

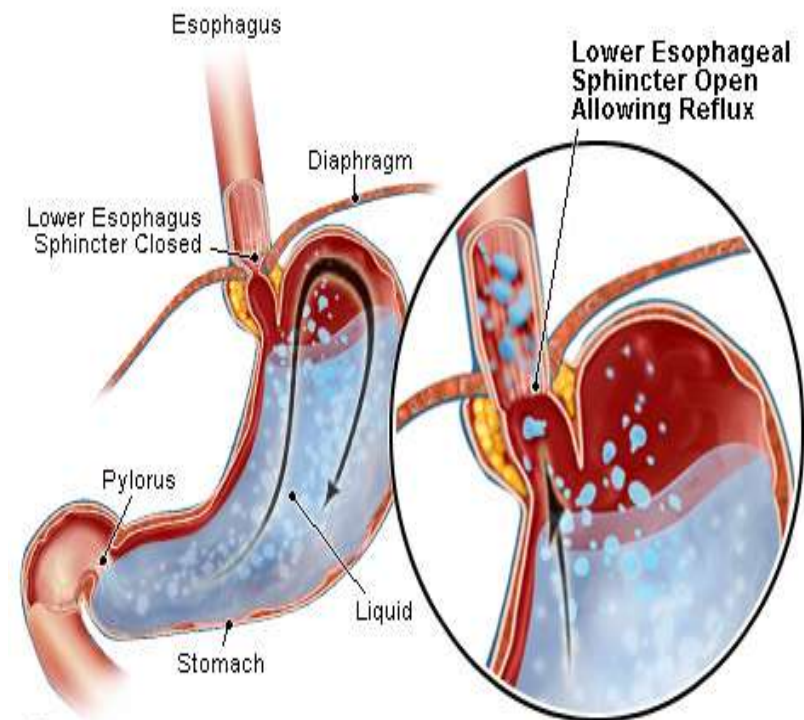
# How to diagnose reflux in 2010 ?

Johannes Gutenberg University Mainz, Germany

***Arthur Hoffman***

# Definition

- American College of Gastroenterology (ACG)
  - Symptoms OR mucosal damage produced by the abnormal reflux of gastric contents into the esophagus
  - Often chronic and relapsing
  - May see complications of GERD in patients who lack typical symptoms



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Gastroesophageal Reflux

# Epidemiology

- about 44% of the US adult population have heartburn at least once a month
- 14% of Americans have symptoms weekly
- 7% have symptoms daily

# Epidemiology and Progress

**50 %** of the western population :  
Axial hernia

**10 % :**  
Pathologic Reflux

**10 % :**  
Reflux Esophagitis

**10 % :**  
Barrett`s-Esophagus

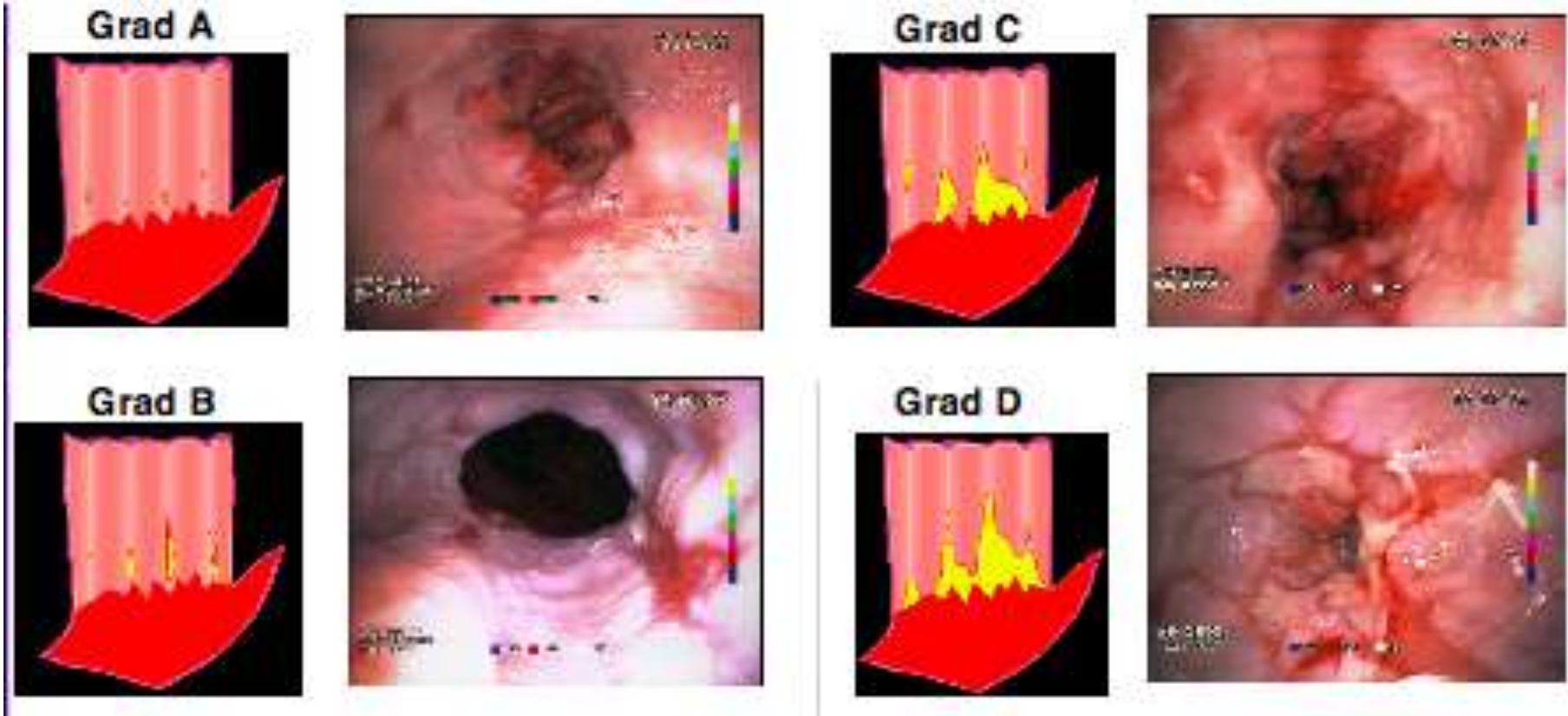
**10 %**  
Barrett-Carcinoma  
(0,4% / year)

# Gastro-Esophageal Reflux Disease

**ERD(40%)** Erosive Reflux Disease

**NERD(60%)** Non-Erosive Reflux Disease

# Los Angeles Classification



# Esophagitis



## Mucosal Break

- An area of slough or erythema with a sharp line of demarcation from adjacent normal mucosa

# Recognition – Technical Evolution



High definition Endoscopy

Video Endoscopy

Fibreoptic Endoscopy

# High resolution Endoscopy

- CCDs in standard videoendoscopes have a total number of pixels of 100,000–300,000.
- Endoscopes containing CCDs with larger numbers of pixels (600,000–1,2 million) are now commercially available.
- These endoscopes are currently denoted as high-resolution endoscopes.

# High definition Endoscopy

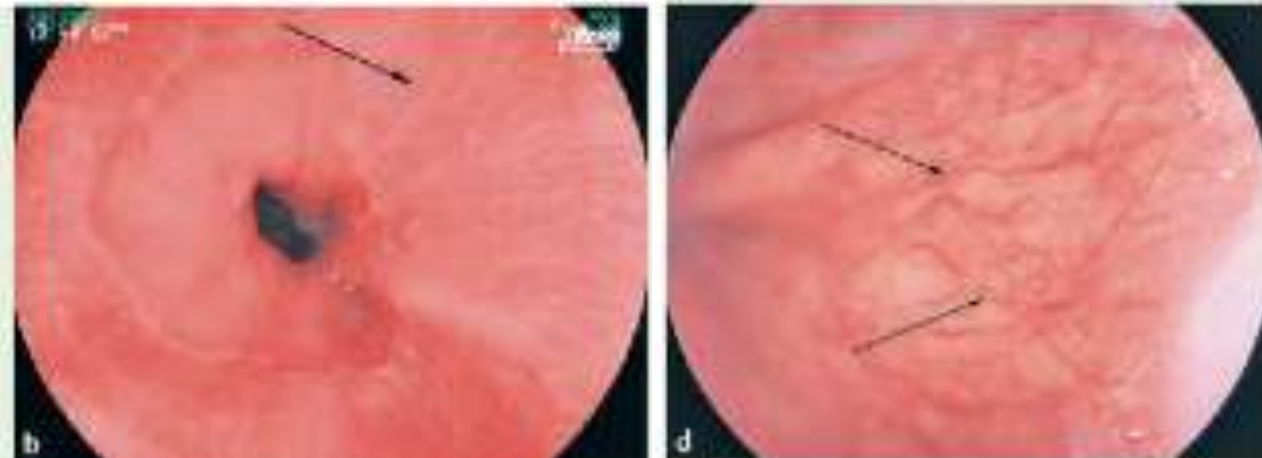
- CCDs convert light information into an electronic signal. This signal is processed in the video-processor into an image.
- The standard analogue broadcasting systems (PAL or NTSC) generate approximately 480–576 scanning lines on a screen.
- High definition endoscopy can generate up to 1080 scanning lines on a screen.

## Magnification endoscopy for diagnosis of nonerosive reflux disease:

- *a proposal of diagnostic criteria and critical analysis of observer variability* -

10 control subjects and 11 Pts. with NERD confirmed by a validated questionnaire, standard endoscopy, and 24-hour pH-metry

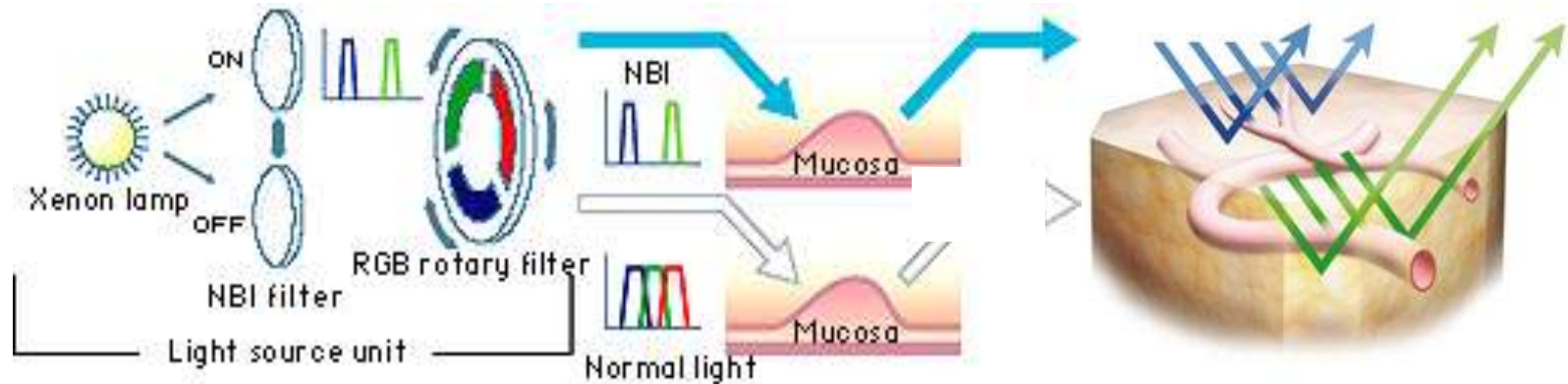
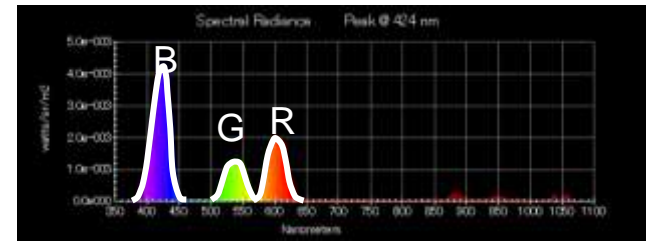
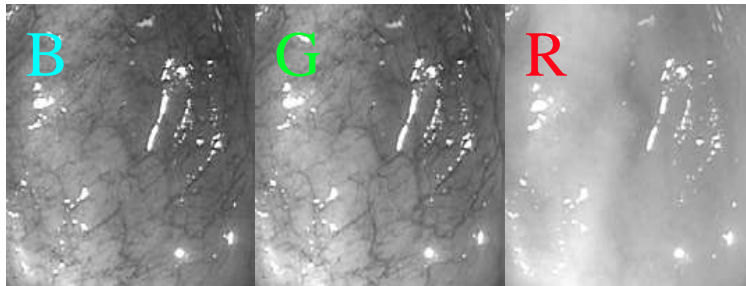
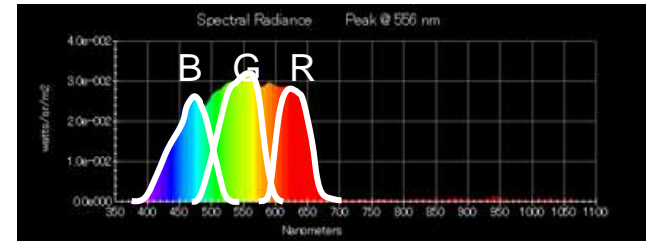
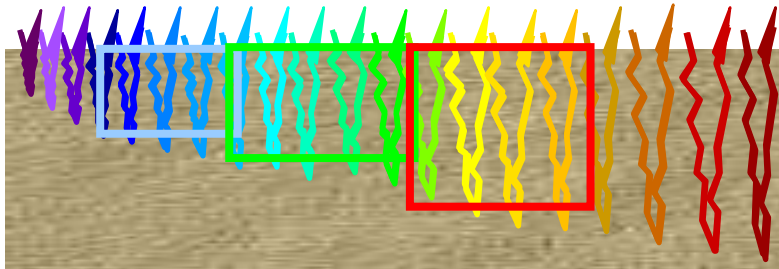
Repeating after 4 weeks of esomeprazole therapy.



The  $\kappa$  value was only high for invisibility of palisade vessels (0.59).

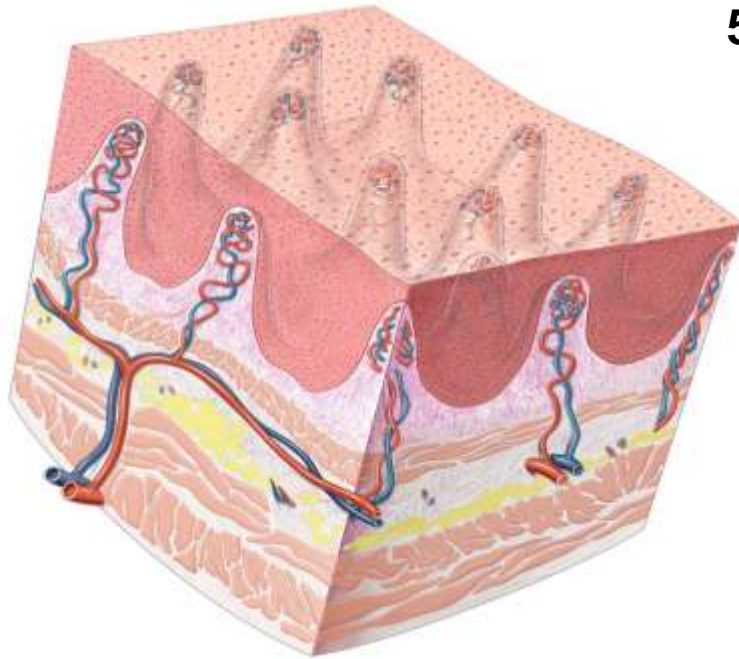
The palisade vessels were significantly less prevalent in reflux patients after therapy  
( $p < 0.01$ ).

# Narrow Band Imaging



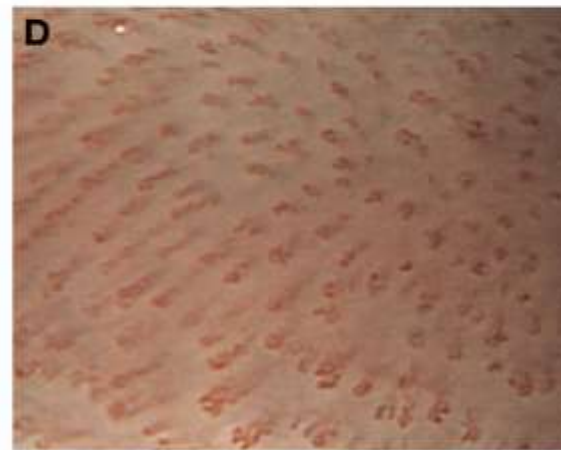
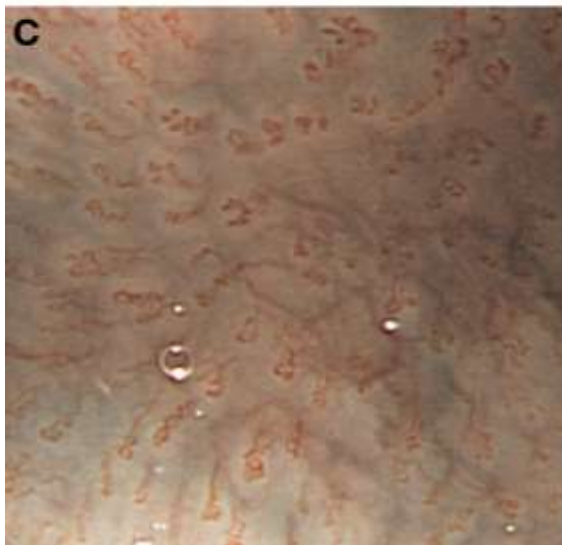
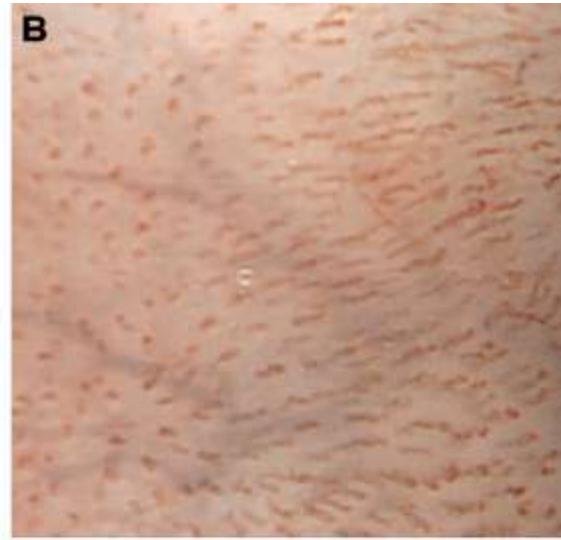
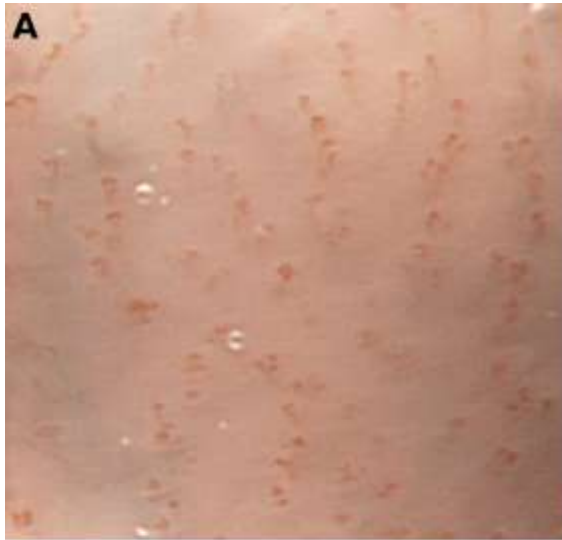
# A Feasibility Trial of Narrow Band Imaging Endoscopy in Patients with Gastroesophageal Reflux Disease

The distal esophagus was examined by standard white light endoscopy followed by NBI. The features seen only by NBI were compared between GERD patients and controls



**50 GERD-Pts., 30 control Pts.**

Significantly more patients with GERD had an **increased number of vessels**, **tortuosity of intrapapillary capillary loops** and **increased vascularity** at the squamocolumnar junction compared with controls.



# High Definition Endoscopy *i scan*



i-scan SE

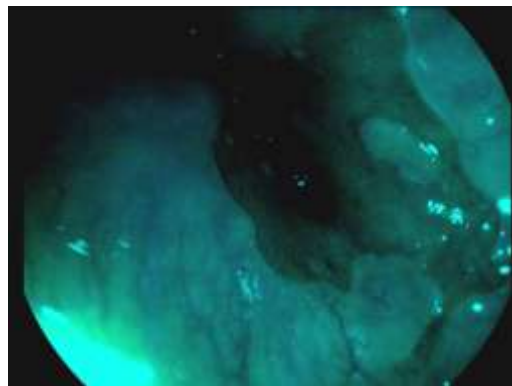
- Off
- Low
- Med
- High

i-scan v

- Off
- On

i-scan p

- Off
- On



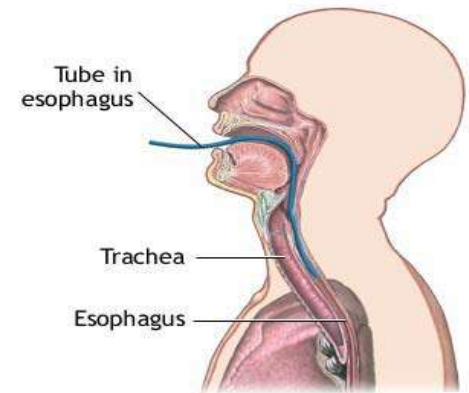
## High definition endoscopy (HD+) with i-scan and Lugol's solution for the detection of inflammation in patients with GERD



Symptoms



Endoscopy



ph-Metry

60 % of patients with reflux symptoms reveal no abnormality under conventional endoscopy

Esophageal mucosal breaks are found in less than half of patients with typical reflux symptom.

Thus, endoscopy appears to be an insensitive test for GERD

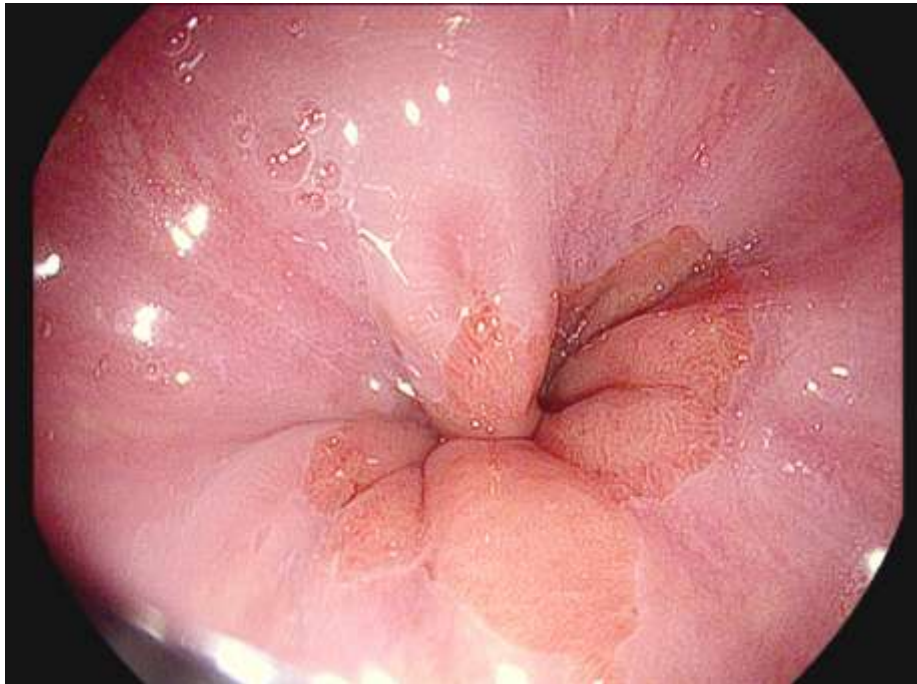
Aim of the study :

Test the efficacy of HD+ EGD in conjunction with *i*-Scan or chromoendoscopy with Lugol´ solution for differentiation NERD patients.

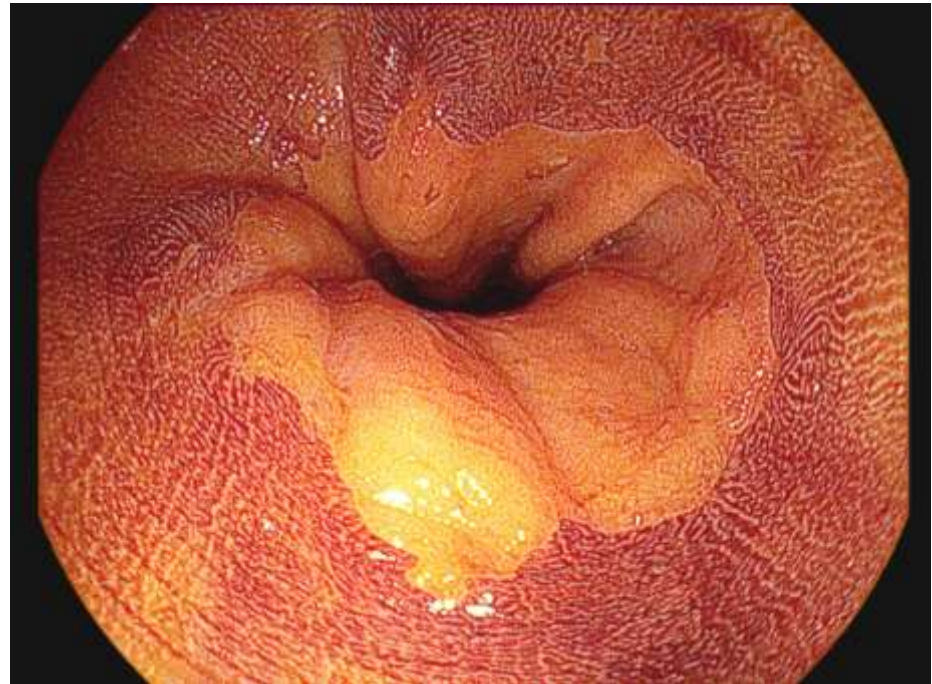
HD+ resolution above  
HDTV standard



## small mucosal breaks



Surface enhancement



Lugol staining

# Patients & Methods

## Patients

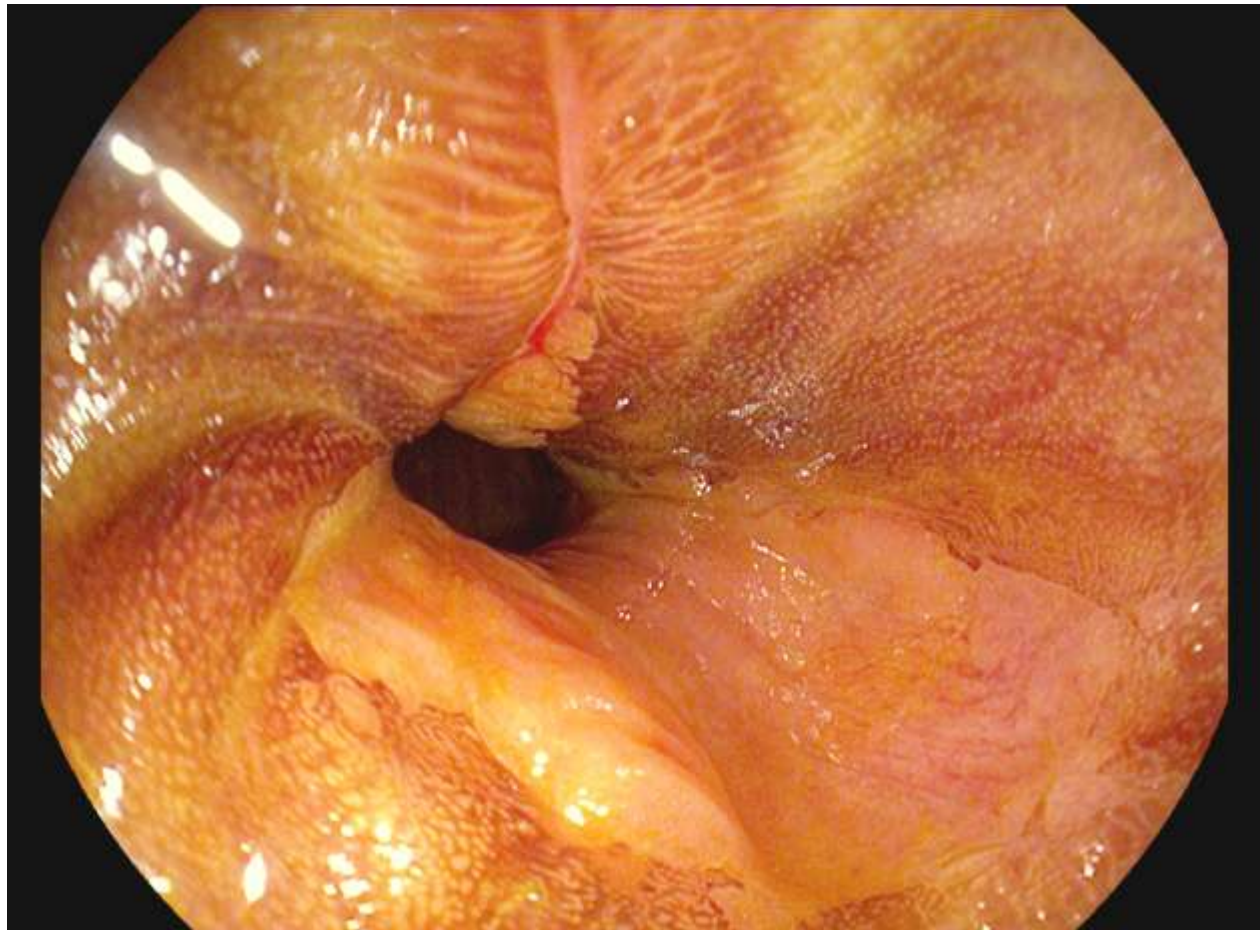
- Patients with typical heartburn ( n=50)  
male 21, female 29; average age 55.9 years

## Methods

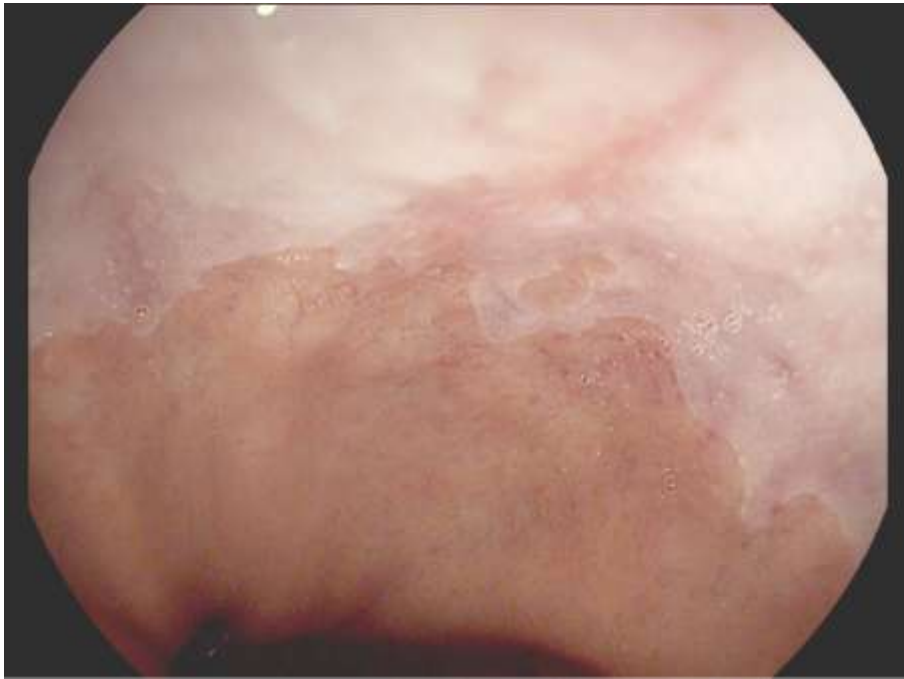
- three different image modalities in one patient
- Endoscopy in the distal esophagus
  - HD+
  - I scan
  - Chromoendoscopy with Lugol's solution
- Inflammation was judged by mucosal breaks Los Angeles Classification (LA).

# NERD

Reflux symptoms, but esophageal histology is normal with no evidence of inflammation on endoscopy



small circumscribed lesions in patients with reflux symptoms

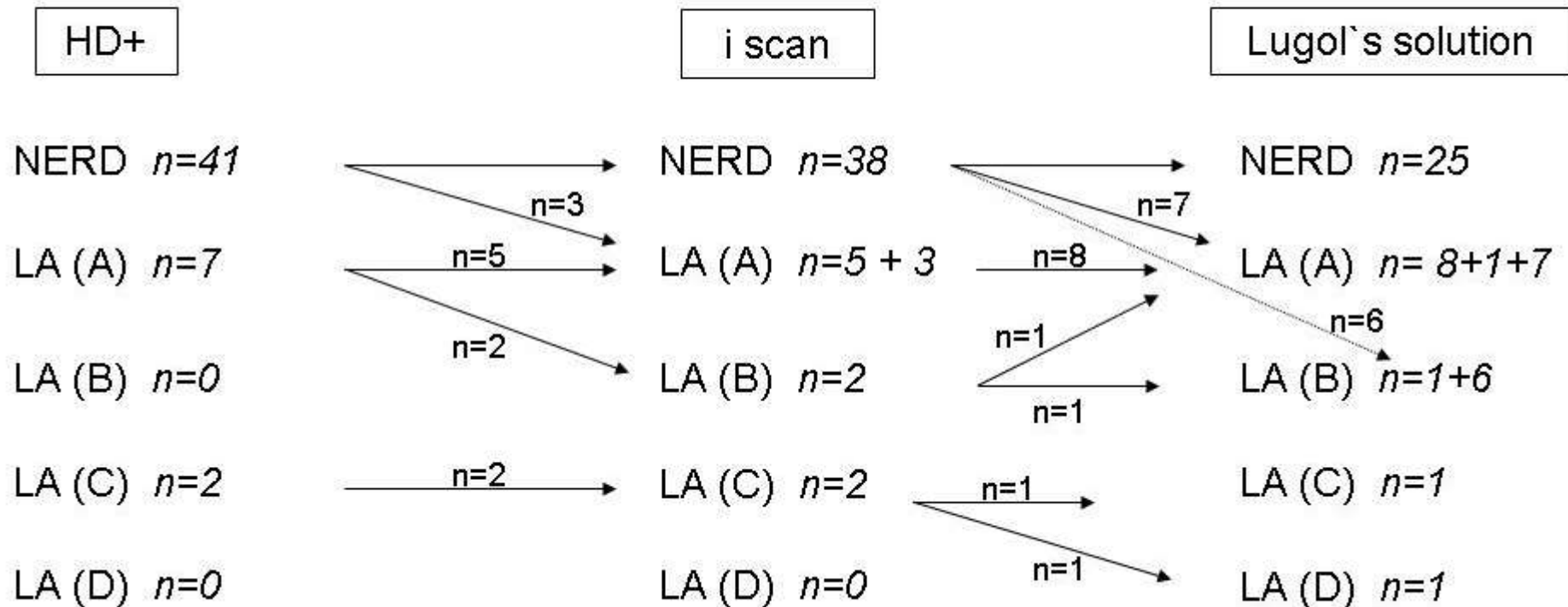


# End points

- Number of patients with esophagitis per method
- Number of visible lesions per method

# results:

## Los Angeles classification



# Results

N = 50 pts.	HD+	Surface	Chromo
Patients with esophagitis	8	12**	25*
Number of lesions	21	58*	85*

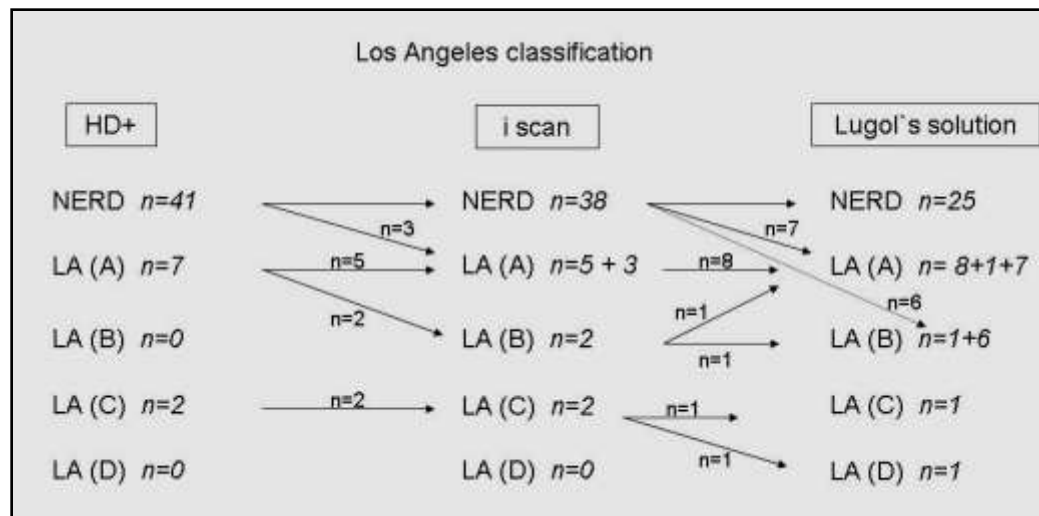
\* Significant  $p < 0.05$

\*\* not significant  $p > 0.05$



# UEGW 2008 Vienna:

Chromoendoscopy with Lugol's solution in conjunction with high definition plus endoscopy significantly improve the detection rate of patients with erosive reflux disease.



Hoffman A et al Endoscopy 2009

Today the diagnostic significance of Lugol chromoendoscopy and *i scan* for NERD compared with histology and a negativ control group can be now presented by our group

# Patients & Methods



## Patients

- 65 consecutive patients with heartburn ( >5 days/week) and
- **inconspicuous first EGD -> NERD patients**
- no PPI intake
- 27 control patients without any symptoms

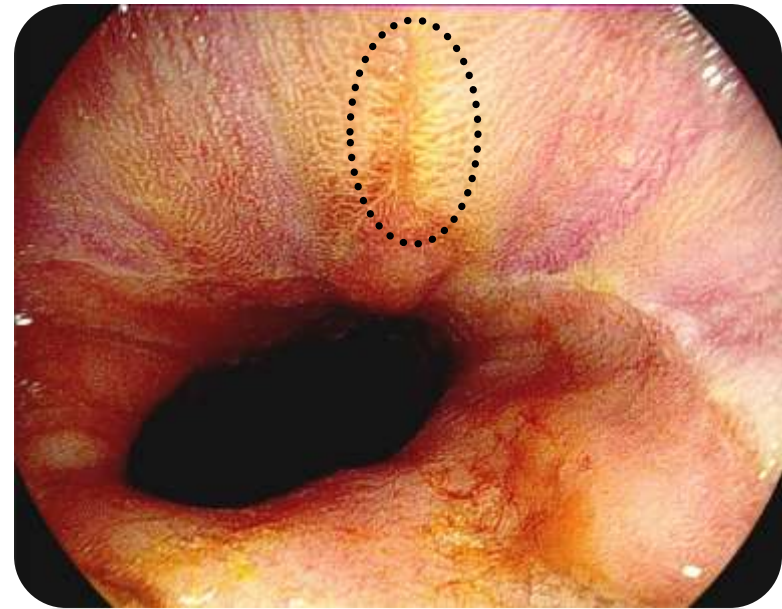
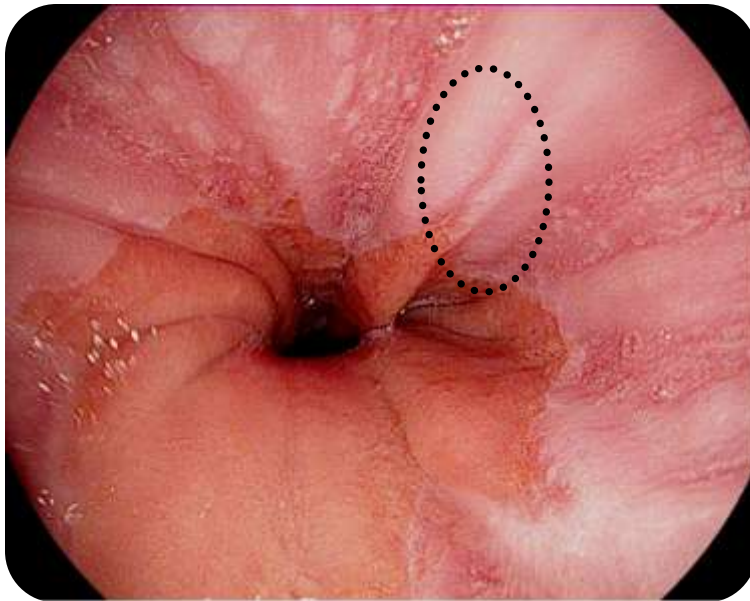
## Methods

- whenever erosions were observed at *i*-scan or chromoendoscopy (Lugol-unstained streaks), targeted biopsy specimens were obtained
- when no lesions were visible, untargeted biopsies were taken from the GI junction
- control patients were judged in the same manner

The distal esophagus was inspected with three imaging modalities.

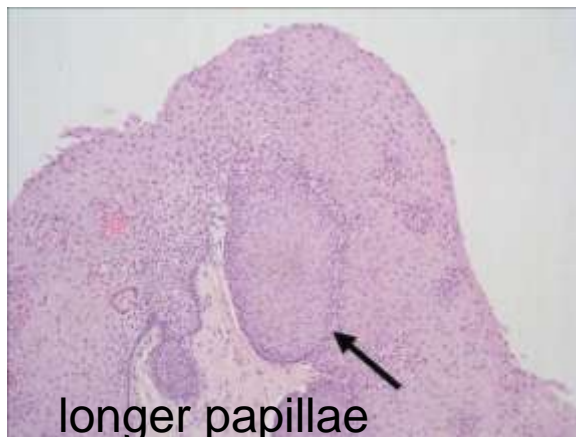
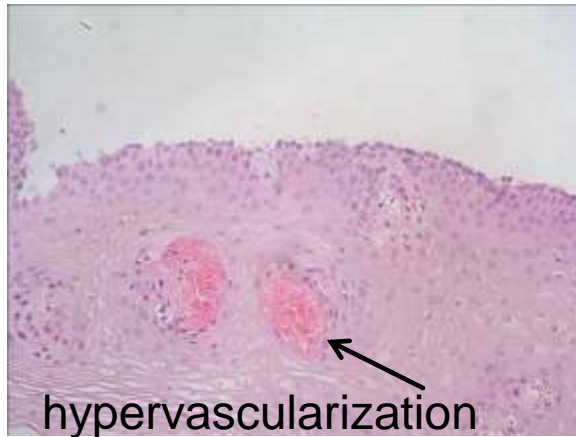
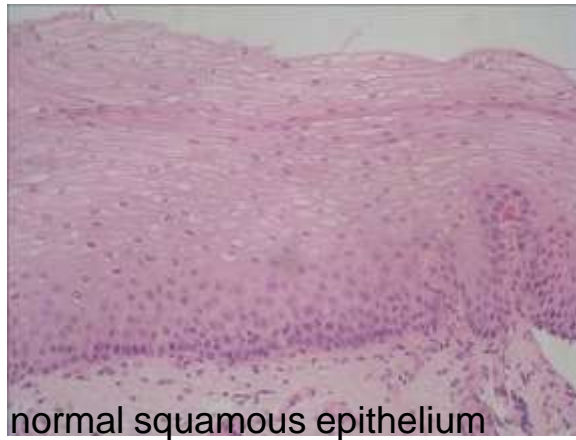
- HD+ was followed by *i*-scan analysis and subsequently Lugol's solution

Subsequent biopsies were taken from new visible erosions in the distal esophagus.



## Histologic Evaluation

biopsy specimens were taken from Lugol-unstained streaks or mucosal breaks under *i* scan :



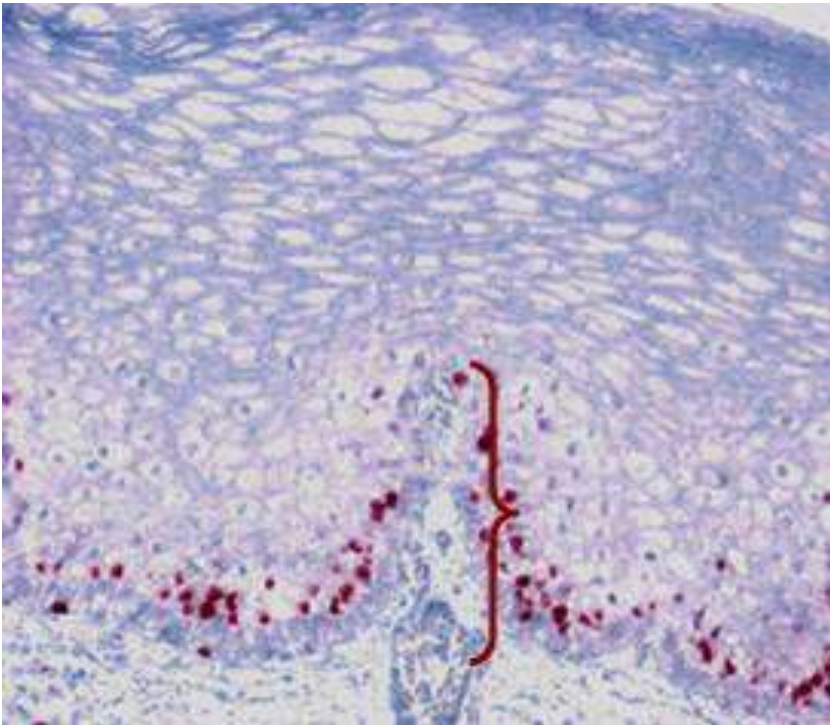
### Histologic criteria for reflux esophagitis:

- basal cell hyperplasia
- vascular dilatation
- elongation of papillae > 50% of epithelium

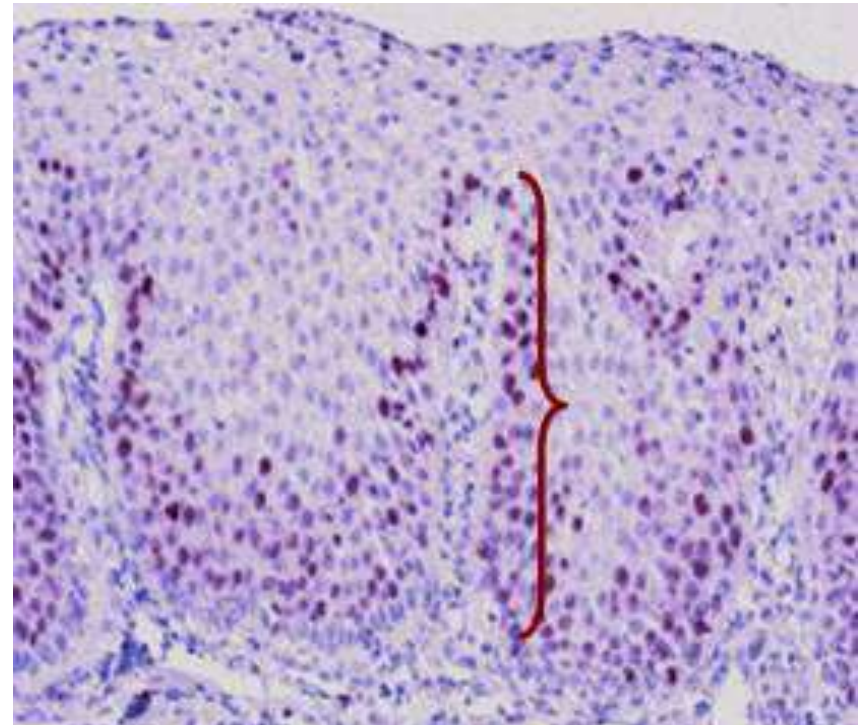
*Vieth M,  
Can an endoscopically negative reflux disease  
be histologically diagnosed ?  
Z Gastroenterol 2000*

# Microscopic Reflux Disease

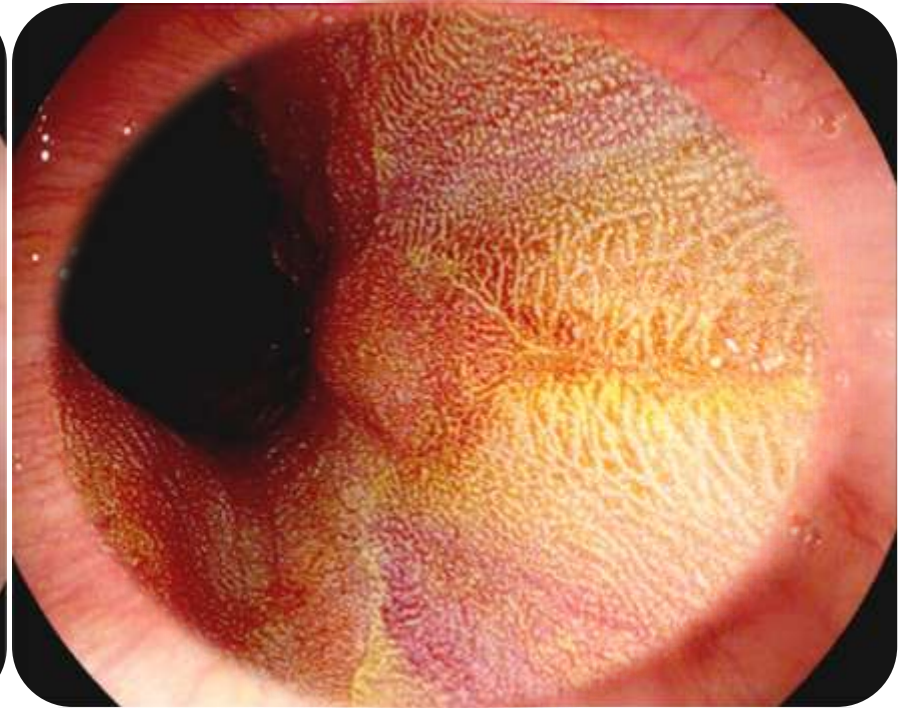
Microscopic changes typical but not always identifiable



Normal



NERD



# Results

## *Endoscopic Evaluation for i-scan*

<b>i scan</b>	<b>Pts. with Symptoms</b>	<b>Pts. without Symptoms</b>
Endoscopy +	52	4
Endoscopy -	13	23
	65	27

Sensitivity: 80%

Specificity: 85%

pos. pred. value: 93% neg. pred. value: 64%

accuracy: 82%

## Results

### *Endoscopic Evaluation for chromoendoscopy with Lugol` solution*

<i>Lugol` solution</i>	<b>Pts. with Symptoms</b>	<b>Pts. without Symptoms</b>
Endoscopy +	59	4
Endoscopy -	6	23
	65	27

Sensitivity: 91%

Specificity: 85%

pos. pred. value: 94% neg. pred. value: 80%

accuracy: 89%

## Endoscopic results according to histologic confirmation

*all symptomatic patients with inconspicuous first EGD*

<b>i scan</b>	<b>Histology +</b>	<b>Histology -</b>
Endoscopy +	52	0
Endoscopy -	11	2

**Sensitivity: 83%**

**Specificity: 100%**

**pos. pred. value: 100%**

**neg. pred. value: 15%**

<b>Lugol</b>	<b>Histology +</b>	<b>Histology -</b>
Endoscopy +	58	1
Endoscopy -	5	1

**Sensitivity: 92%**

**Specificity: 50%**

**pos. pred. value: 98%**

**neg. pred. value: 17%**

# Results

65 symptomatic NERD Pts.

HD+ with *i* scan

Lugol's solution

52/65 with mucosal breaks

*80% of NERD up-graded to LA A*

59/65 with unstained streaks

*89% of NERD up-graded to LA A*

52 Pts with pos. histology  
100% pos. predictive value

58 Pts with pos. histology  
98% pos. predictive value

Visible unstained streaks by Lugol chromoendoscopy or small mucosal breaks after *i* scan seem to be indicative of mucosal injury, which was not detectable by conventional endoscopy.

There no significant difference in detection of minimal change esophagitis between *i* scan and Lugol chromoendoscopy  
(p=ns)

# I-Scan

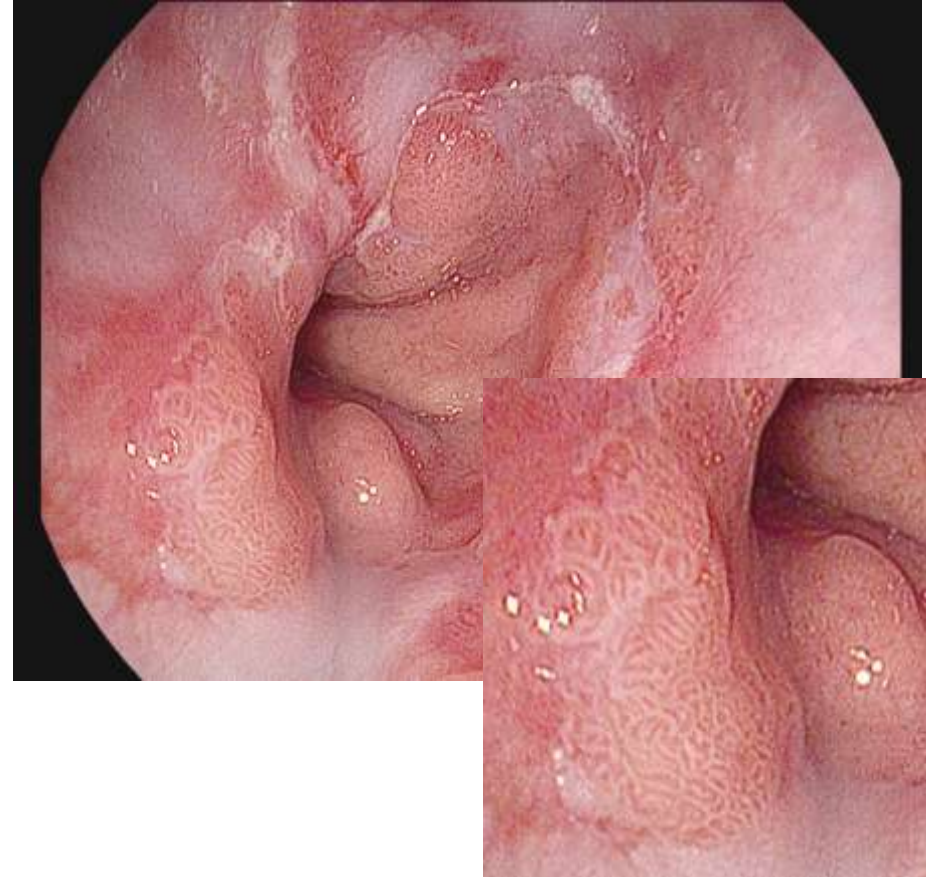
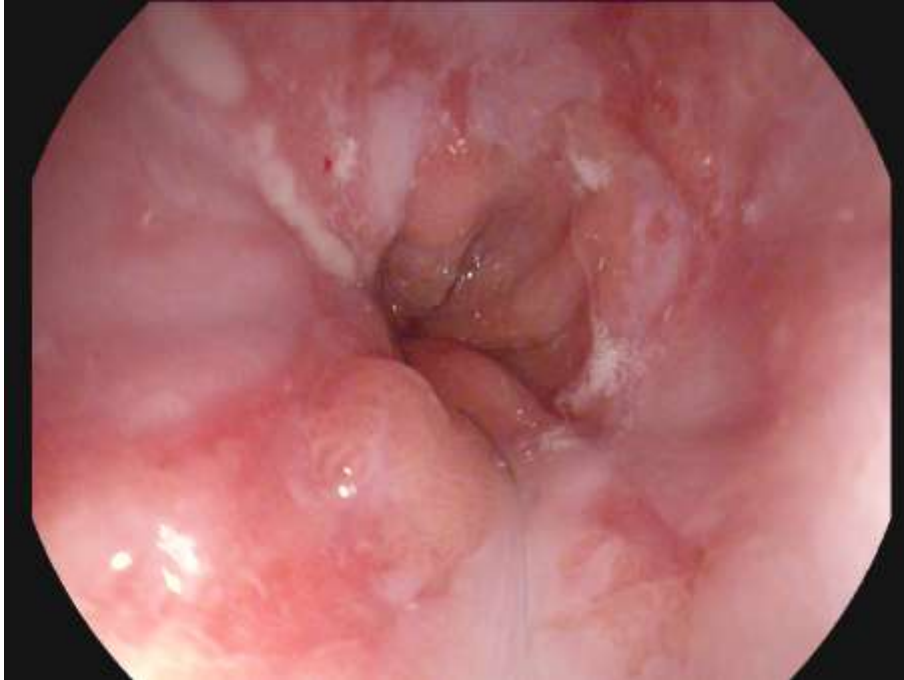


## Conclusion

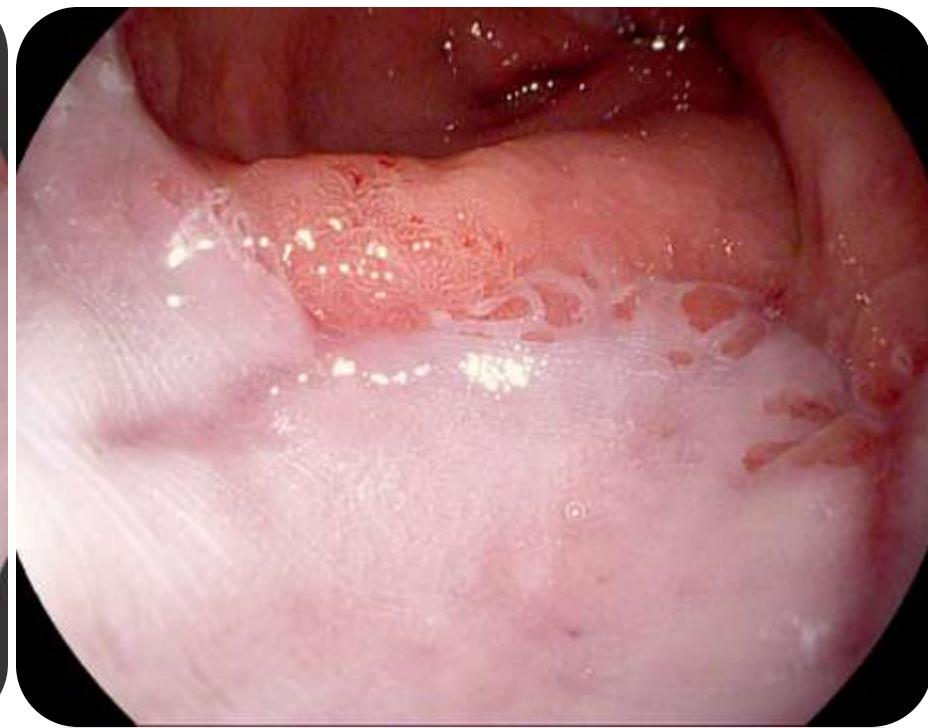
The present study suggests that most of the patients with so called NERD with typical symptoms of reflux disease can be diagnosed by Lugol chromoendoscopy or *i* scan as ERD patients

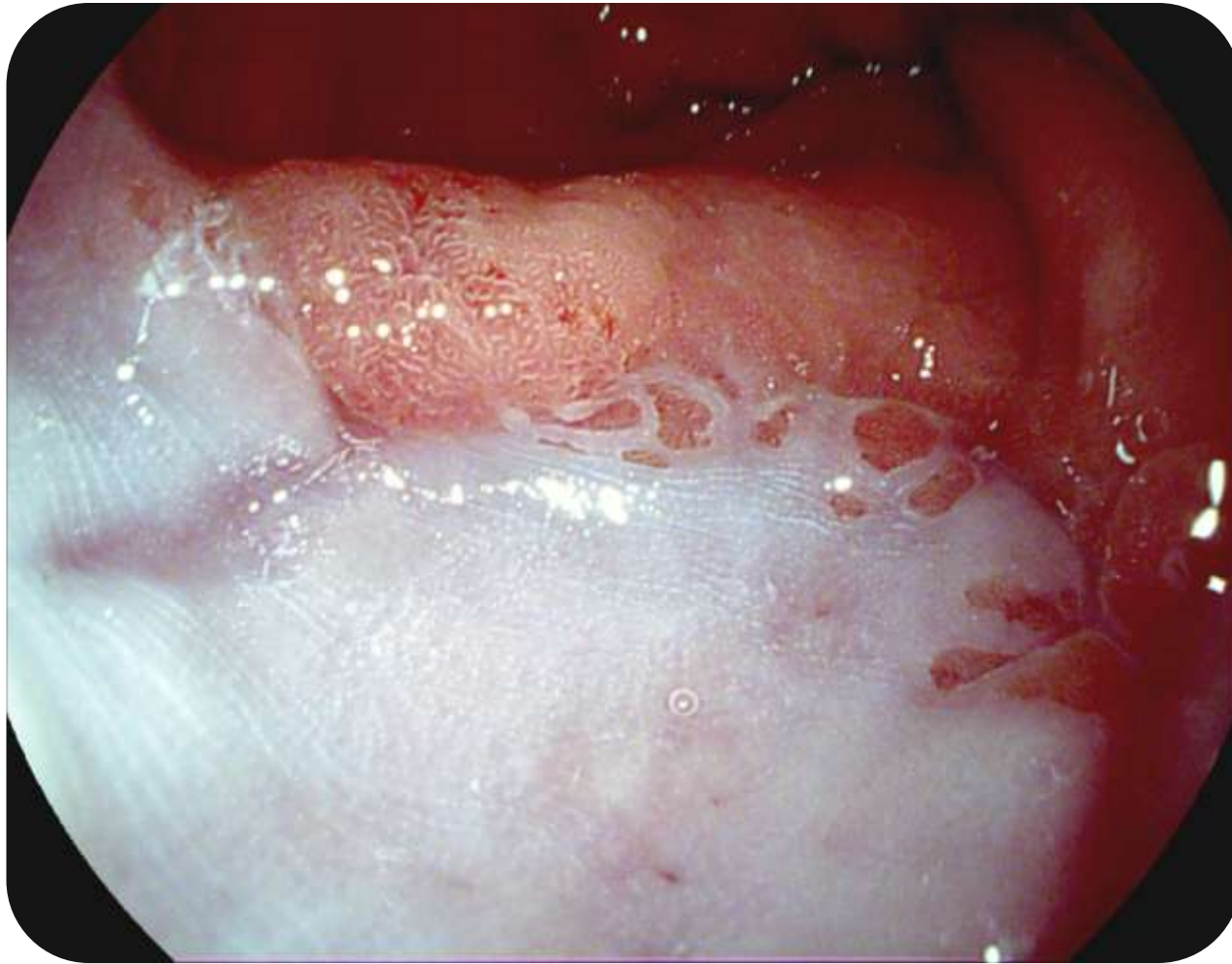
Both methods could be appealing for the endoscopists as they are easy, safe, and can be performed at the same endoscopic session.

# Lesion & Esophagitis

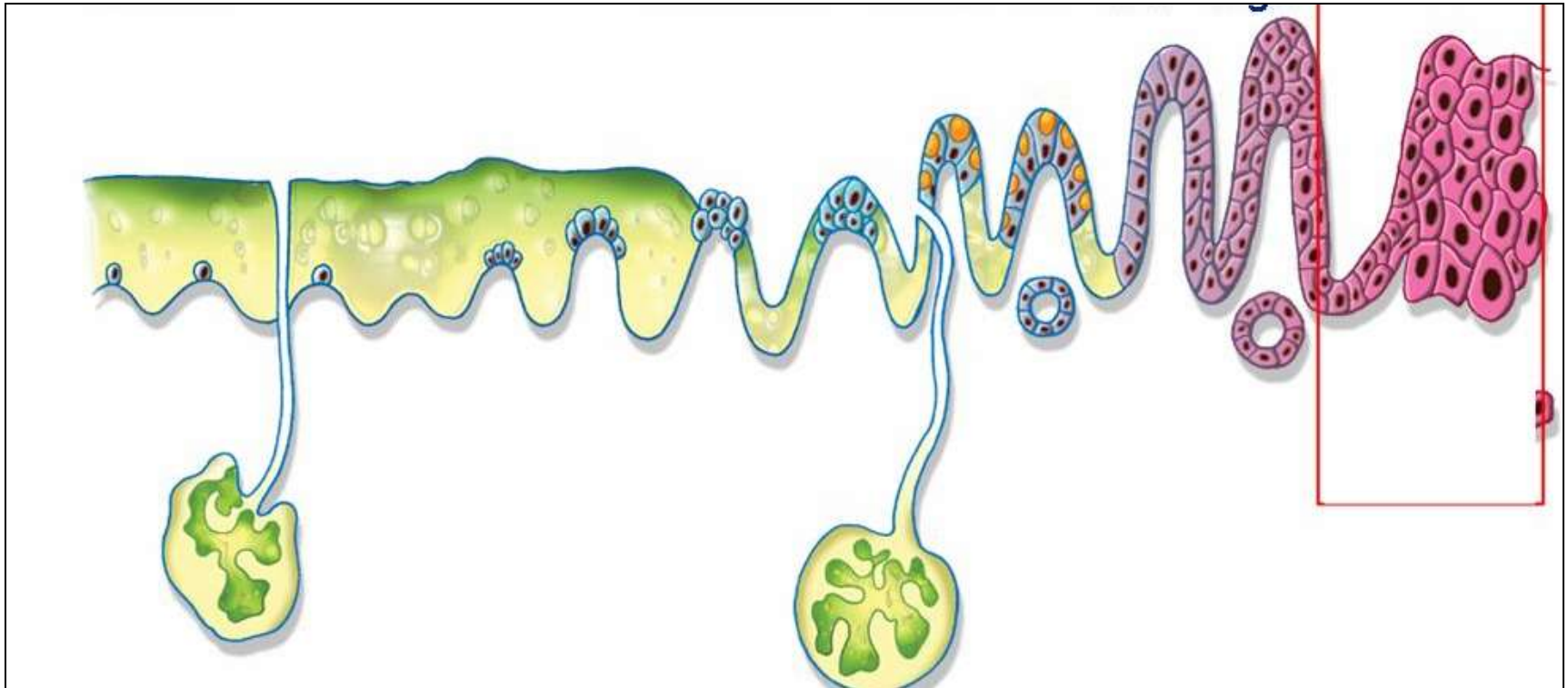


# Barrett`s Esophagus and *i*-scan

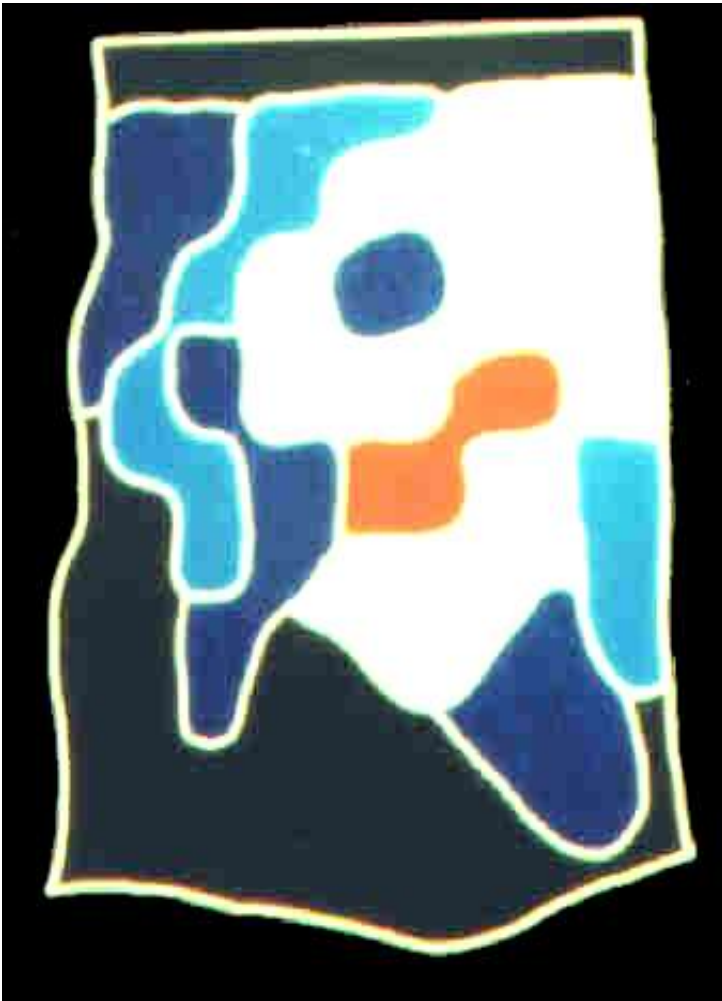




## Barrett`s Esophagus and cancer risk



# Distribution Barrett's tissue



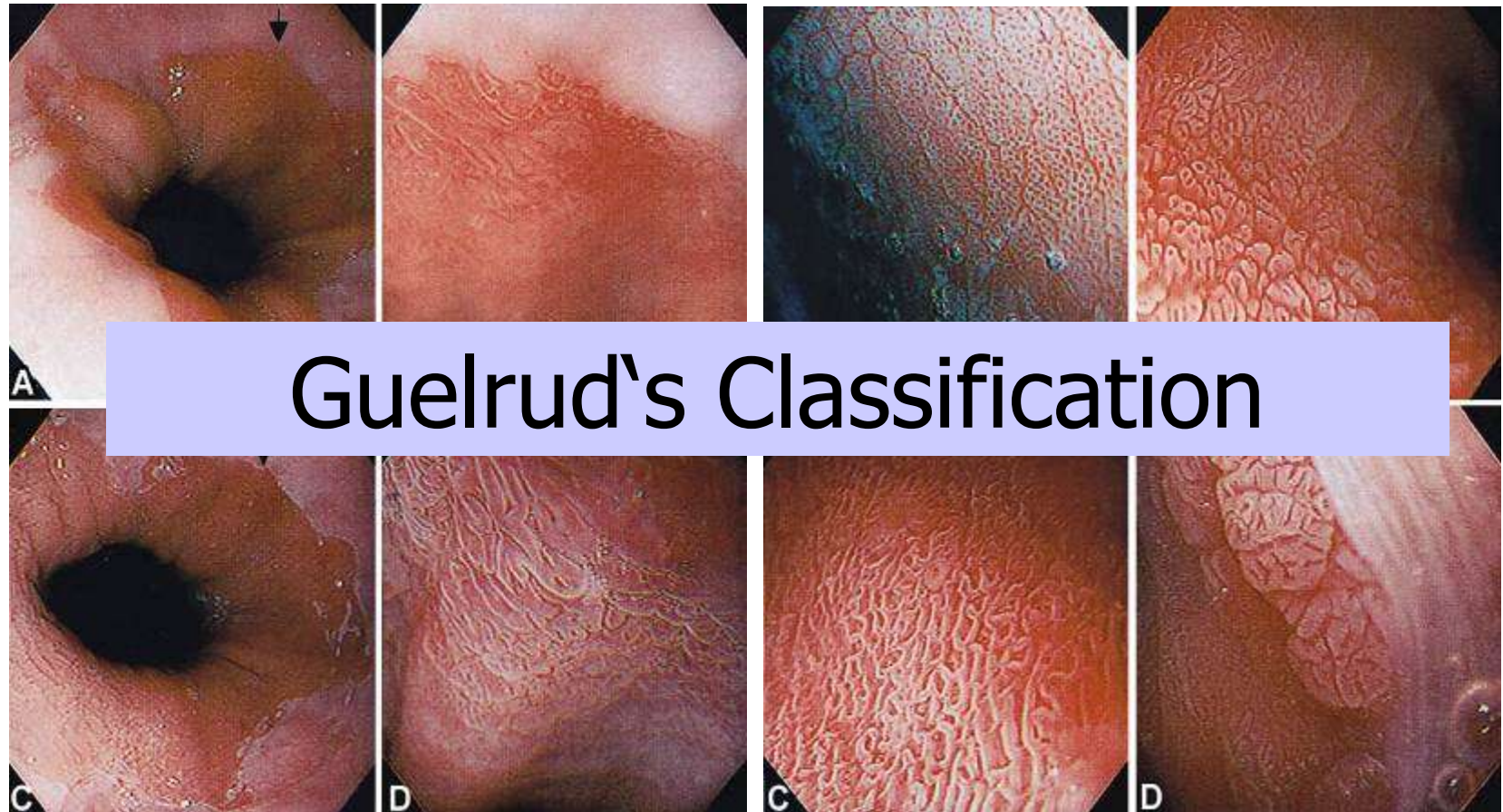
Metaplasia

Low-grade Dysplasia

High-grade Dysplasia

Cancer

# Acetic Acid



# Acetic Acid

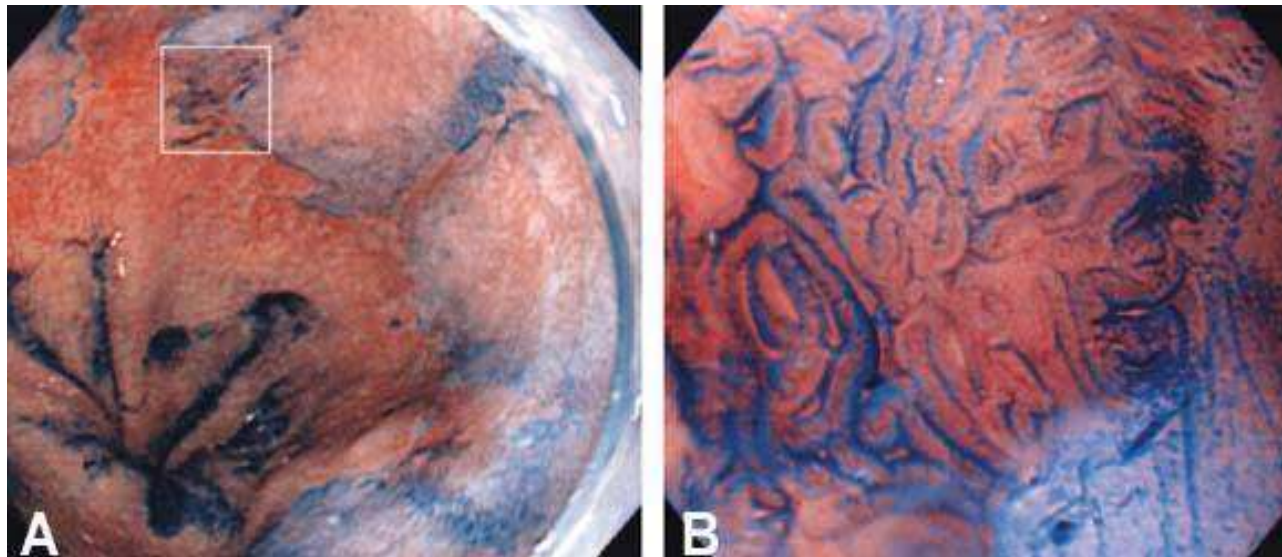
Barrett's epithelium (villous/ridged surface)

Study	Sample Size	Sensitivity, %	Specificity, %	Accuracy, %
Guelrud et al, <sup>7</sup> 2001	49	96.5	88.7	92.2
Toyoda et al, <sup>10</sup> 2004	67	88.5	90.2	90.0
Meining et al, <sup>11</sup> 2004	51	77.0	15.0	52.3
Hoffman et al, <sup>9</sup> 2006	31	88.0	86.0	83.0

Barrett's dysplasia (dysorganised surface structure)

Sensitivity: 40-80% kappa values <0.4

# Methylene blue

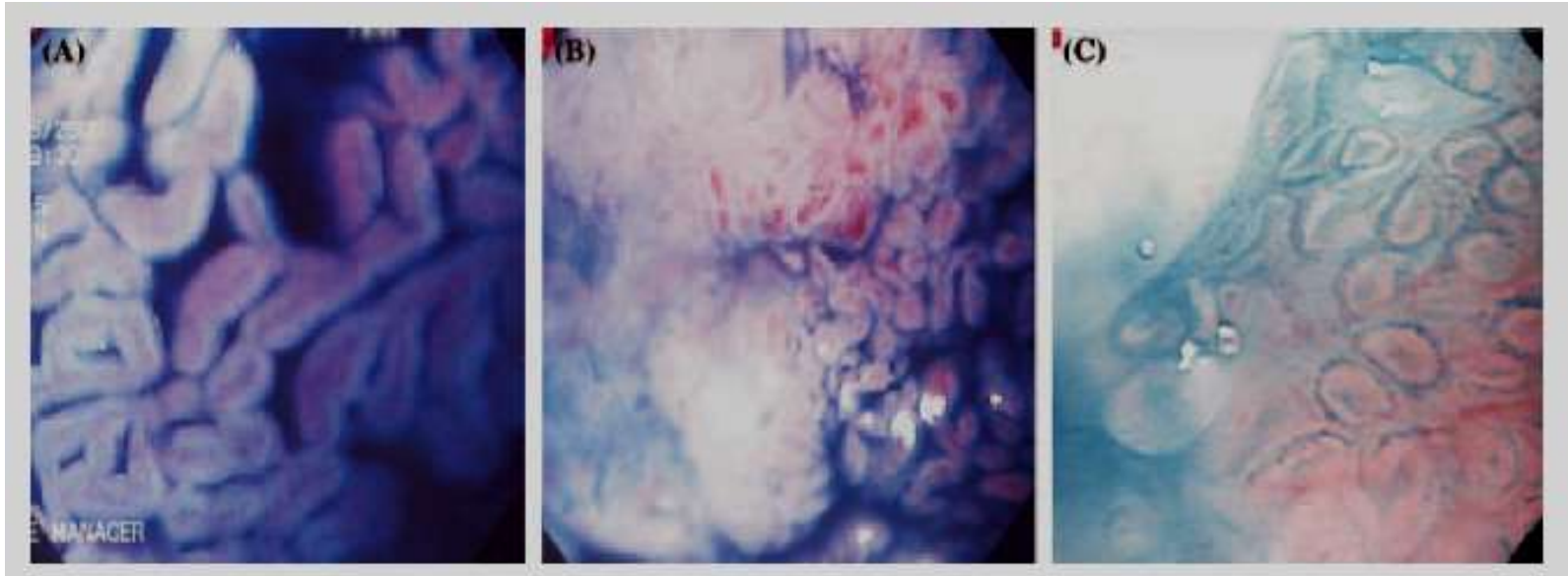


Endo's Classification

# Methylene blue

- Endo et al. Gastrointest Endosc 2002  
**Prediction of Barrett's epithelium; Accuracy: 83%**
- Gossner et al. Dig Liv Dis 2006  
**MB improves detection of dysplasia**
- Lim et al. Gastrointest Endosc 2006  
**MB makes detection of dysplasia worse  
(cross over trial)**

# Indigo carmine

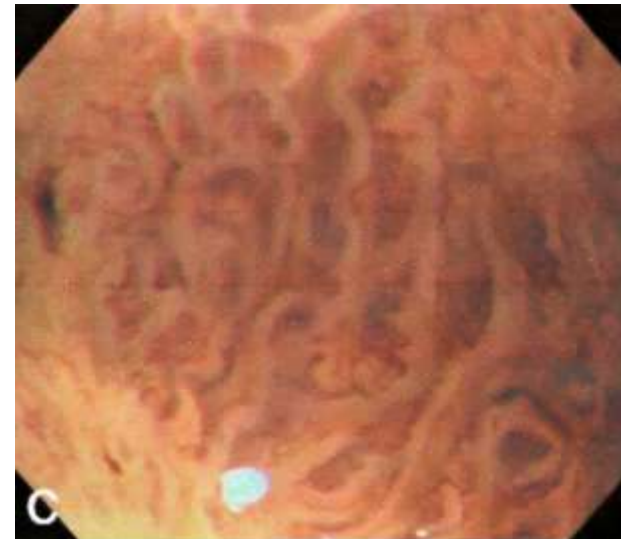


## Sharma's Classification

Barrett: Sensitivity 97%; Specificity 76%

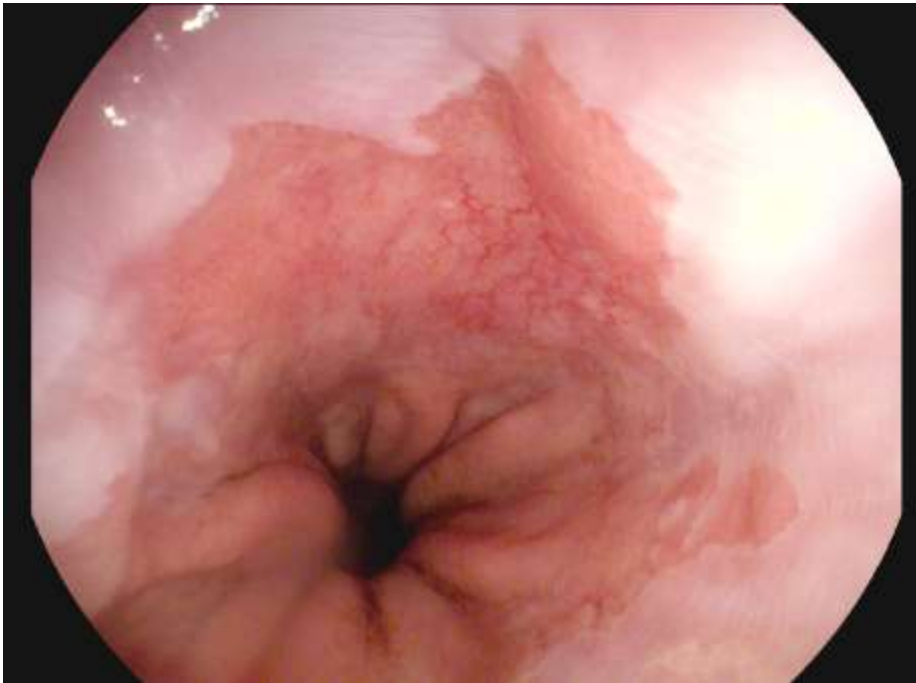
HGD: Sensitivity 97%; Specificity 100%

## The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus

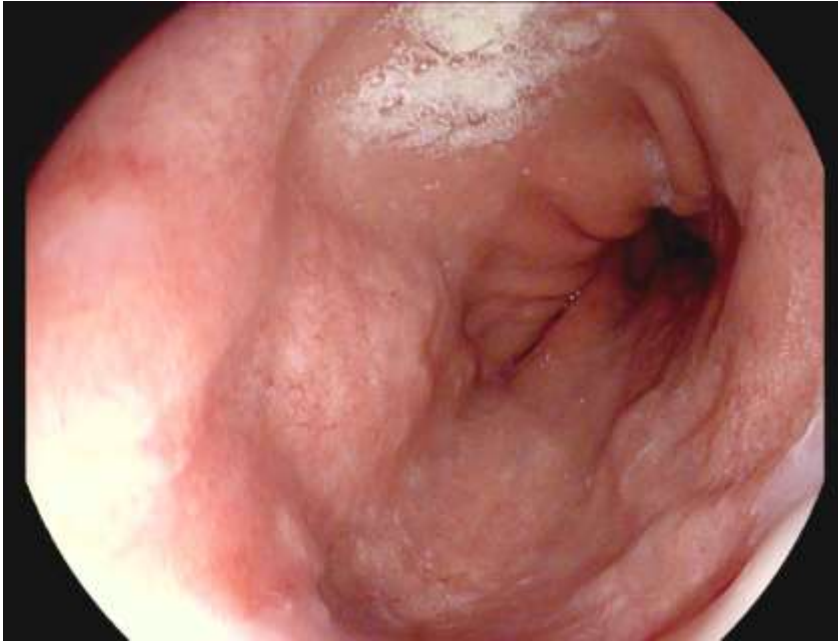


Sensitivity, Specificity, and positive pre-dictive value of ridge/villous pattern for diagnosis of IM without HGD were 93.5%, 86.7%, and 94.7% .

# Barrett's esophagus



# Barrett`s Esophagus and *i*-scan

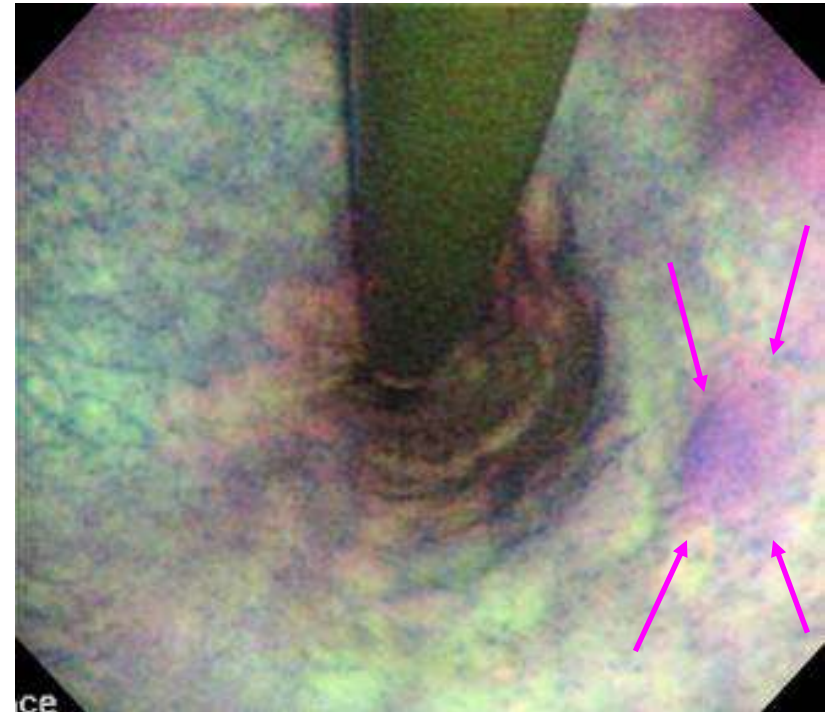
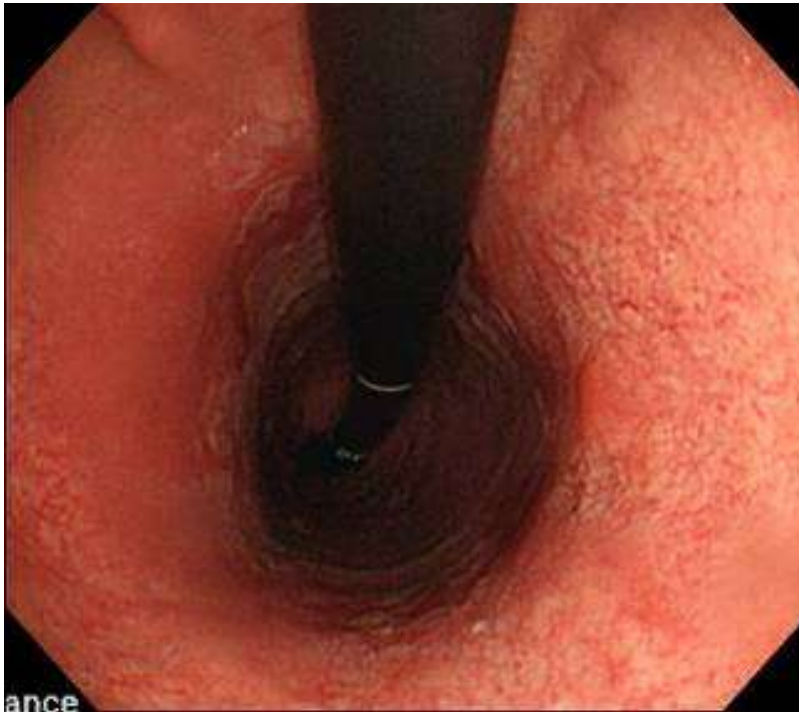


HD white Light



SE + TE with acetic acid

# Autofluorescence & Videoendoscopy

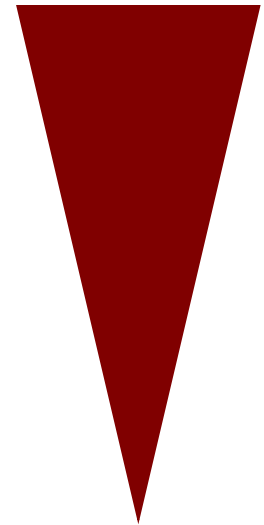


## Possible red flag technology:

Sensitivity 100%, but false positive results in 40%

# Combined approach for characterizing neoplasia

- White light Endoscopy
- Autofluorescence False positive 40%
- Narrow band imaging False positive 10%



**Draw back – two endoscopes needed**

# Endoscopic tri-modality imaging (ETMI).

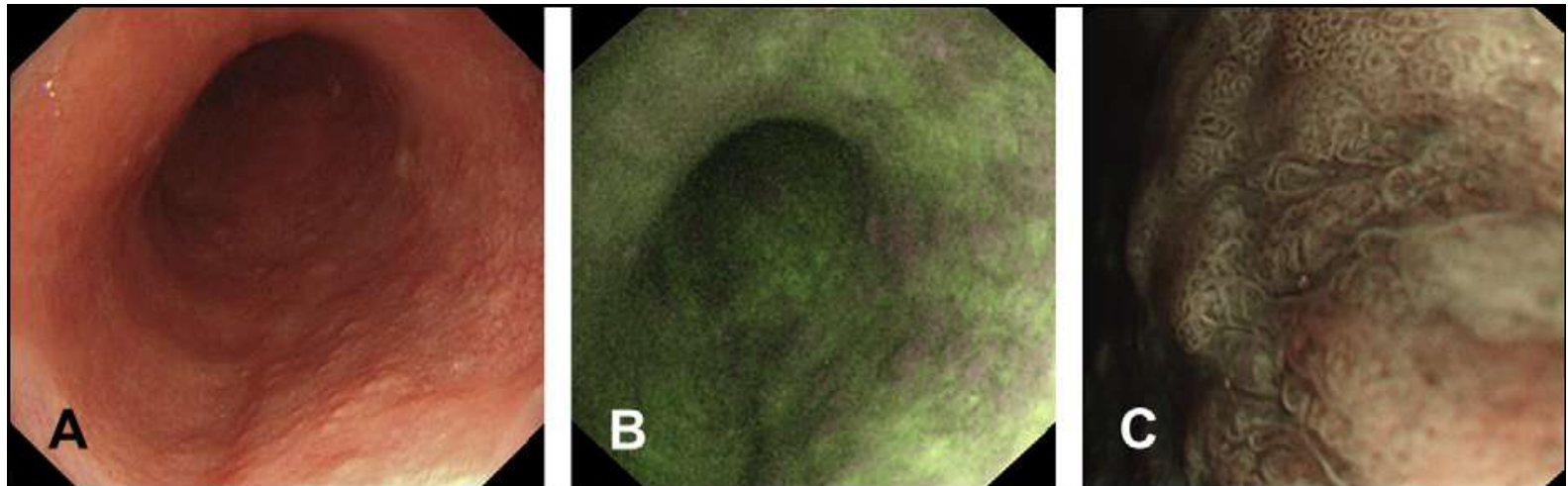
- White light Endoscopy
- Autofluorescence
- Narrow band imaging

Sensitivity 53%

Sensitivity 90%

False positive 81%

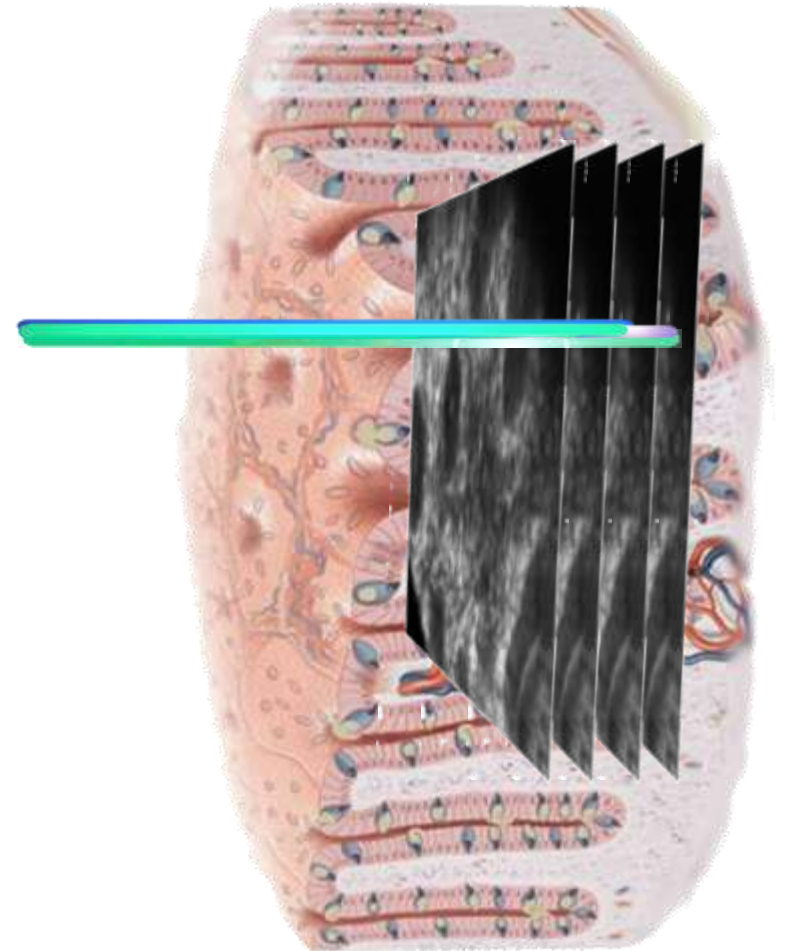
False positive 26%



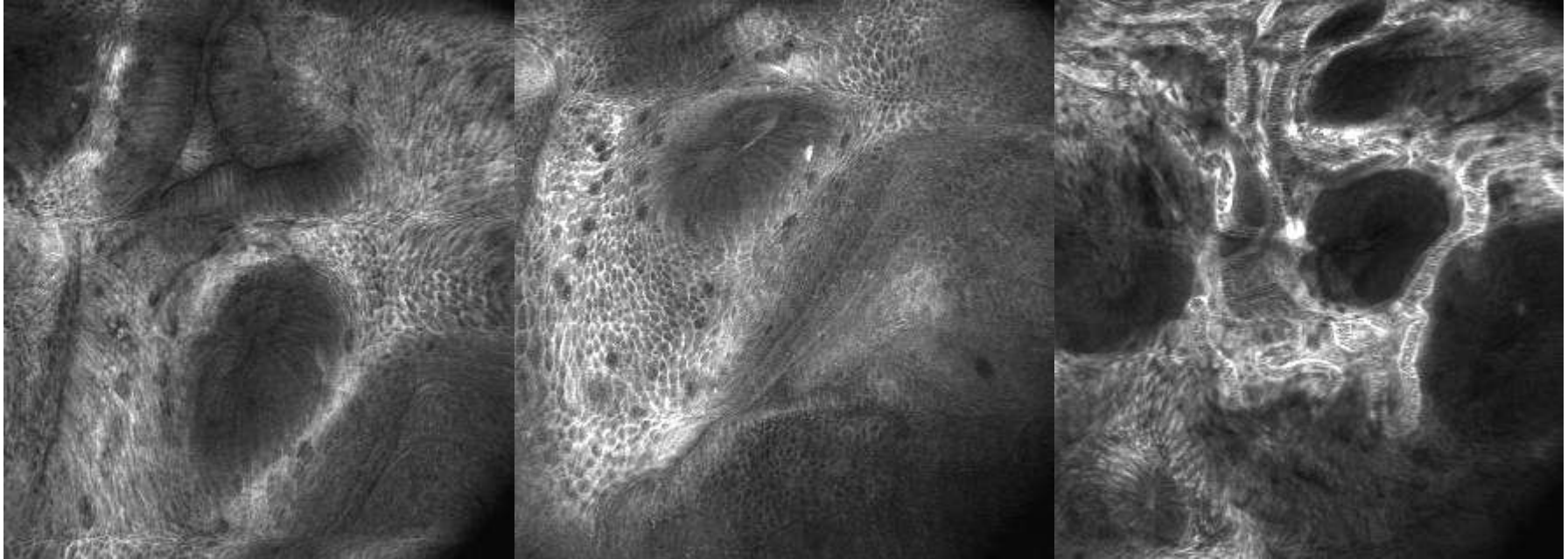
# Endomicroscopy



Field of view:  $475 \times 475 \mu\text{m}$   
Range:  $0\text{-}250 \mu\text{m}$   
Lateral resolution:  $<1 \mu\text{m}$



# Barrett Esophagus without dysplasia



# Barrett Esophagus: First data

**Table 2:** Correlation between confocal imaging and histology (156 areas in 63 patients)

Confocal diagnosis	Sites	Histology				
		Gastric Epithelium	SCE	LGIN	HGIN	Cancer
Gastric Epithelium	50	48	2	0	0	0
Barrett's epithelium	78	3	73	1	1	0
Neoplasia	28	0	2	6	12	8

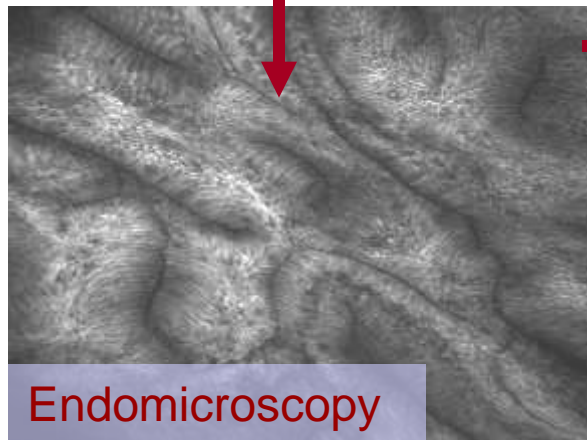
Blinded prediction of Barrett' epithelium:

Sensitivity: 98.1%; Specificity: 94.1%, Accuracy: 96.8%

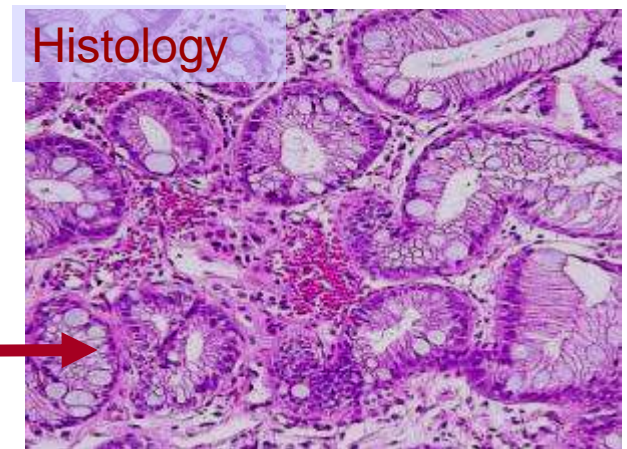
Blinded prediction of Barrett's associated neoplasias:

Sensitivity: 92.9%; Specificity: 98.4%, Accuracy: 97.4%

# Barrett Esophagus: Work flow



Targeted Biopsy



For any new endoscopic technology to be useful in NERD patients, the grading system it uses must be accurate, reproducible, easy to remember and easy to interpret.

These requirements represent a high bar indeed for any new approach to non-erosive reflux disease.

Current techniques under investigation include high-resolution endoscopy, magnification endoscopy, chromoendoscopy, narrow-band imaging and confocal endomicroscopy.