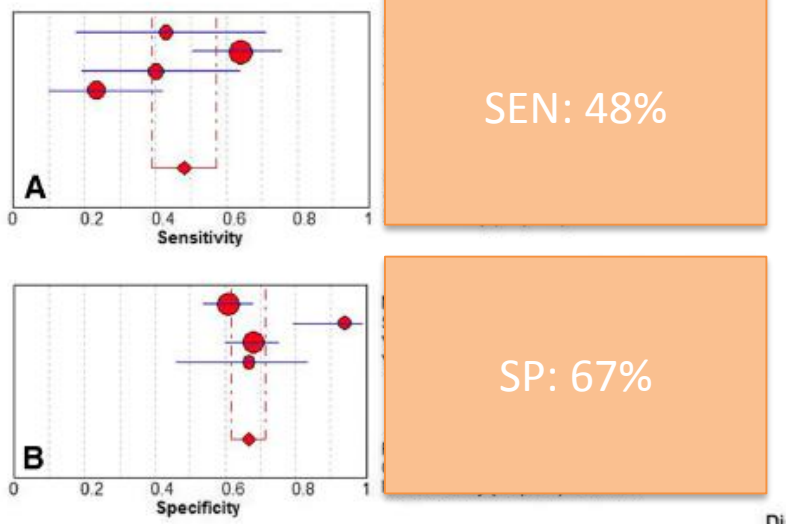
Gastric Cancer (2016) 19:543–552
DOI 10.1007/s10120-015-0500-5

ORIGINAL ARTICLE

Comparison of the diagnostic efficacy of white light endoscopy and magnifying endoscopy with narrow band imaging for early gastric cancer: a meta-analysis

Qiang Zhang[1] · Fei Wang[1] · Zhen-Yu Chen[1] · Zhen Wang[1] · Fa-Chao Zhi[1] · Si-De Liu[1] · Yang Bai[1]

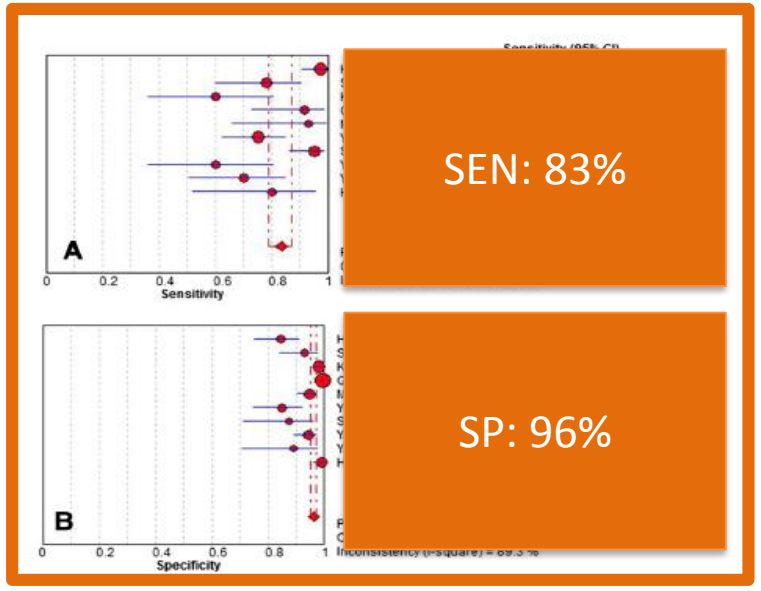
White Light Endoscopy



SEN: 48%

SP: 67%

ME-NBI

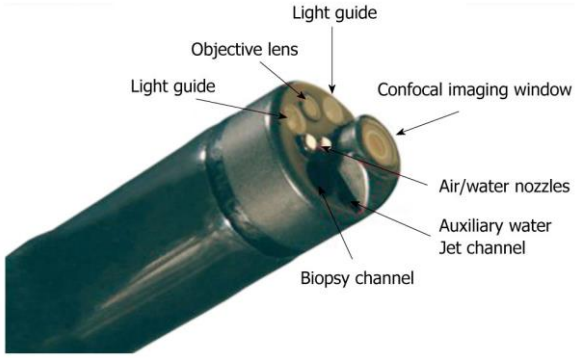


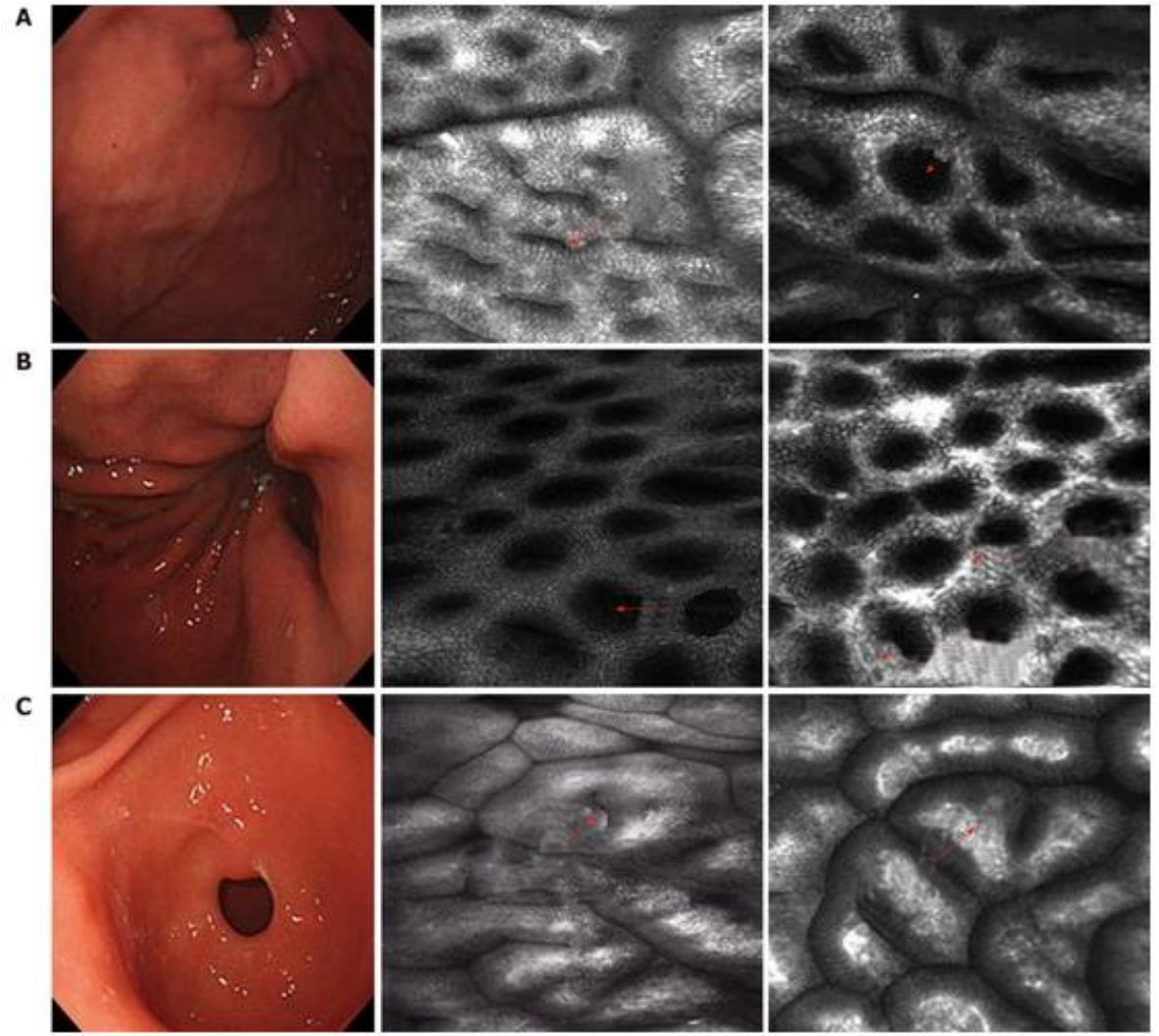
SEN: 83%

SP: 96%

- ❑ WLI has poor performance in the diagnosis of early gastric cancer.
- ❑ ME-NBI is an effective tool for real-time endoscopic diagnosis of early gastric cancer

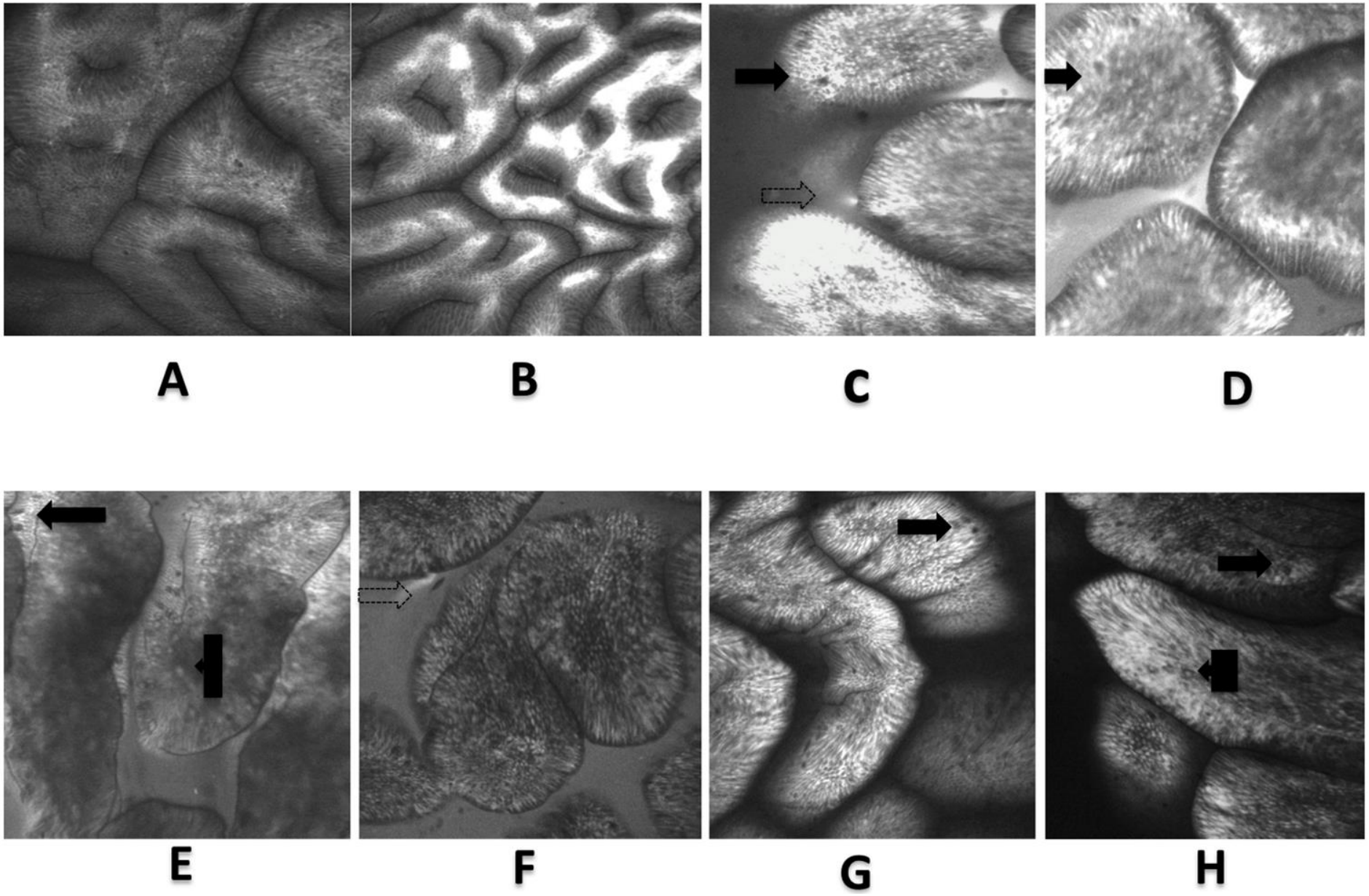
EARLY GASTRIC CANCER (EGC) : CONFOCAL LASER ENDOMICROSCOPY (CLE)





X 1000 fold magnification

Real-time histology


A
B
C
D
E
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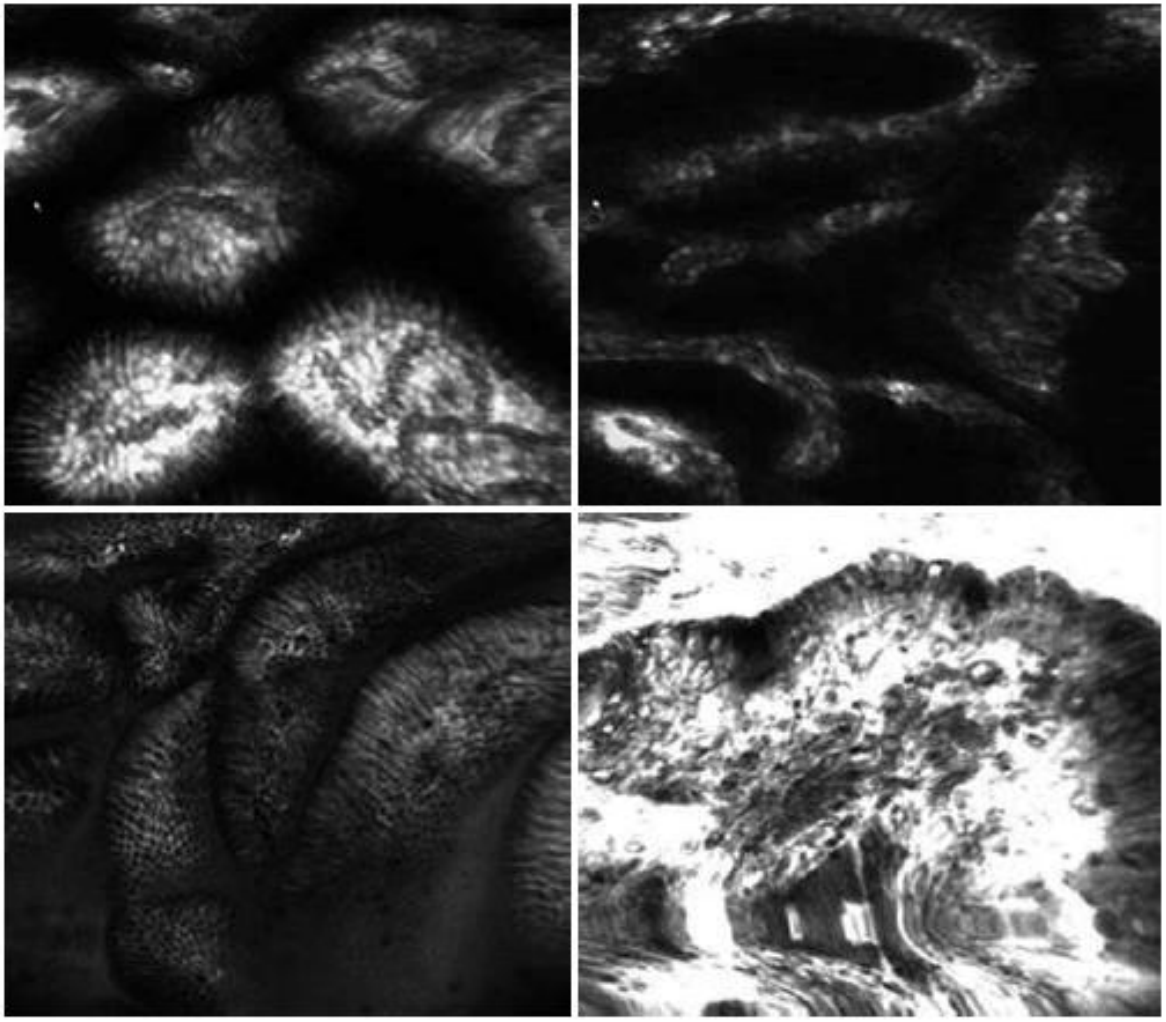
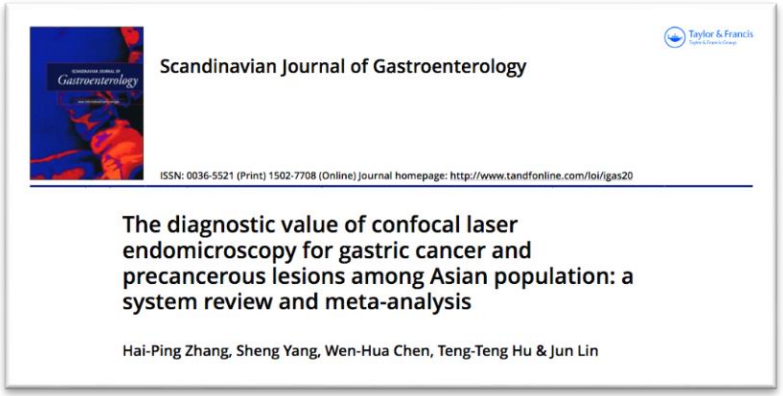
G
H

EARLY GASTRIC CANCER (EGC) : CONFOCAL LASER ENDOMICROSCOPY (CLE)





Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: http://www.tandfonline.com/loi/igas20

The diagnostic value of confocal laser endomicroscopy for gastric cancer and precancerous lesions among Asian population: a system review and meta-analysis

Hai-Ping Zhang, Sheng Yang, Wen-Hua Chen, Teng-Teng Hu & Jun Lin

Table 2. Subgroup analysis of CLE for diagnosing GC, GIM and GIN lesions.

		Pooled sensitivity	Heterogeneity	Pooled specificity	Heterogeneity
GC	Diagnostic criterion				
	Criteria in references [20,32]	89% (84–94%)	$I^2 = 0.0\%$, $p = 0.9832$	98% (96–99%)	$I^2 = 79.3\%$, $p = 0.0002$
	Criteria in other reference	93% (89–95%)	$I^2 = 44.1\%$, $p = 0.1047$	100% (99–100%)	$I^2 = 81.6\%$, $p = 0.0000$
	Real-time diagnosis				
	Yes	93% (89–96%)	$I^2 = 0.0\%$, $p = 0.5157$	100% (99–100%)	$I^2 = 82.1\%$, $p = 0.0000$
	No	90% (86–93%)	$I^2 = 15.0\%$, $p = 0.3121$	96% (93–98%)	$I^2 = 49.8\%$, $p = 0.0524$
GIM	Diagnostic criterion				
	Criteria in reference 19	92% (90–94%)	$I^2 = 69.1\%$, $p = 0.0035$	93% (92–95%)	$I^2 = 21.2\%$, $p = 0.2680$
	Criteria in other references	93% (89–95%)	$I^2 = 0.0\%$, $p = 0.5546$	99% (98–99%)	$I^2 = 94.9\%$, $p = 0.0000$
	Real-time diagnosis				
	Yes	91% (89–93%)	$I^2 = 0.0\%$, $p = 0.5492$	98% (97–98%)	$I^2 = 94.1\%$, $p = 0.0000$
	No	94% (91–97%)	$I^2 = 77.4\%$, $p = 0.0041$	94% (91–96%)	$I^2 = 0.0\%$, $p = 0.7027$
GIN	Diagnostic criterion				
	Criteria in reference [25]	77% (69–84%)	$I^2 = 76.1\%$, $p = 0.0022$	87% (82–90%)	$I^2 = 83.1\%$, $p = 0.0001$
	Criteria in other references	84% (77–90%)	$I^2 = 50.5\%$, $p = 0.0886$	100% (99–100%)	$I^2 = 86.3\%$, $p = 0.0000$
	Real-time diagnosis				
	Yes	84% (76–89%)	$I^2 = 0.0\%$, $p = 0.5168$	99% (98–99%)	$I^2 = 96.3\%$, $p = 0.0000$
	No	78% (70–84%)	$I^2 = 78.5\%$, $p = 0.0003$	91% (87–93%)	$I^2 = 78.6\%$, $p = 0.0003$

	sensibility	Specificity
Gastric cancer	**89-93%**	**98-100%**
Intestinal metaplasia	92-93%	93-99%
Intraepithelial neoplasia	77-84%	87-100%

Zhang 2016

*Take home message

- **Carefully inspection whit routine WLE** should be done to detect suspicious areas of malignancy especially in high risk patients (pre-malignant conditions)

- In superficial neoplasms, **New advanced imaging endoscopy** (Magnification endoscopy with chromoendoscopy or Narrow Band Imaging, or CLE) **is recomended to confirm the diagnosis and delimitate the extension**, especially when local endoscopic resection is planed

3.Staging

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi57–vi63, 2013
doi:10.1093/annonc/mdt344

Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

T. Waddell[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6*]

Table 1.
Diagnostic and staging investigations in gastric cancer

Procedure	Purpose
Full blood count	Assess for iron deficiency anaemia
Renal and liver function	Assess renal and liver function to determine appropriate therapeutic options
Endoscopy and biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers, e.g. HER2 status
CT thorax + abdomen ± pelvis	Staging of tumour—to detect local/distant lymphadenopathy and metastatic disease or ascites
EUS	Accurate assessment of T and N stage in potentially operable tumours
	Determine the proximal and distal extent of tumour
Laparoscopy ± washings	Exclude occult metastatic disease involving peritoneum/diaphragm
PET, if available	May improve detection of occult metastatic disease in some cases

CT, computed tomography; EUS, endoscopic ultrasound; PET, positron emission tomography

clinical practice guidelines

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clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v38–v49, 2016
doi:10.1093/annonc/mdw350

Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. C. Smyth[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6] on behalf of the ESMO Guidelines Committee*

CT (TAP)
Consider PET if CT-

- Rule out M+

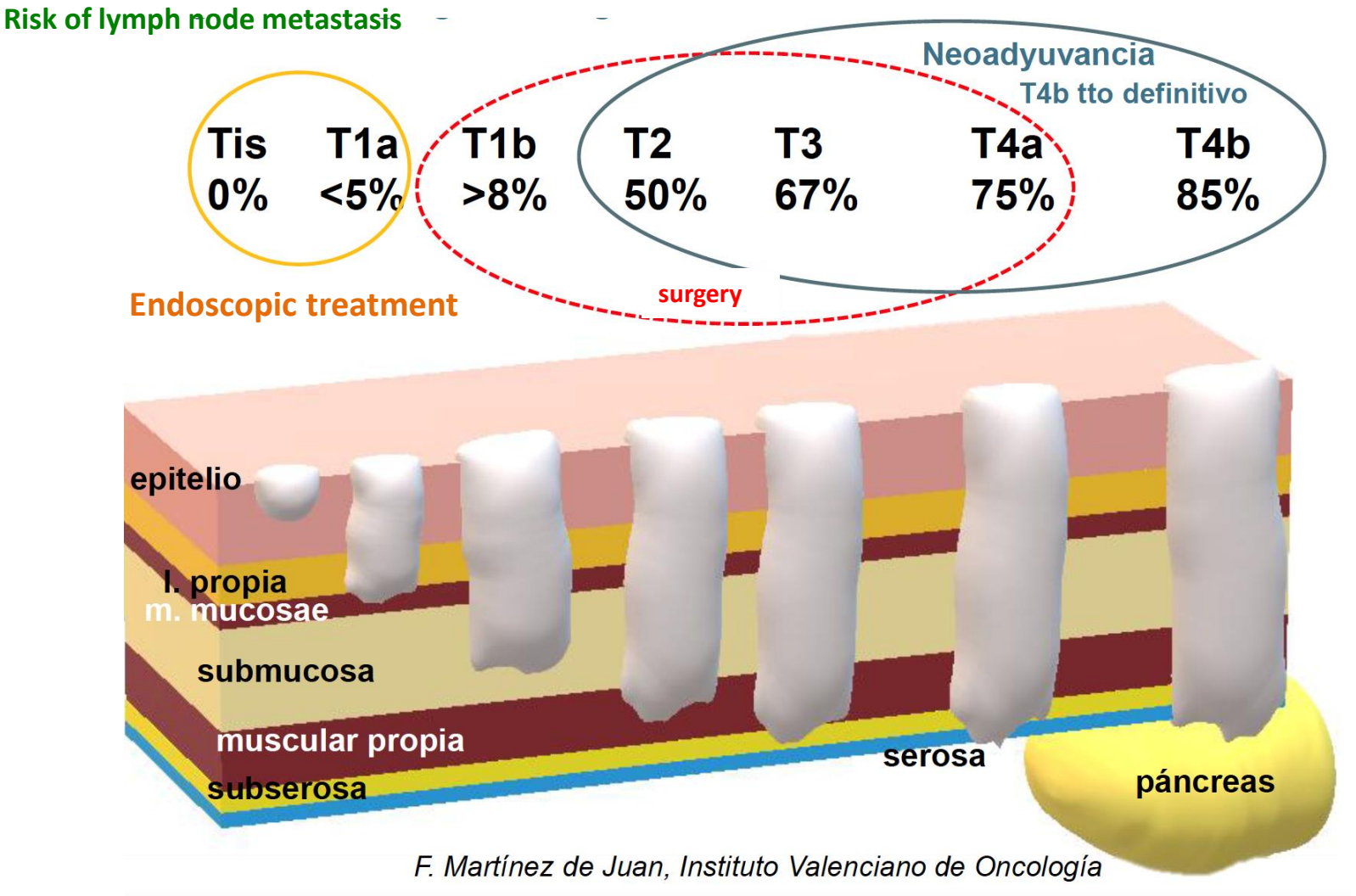
EUS

- Locorregional staging/extent

Consider
LAPAROSCOPY

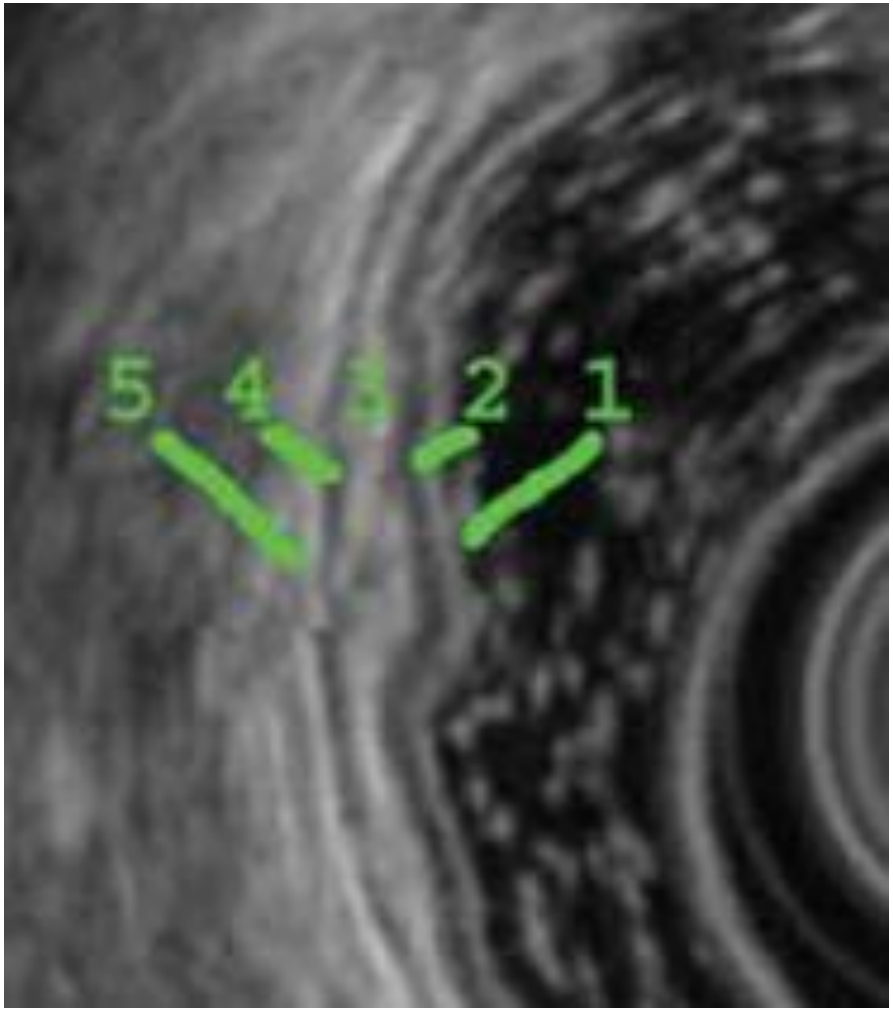
- Exclude occult metastatic disease in some cases
- (pre or during surgery)

IMPORTANCE OF T- STAGING OF GASTRIC CANCER

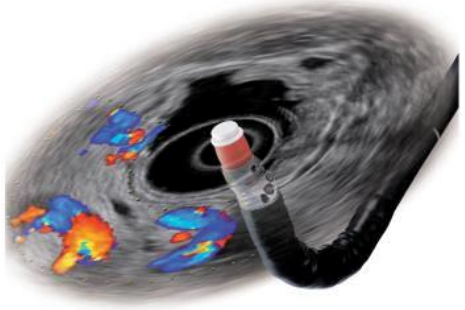


F. Martínez de Juan, Instituto Valenciano de Oncología

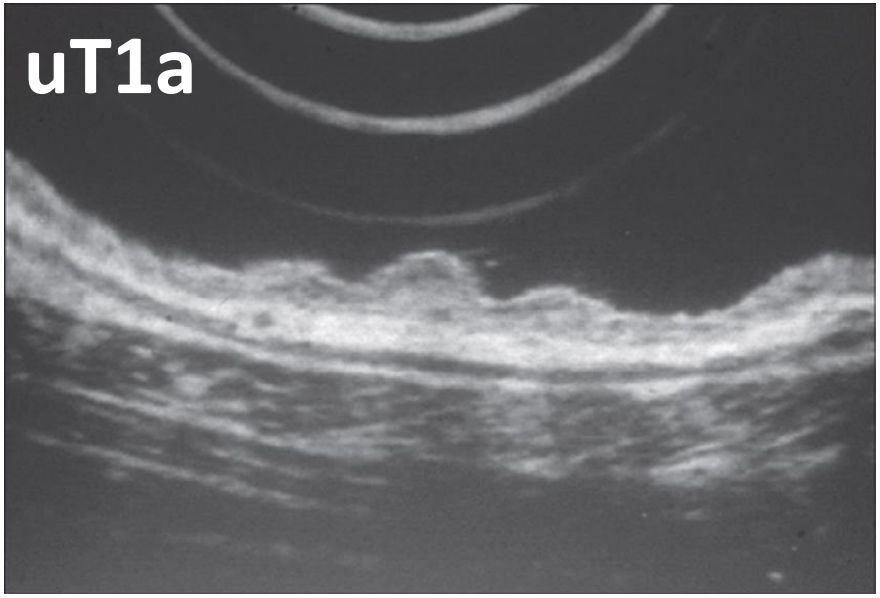
EUS T-STAGING. NORMAL GASTRIC WALL

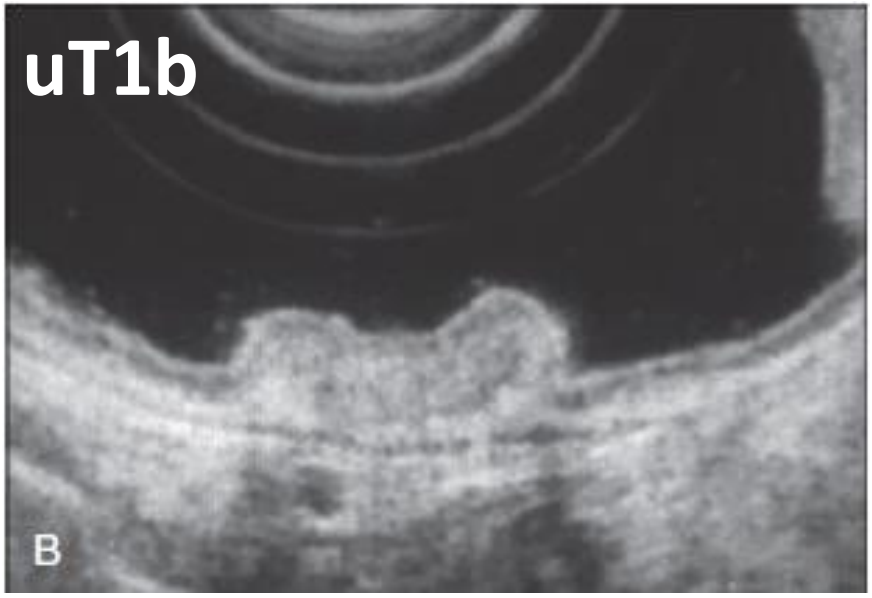


EUS Layer and Echo Features	Histologic Correlation
First (hyperechoic)	Superficial mucosa
Second (hypoechoic	Deep mucosa
Third (hyperechoic)	Submucosa
Fourth (hypoechoic)	Muscularis propria
Fifth (hyperechoic)	Serosa

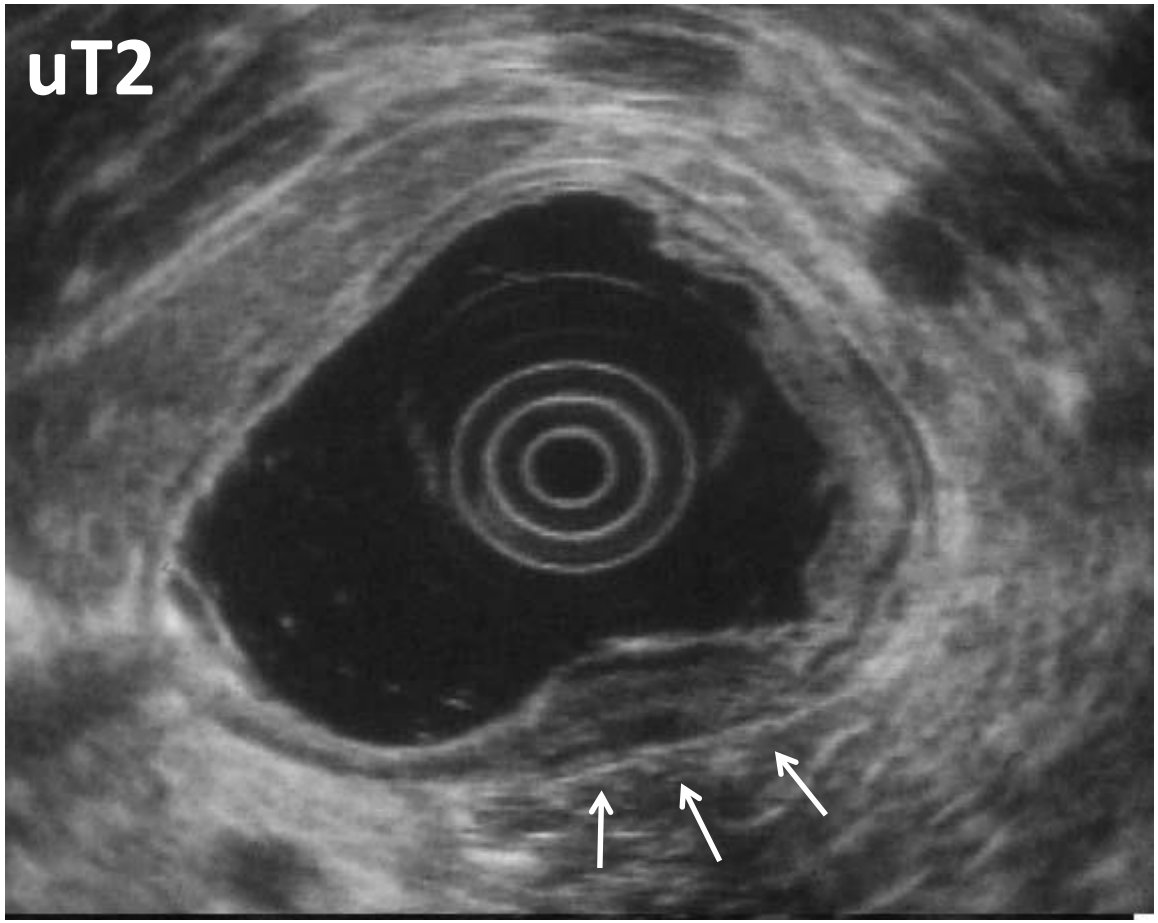


EUS T-STAGING. T1 (miniprobes 20 Hz)



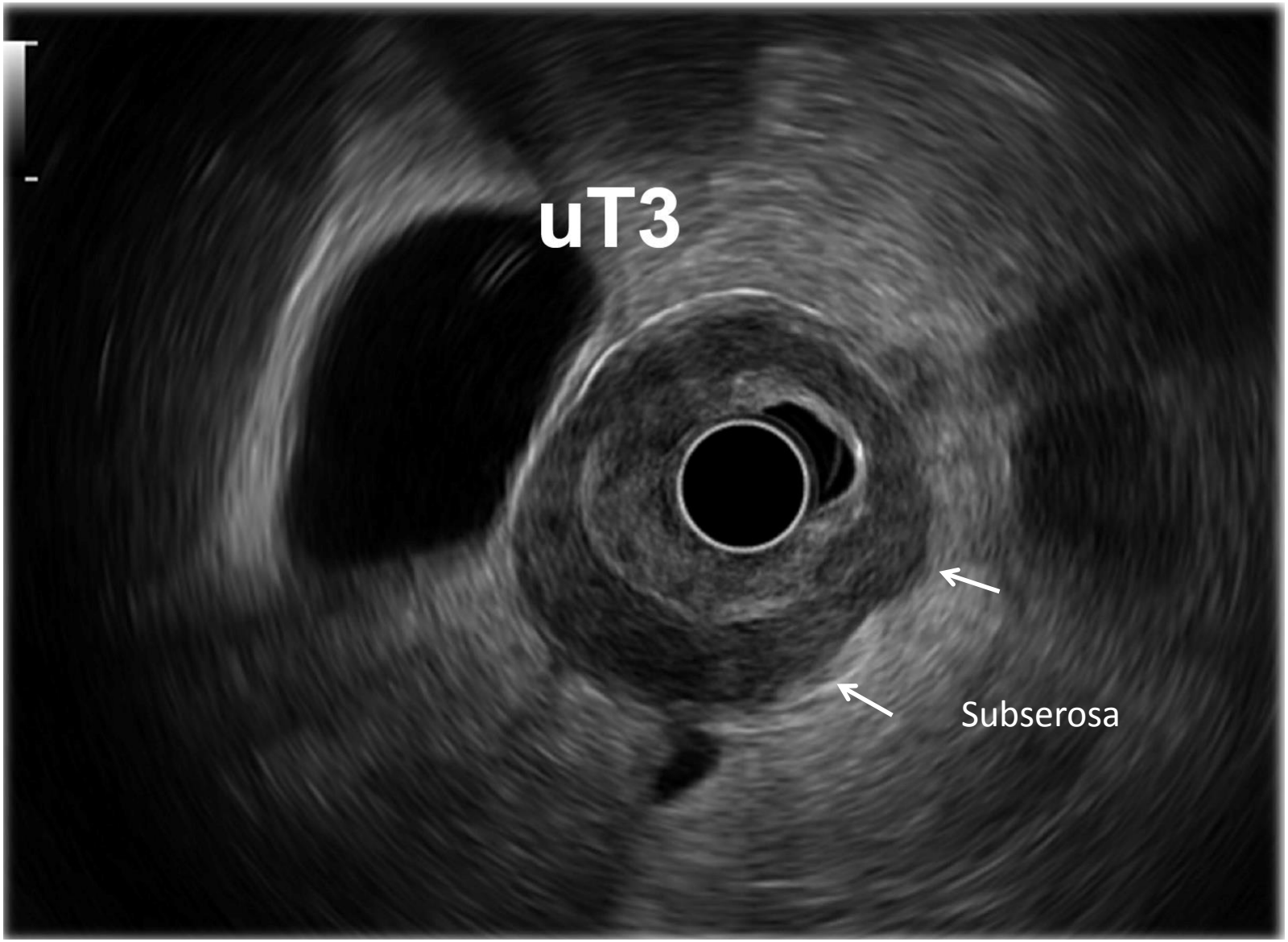


EUS T-STAGING. T2 (radial EUS)



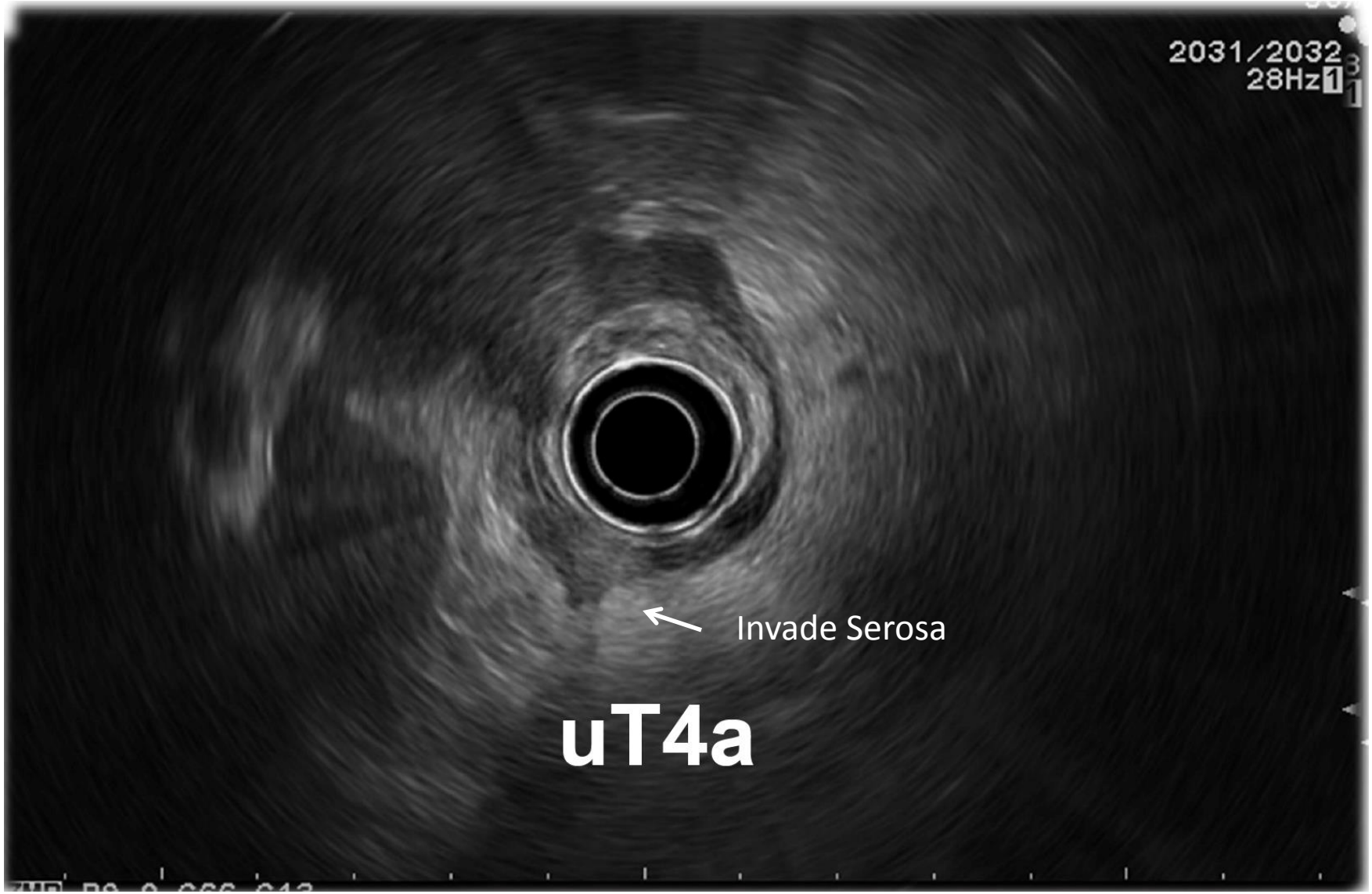
Courtesy of Fernando Martinez de Juan. Insituto Valenciano de Oncología (IVI)

EUS T-STAGING. T3 (radial EUS)



Courtesy of Fernando Martinez de Juan. Insituto Valenciano de Oncología (IVI)

EUS T-STAGING. T4a (radial EUS)



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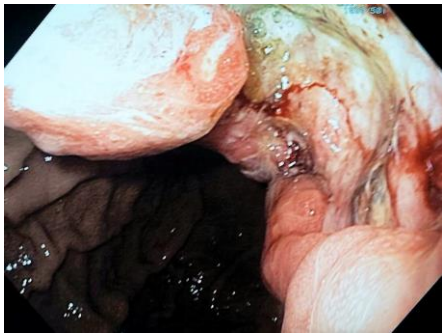
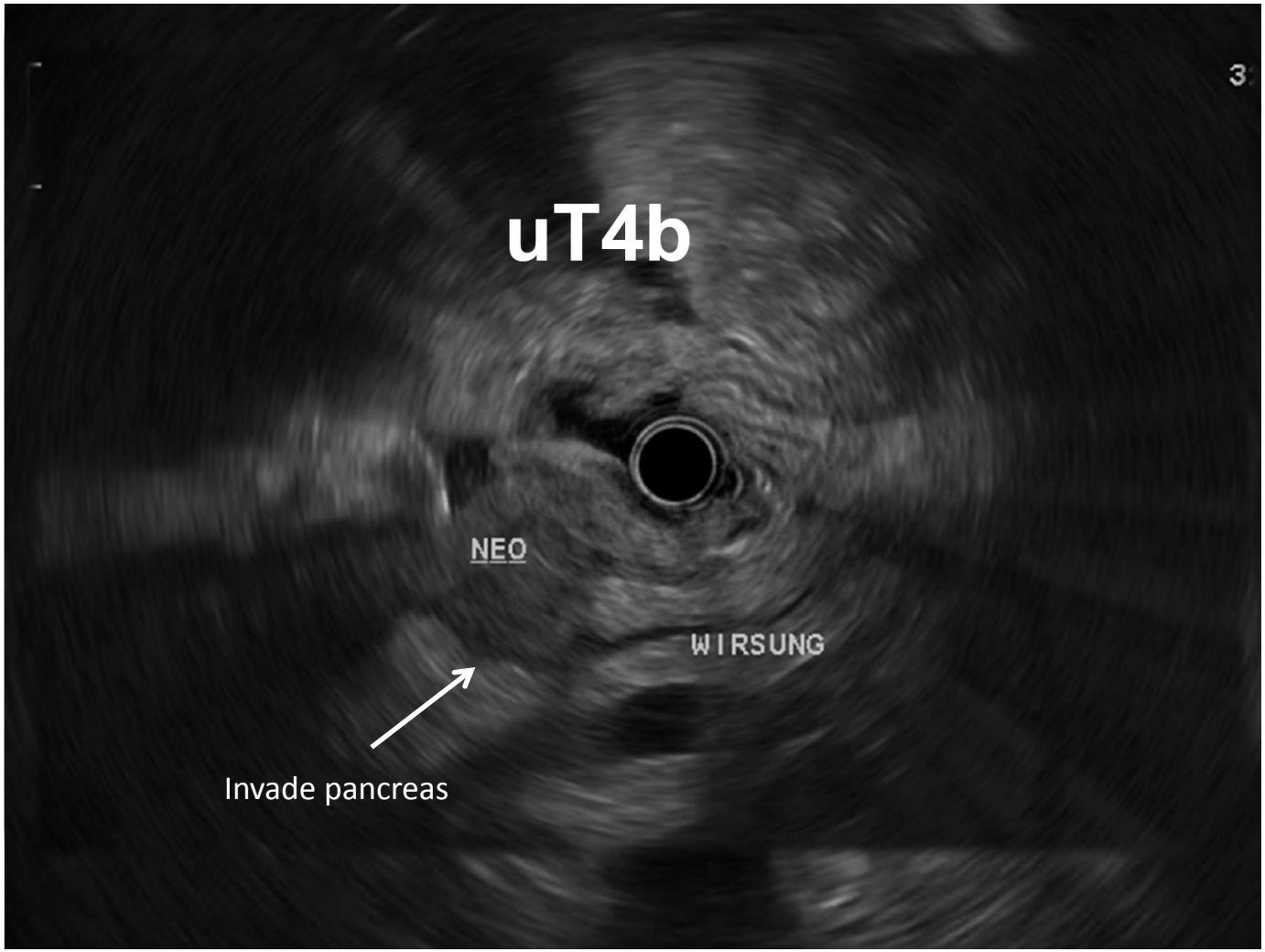
EUS T-STAGING. T4b (radial EUS)





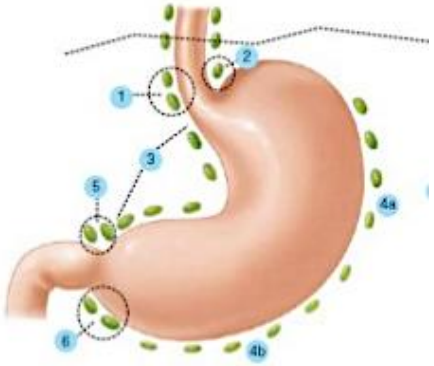
Courtesy of Fernando Martinez de Juan. Insituto Valenciano de Oncología (IVI)

EUS IN N- STAGING OF GASTRIC CANCER

LN stations

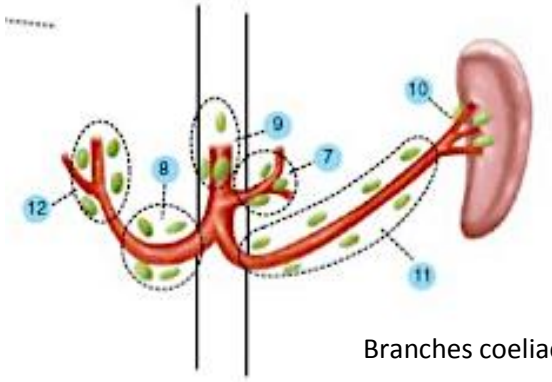
LYMPH NODE STATION (NO.)	DESCRIPTION	LOCATION OF PRIMARY TUMOR IN STOMACH		
		Upper Third	Middle Third	Lower Third
1	Right paracardial	1	1	2
2	Left paracardial	1	3	M
3	Lesser curvature	1	1	1
4sa	Short gastric	1	3	M
4sb	Left gastroepiploic	1	1	3
4d	Right gastroepiploic	2	1	1
5	Suprapyloric	3	1	1
6	Infrapyloric	3	1	1
7	Left gastric artery	2	2	2
8a	Anterior comm. hepatic	2	2	2
8p	Posterior comm. hepatic	3	3	3
9	Celiac artery	2	2	2
10	Splenic hilum	2	3	M
11p	Proximal splenic	2	2	2
11d	Distal splenic	2	3	M
12a	Left hepatoduodenal	3	2	2
12b,p	Posterior hepatoduodenal	3	3	3
13	Retropancreatic	M	3	3
14v	Superior mesenteric vein	M	3	2
14a	Superior mesenteric artery	M	M	M
15	Middle colic	M	M	M
16al	Aortic hiatus	3	M	M
16a2,b1	Para-aortic, middle	M	3	3
16b2	Para-aortic, caudal	M	M	M

Lymphatic drainage



N1

Perigastric



N2

Branches coeliac axis

EUS IN N- STAGING OF GASTRIC CANCER

LN stations

LYMPH NODE STATION (NO.)	DESCRIPTION	LOCATION OF PRIMARY TUMOR IN STOMACH		
		Upper Third	Middle Third	Lower Third
1	Right paracardial	1	1	2
2	Left paracardial	1	3	M
3	Lesser curvature	1	1	1
4sa	Short gastric	1	3	M
4sb	Left ga	1	1	3
4d	Right g	2	1	1
5	Suprap	3	1	1
6	Infrapyl	3	1	1
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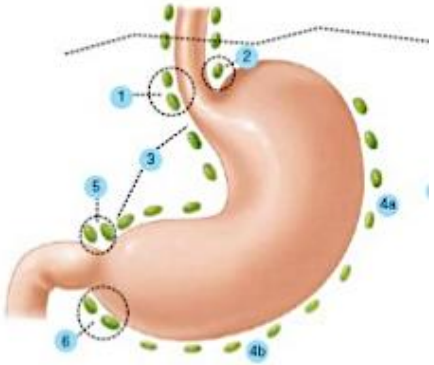
13	Retropancreatic	M	3	3
14v	Superi	M	3	2
14a	Superi	M	M	M
15	Middle	M	M	M
16al	Aortic h	3	M	M
16a2,b1	Para-a	M	3	3
16b2	Para-a	M	M	M

N+

M+

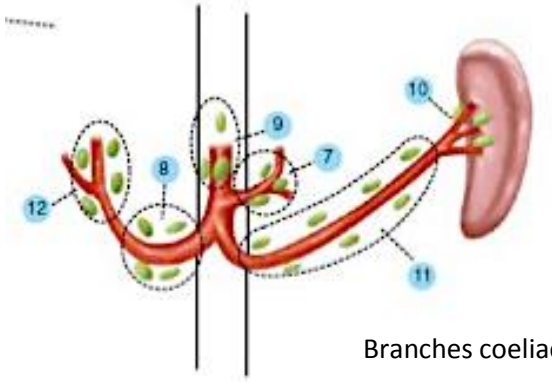
Lymphatic drainage



N1

Perigastric

D1

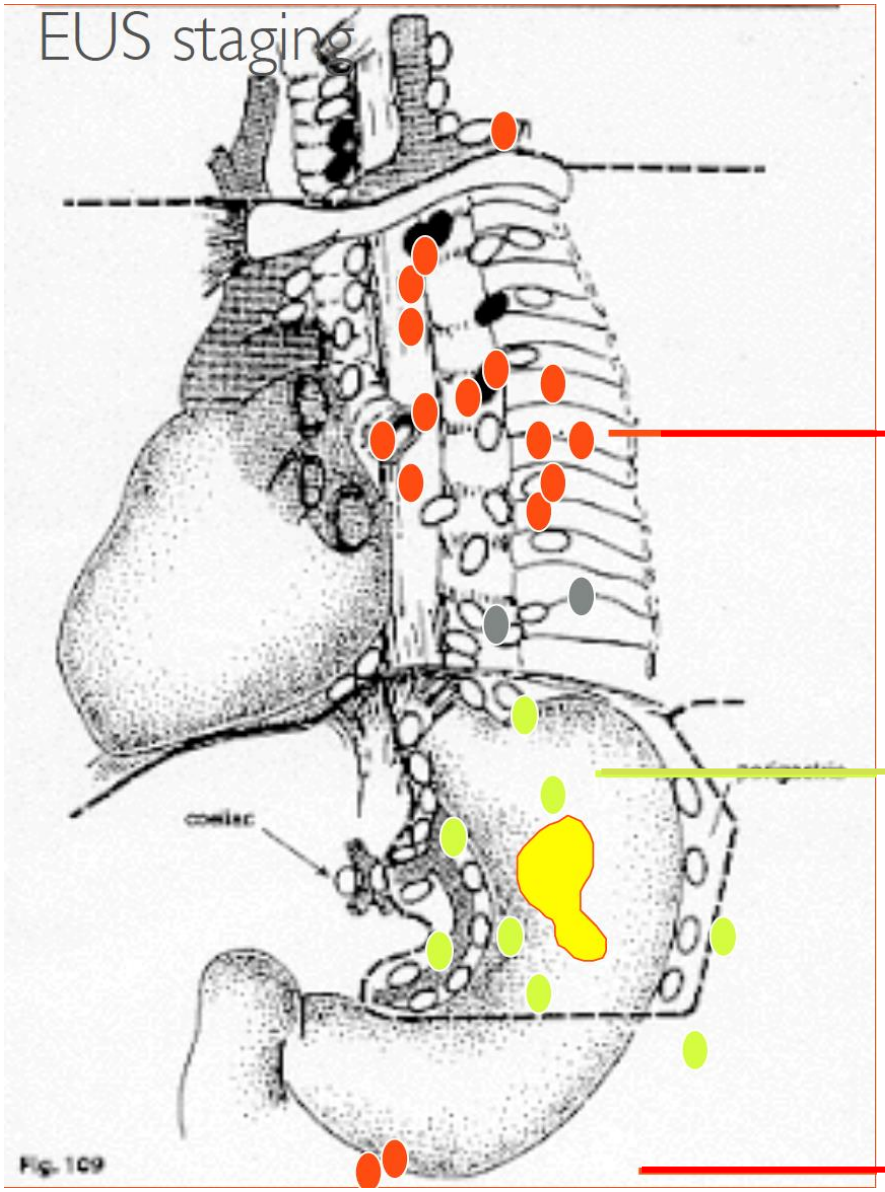


N2

D2

Branches coeliac axis

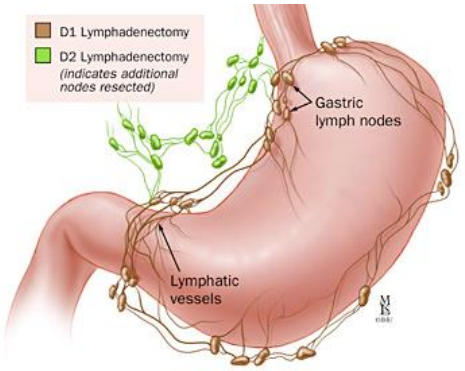
EUS IN N- STAGING OF GASTRIC CANCER



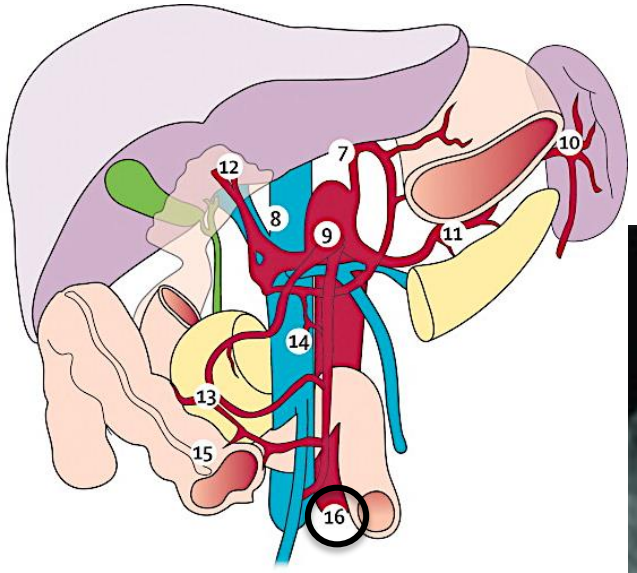
Mediastinum → **M+**

1-12 → **N+**

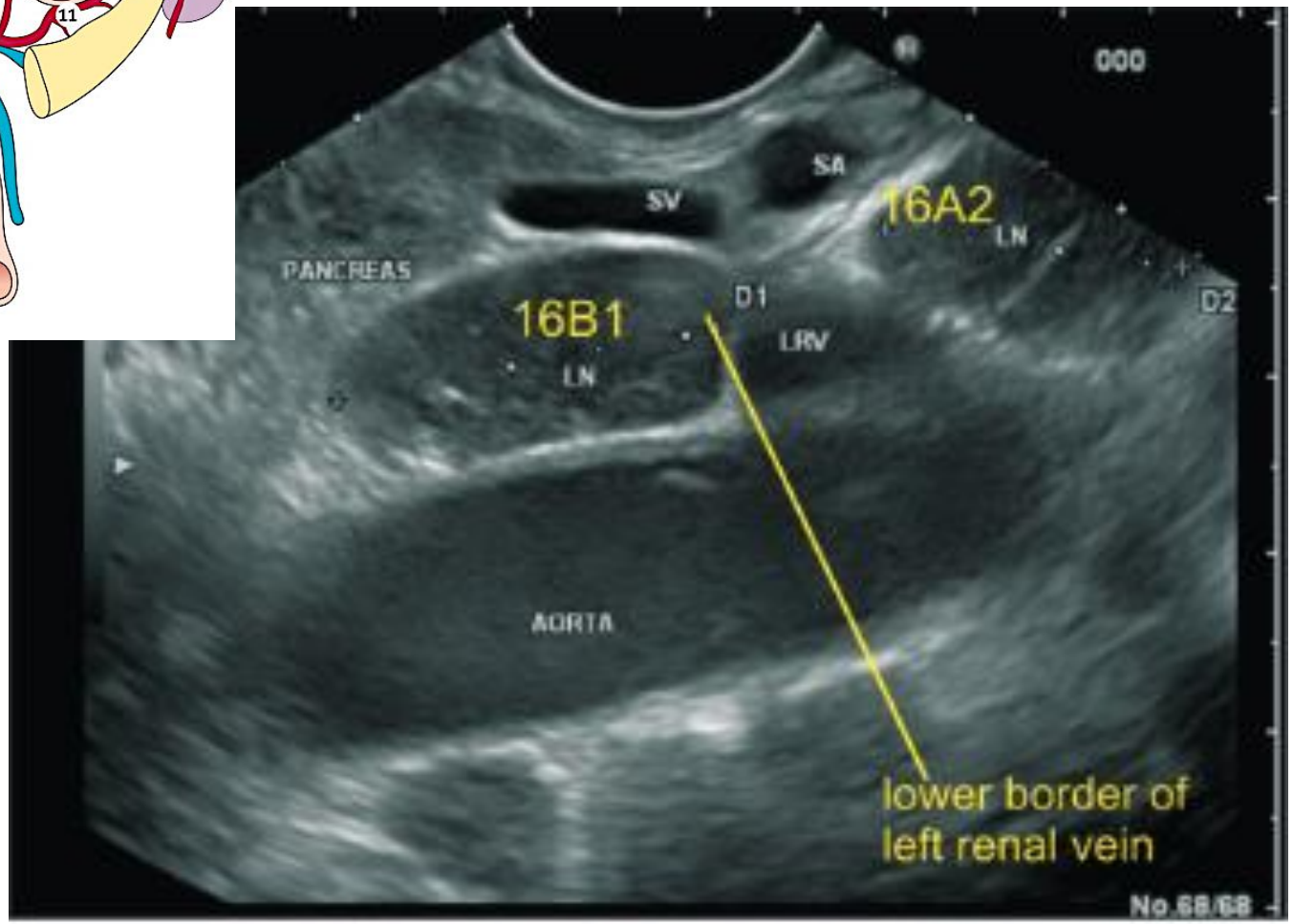
13-16 → **M+**



EUS IN N- STAGING OF GASTRIC CANCER

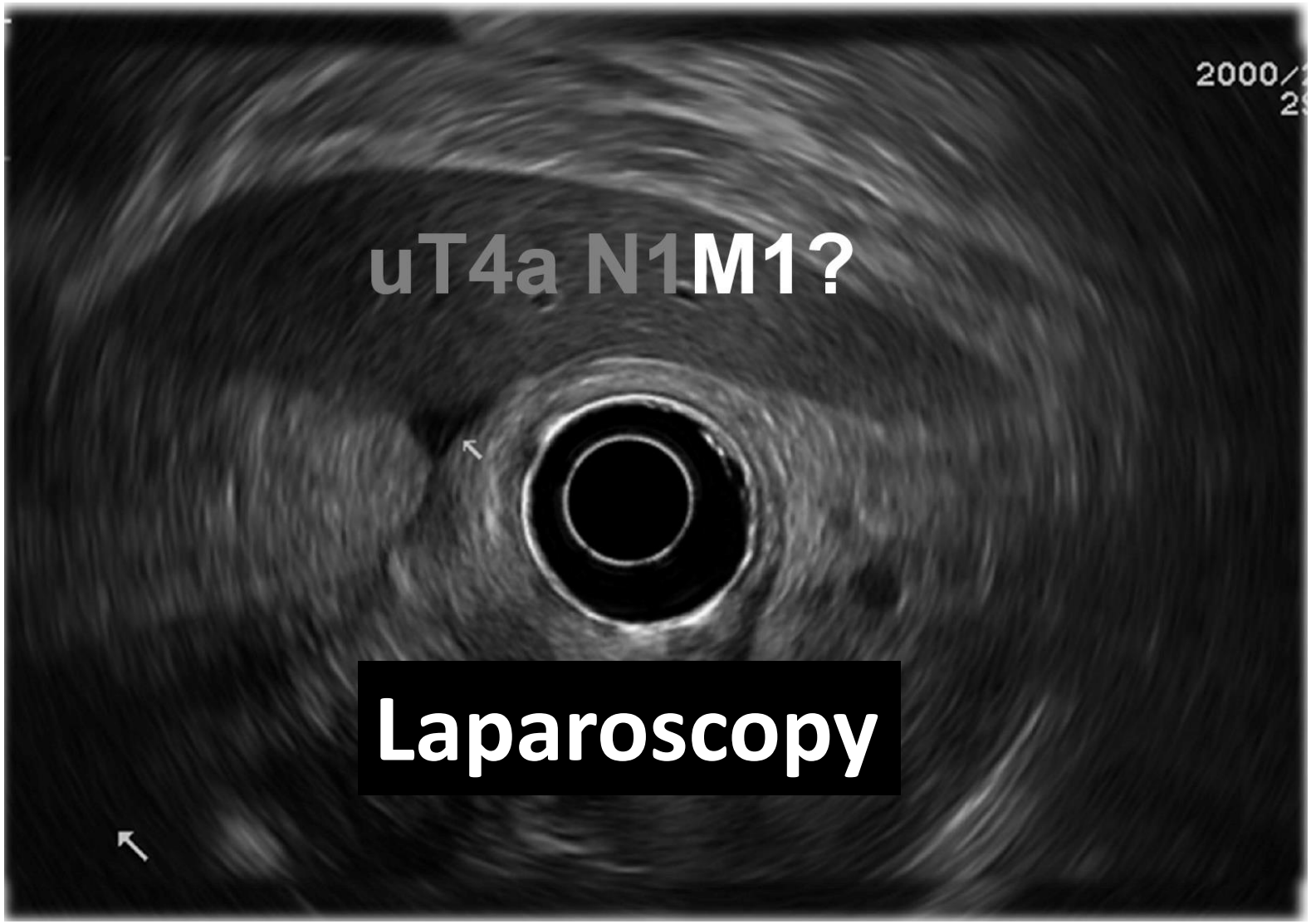


M+



Techniques of imaging of nodal stations of gastric cancer by endoscopic ultrasound. Sharma M. eusjournal 2018

EUS IN M- STAGING OF GASTRIC CANCER



Courtesy of Fernando Martinez de Juan. Insituto Valenciano de Oncología (IVI)

EUS IN M- STAGING OF GASTRIC CANCER

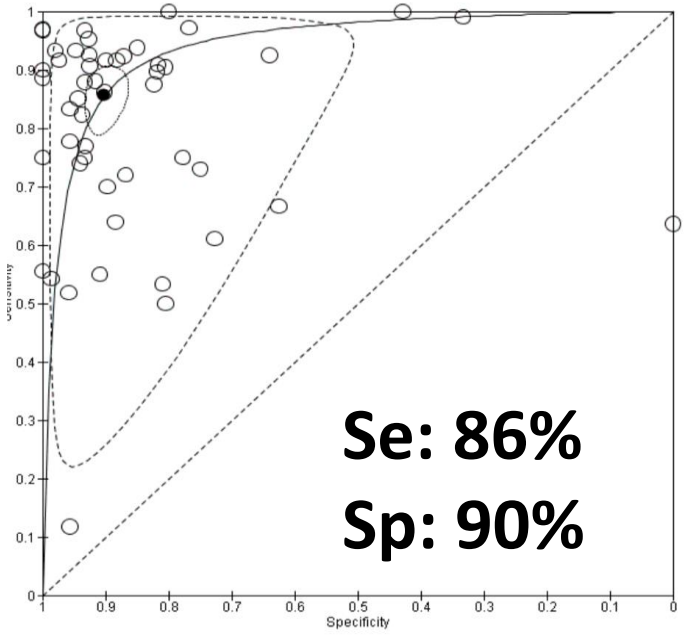
M+

Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer (Review)

Mocellin S, Pasquali S

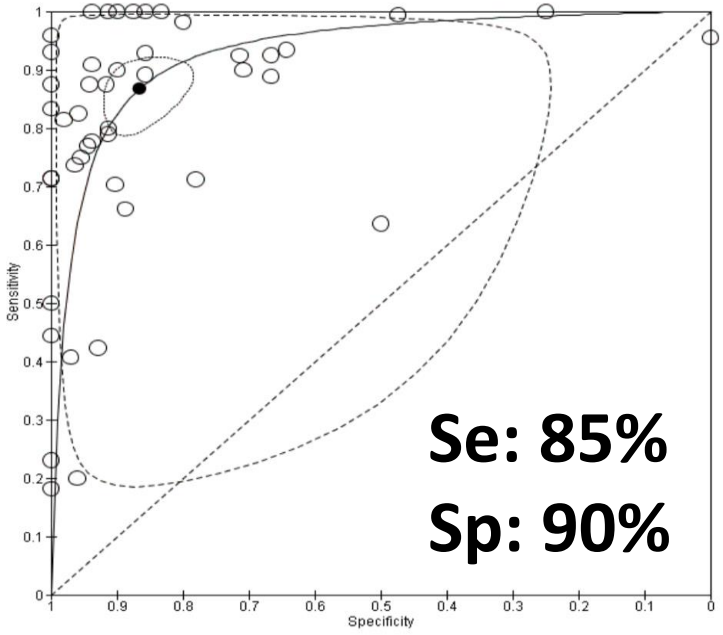
2015 meta-analysis, 66 studies, 7747 patients

T1-T2 vs T3-T4



Se: 86%
Sp: 90%

T1 vs T2



Se: 85%
Sp: 90%

Mocellin 2015

Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer (Review)

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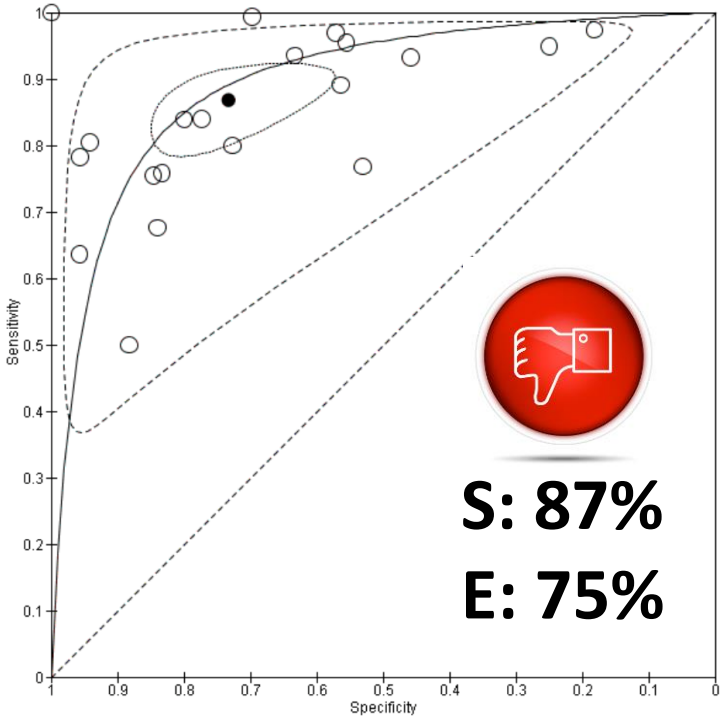
T1a vs T1b



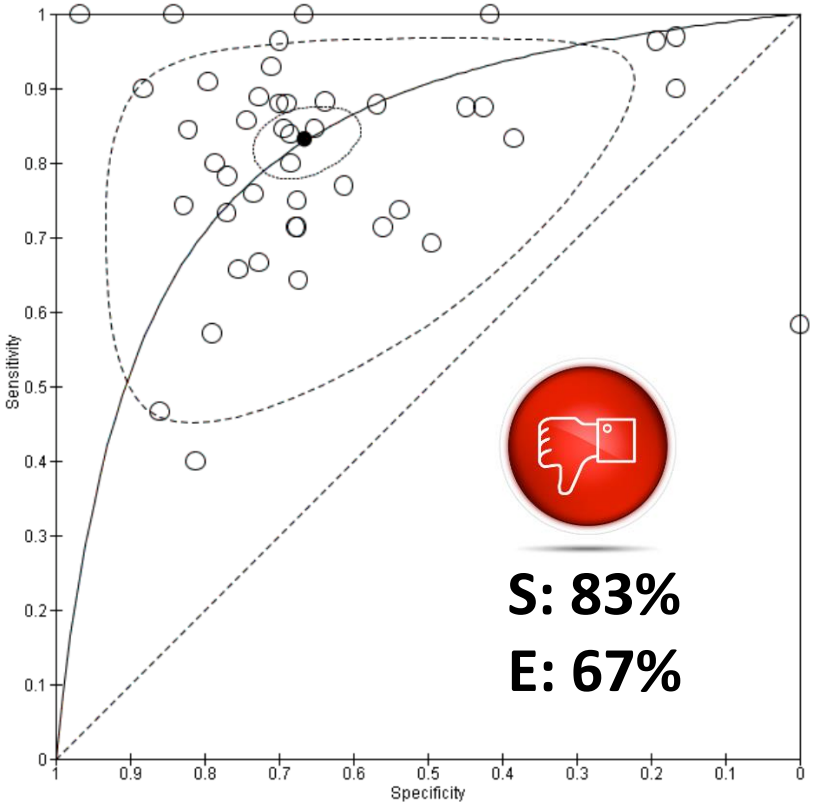
S: 87%

E: 75%

Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer (Review)

Mocellin S, Pasquali S

N+ vs N-



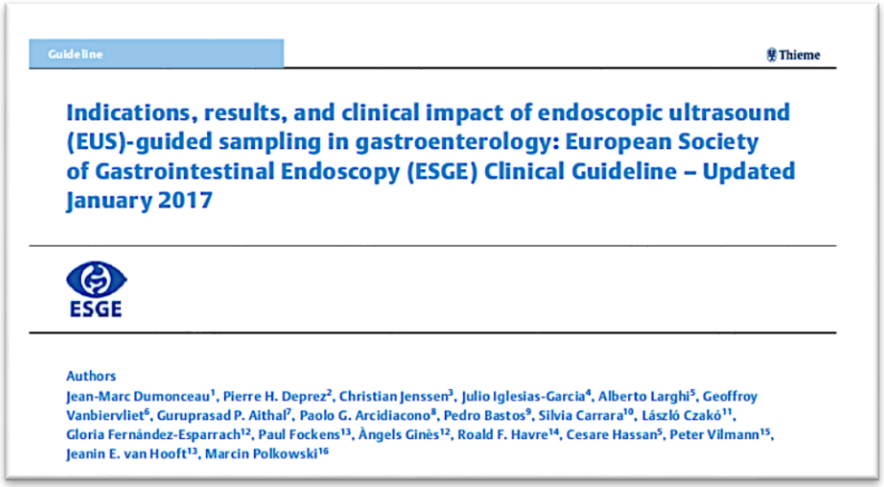
EUS N-STAGING: RELIABILITY OF BIOPSY

FNA Lymph nodes:

- **Specificity** for adenocarcinoma is considered around of 100%.
- **Sensitivity** varies from 87 to 100%

IS IT NECESSARY TO PUNCTURE ALL THE LYMPH NODES?

EUS N-STAGING: RELIABILITY OF BIOPSY



Guideline

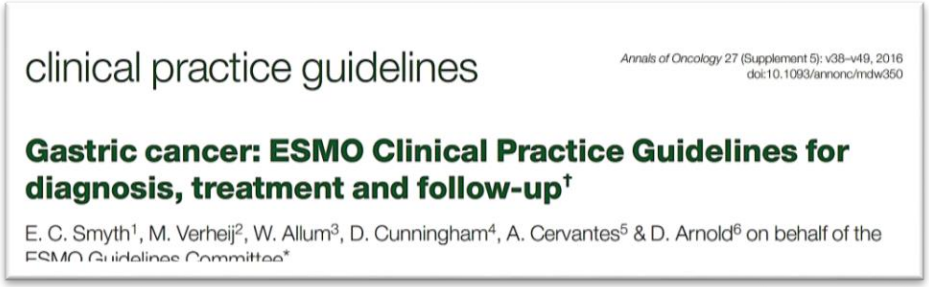
Thieme

Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline – Updated January 2017

ESGE

Authors

Jean-Marc Dumonceau[1], Pierre H. Deprez[2], Christian Jenssen[3], Julio Iglesias-Garcia[4], Alberto Larghi[5], Geoffroy Vanbiervliet[6], Guruprasad P. Aithal[7], Paolo G. Arcidiacono[8], Pedro Bastos[9], Silvia Carrara[10], László Czakó[11], Gloria Fernández-Esparrach[12], Paul Fockens[13], Àngels Ginès[12], Roald F. Havre[14], Cesare Hassan[5], Peter Vilmann[15], Jeanin E. van Hooft[13], Marcin Polkowski[16]



clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v38–v49, 2016
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Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

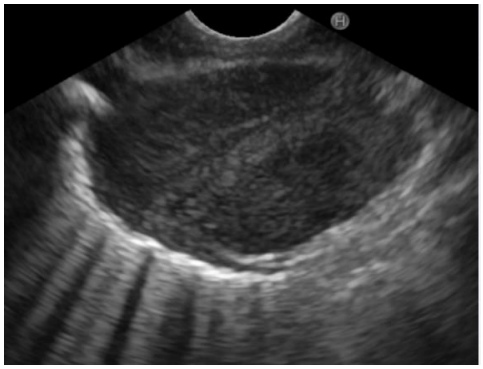
E. C. Smyth[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6] on behalf of the ESMO Guidelines Committee*

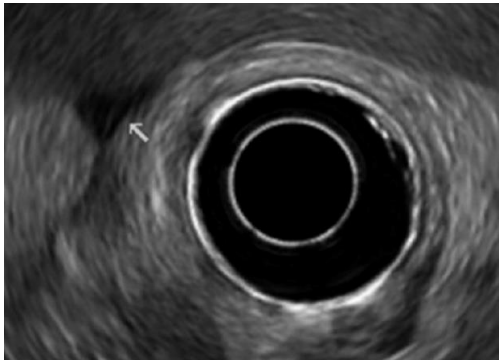
- **No rutine EUS-guide sampling.**
- **Only if impact in treatment decisions (prognosis)**

EUS N-STAGING: RELIABILITY OF BIOPSY

- **Mortensen et al:** Prospective study of 62 patients. Therapeutic changed in **8%** of the patients after exclusion of suspected metastasis lesions on CT-scan
- **Hassan et al:** retrospective study of 234 patients. Therapeutic management changed in **15%** of the patients
- **Araujo et al:** Retrospective study of 115 patients. Therapeutic management changes in **23%** of the patients

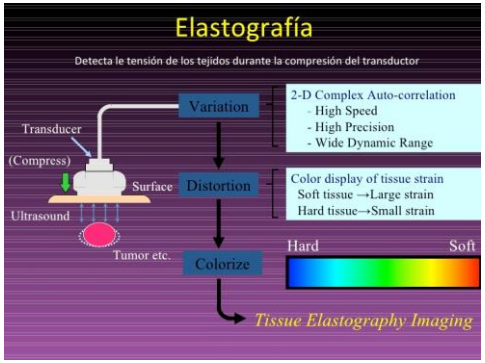
EUS staging, looking for distant lesions will **change your therapeutic management in 8 to 23%** finding lesion which will change the status of the patient (local disease to metastatic disease)



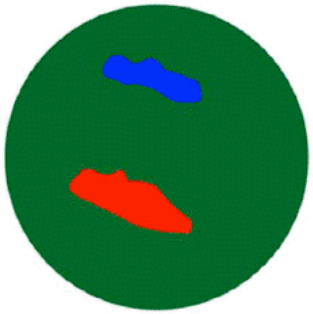


Mortensen Mb et al . Endoscopy, 2001;
Hassan C et al GIE, 2010;
Araujo J et al. Ends Ultrasound, 2014;
Dumonceau JM et al. Endoscopy 2011.

EUS N-STAGING: ELASTOSONOGRAPHY



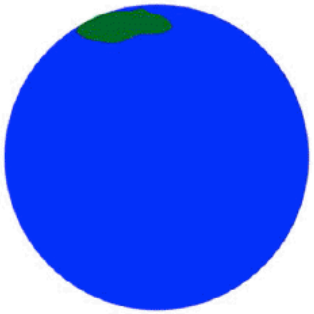
ES 1



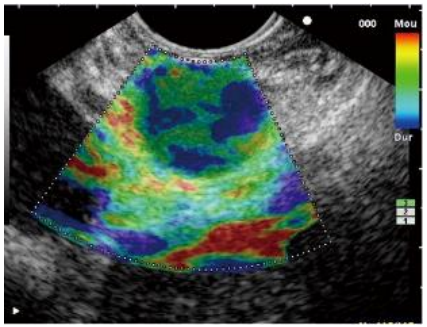
ES 2

ES 3

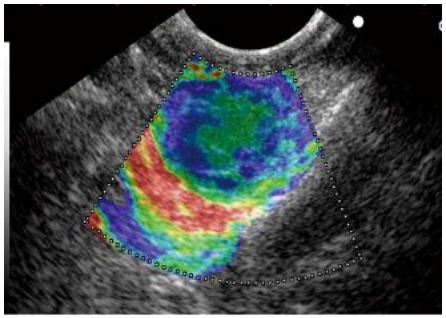
ES 4



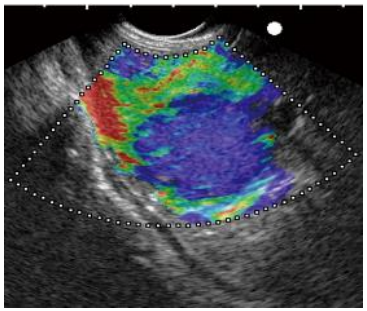
Normal LN



inflammatory LN



Malignant
(central necrosis)



Malignant
(homogeneus)

EUS N-STAGING: ELASTOSONOGRAPHY

ELASTOGRAPHY VS CONVENTIONAL B-MODE :

SEN: 83,6%
SPE: 95%

SEN: 78.6%;
SPE: 50%

US elastography is **superior** compared to conventional B-mode imaging and appears to be able to distinguish benign from malignant lymph nodes
But….EUS elastography is not considered a modality that can replace biopsy. it should be considered as **complementary** to other imaging techniques rather than a replacement for tissue confirmation EUS-e has the potential to be useful for **target selection** prior to endosonographic guided tissue sampling

Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: A multicenter study. Giovannini M. 2009

Endoscopic ultrasound elastography: current status and future perspectives Xin-Wu Cui. 2015

EUS N-STAGING: ELASTOSONOGRAPHY

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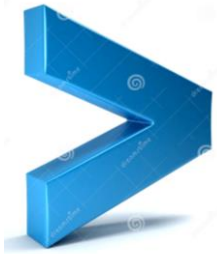

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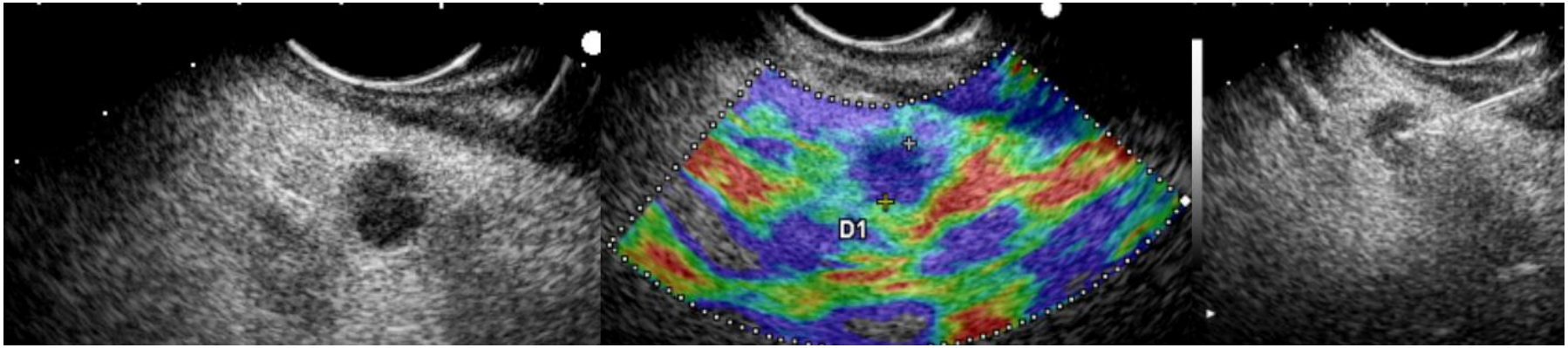

Endoscopic ultrasound elastography for evaluation of lymph nodes and pancreatic masses: A multicenter study. Giovannini M. 2009

Endoscopic ultrasound elastography: current status and future perspectives Xin-Wu Cui, Jian-Min Chang, Quan-Cheng Kan, Liliana Chiorean, Andre Ignee, Christoph F Dietrich 2015

*Take home message

- **EUS staging** is **more reliable than others techniques** to differentiate T1 from T2 and superficial versus advanced gastric tumors but has a moderate/low sensibility and specificity to differentiate between mucosal and submucosal in T1 cancers or in lymph node involvement

- EUS staging **will not change the therapeutic management** in most cases. Neoadjuvant chemotherapy is already decided.

- But… EUS staging, looking for distant lesions will **change the therapeutic management in 8 to 23%** finding lesion which will change the status of the patient (local disease to metastatic disease)

4.Treatment

clinical practice guidelines

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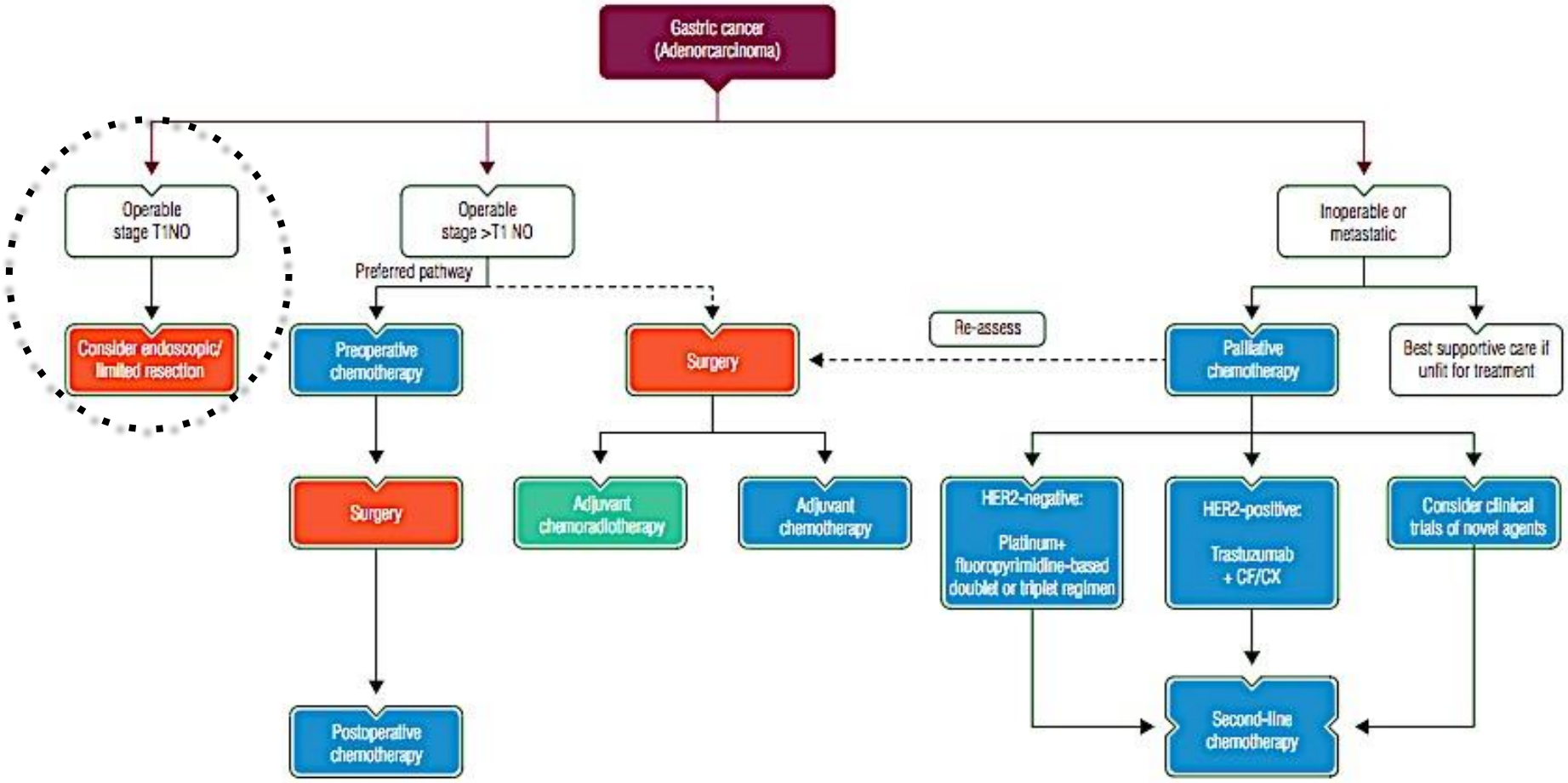

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Annals of Oncology 27 (Supplement 5): v38–v49, 2016
doi:10.1093/annonc/mdw350

Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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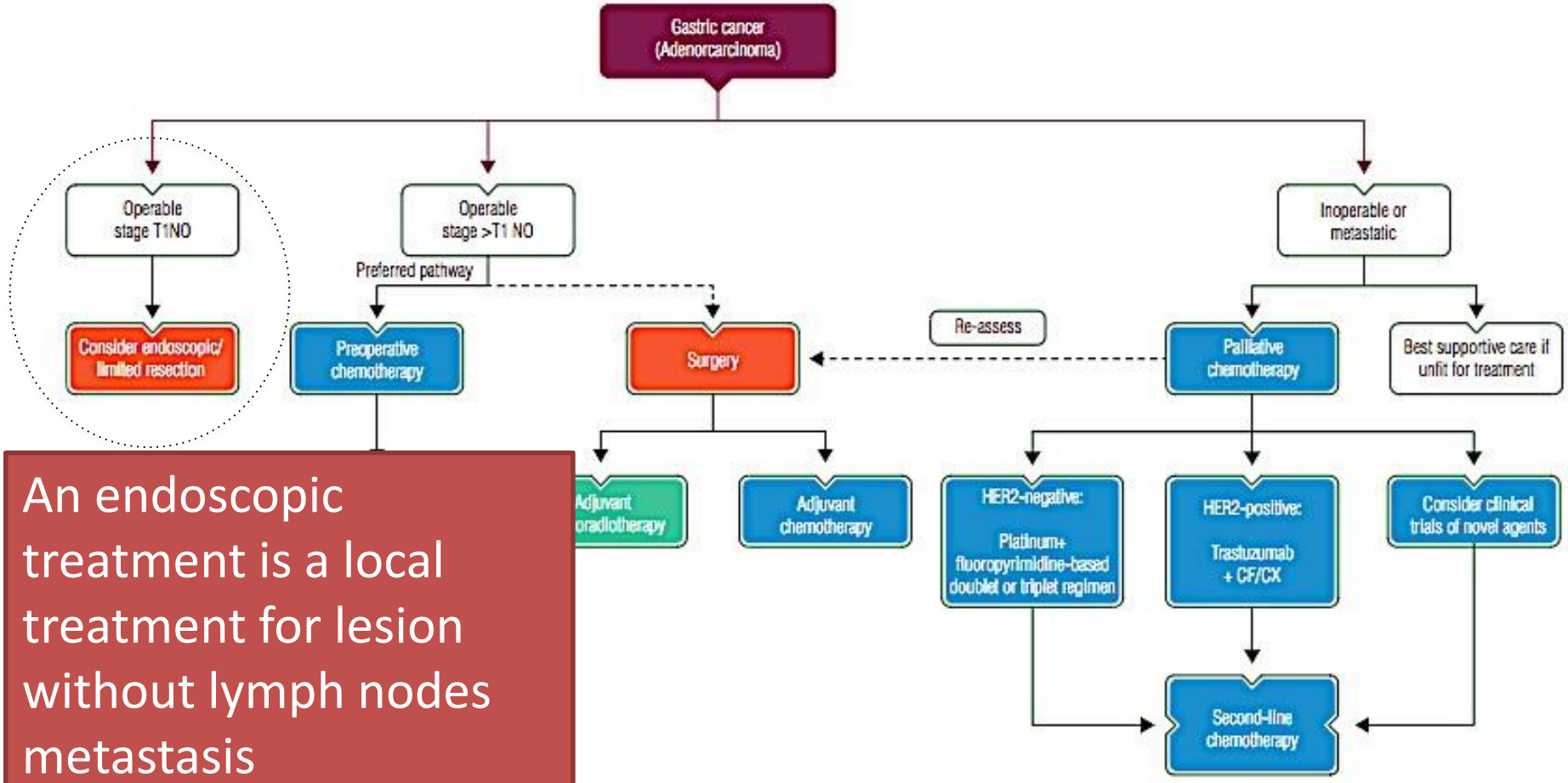

An endoscopic treatment is a local treatment for lesion without lymph nodes metastasis

Digestive Endoscopy 2016; **28**: 3–15 doi: 10.1111/den.12518

Guideline

*Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer**

Hiroyuki Ono,[1,2] Kenshi Yao,[1,2] Mitsuhiro Fujishiro,[1,2] Ichiro Oda,[1,2] Satoshi Nimura,[2] Naohisa Yahagi,[1,2] Hiroyasu Iishi,[1,2] Masashi Oka,[1,2] Yoichi Ajioka,[2] Masao Ichinose[1] and Toshiyuki Matsui[1]

[1]*Japan Gastroenterological Endoscopy Society, Tokyo, and* [2]*Japanese Gastric Cancer Association, Kyoto, Japan*

Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

ESGE

Authors

Pedro Pimentel-Nunes[1], Mário Dinis-Ribeiro[1], Thierry Ponchon[2], Alessandro Repici[3], Michael Vieth[4], Antonella De Ceglie[5], Arnaldo Amato[6], Frieder Berr[7], Pradeep Bhandari[8], Andrzej Bialek[9], Massimo Conio[10], Jelle Haringsma[11], Cord Langner[12], Søren Meisner[13], Helmut Messmann[14], Mario Morino[15], Horst Neuhaus[16], Hubert Piessevaux[17], Massimo Rugge[18], Brian P. Saunders[19], Michel Robaszkiewicz[20], Stefan Seewald[21], Sergey Kashin[22], Jean-Marc Dumonceau[23], Cesare Hassan[24], Pierre H. Deprez[17]

INDICATIONS FOR ENCOSCOPIC RESECTION?

ESGE recommends endoscopic resection for the treatment of ***gastric superficial neoplastic lesions*** that possess a **very low risk of lymph node metastasis**

Endoscopy in gastric cancer: new treatment modalities (EMR, ESD)

INDICATIONS FOR ENCOSCOPIC RESECTION?

ESGE recommends endoscopic resection for the treatment of ***gastric superficial neoplastic lesions*** that possess a **very low risk of lymph node metastasis**

Tumor-related factors

- **Grade of difererentiation** (diferentiated/diffuse)
- **Size** (horizontal expansion)
- **Depth** (vertical invasion)
- **Morphology** (ulcerated/non-ulcerated)
- **Lympho-Vascular invasion** (+/-)

Technique-related factors

- **Resection** ("en bloc" vs piecemeal)
- **Margins** (free)

Final Objetive: **Negligible Risk** of lymph node methastasis after resection

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ABSOLUTE INDICATIONS

- **Macroscopically intramucosal (cT1a) differentiated carcinomas measuring less than 2cm**

EXPANDED INDICATIONS

- Macroscopically intramucosal (cT1a) UL-, differentiated carcinomas >2cm, LV-
- Macroscopically intramucosal (cT1a) UL+, differentiated carcinomas <3cm, LV-
- Macroscopically intramucosal (cT1a) UL-, undifferentiated carcinomas <2cm, LV-

Differentiated-type adenocarcinoma with superficial submucosal invasion (sm1 ≤ 500μm), and size ≤3cm

Preoperative diagnosis

Depth of invasion	Ulceration	Differentiated		Undifferentiated	
		≤ 2 cm	> 2 cm	≤ 2 cm	> 2 cm
cT1a (M)	UL(−)				
	UL(+)	≤ 3 cm	> 3 cm		
cT1b (SM)					

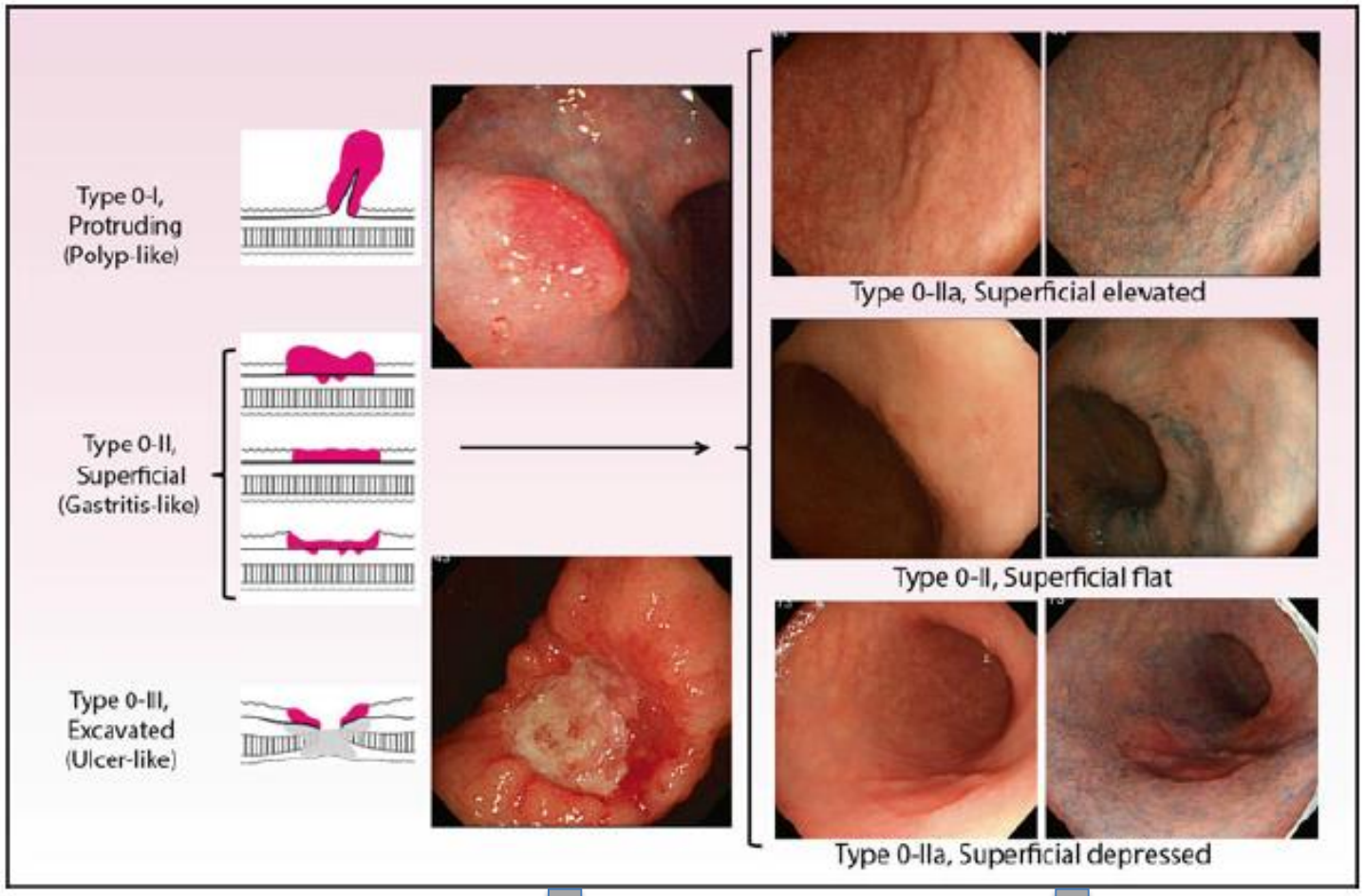
Histopathological diagnosis

Curative resection (R0)

Depth of invasion	Ulceration	Predominantly differentiated		Predominantly Undifferentiated	
		≤ 2 cm	> 2 cm	≤ 2 cm	> 2 cm
pT1a (M)	UL(−)				
	UL(+)	≤ 3 cm	> 3 cm		
pT1b (SM1)		≤ 3 cm	> 3 cm		

EVALUATION BEFORE RESECTION (PREOPERATIVE DIAGNOSIS) IS ESD OR EMR INDICATED?

Inspectión: Morphology



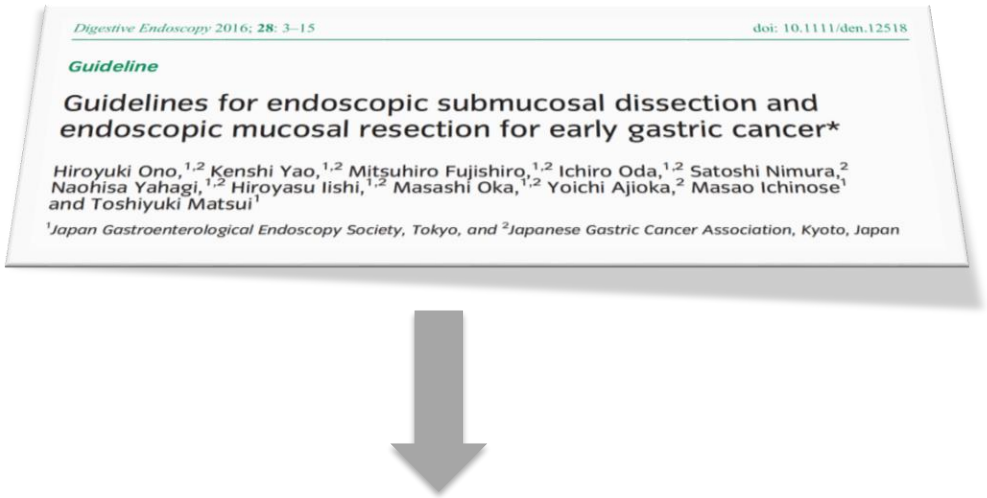
JAPANESE CLASSIFICATION

90-95% SM+

80-85% IE

EVALUATION BEFORE RESECTION (PREOPERATIVE DIAGNOSIS) IS ESD OR EMR INDICATED?

DEPTH OF INVASION



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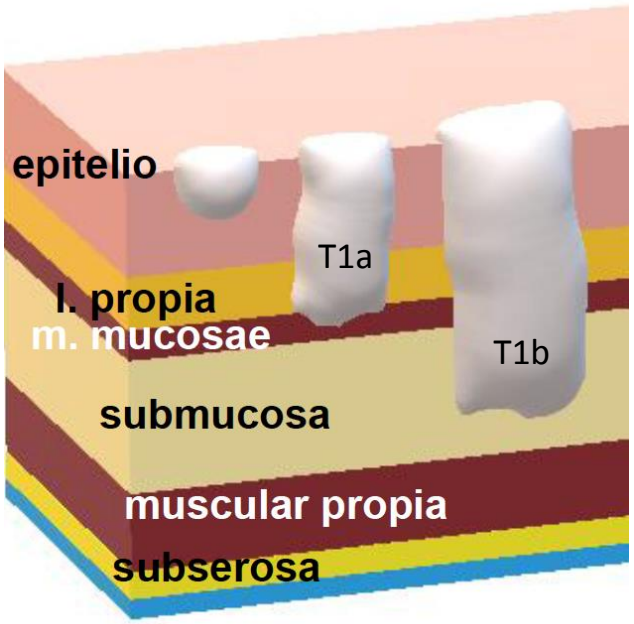
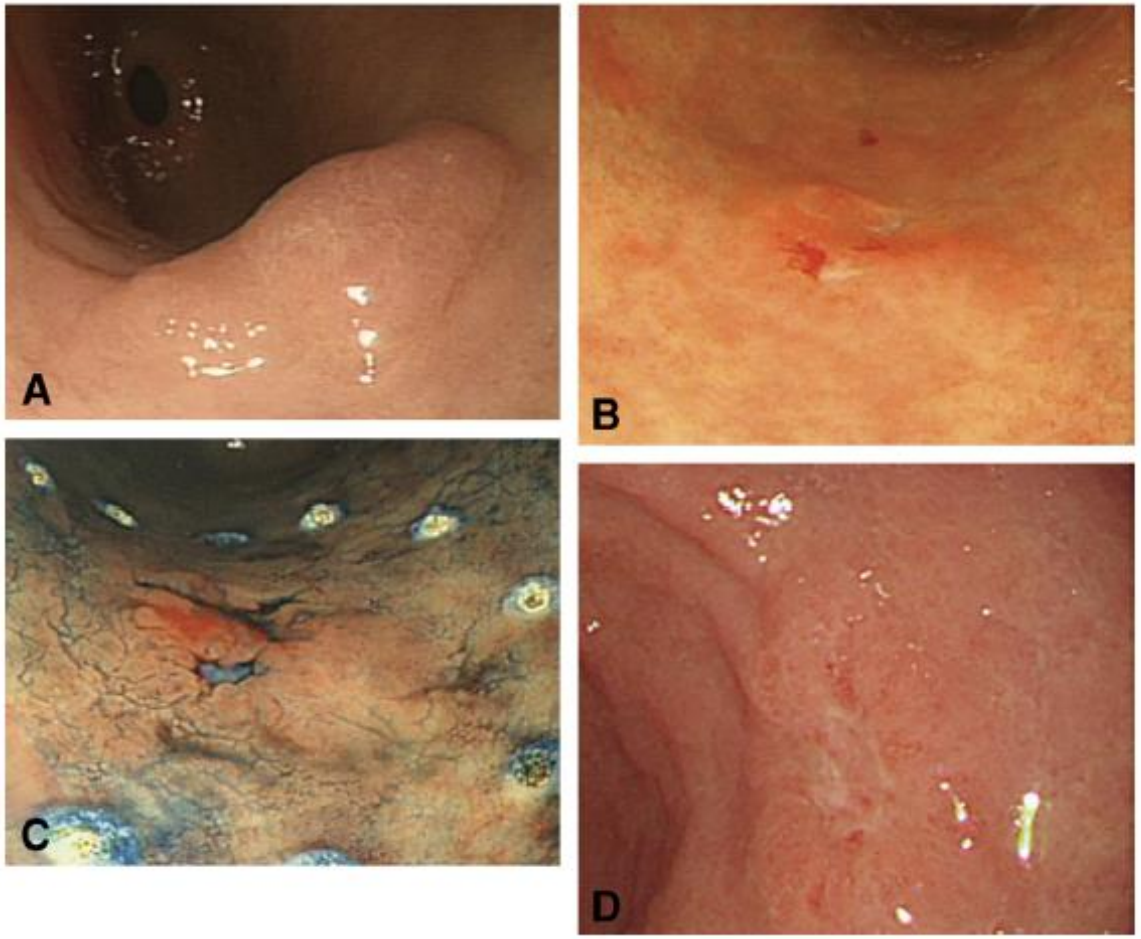


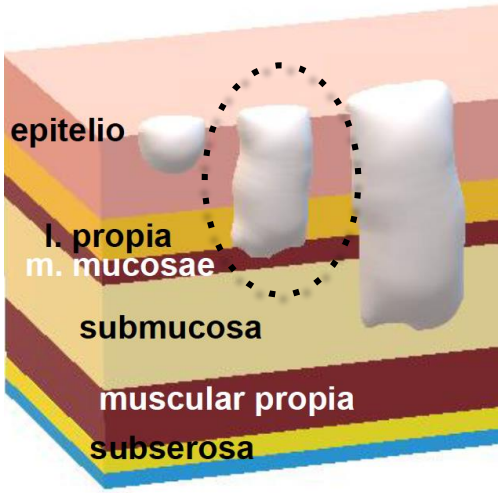
"Determination of the depth of invasion by EGC is generally carried out using **conventional endoscopy with additional indigo-carmine dye spraying** being recommended"

Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Ono 2015

DEPTH OF INVASION

Characteristic **endoscopic features** of **mucosal** cancer



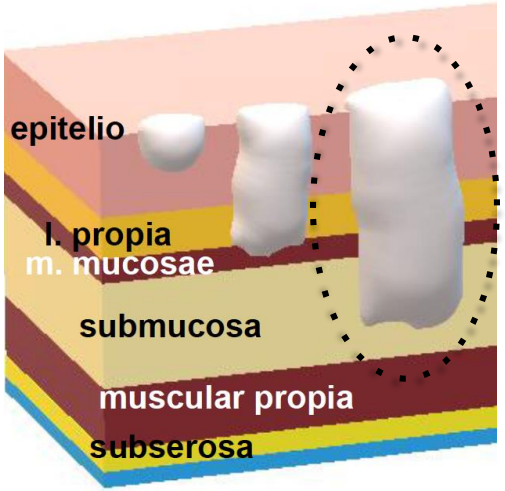


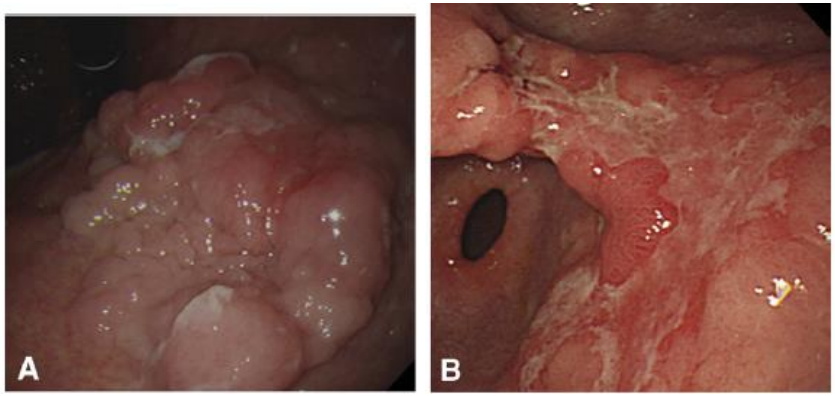
- Smooth surface protrusion
- Shallow and even depression
- slight marginal elevation

Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Ono 2015

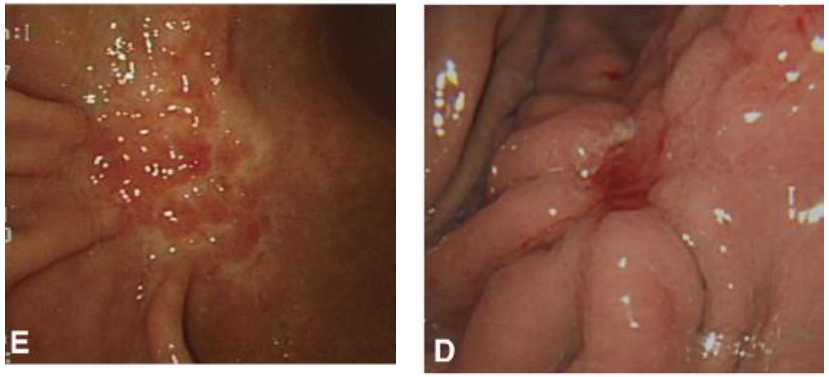
DEPTH OF INVASION

Characteristic endoscopic features of **submucosal invasive** cancer

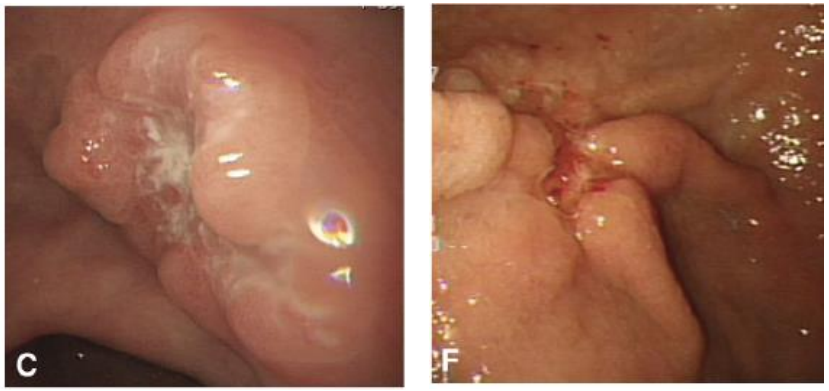




Irregular/nodular surface protrusion



Fusion of converging folds
Abrupt cutting of converging folds
Clubbing of converging folds.

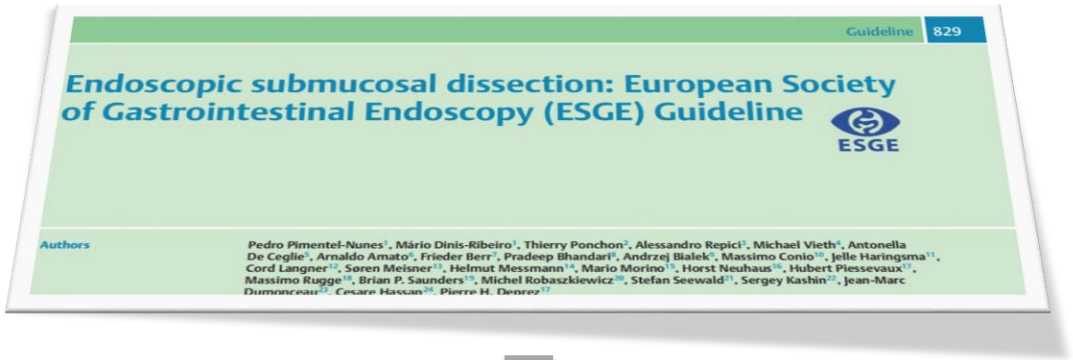


Deep ulcer with marked marginal elevation

Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Ono 2015

EVALUATION BEFORE RESECTION (PREOPERATIVE DIAGNOSIS) IS ESD OR EMR INDICATED?

3) DEPTH OF INVASION


Guideline 829

Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

ESGE

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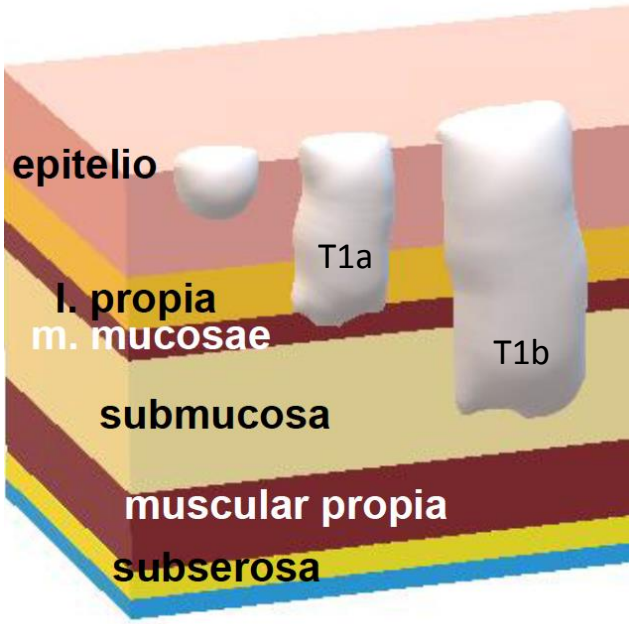


Evaluation before endoscopic resection: stomach

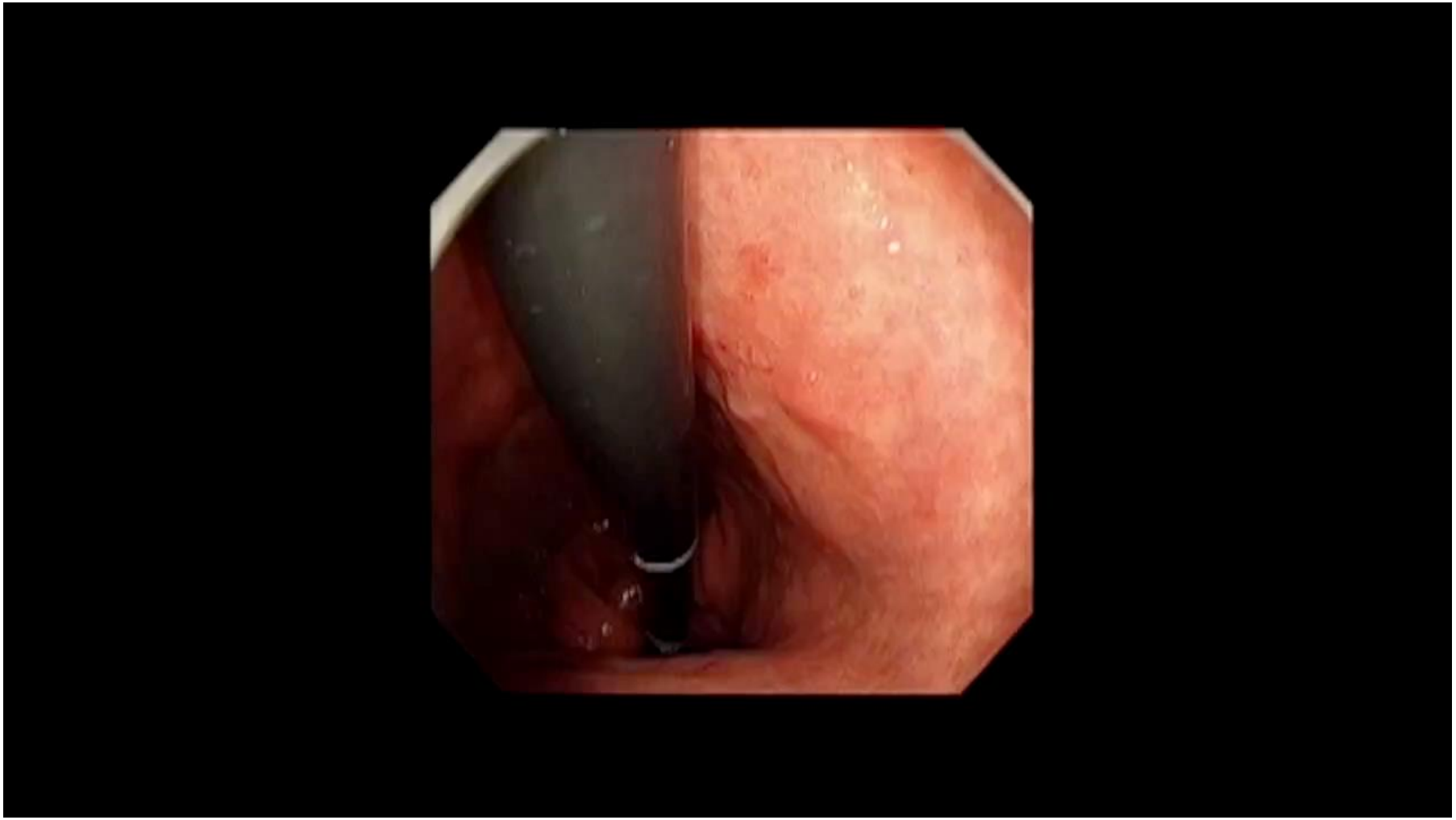
ESGE recommends a high quality endoscopy, ideally with contrast or digital chromoendoscopy, by an experienced endoscopist in order to establish the feasibility of gastric endoscopic resection (strong recommendation, moderate quality evidence).

US, CT, or other procedures are not routinely recommended for the assessment of gastric superficial lesions prior to endoscopic resection (strong recommendation, moderate quality evidence).

- High quality endoscopy ideally with **contrast or digital chromoendoscopy (NBI)**
- Experienced endoscopist

EVALUATION BEFORE RESECTION (PREOPERATIVE DIAGNOSIS) IS ESD OR EMR INDICATED?

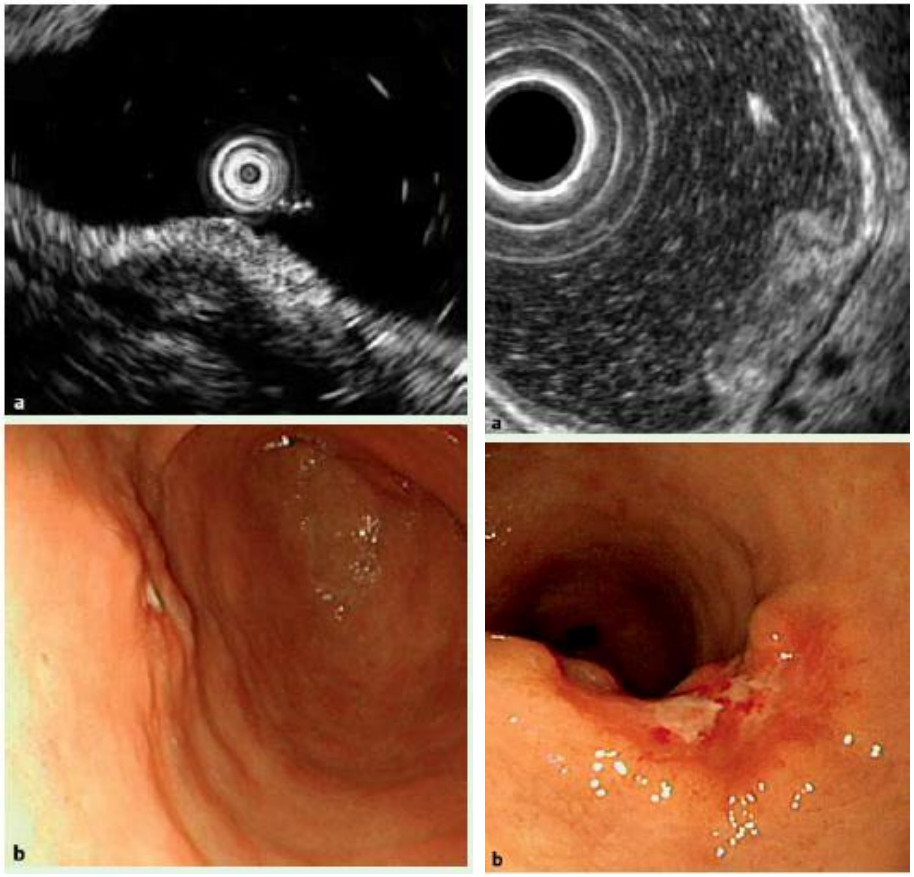
DEPTH OF INVASION

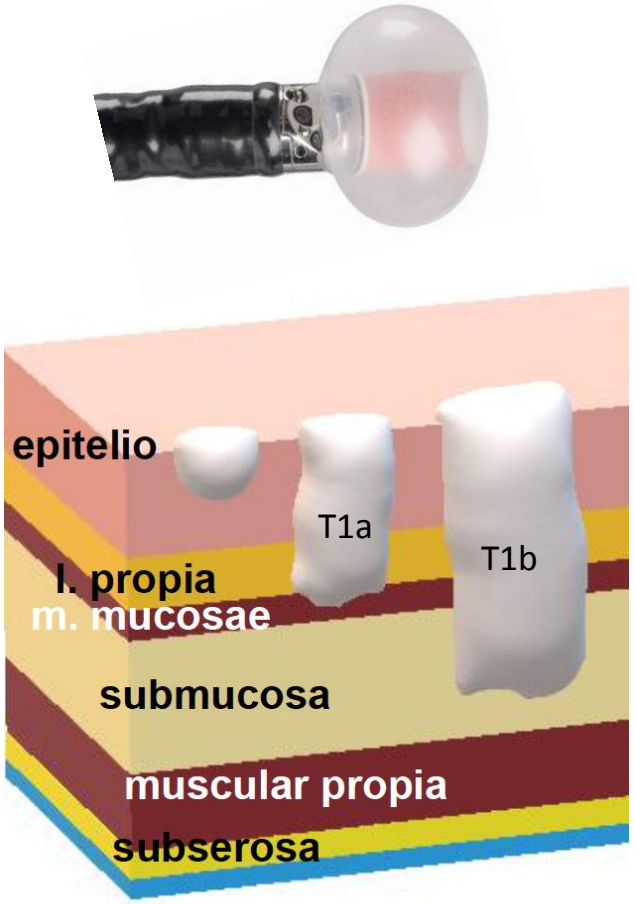


EVALUATION BEFORE RESECTION (PREOPERATIVE DIAGNOSIS) IS ESD OR EMR INDICATED?

DEPTH OF INVASION

ROLE FOR EUS???





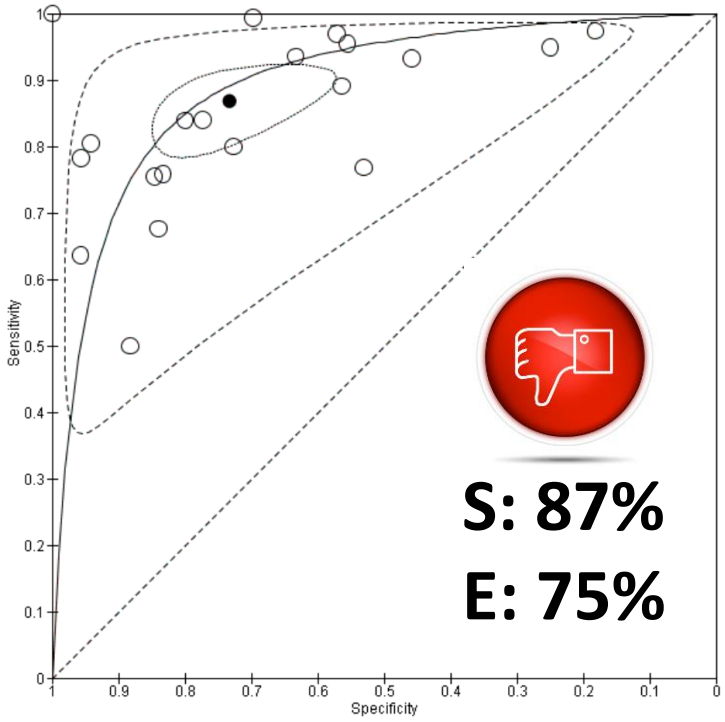
Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer Choi 2010 Endoscopy

EVALUATION BEFORE RESECTION (PREOPERATIVE DIAGNOSIS) IS ESD OR EMR INDICATED?

DEPTH OF INVASION

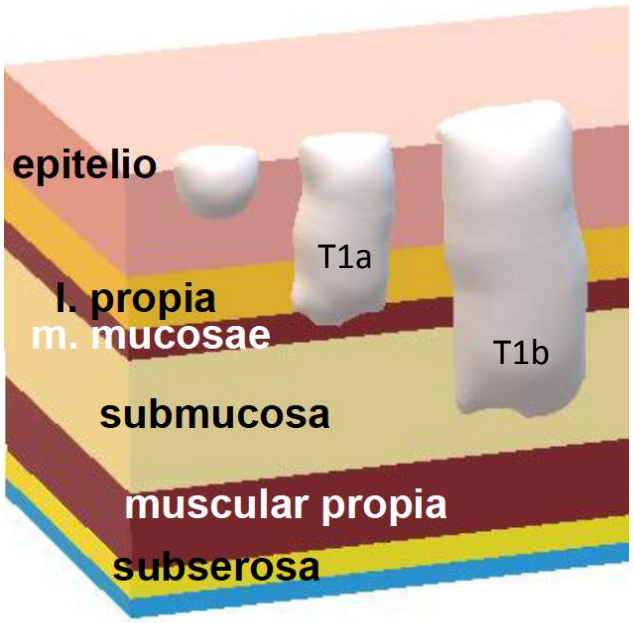
ROLE FOR USE???

T1a (m) vs T1b (Sbm)



S: 87%

E: 75%



"Over and under diagnosis"

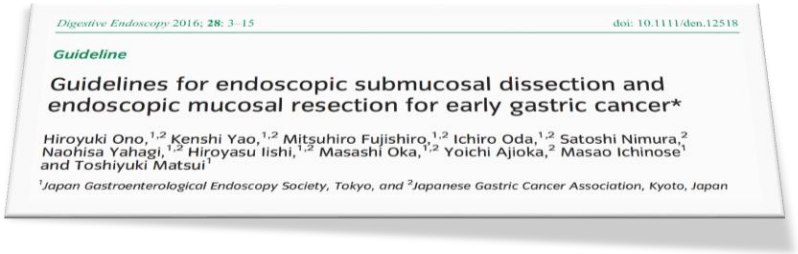
Mocellin S 2015

EVALUATION BEFORE RESECTION (PREOPERATIVE DIAGNOSIS) IS ESD OR EMR INDICATED?

3) DEPTH OF INVASION

ROLE FOR EUS???

USE in EGC is not neccessary….Only for selected cases……



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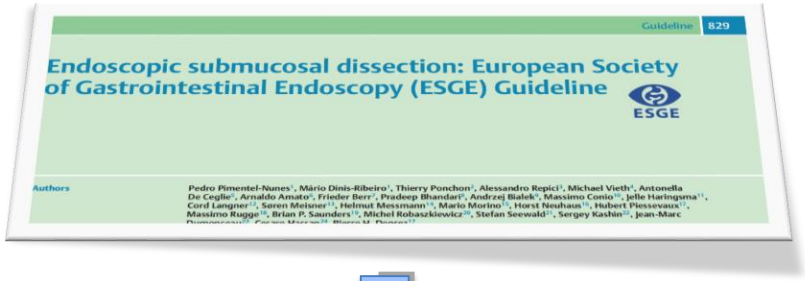

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EUS in EGC may not be necessary routinely……

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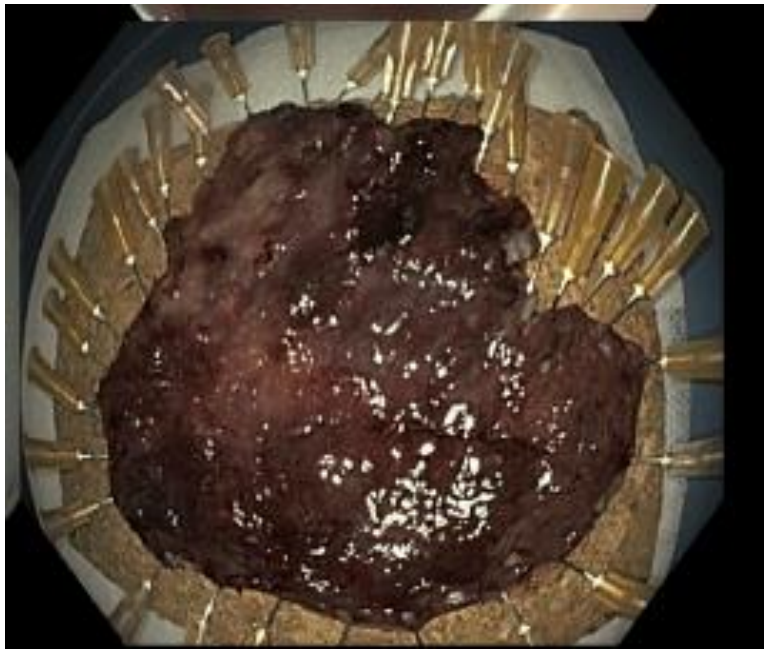
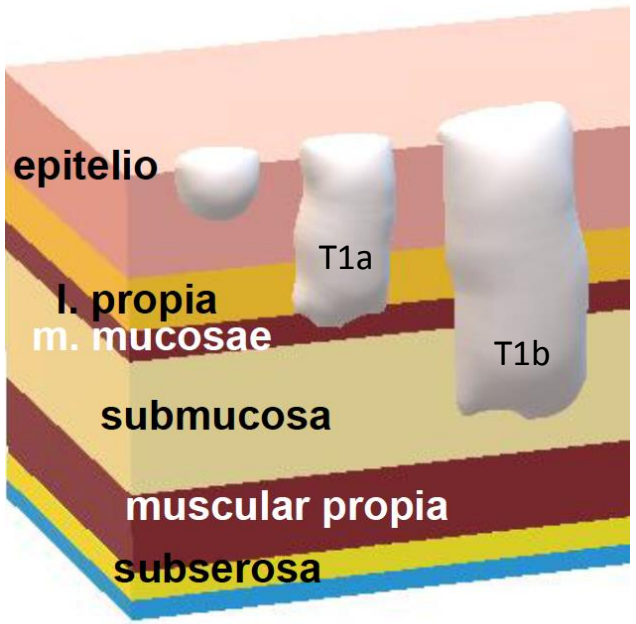


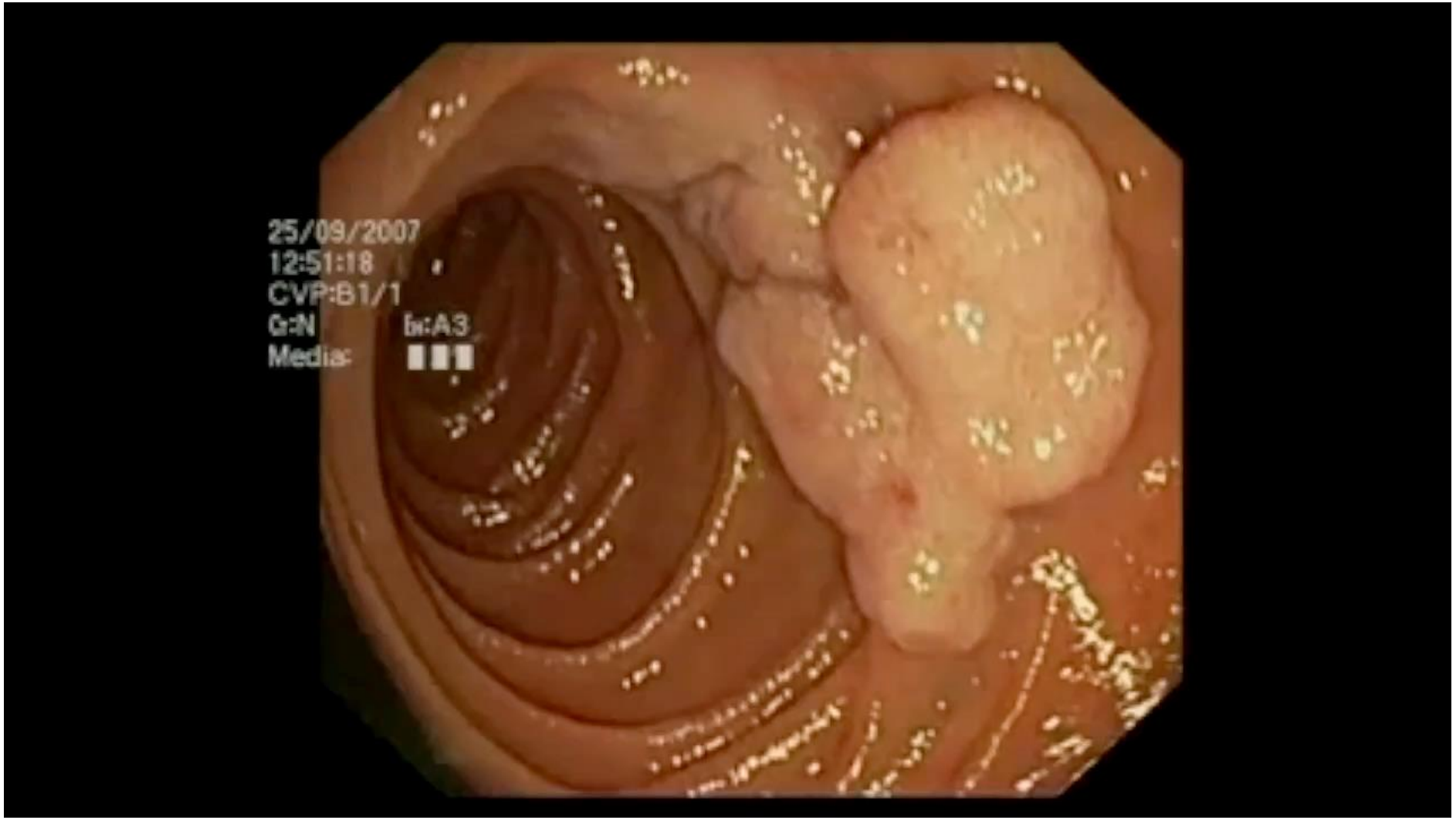


But….histopathological analysis of endoscopically resected specimens is the gold standard reference for tumor staging

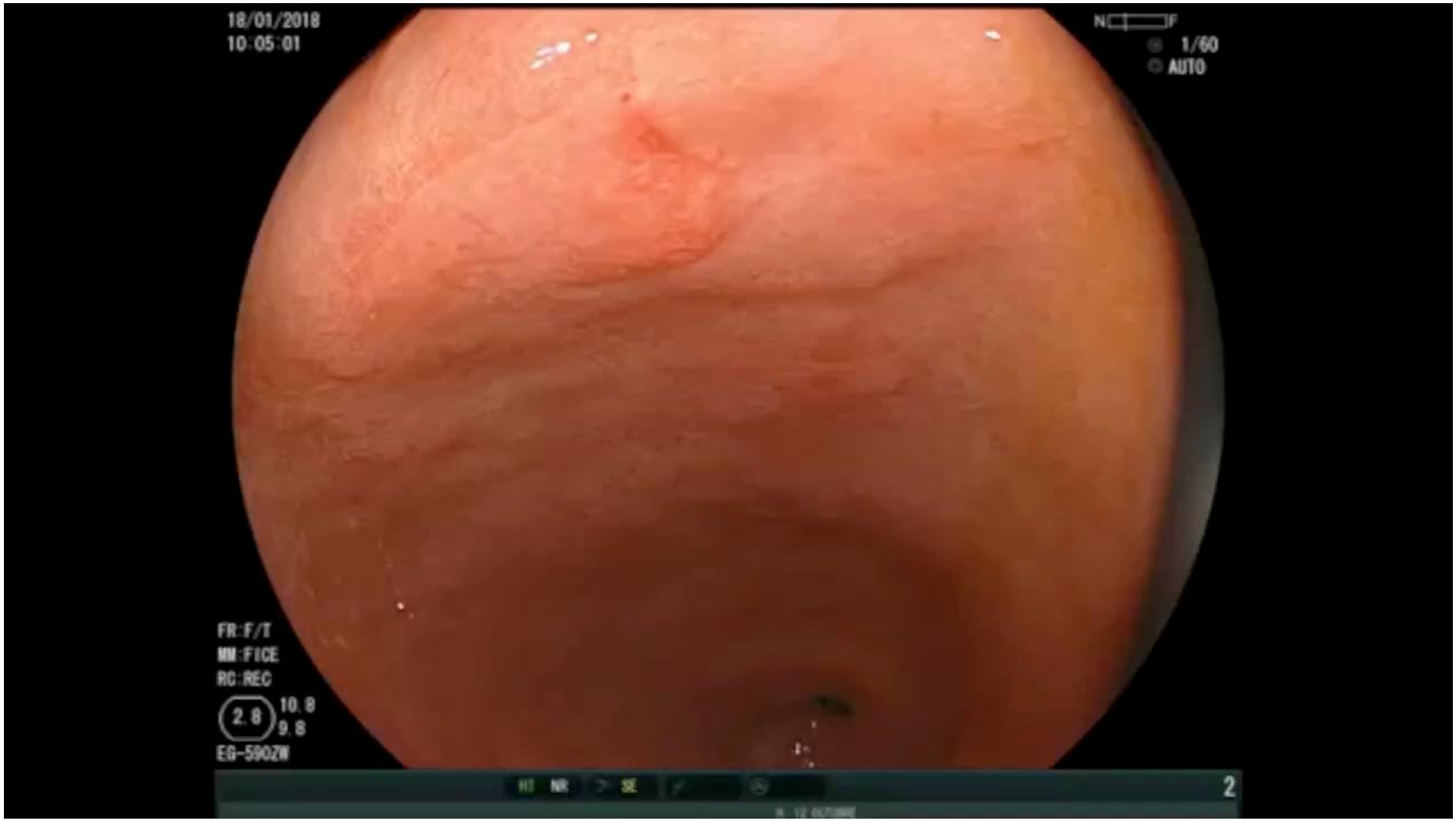
ENDOSCOPICAL MUCOSAL RESECTION (EMR)
VS
ENDOSCOPICAL SUBMUCOSAL DISECTION (ESD)

ENDOSCOPIC MUCOSAL RESECTION: TECHNIQUE

STANDAR



ENDOSCOPIC SUBMUCOSAL DISSECTION



Courtesy of Dr juan Carlos Marín (H.12 Octubre Madrid)

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META-ANALYSIS

Endoscopic submucosal dissection *vs* endoscopic mucosal resection for early gastric cancer: A meta-analysis

Antonio Facciorusso, Matteo Antonino, Marianna Di Maso, Nicola Muscatiello

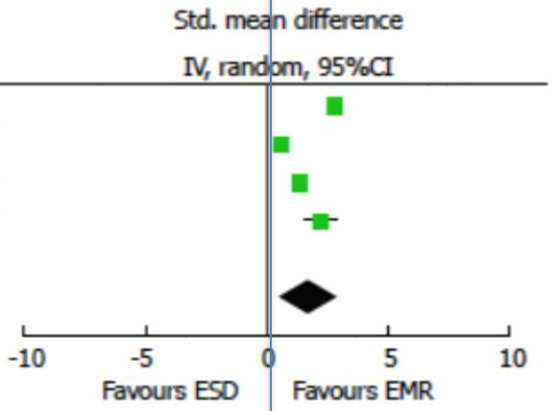
EMR/ESD: DURATION OF THE PROCEDURE

ESD VS EMR

Study or subgroup	ESD Mean	ESD SD	ESD Total	EMR Mean	EMR SD	EMR Total	Weight	Std. mean difference IV, random, 95%CI	Year
Oka	84.4	55.3	195	12.6	9.3	825	25.50%	2.81 [2.61, 3.01]	2006
Nakamoto	84.4	61.9	122	17.2	18.5	80	25.20%	1.35 [1.04, 1.66]	2009
Min	33.6	16.6	243	24.3	16.2	103	25.40%	0.56 [0.33, 0.80]	2009
Hoteya 2010	115.8	48.8	40	25.3	11.6	22	23.90%	2.24 [1.58, 2.90]	2010
Total (95%CI)			600			1030	100.00%	1.73 [0.52, 2.95]	

Heterogeneity: Tau² = 1.51; χ^2 = 216.15, df = 3 (P < 0.00001); I^2 = 99%

Test for overall effect: Z = 2.79 (P = 0.005)



EMR

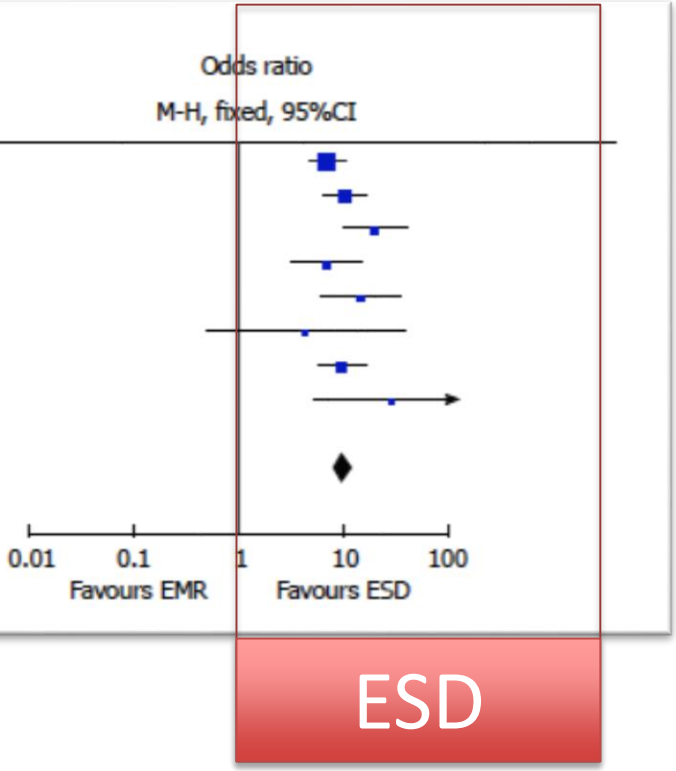
EMR/ESD: “EN BLOC RESECTION RATE”

EMR VS ESD

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Oka	162	195	347	825	36.80%	6.76 [4.54, 10.08]	2006
Oda	281	303	230	411	23.20%	10.05 [6.25, 16.17]	2006
Hoteya	294	303	219	350	9.90%	19.54 [9.73, 39.26]	2007
Nakamoto	115	122	43	80	4.90%	14.14 [5.86, 34.10]	2009
Min	233	243	80	103	7.60%	6.70 [3.06, 14.68]	2009
Catalano	11	12	26	36	1.80%	4.23 [0.48, 37.17]	2009
Watanabe	194	219	66	146	14.80%	9.41 [5.54, 15.96]	2010
Hoteya 2010	38	40	9	22	1.00%	27.44 [5.24, 143.84]	2010
Total (95%CI)		1473		1973	100.00%	9.69 [7.74, 12.13]	
Total events	1328		1020				

Heterogeneity: $\chi^2 = 10.67$ df = 7 ($P = 0.15$); $I^2 = 34\%$

Test for overall effect: $Z = 19.84$ ($P < 0.00001$)



ESD

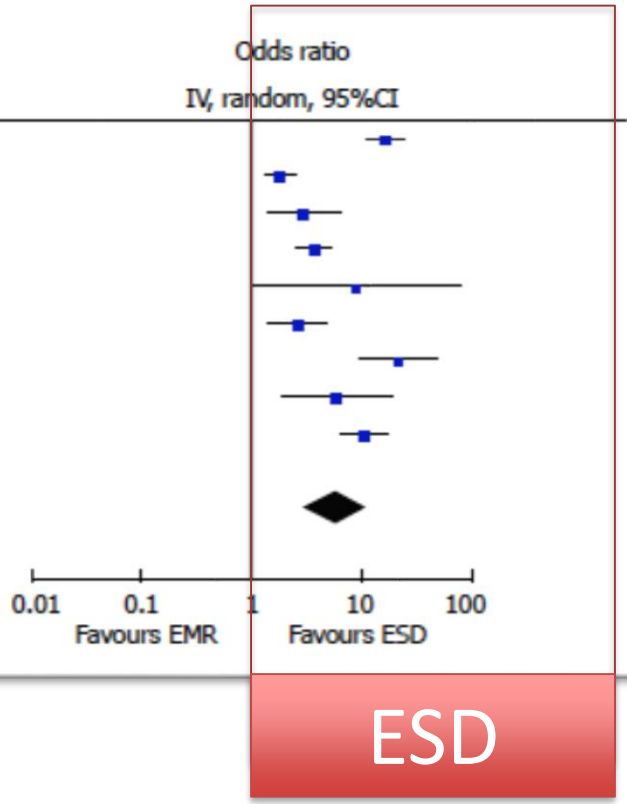
EMR/ESD: COMPLETE HISTOLOGIC RESECTION RATE

EMR VS ESD

	ESD		EMR			Odds ratio	
Study or subgroup	Events	Total	Events	Total	Weight	IV, random, 95%CI	Year
Oka	162	195	195	825	12.60%	15.86 [10.55, 23.83]	2006
Odashima	43	57	41	80	11.40%	2.92 [1.39, 6.16]	2006
Oda	223	303	251	411	12.90%	1.78 [1.29, 2.46]	2006
Hoteya	254	304	204	350	12.80%	3.64 [2.51, 5.26]	2007
Catalano	11	12	20	36	5.50%	8.80 [1.02, 75.55]	2009
Nakamoto	113	122	30	80	11.00%	20.93 [9.25, 47.32]	2009
Min	216	243	78	103	12.00%	2.56 [1.40, 4.68]	2009
Hoteya 2010	32	40	9	22	9.50%	5.78 [1.83, 18.25]	2010
Watanabe	173	219	39	146	12.40%	10.32 [6.32, 16.84]	2010
Total (95%CI)		1495		2053	100.00%	5.66 [2.92, 10.96]	
Total events	1227		867				

Heterogeneity: $Tau^2 = 0.85$; $\chi^2 = 99.48$ df = 8 ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 5.14$ ($P < 0.00001$)



ESD

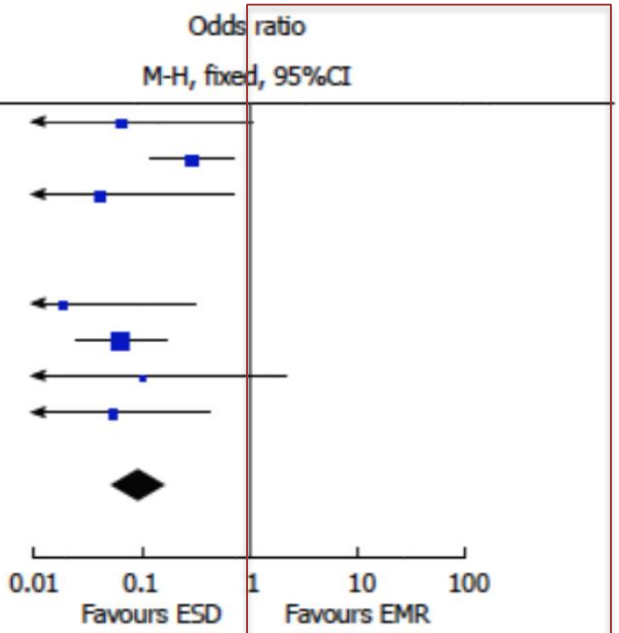
EMR/ESD: LOCAL RECURRENCE RATE

EMR VS ESD

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Oka	0	195	31	825	9.30%	0.06 [0.00, 1.06]	2006
Oda	6	303	27	411	17.30%	0.29 [0.12, 0.70]	2006
Hoteya	0	304	13	350	9.70%	0.04 [0.00, 0.69]	2007
Nakamoto	0	122	14	80	13.40%	0.02 [0.00, 0.32]	2009
Min	0	243	0	103		Not estimable	2009
Catalano	0	12	0	36		Not estimable	2009
Watanabe	5	219	39	146	35.30%	0.06 [0.02, 0.17]	2010
Hoteya 2010	0	40	2	22	2.40%	0.10 [0.00, 2.21]	2010
Tanabe	1	421	15	359	12.50%	0.05 [0.01, 0.42]	2014
Total (95%CI)		1859		2332	100.00%	0.09 [0.05, 0.17]	
Total events	12		141				

Heterogeneity: $\chi^2 = 8.48$ df = 6 ($P = 0.21$); $I^2 = 29\%$

Test for overall effect: $Z = 8.18$ ($P < 0.00001$)



ESD

EMR/ESD: COMPLICATION RATE

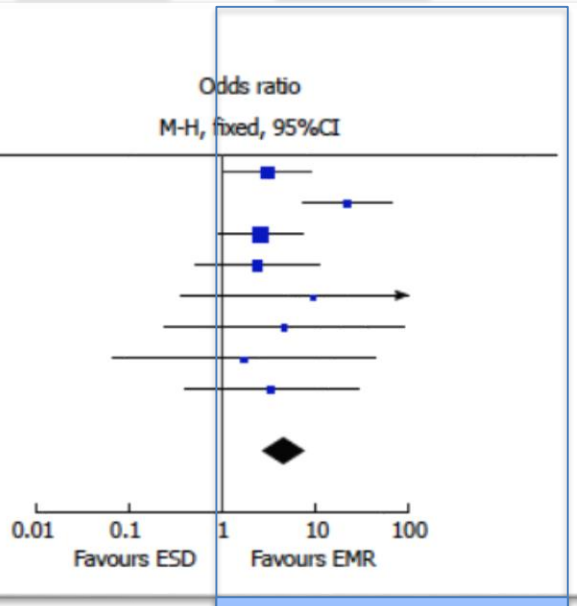
Perforation rate

ESD VS EMR

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Oda	11	303	5	411	26.80%	3.06 [1.05, 8.90]	2006
Oka	19	195	4	825	9.10%	22.16 [7.45, 65.93]	2006
Hoteya	11	304	5	350	29.40%	2.59 [0.89, 7.54]	2007
Catalano	1	12	0	36	1.50%	9.52 [0.36, 250.16]	2009
Min	11	243	2	103	17.60%	2.39 [0.52, 11.00]	2009
Nakamoto	3	122	0	80	3.80%	4.72 [0.24, 92.53]	2009
Watanabe	5	219	1	146	7.70%	3.39 [0.39, 29.30]	2010
Hoteya 2010	1	40	0	22	4.10%	1.71 [0.07, 43.73]	2010
Total (95%CI)		1438		1973	100.00%	4.67 [2.77, 7.87]	
Total events	62		17				

Heterogeneity: $\chi^2 = 10.98$ df = 7 ($P = 0.14$); $I^2 = 36\%$

Test for overall effect: $Z = 5.77$ ($P < 0.00001$)



EMR

Favours EMR…… but most fo perforations in ESD group are managed conservatory without the need of surgery

EMR/ESD: COMPLICATION RATE

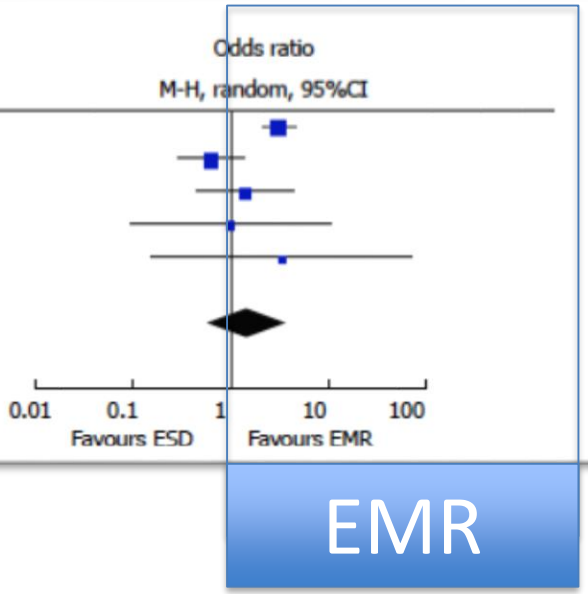
Bleeding rate

ESD VS EMR

Study or subgroup	ESD Events	ESD Total	EMR Events	EMR Total	Weight	Odds ratio M-H, random, 95%CI	Year
Oka	56	195	95	825	32.70%	3.10 [2.12, 4.51]	2006
Hoteya	10	304	18	350	27.50%	0.63 [0.29, 1.38]	2007
Min	13	243	4	103	22.40%	1.40 [0.45, 4.40]	2009
Nakamoto	2	122	0	80	7.10%	3.34 [0.16, 70.49]	2009
Catalano	1	12	3	36	10.40%	1.00 [0.09, 10.63]	2009
Total (95%CI)		876		1394	100.00%	1.49 [0.60, 3.71]	
Total events	82		120				

Heterogeneity: Tau² = 0.62; χ^2 = 14.14 df = 4 (P = 0.007); I^2 = 72%

Test for overall effect: Z = 0.87 (P = 0.39)



Favours EMR…… but non significant difference

Long-term follow-up after endoscopic resection of gastric superficial neoplastic lesions in Portugal

Resection	R0 RESECTION RATE	RECURRENCE RATE
EMR	54%	15%
ESD	**91%**	**4%**

But……. no differences in survival

Pimentel-Nunes Endoscopy 2014

Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

ESGE

Authors

Pedro Pimentel-Nunes[1], Mário Dinis-Ribeiro[1], Thierry Ponchon[2], Alessandro Repici[3], Michael Vieth[4], Antonella De Ceglie[5], Arnaldo Amato[6], Frieder Berr[7], Pradeep Bhandari[8], Andrzej Bialek[9], Massimo Conio[10], Jelle Haringsma[11], Cord Langner[12], Søren Meisner[13], Helmut Messmann[14], Mario Morino[15], Horst Neuhaus[16], Hubert Piessevaux[17], Massimo Rugge[18], Brian P. Saunders[19], Michel Robaszkiewicz[20], Stefan Seewald[21], Sergey Kashin[22], Jean-Marc Dumonceau[23], Cesare Hassan[24], Pierre H. Deprez[17]

ESGE recommends endoscopic resection for the treatment of gastric superficial neoplastic lesions that possess a very low risk of lymph node metastasis (strong recommendation, high quality evidence).

EMR is an acceptable option for lesions smaller than 10–15 mm with a very low probability of advanced histology (Paris 0-IIa). However, ESGE recommends ESD as treatment of choice for most gastric superficial neoplastic lesions (strong recommendation, moderate quality evidence).

EMR

- ✓ <10-15mm
- ✓ Low probability of advanced histology (0-IIa)

ESD

Treatment of choice

Digestive Endoscopy 2016; **28**: 3–15 doi: 10.1111/den.12518

Guideline

Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer*

Hiroyuki Ono,[1,2] Kenshi Yao,[1,2] Mitsuhiro Fujishiro,[1,2] Ichiro Oda,[1,2] Satoshi Nimura,[2] Naohisa Yahagi,[1,2] Hiroyasu Iishi,[1,2] Masashi Oka,[1,2] Yoichi Ajioka,[2] Masao Ichinose[1] and Toshiyuki Matsui[1]

[1]*Japan Gastroenterological Endoscopy Society, Tokyo, and* [2]*Japanese Gastric Cancer Association, Kyoto, Japan*

The risk of incomplete resection is high when using EMR for lesions with expanded indications, so ESD should be carried out instead of EMR for these lesions (evidence level V, grade of recommendation C1).

EMR

- ✓ <10 mm
- ✓ Absolute indications (non expanded)

ESD

Treatment of choice

“ESD should be the first-line therapy for all potentially endoscopically resectable superficial gastric neoplasia. Surgery can be reserved and used as a rescue therapy”

Thank you