

# Barrett's Esophagus

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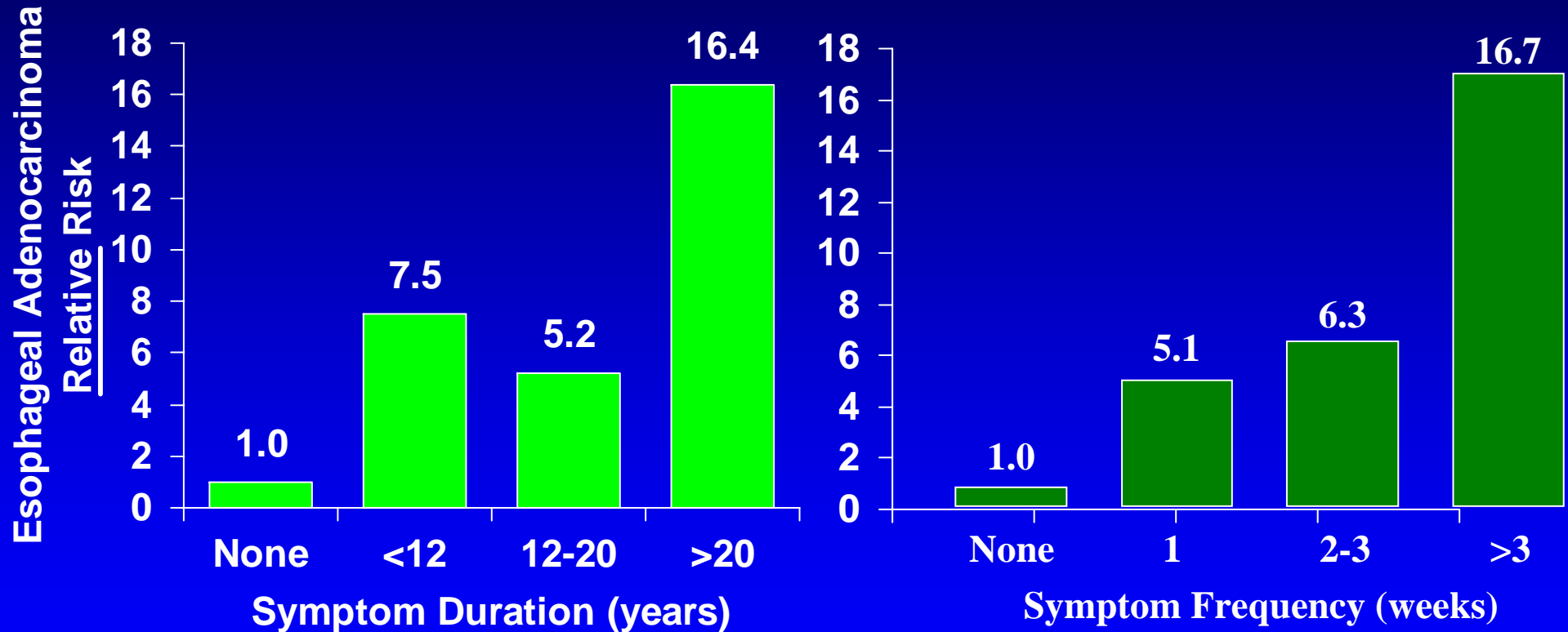
September 10, 2009



# Optimal Surveillance and Management of Barrett's Esophagus

- What is Barrett's Esophagus?
- Carcinogenesis of Barrett's
- Surveillance
- Management of high grade dysplasia
  - Endoscopic mucosal resection
  - Ablation

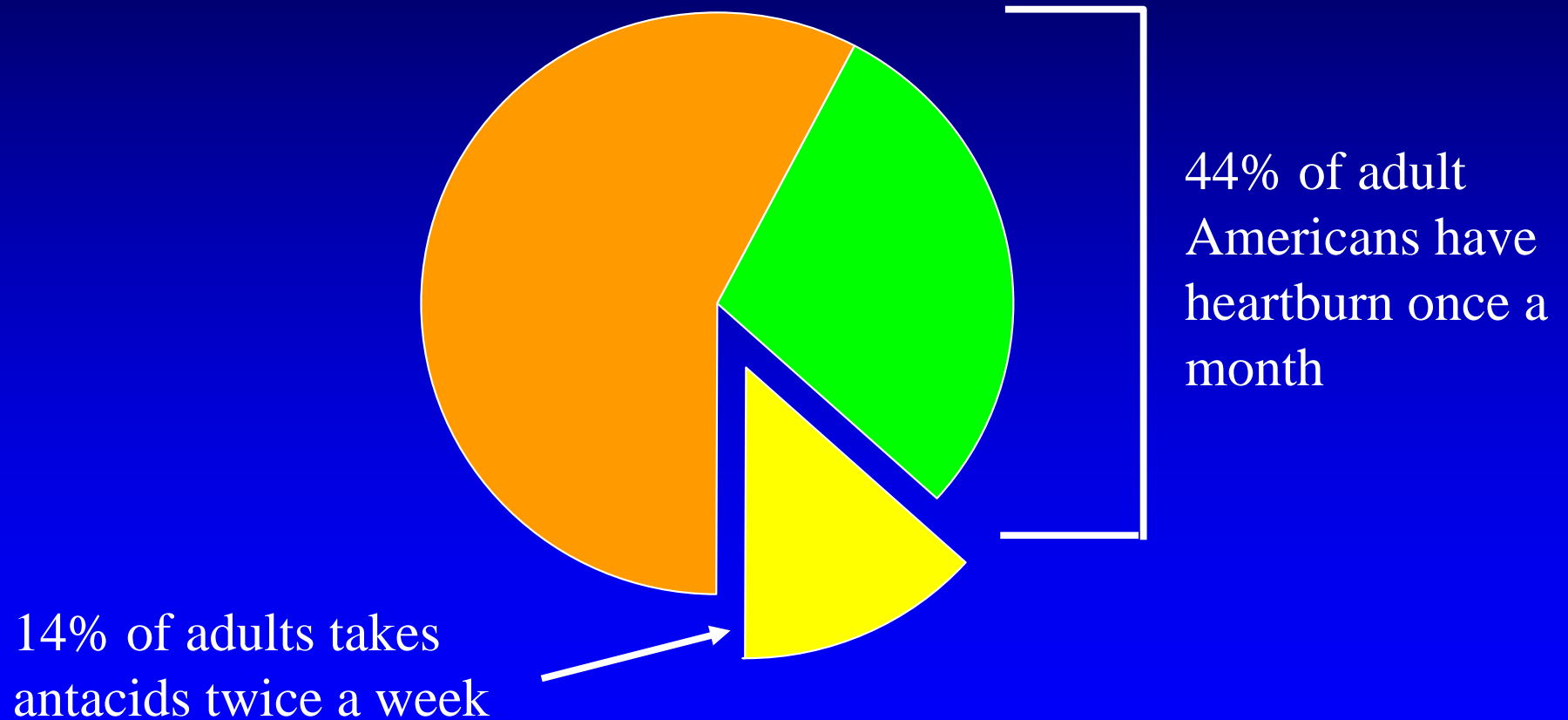
# Duration and Frequency of Heartburn is Associated with Esophageal Adenocarcinoma



N = 1,438 (n = 189 with esophageal adenocarcinoma).

Lagergren et al. *N Engl J Med*. 1999;340:825-831.

# Heartburn is Very Common in the US

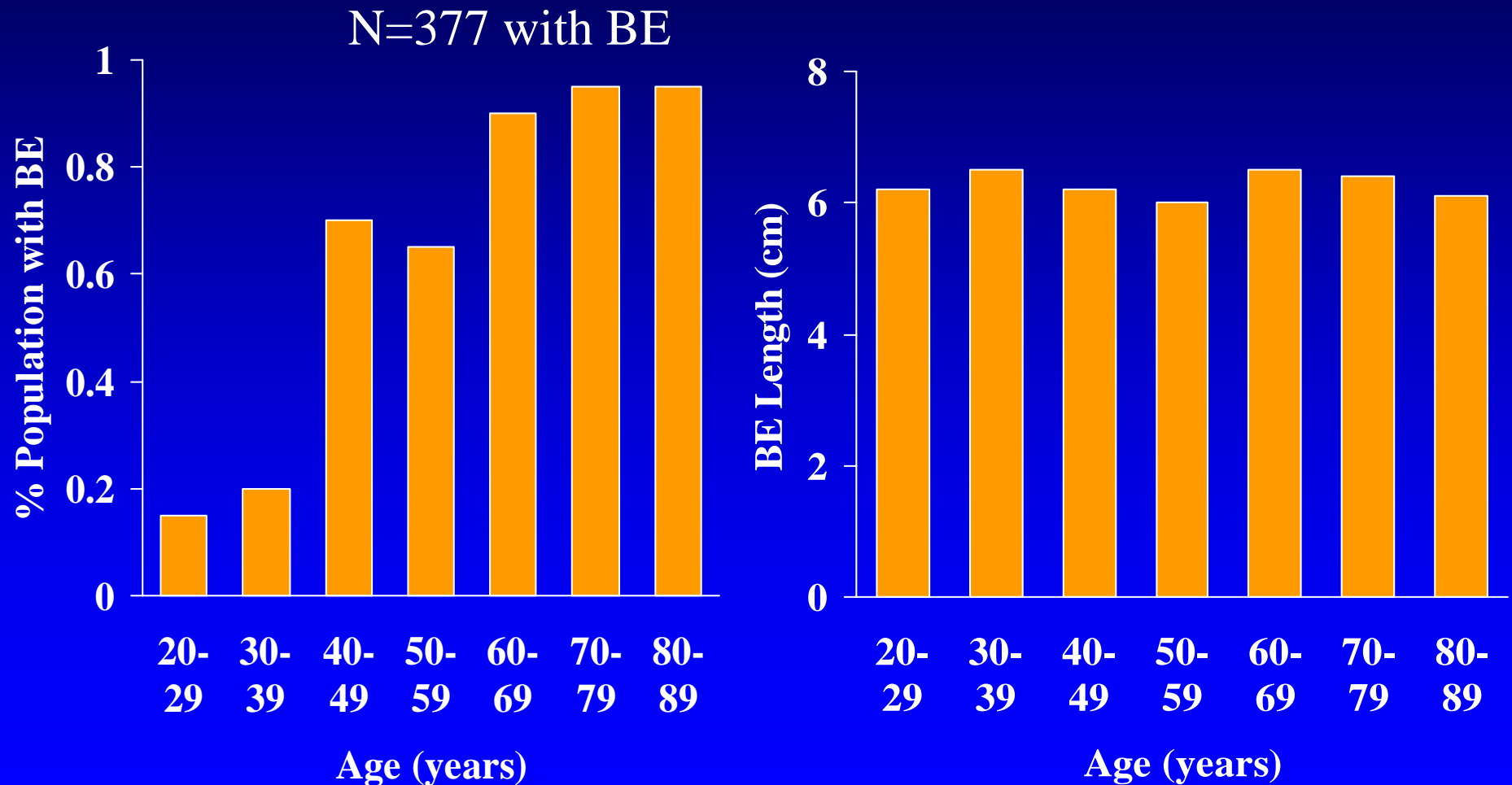


# Complications of Gastroesophageal Reflux Disease

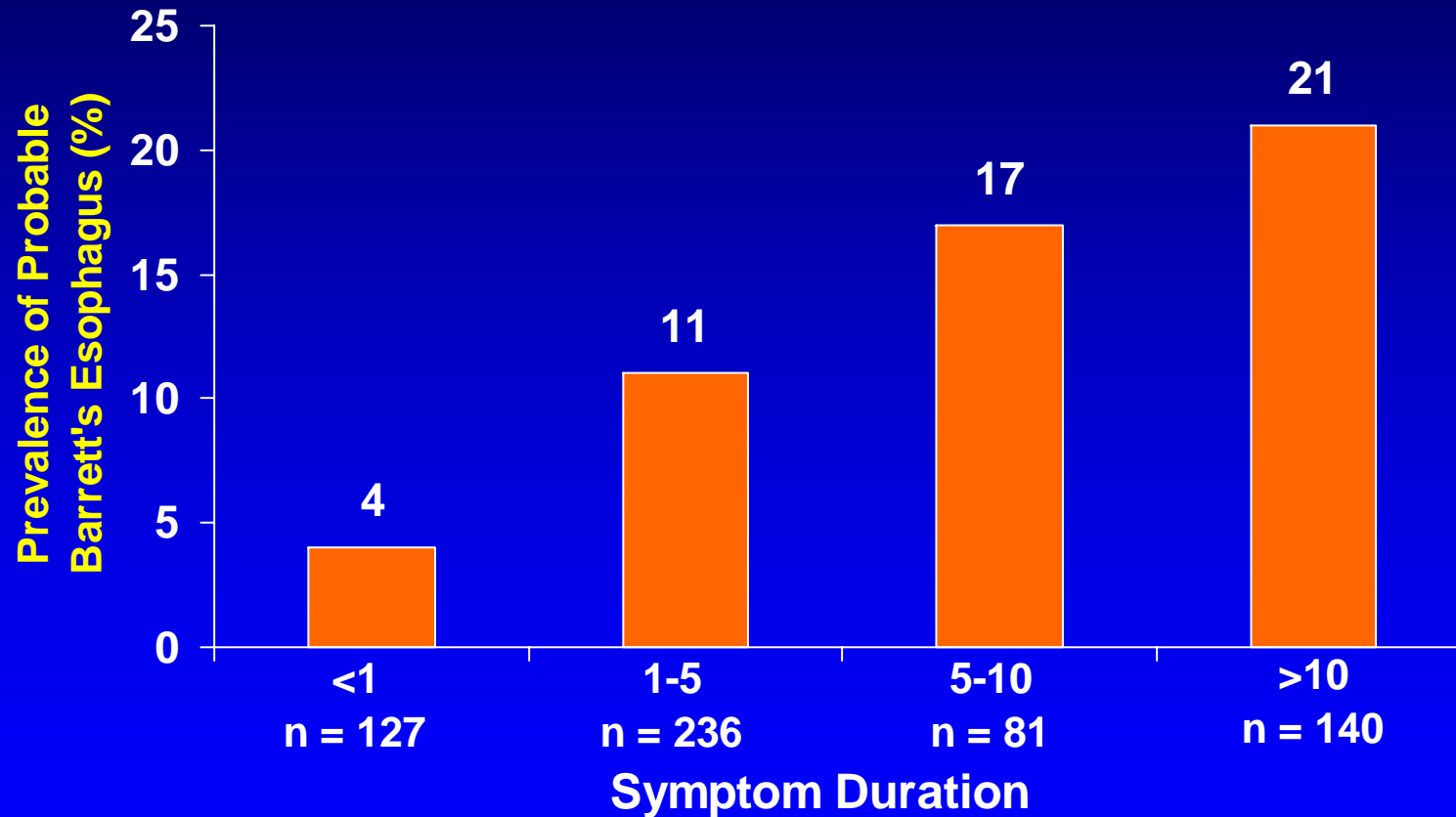
## Incidence

- Esophagitis 20 - 40 %
- Bleeding < 5 %
- Esophagus Stricture 4 - 20 %
- **Barrett's Esophagus 8 - 15 %**
- Esophageal adenocarcinoma ?

# Barrett's Esophagus Occurred Early in Patients with Chronic Heartburn



# Prevalence of Barrett's Esophagus is Associated with Duration of Heartburn



# Recommended Screening for Barrett's Esophagus

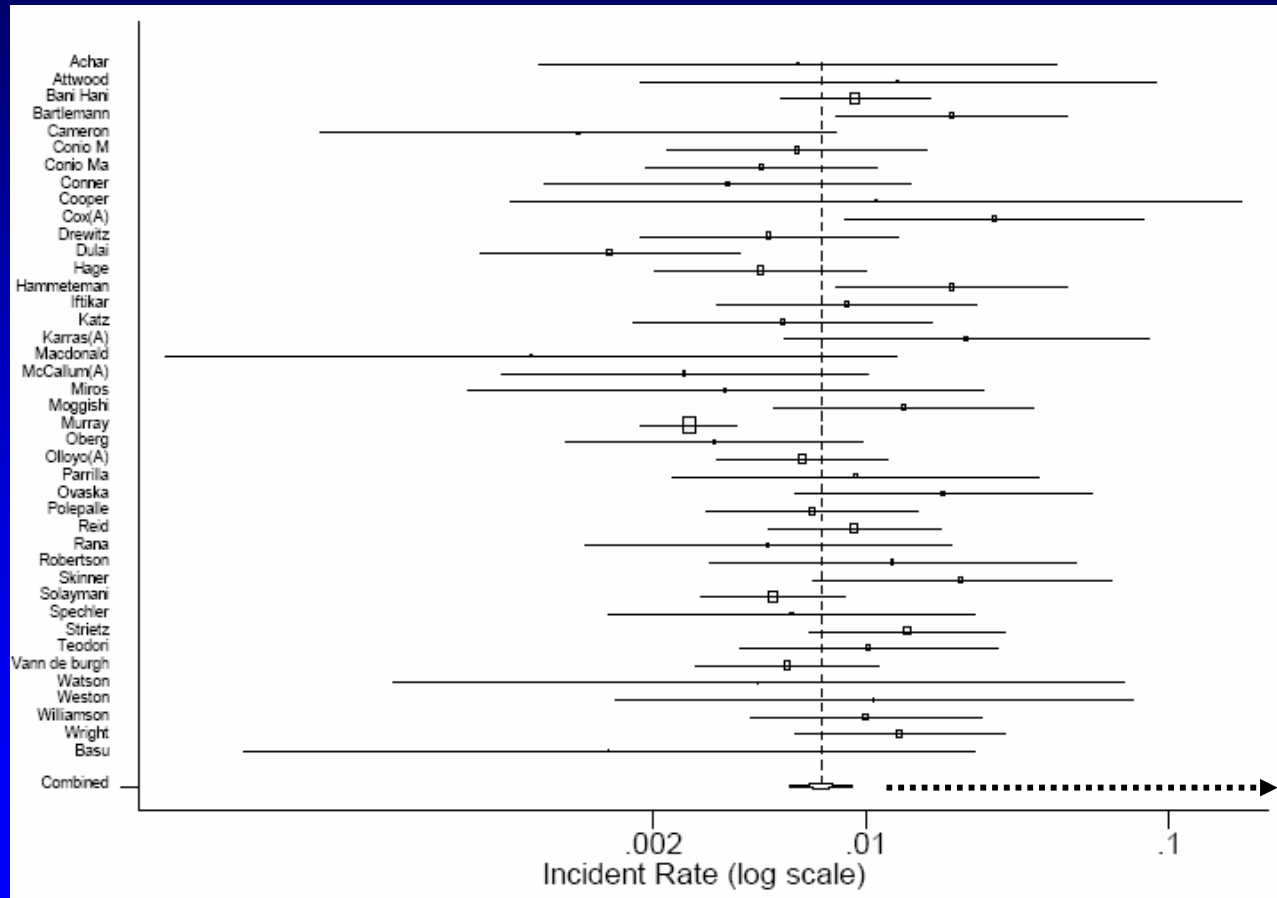
- > 10 years of heartburn
- > 50 years old
- Caucasians
- Males
- *\*Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper endoscopy.*

Sampliner RE. ACG Practice Guideline. Am J Gastroenterol 1998;93: 1028-32.

\*Sampliner RE. Updated ACG Practice Guideline. Am J Gastroenterol 2002;97:1888-95.



# Risk of Adenocarcinoma in Patients with Barrett's Esophagus



Average risk of developing AdenoCa: 0.7% per patient-year follow-up

Meta-Analysis of 41 studies

Thomas T et al. Aliment Pharmacol Therapt 2007.

# Patient Education is Very Important for Barrett's Esophagus

- 8 to 15 % of patients with chronic heartburn have Barrett's esophagus
- On average, a patient with BE has only a 0.5% risk per year for developing esophageal adenocarcinoma
  - Lower risk for short segment BE
  - Higher risk for dysplastic BE

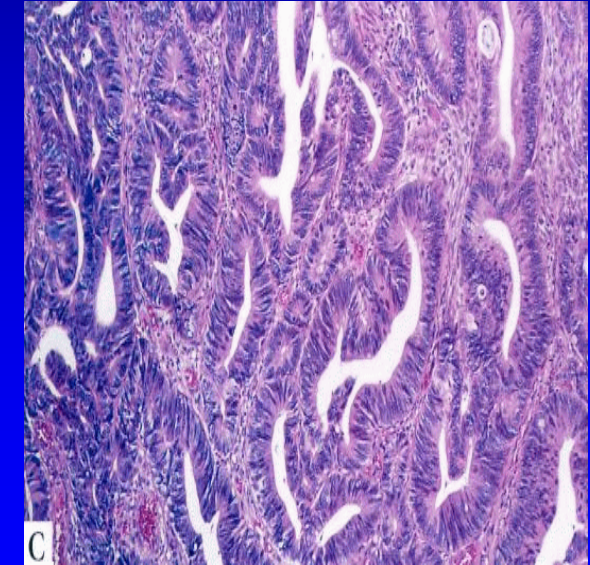
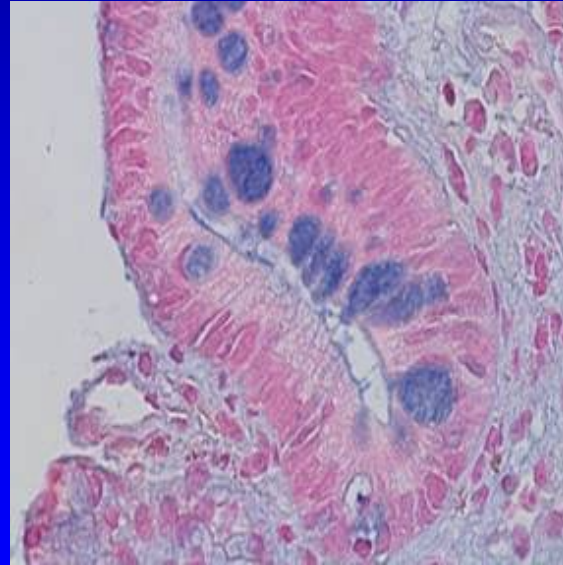
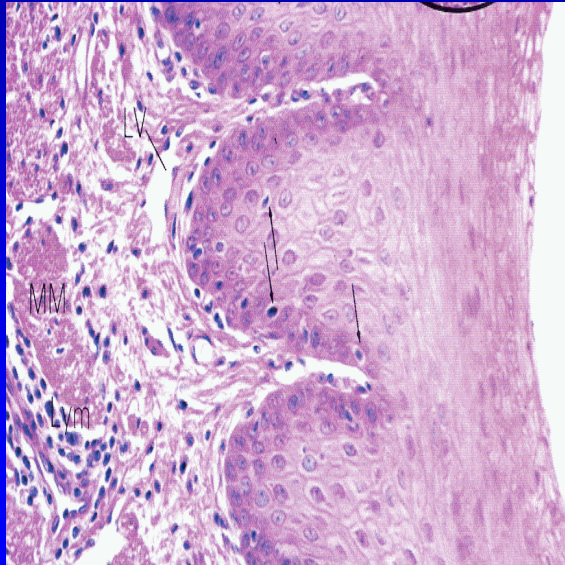
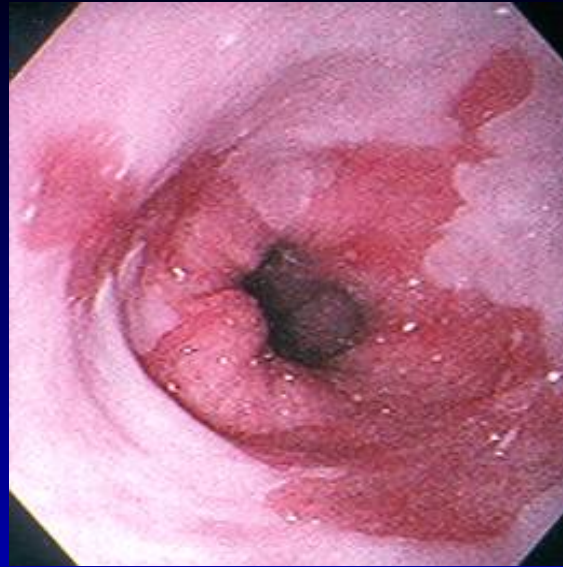
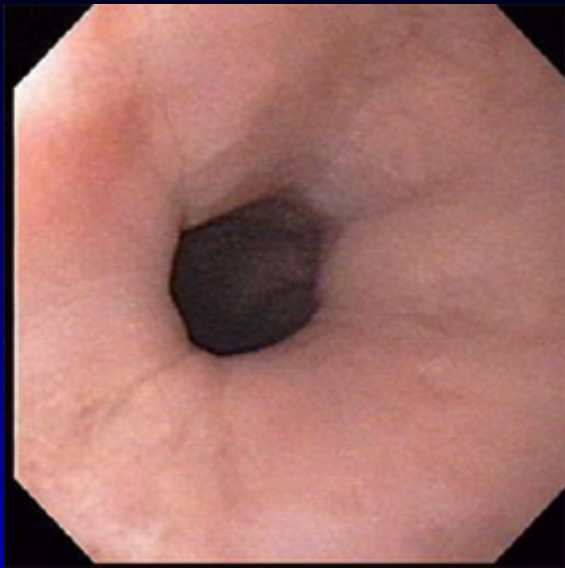
# Questions to Answer?

- What is Barrett's esophagus, and why it turns into cancer?
- How to diagnose BE and identify patients with dysplasia?
- What is the optimal surveillance strategy?
- What is the management of high grade dysplasia?

**What is Barrett's esophagus, and  
why it turns into cancer?**

# Barrett's Esophagus: Definition

- A change in the esophageal epithelium of any length that
  - Can be recognized at endoscopy
  - Confirmed by biopsy to have specialized intestinal metaplasia
  - Not intestinal metaplasia of the cardia



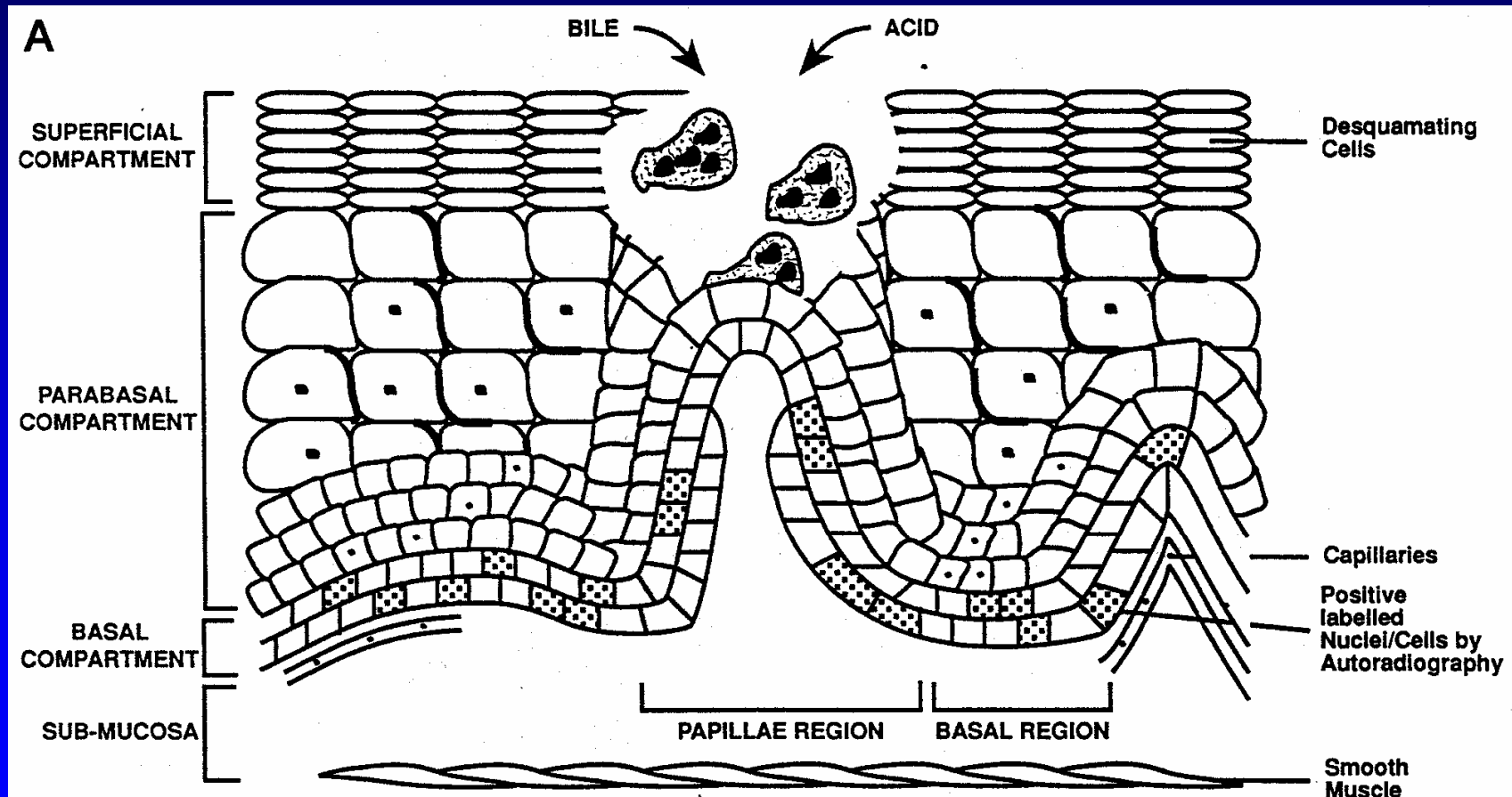
**Normal  
Esophagus**

**Barrett's  
Esophagus**

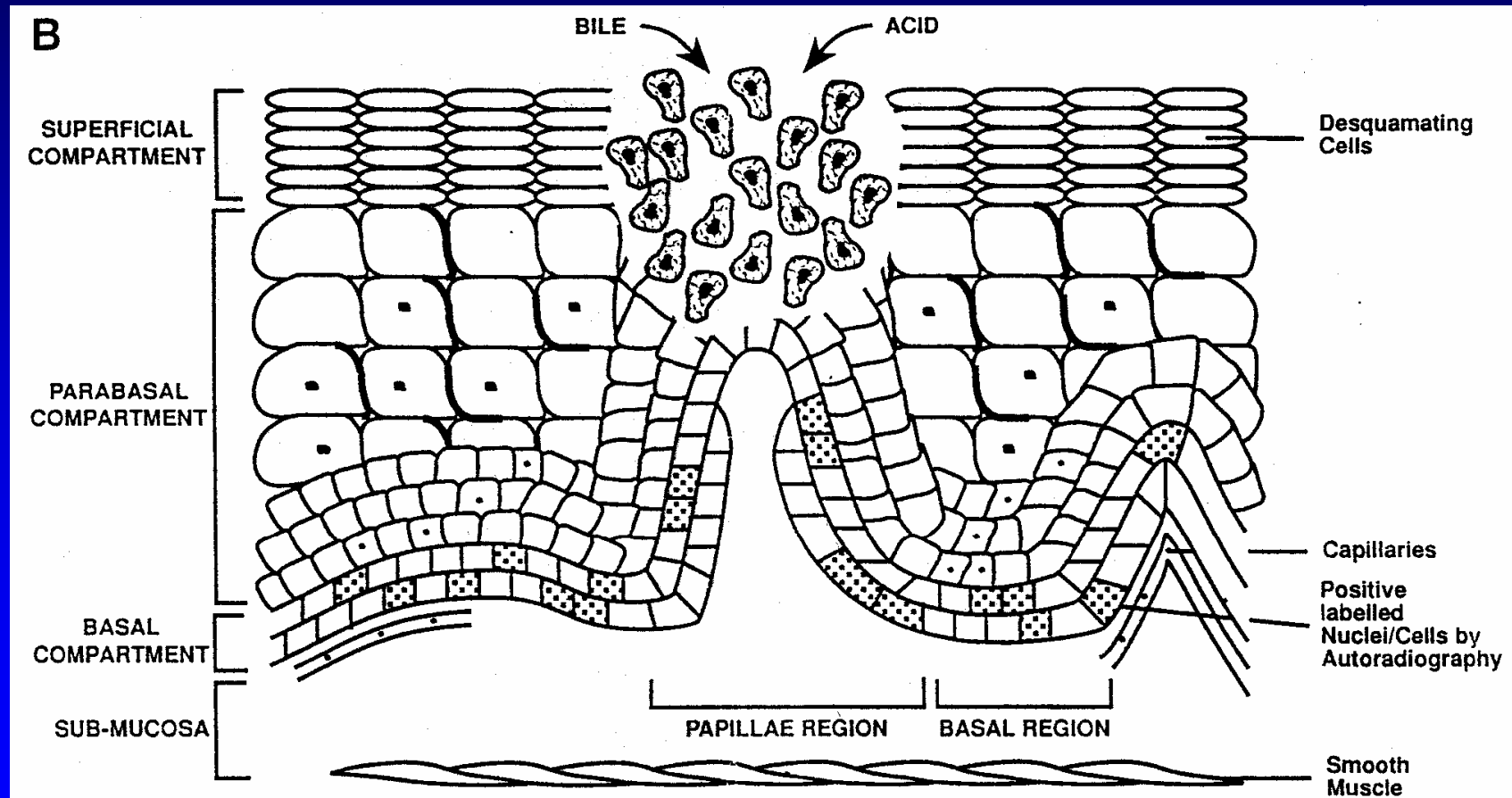
**Esophageal  
Adenocarcinoma**



# Esophagus Lining is Damaged by Acid Reflux

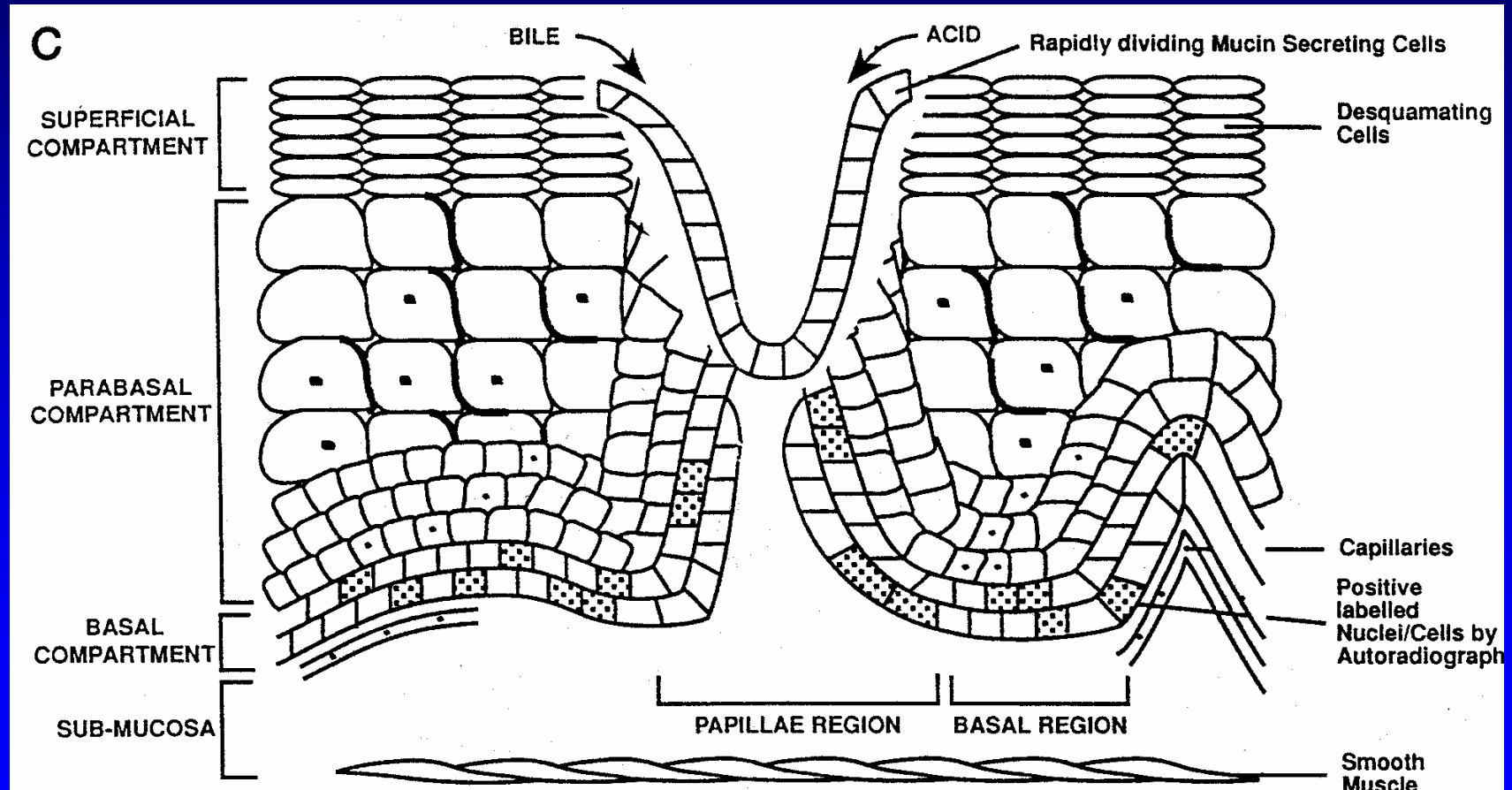


# Hyperproliferation Occurs, Esophagus Stem Cells are Damaged

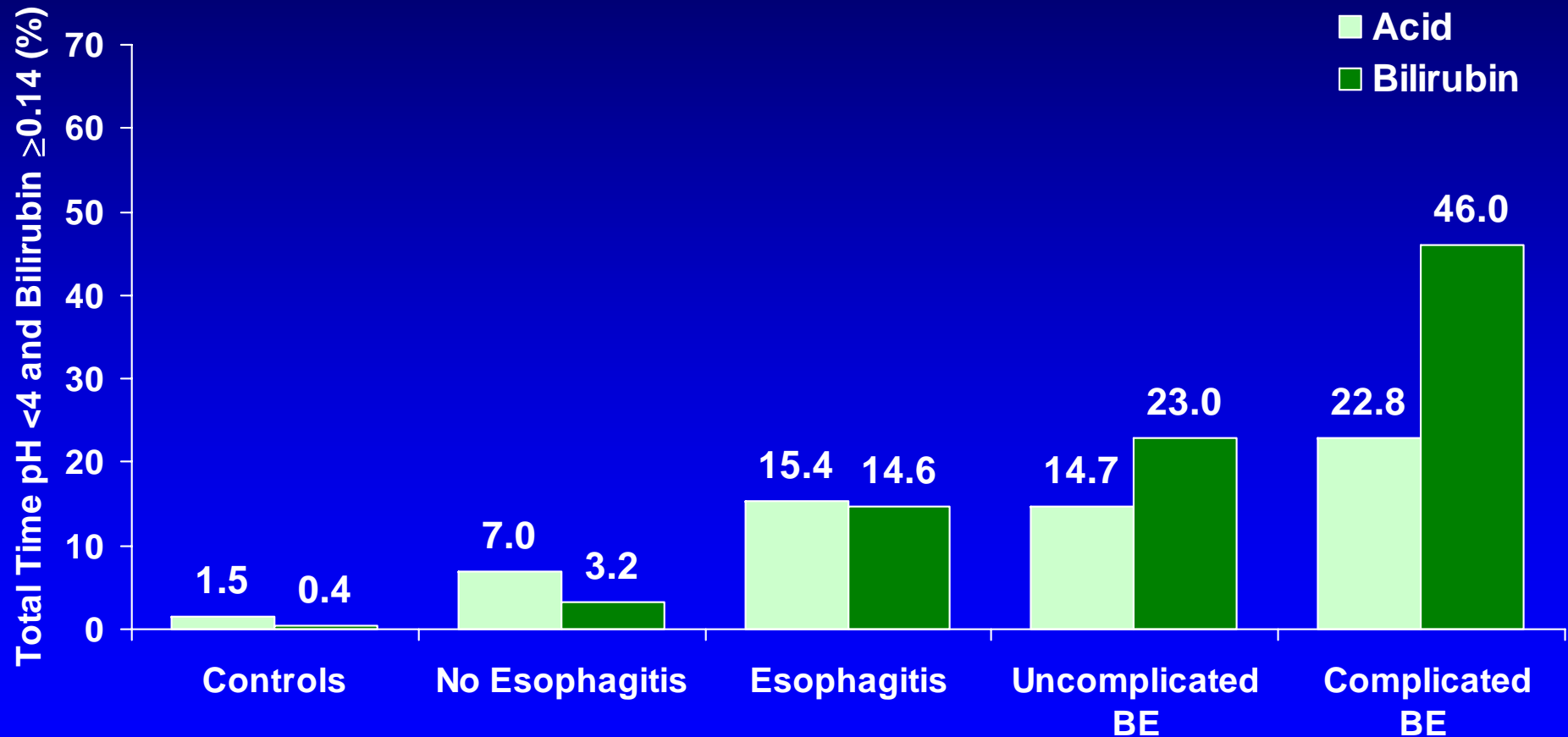




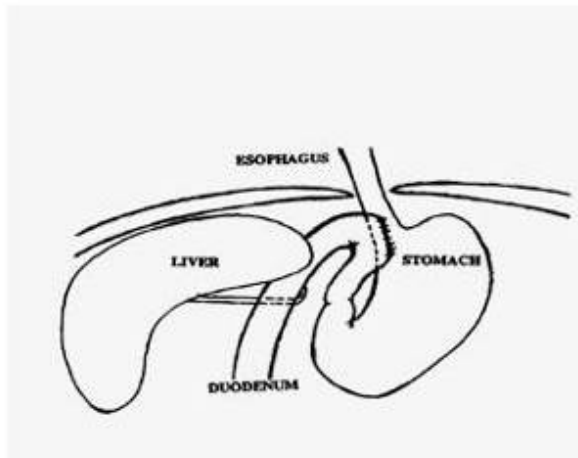
# Instead of Healing with Squamous Cells, Mucous-Secreting Cells are Generated



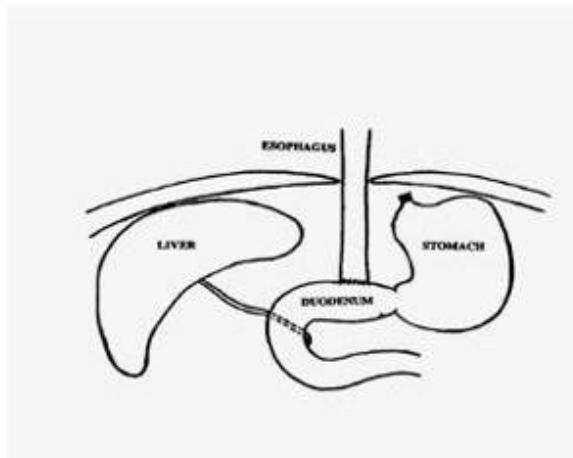
# Relationship of Acid and Bile Exposure to Barrett's Esophagus



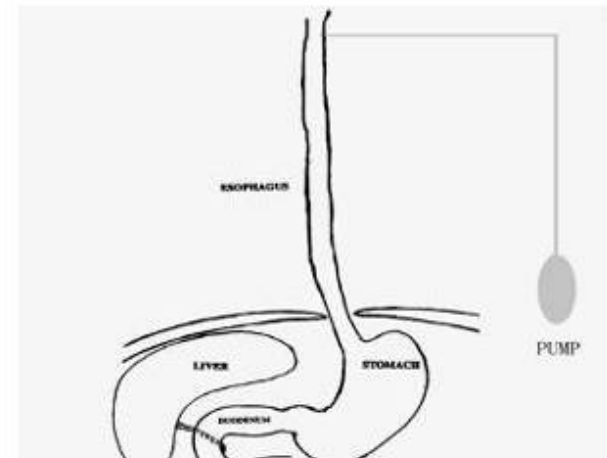
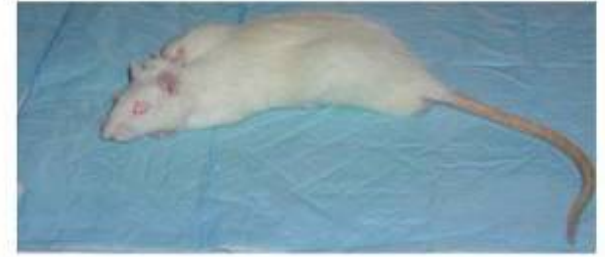
## Esophagogastroduodenostomy



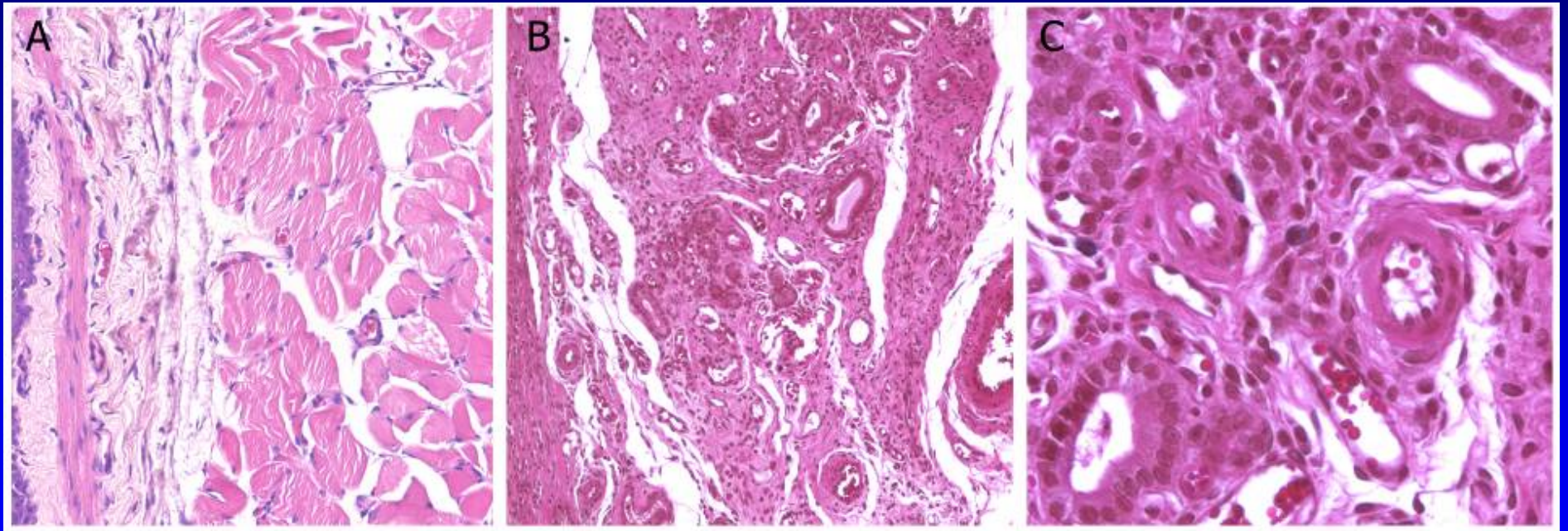
## Esophagoduodenostomy



## External Esophageal Perfusion

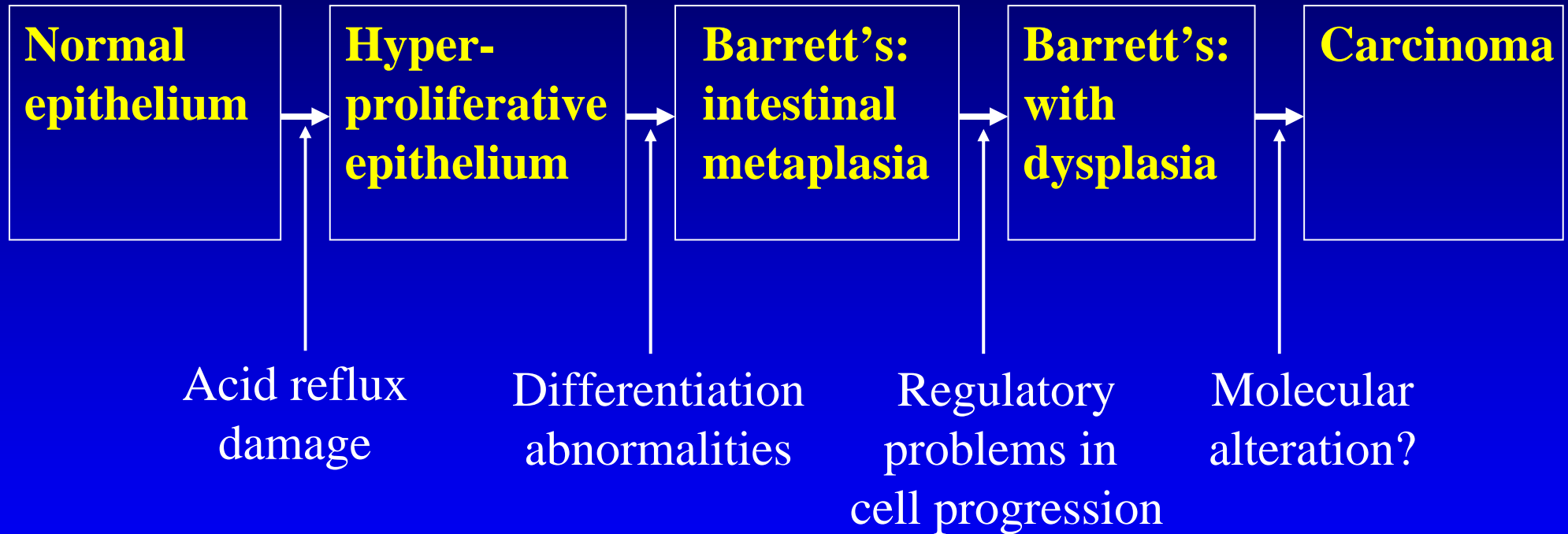


# External Esophageal Perfusion Model with Implantation of Bone Marrow Cells



# Metaplasia-Dysplasia-Adenocarcinoma

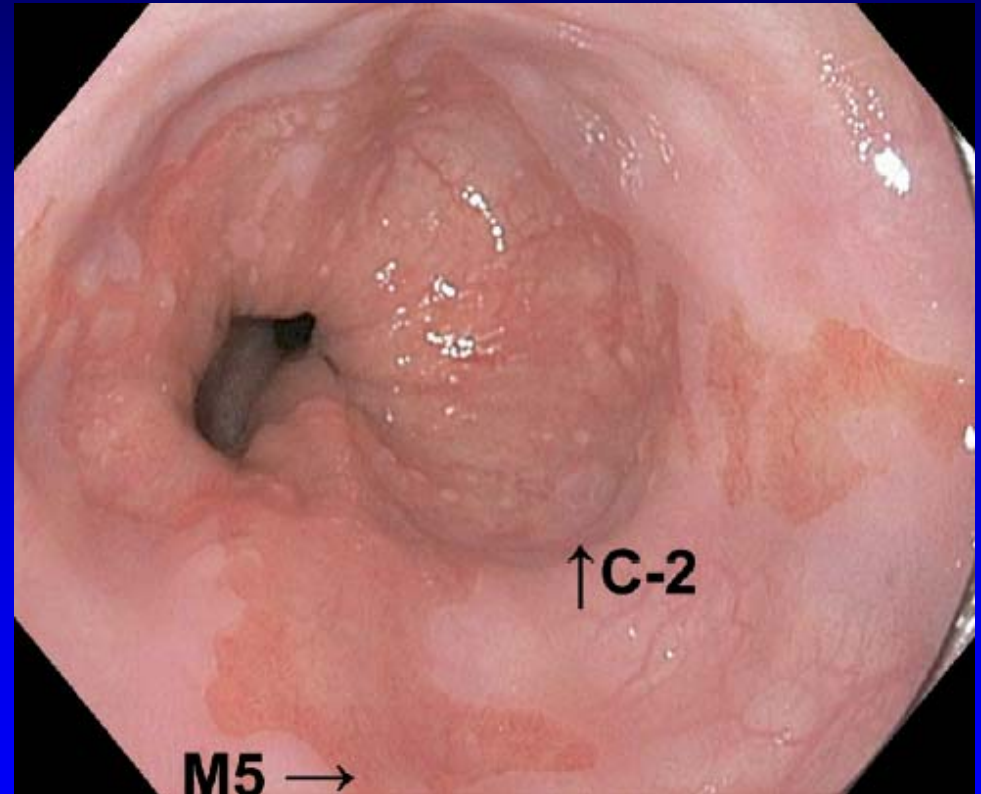
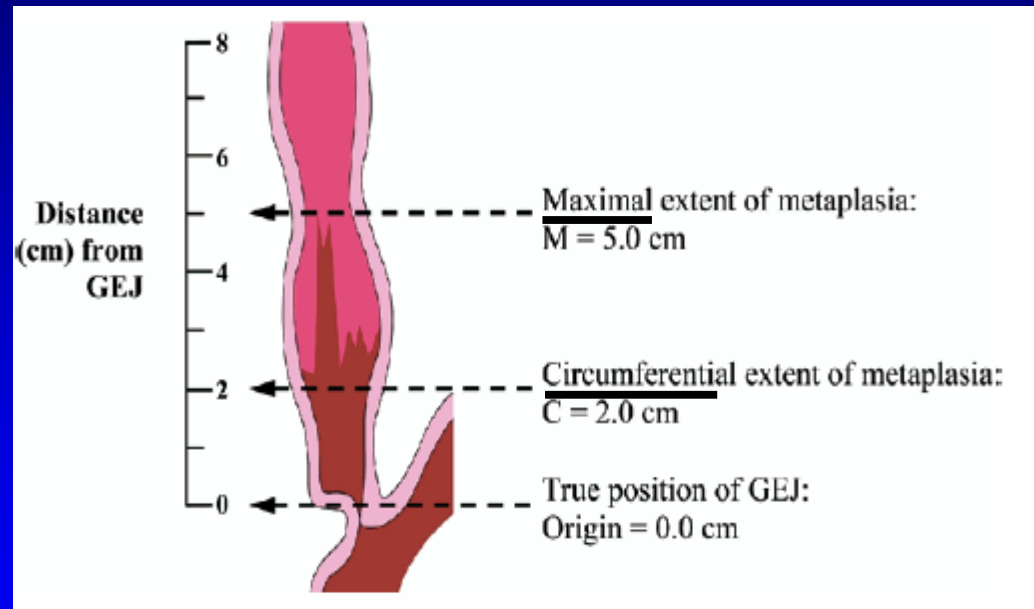
## Sequence of Barrett's Esophagus





**How to diagnose BE and  
identify patients with dysplasia?**

# Prague's C & M Criteria



C2 M5

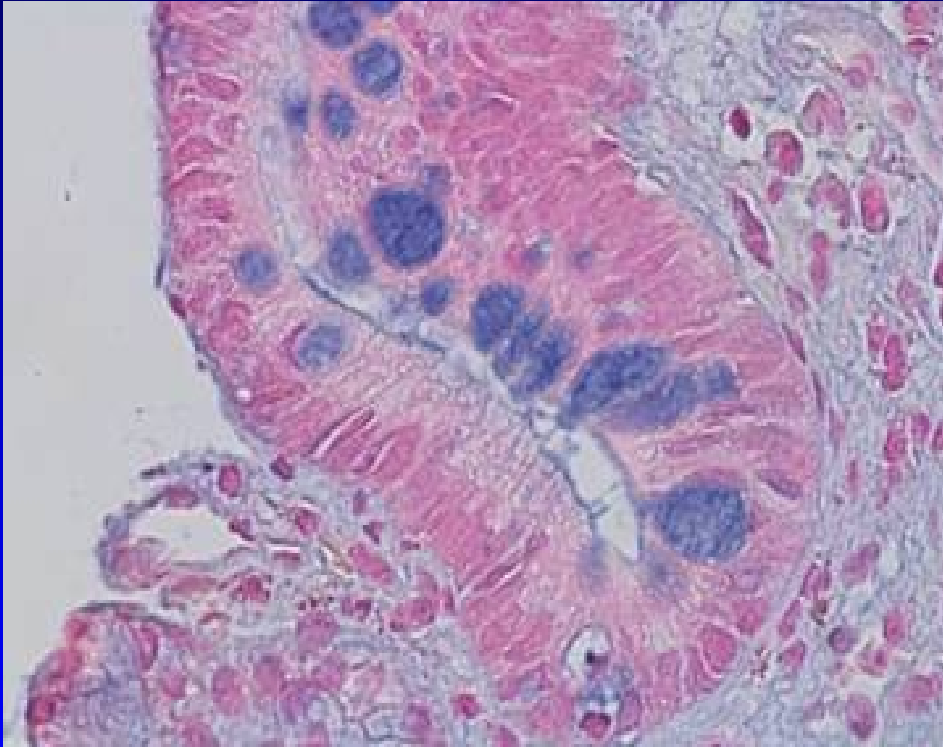
# Prague's C & M Criteria

**Table 5.** Percentage Agreement for C & M Values

	Percentage agreement
Exact agreement: C	53
1-cm difference: C	88
2-cm difference: C	97
Exact agreement: M	38
1-cm difference: M	82
2-cm difference: M	95

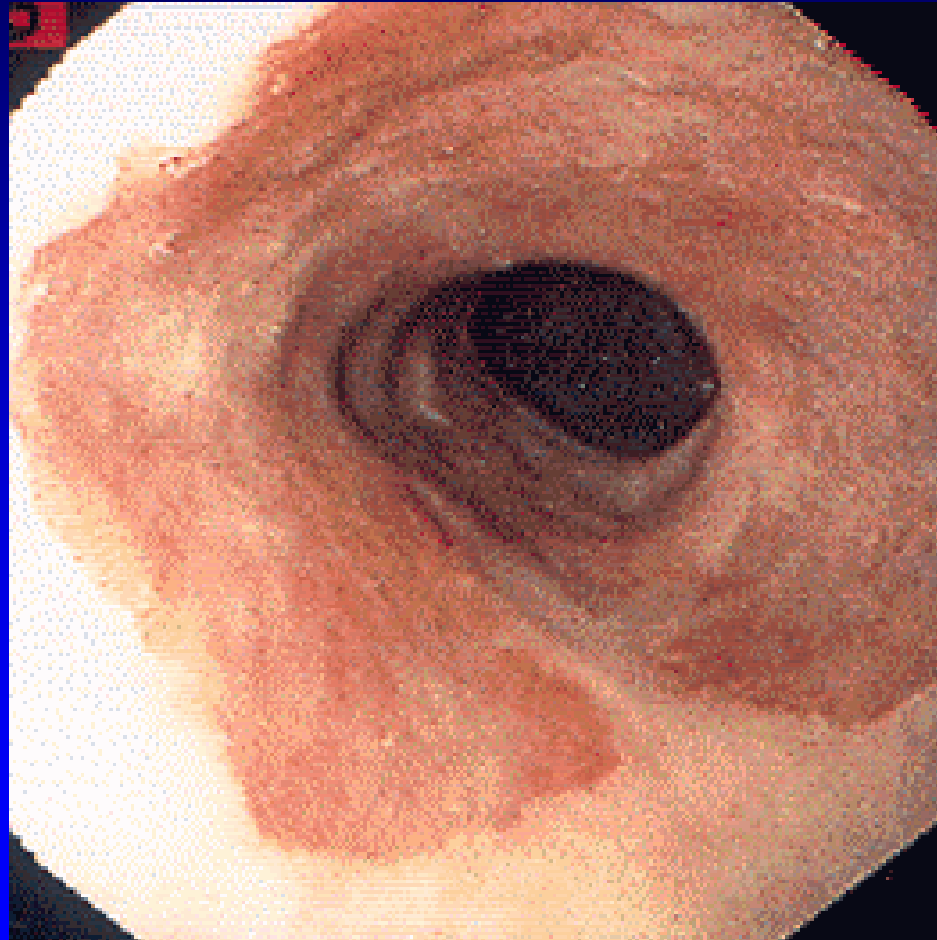


# Diagnosis of Barrett's Esophagus:



- Not just columnar epithelium
- Intestinal metaplasia must be present
- Presence of goblet cells

# Where is the Dysplasia?



# Systematic Mapping of Esophagectomy Specimens

	<u>Surface Area</u>
Total Barrett's mucosa	32 cm <sup>2</sup>
Low grade dysplasia	13 cm <sup>2</sup>
High grade dysplasia	1.3 cm <sup>2</sup>
Adenocarcinoma	1.1 cm <sup>2</sup>

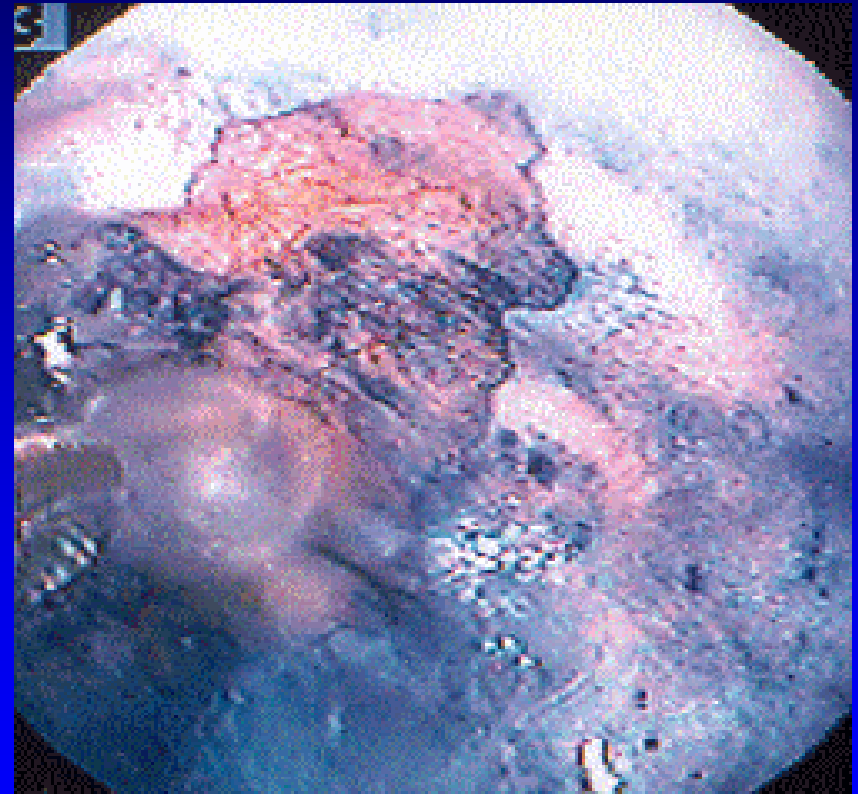
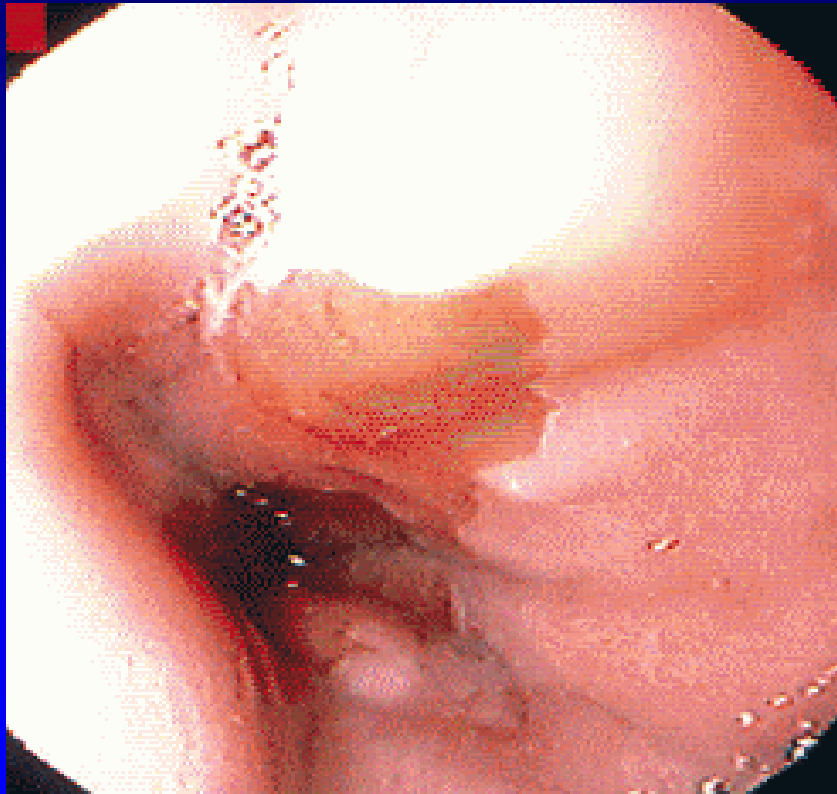
# **Current Recommendation for Surveillance Biopsy in Barrett's Esophagus**

- 4-quadrant, “random,” jumbo biopsy every 2 cm along the length of Barrett's Esophagus

# Real-Time Endoscopy to Detect Dysplasia

- Chromoendoscopy
  - Methylene blue, crystal violet, indo
- Optical devices
  - Fluorescence spectroscopy
  - Confocal fluorescence microendoscopy
  - Light scattering spectroscopy
  - Raman spectroscopy
- Magnification endoscopy
- Blue-light endoscopy

# Methylene-Blue Chromoendoscopy

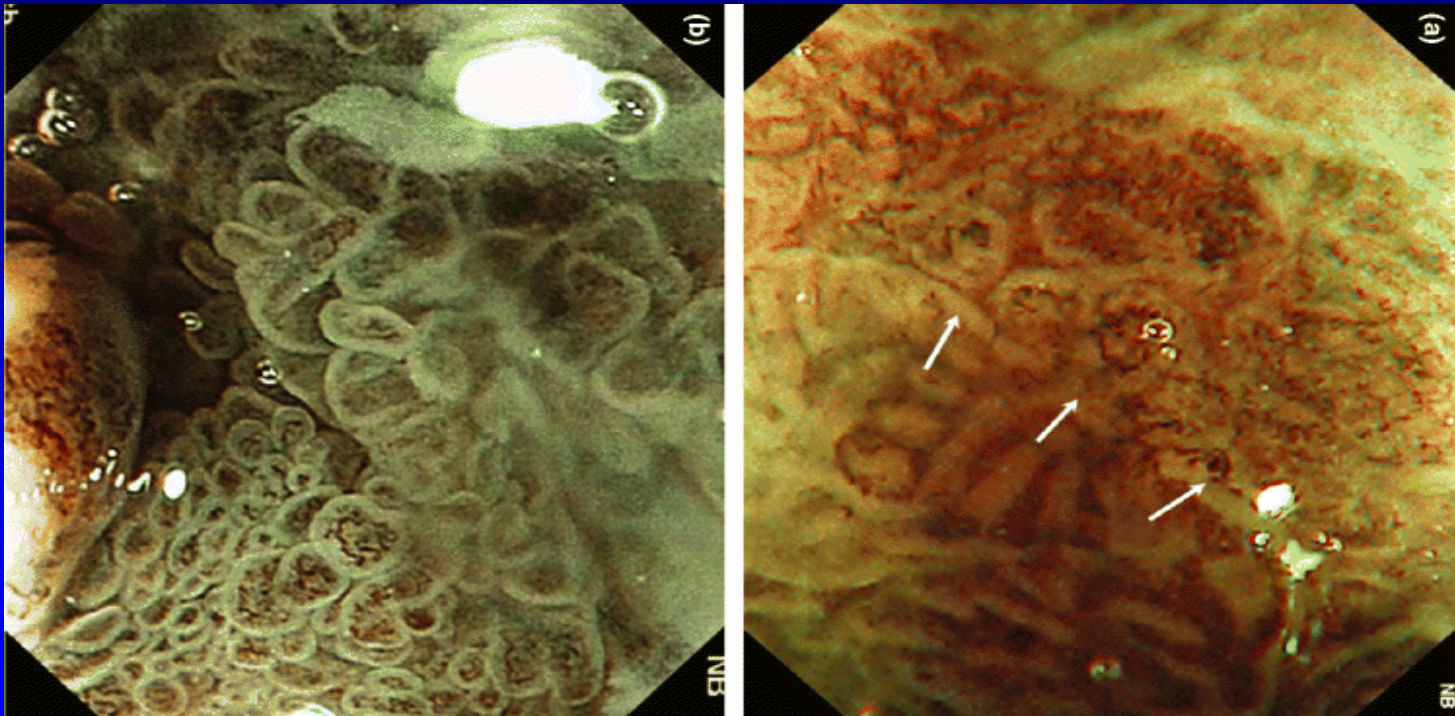


# Crystal Violet and Magnification Endoscopy





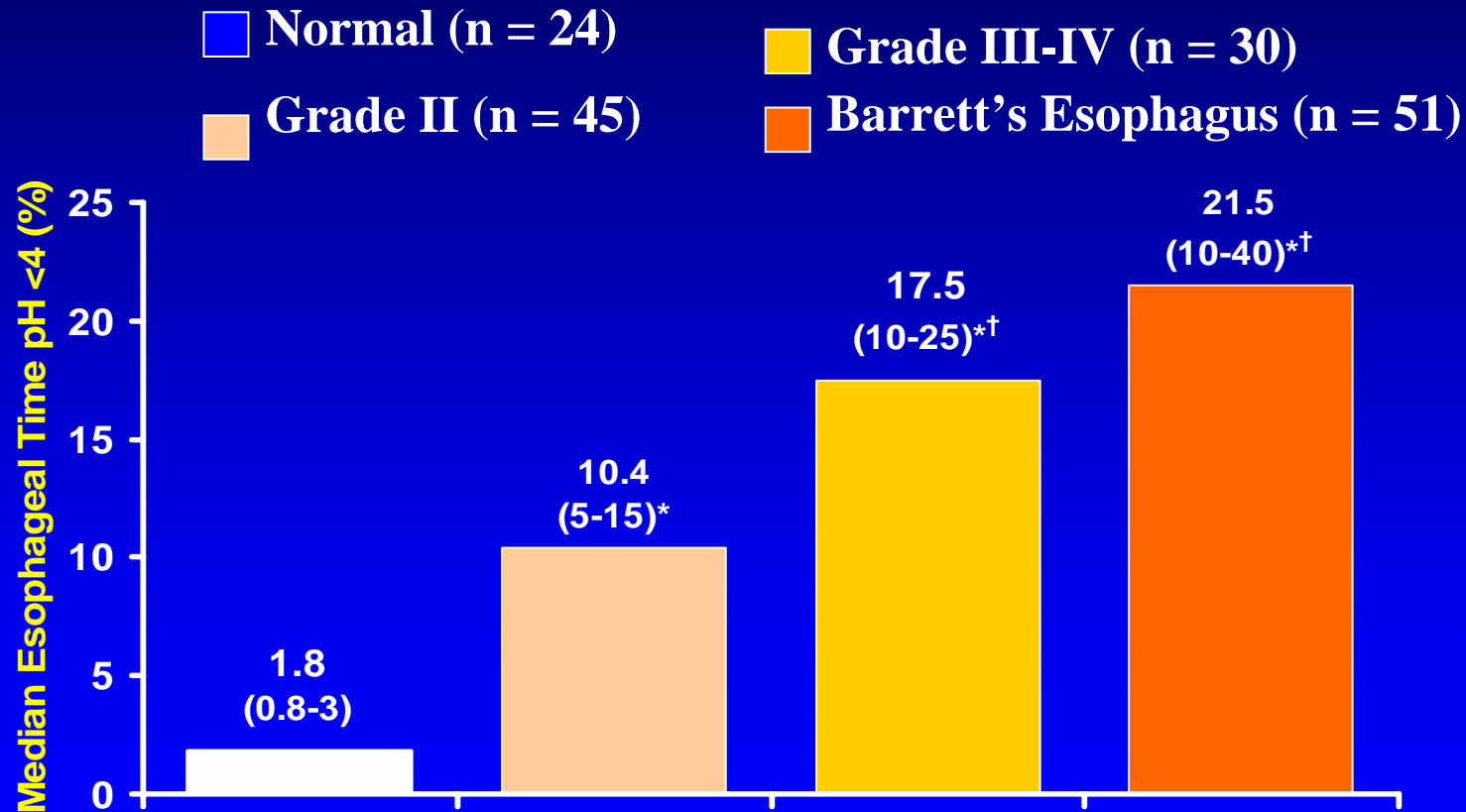
# Narrow Band Imaging and Magnification





**What is the optimal surveillance  
strategy for BE?**

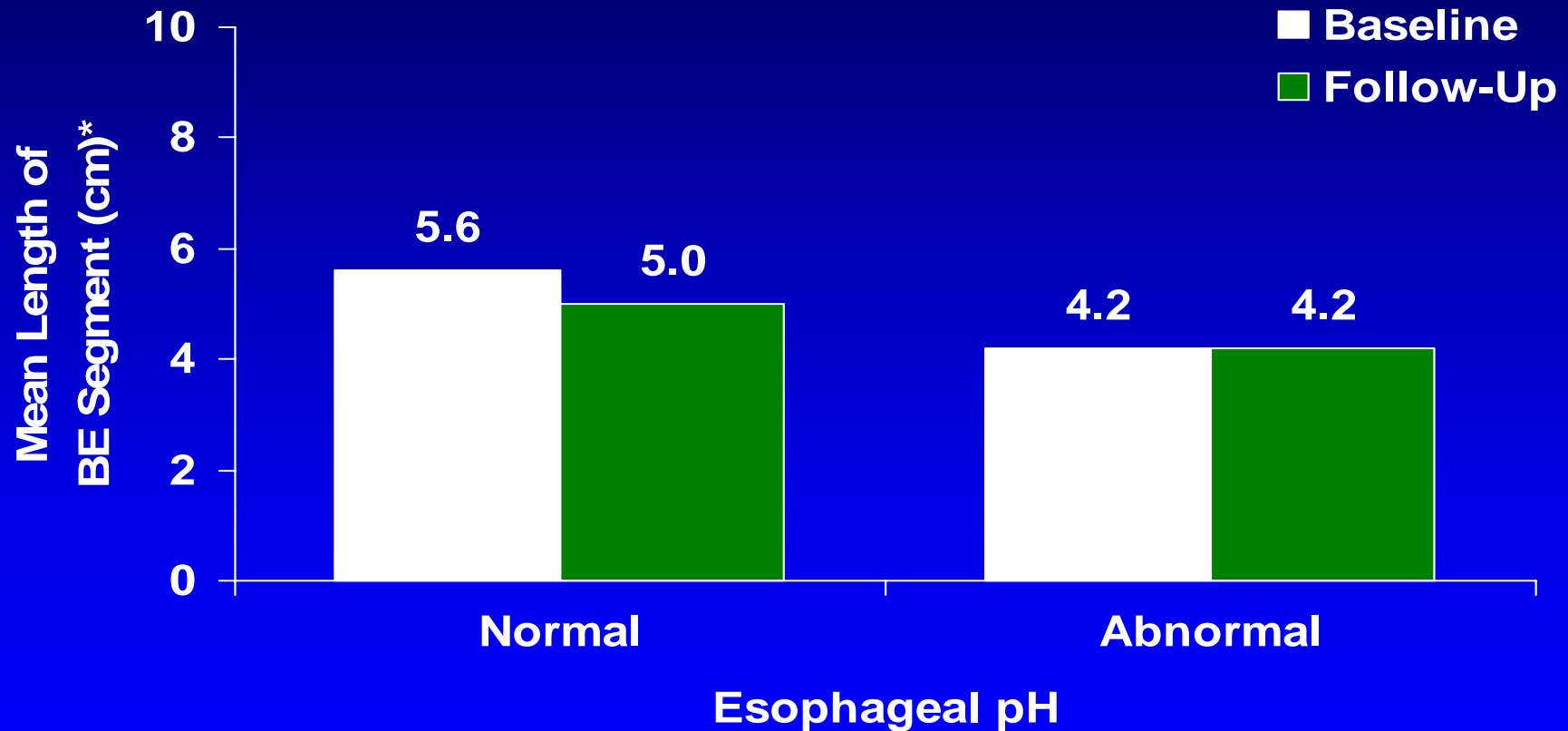
# Patients with Barrett's Esophagus have Severe Acid Reflux



\* $P < 0.0001 - 0.05$  vs Normal. † $P < 0.001 - 0.05$  vs Grade II.

Coenraad et al. *Am J Gastroenterol*. 1998;93:1068-1072.

# High-Dose PPI Does Not Regress Barrett's Esophagus



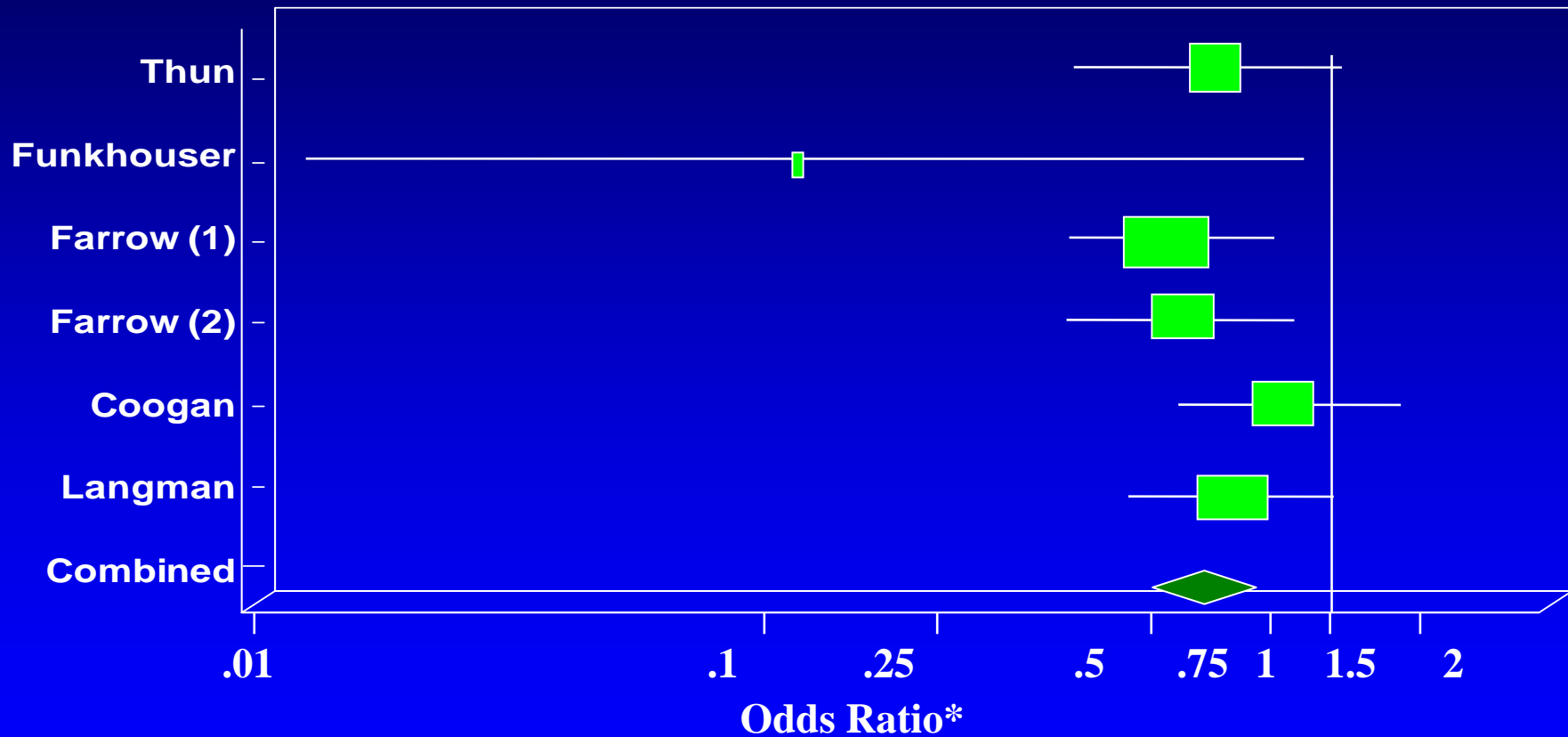
N = 13 patients treated with lansoprazole 60 mg daily for a mean of 5.7 years.

Sharma et al. *Am J Gastroenterol*. 1997;92:582-585.

# Acid Suppression for Barrett's Esophagus

- No clear evidence that antireflux therapy or antireflux surgery reduces the extent of Barrett's esophagus or the risk of adenocarcinoma

# Protective Effect of Aspirin/NSAIDs in Esophageal Cancer: A Meta-Analysis

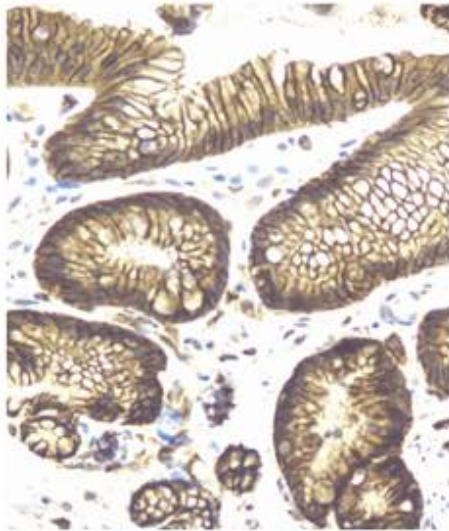


\*Adjusted for potential confounders, odds ratios, and 95% confidence intervals (CIs).

Corley et al. *Gastroenterology*. 2003;124:47-56.

# COX-2 Expression and Barrett's Esophagus

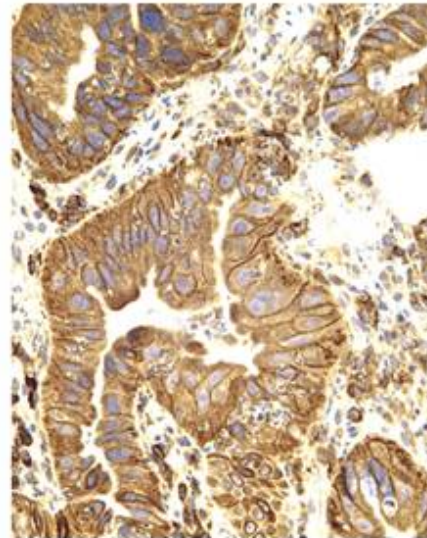
**SIM**



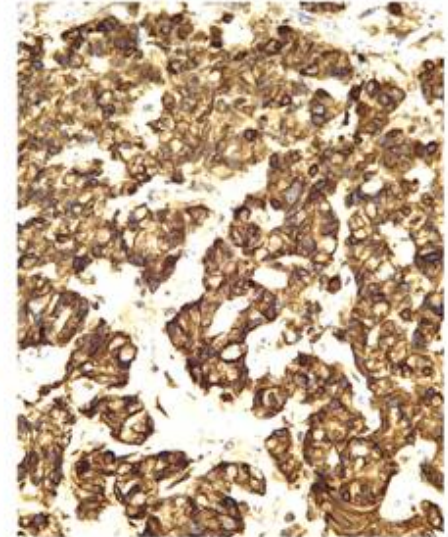
**LGD**



**HGD**



**EAC**



# Goals for Surveillance EGD's in Barrett's Esophagus

- Detect dysplasia before becoming cancer
- Identify which patient is at high risk for developing cancer
- Early intervention to prolong quality of life

# “Natural” History of Barrett’s Esophagus

**Table 1.** Grade of Dysplasia and Development of Esophageal Adenocarcinoma

Dysplasia (%)	n	Cancer (%)
None	382	9 (2)
Low grade	72	5 (7)
High grade	170	37 (22)

A total of 783 patients followed a mean of 2.9–7.3 yr (61–65).

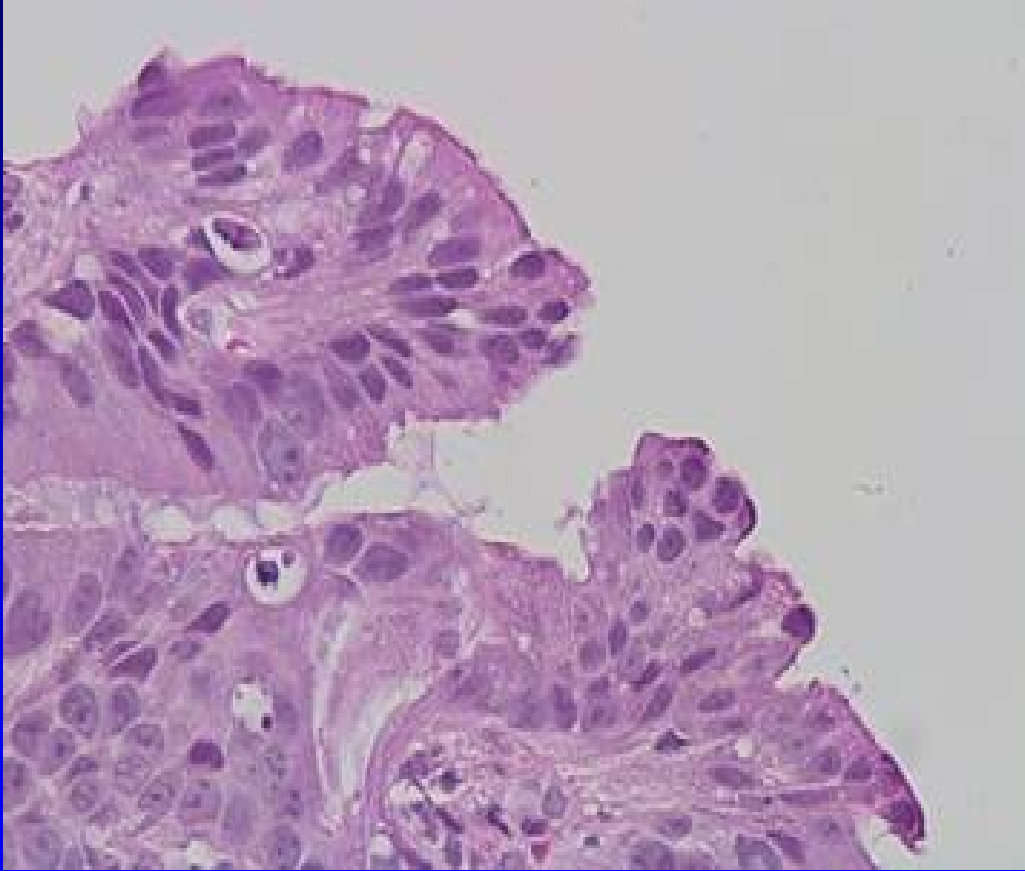


# Management of Barrett's Esophagus with No Dysplasia

ACG Practice Guidelines for No Dysplasia	
New diagnosis	Repeat in 1 year*
Confirm on repeat	Surveillance every 3 years

\*To avoid sampling error; repeat in 3 years for short segment BE may be adequate

# Barrett's Esophagus: Low Grade Dysplasia



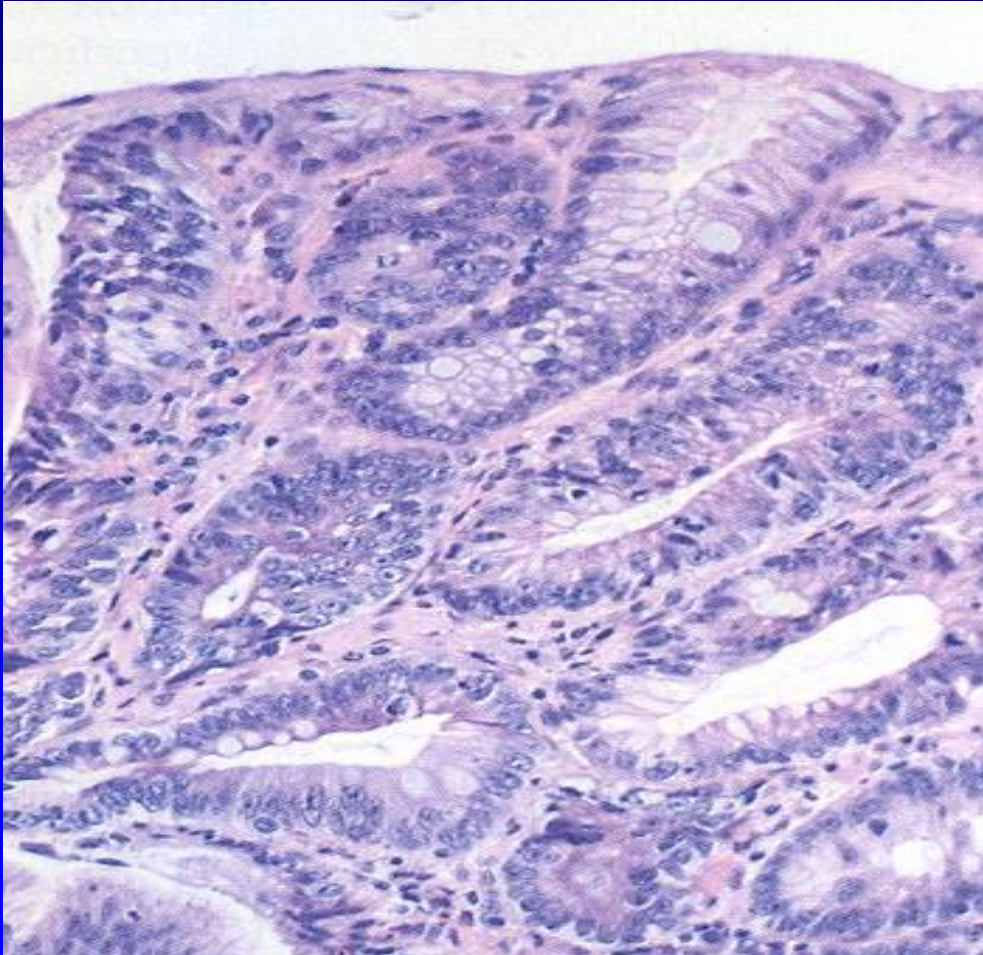
- Architecture mildly altered
  - Glandular crowding
  - But identifiable lamina propria
- Surface maturation distorted
  - Surface similar to deeper glands
- Cytology with mild alterations
  - Nuclear hyperchromasia
  - Nuclear membrane irregularities
  - Normal nuclear polarity

# Management of Barrett's Esophagus with Low-Grade Dysplasia

- Prescribe aggressive antisecretory therapy to eliminate confounding inflammation

ACG Practice Guidelines for Low Grade Dysplasia	
New diagnosis	Repeat in 6 months
Confirm on repeat	Surveillance every 1 year

# Barrett's Esophagus: High Grade Dysplasia

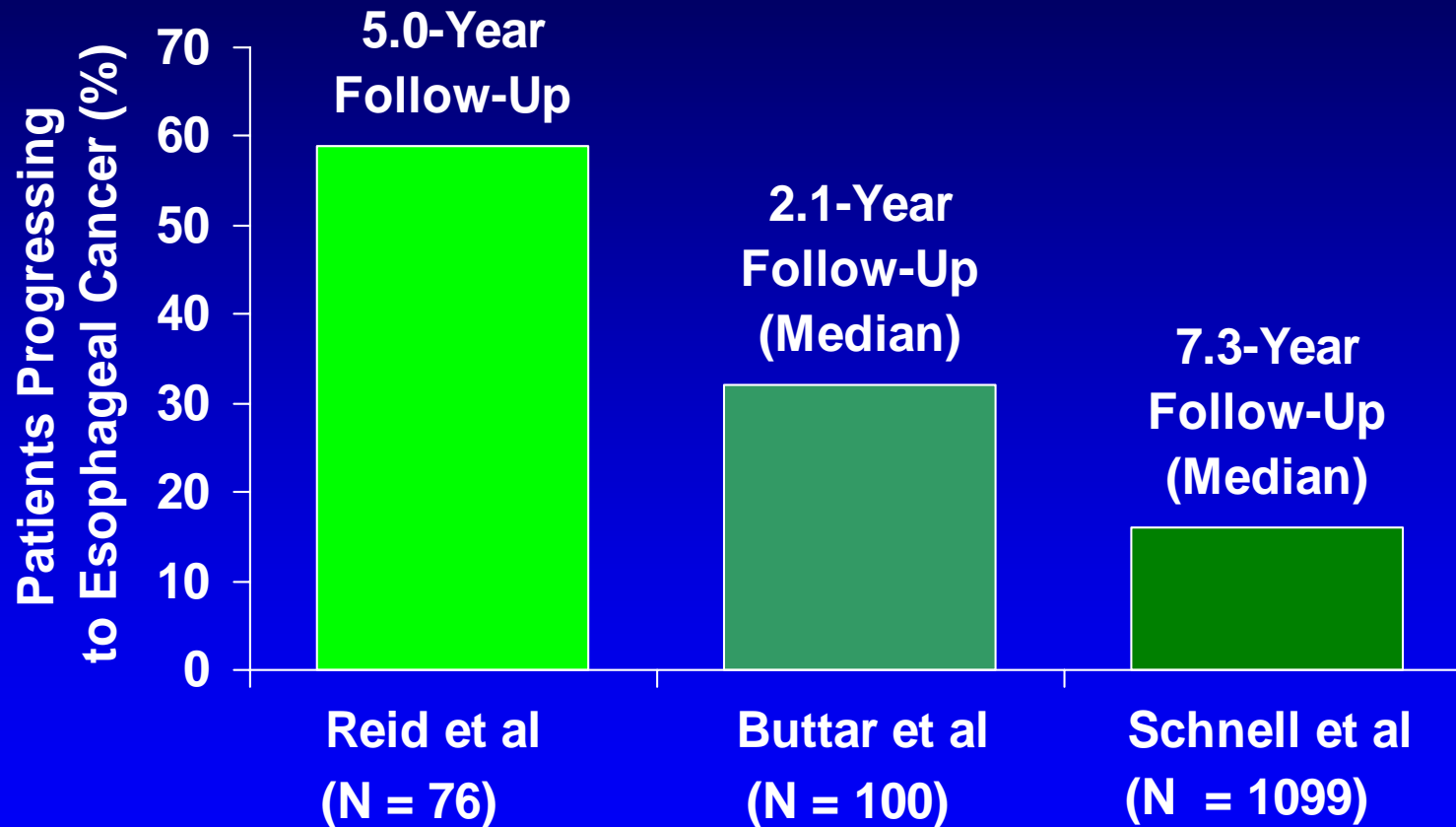


- Architecture marked altered
  - Crowding of abnormal glands
- Surface maturation lacking
- Cytology with marked alterations
  - Nuclear hyperchromasia
  - Prominent irregular nucleoli with clumped chromatin
  - Loss of nuclear polarity

# Substantial Inter-Observer Variation of BE between General and GI Pathologists

(General pathologist) Initial diagnosis	Final diagnosis (GI pathologist)			
	ND	IND/LGD	HGD/AC	Total
ND	546	19	2	567
IND/LGD	111	94	5	210
HGD/AC	0	1	15	16
Total	657	114	22	793

# Progression of HGD to Cancer

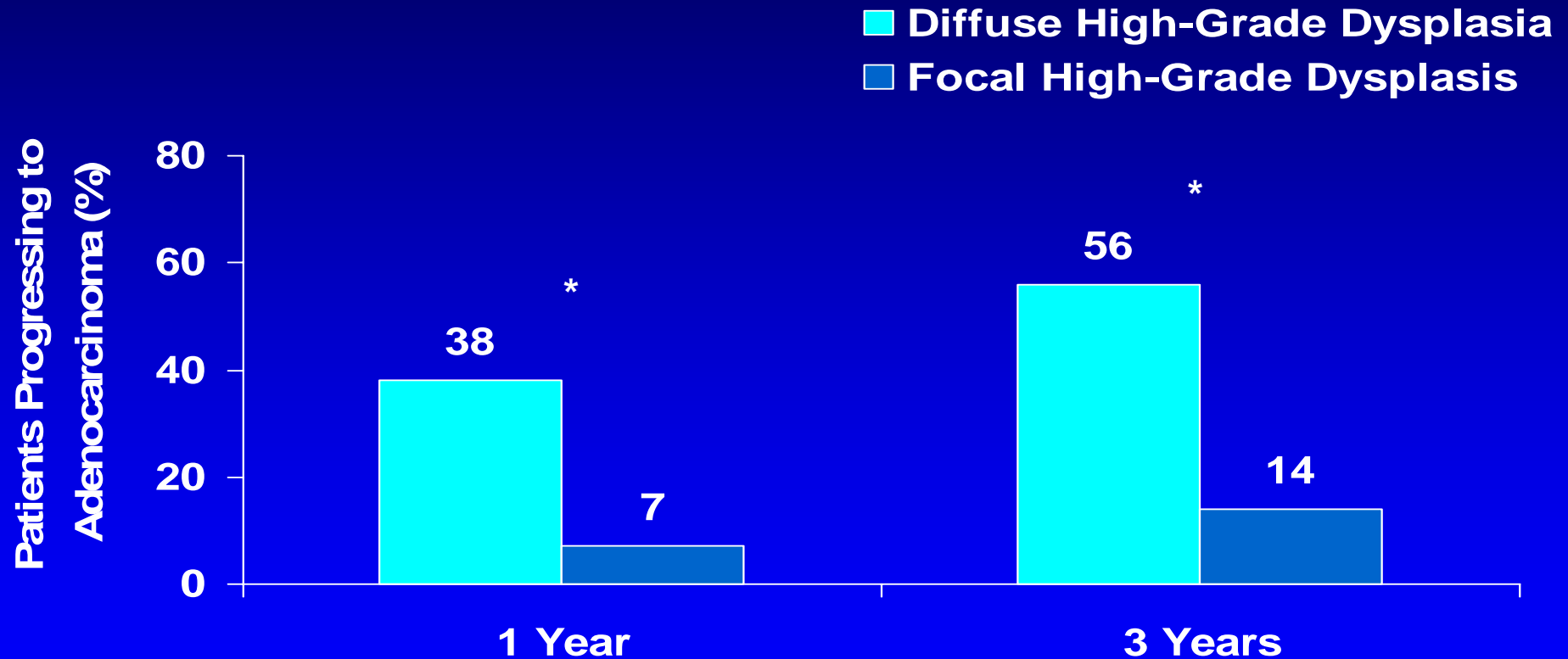


Buttar et al. *Gastroenterology*. 2001;120:1630-1639.

Reid et al. *Am J Gastroenterol*. 2000;95:1669-1676.

Schnell et al. *Gastroenterology*. 2001;120:1607-1619.

# Risk of Adenocarcinoma in Focal vs. Diffuse HGD



\* $P < 0.001$ .

Buttar et al. *Gastroenterology*. 2001;120:1630-1639.

# Management of Barrett's Esophagus with High-Grade Dysplasia

- Difficult to differentiate from cancer; requires intensive biopsy protocol; confirm by expert pathologist
- 6 - 40% of HGD BE has adenocarcinoma at surgery

## ACG Practice Guidelines for HGD

Mucosal irregularity	Endoscopic mucosal resection
Focal high-grade dysplasia	Follow-up EGD every 3 months
Multifocal (diffuse) high-grade dysplasia	a. Surgery <u>or</u> b. Photodynamic therapy <u>or</u> c. EGD every 3 months



**What is the management of  
high grade dysplasia?**

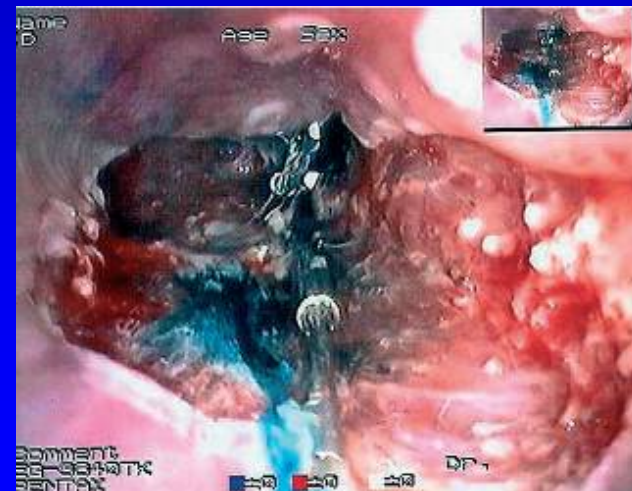
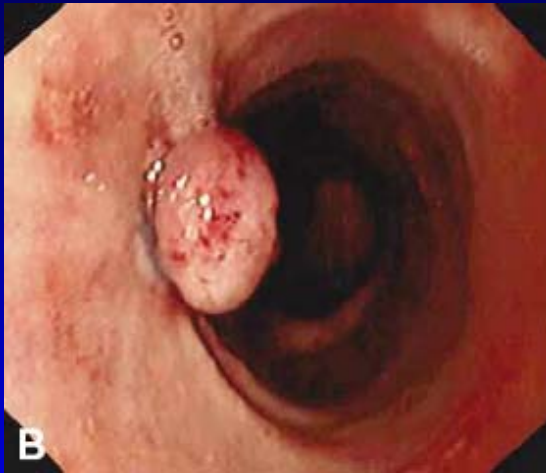
# Treatment Options for High Grade Dysplasia

1. Do nothing, “watchful waiting”
2. Endoscopic ablation
3. Surgical resection

# Important Principals for Endoscopic Treatment of BE

- Make sure there is no cancer
- Diffuse vs. focal dysplasia
- Make sure acid suppression is adequate
- Treat the patient, not the Barrett's!
  - Risk vs. Benefit

# Endoscopic Mucosal Resection for Barrett's Esophagus



# Endoscopic Mucosa Resection for BE

- To obtain better tissue to differentiate dysplasia and adenocarcinoma
- Can treat focal or diffuse dysplasia
- Combine EMR with diffuse ablation

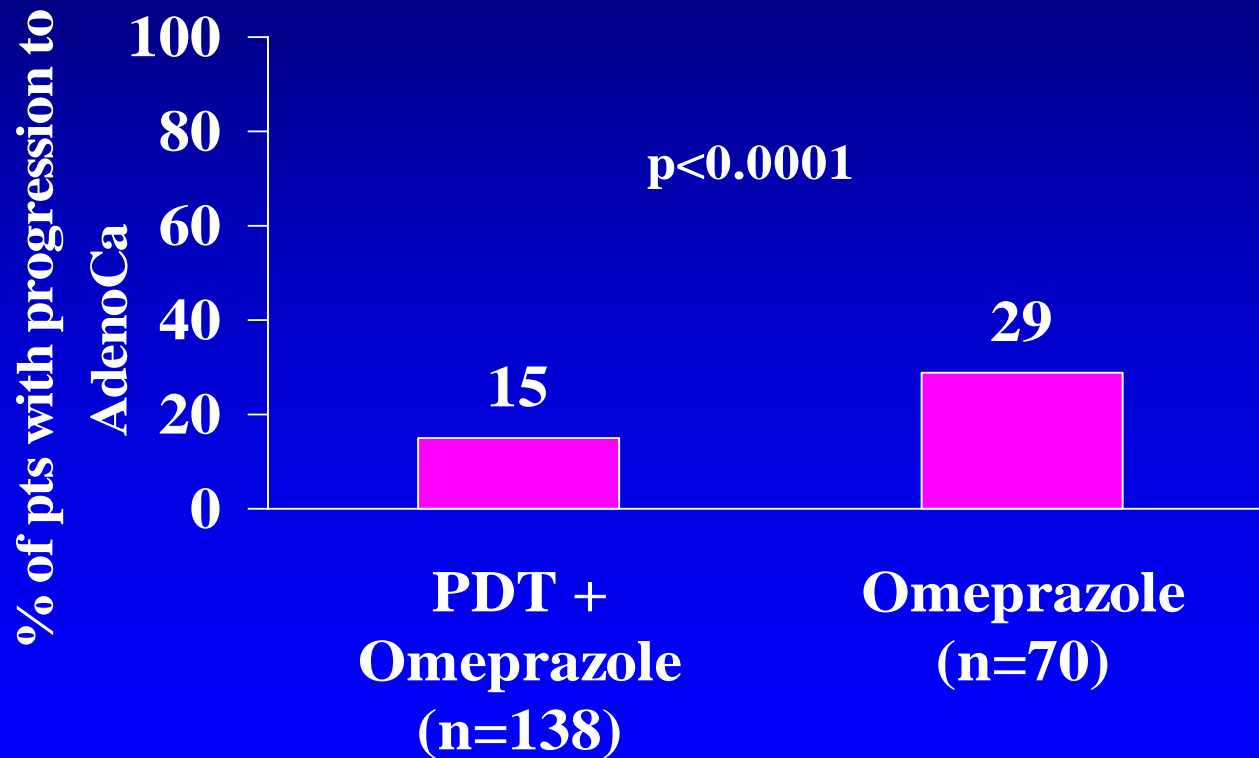
# Endoscopic Ablation for Barrett's Esophagus

- Diffuse treatment
  - Photodynamic therapy (PDT)
  - Radiofrequency ablation (RFA)
  - Cryotherapy
- Focal treatment
  - Radiofrequency ablation (RFA)
  - Heater probe
  - Argon plasma coagulation
  - Laser

# Photodynamic Therapy for HGD in Barrett's Esophagus

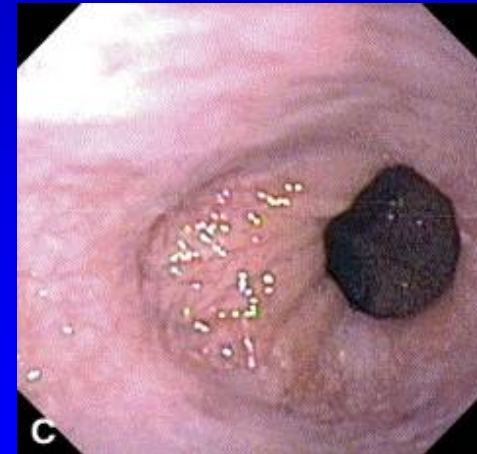
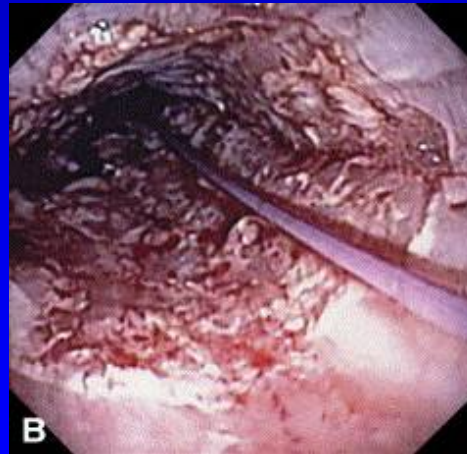
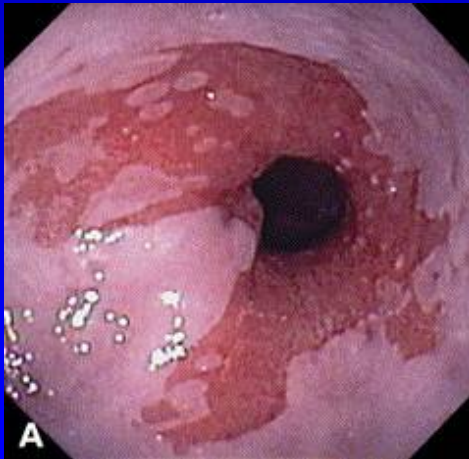
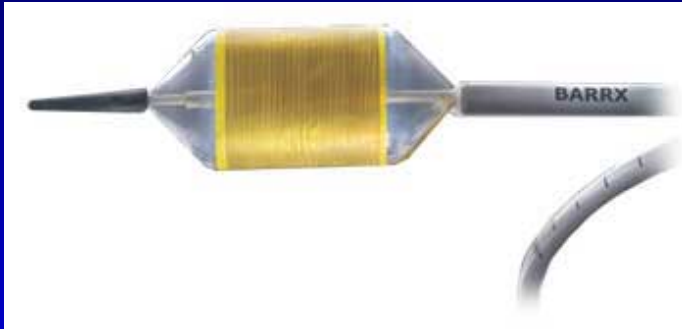
- N= 208 patients with HGD
- 2:1 randomization to
  - PDT/Photofrin (2 mg/kg IV) + Omeprazole 20 bid or
  - Omeprazole 20 bid only
- Methods
  - Laser exposure within 40-50 hrs after Photofrin
  - Multiple PDT sessions allowed
  - Single center pathologists blinded to treatment arms

# PDT with Photofrin: 5-Year Follow-Up of RCT for HGD in BE





# Radiofrequency Ablation for Barrett's Esophagus



Ablation to the muscularis mucosae  
but preserving submucosa.

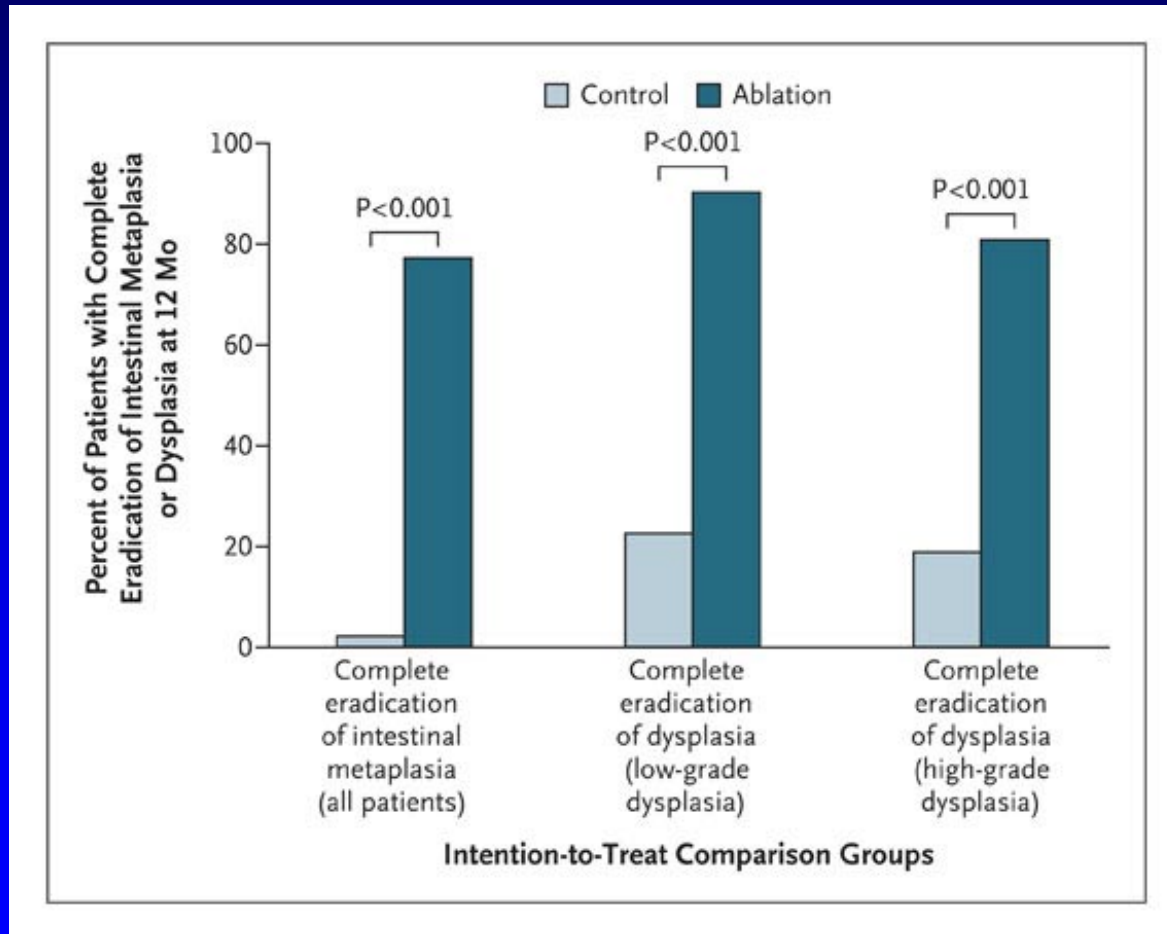
# Radiofrequency Ablation for High-Grade Dysplasia in BE

- Open label U.S. registry
- 57 patients with HGD
  - Mean follow-up 9.5 months
  - Average of 1.4 ablation sessions
- Response (no HGD): 88%
  - 53% squamous, 23% non-dysplastic, 13% I/LGD
  - 9% HGD, 4% intramucosal cancer
- Adverse effects
  - Only 1 stricture (1.1%)
- Conclusions
  - Safe and effective for HGD
  - Long term and randomized controlled trials are needed

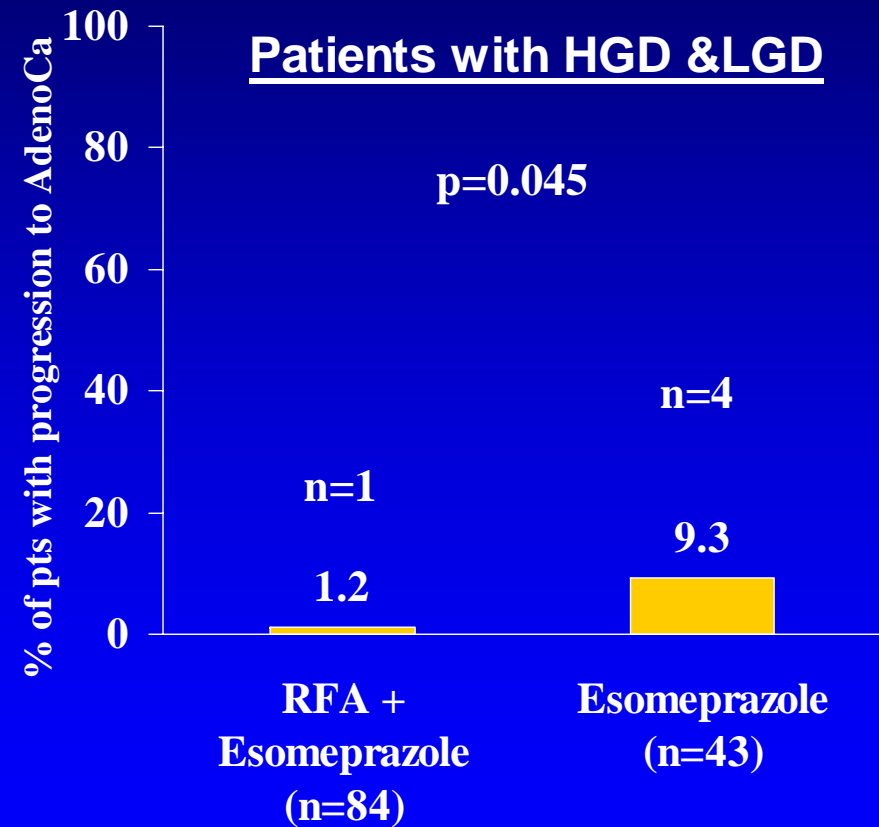
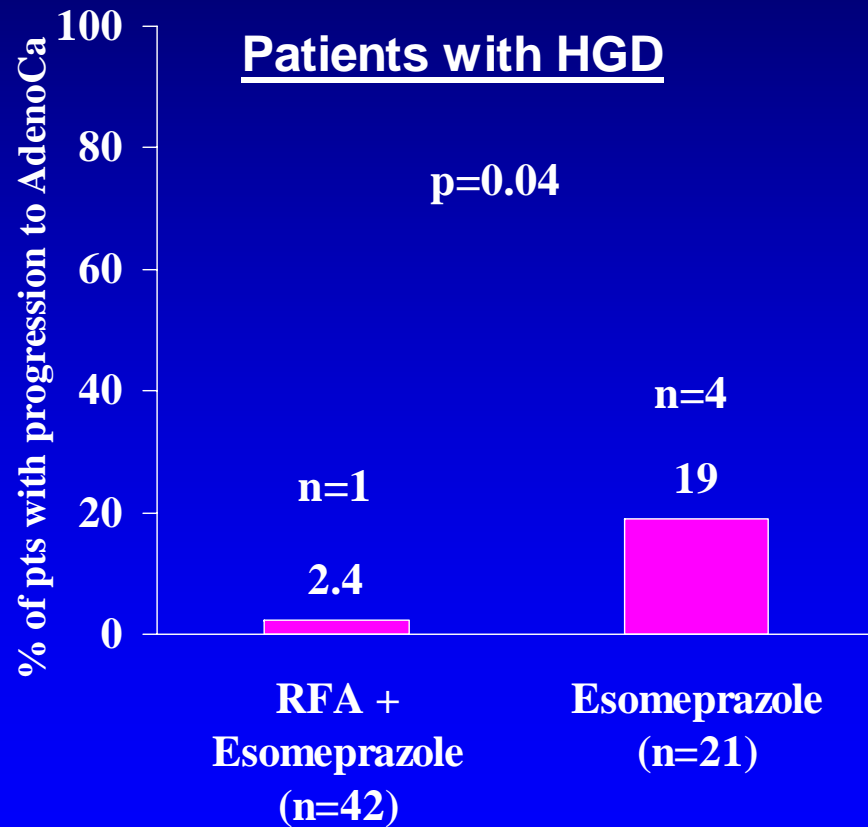
# Radiofrequency Ablation (RFA) for Dysplastic BE

- Primary outcome variables
  - % of patients with LDG with complete eradication of dysplasia at 12 months
  - % of patients with HGD with complete eradication of dysplasia at 12 months
  - % of all patients who had complete eradication of IM 12 months.
- Study
  - Non-nodular BE
  - Excluded BE >8 cm
  - Excluded lymphadenopathy and wall abnormalities by EUS

# Radiofrequency Ablation (RFA) for Dysplastic BE



# RFA: 1-Year Data for Dysplastic BE



# **Criteria for an “Ideal” Ablation Technique for BE**

- Completely remove Barrett’s esophagus and dysplasia and replace it with normal epithelium
- Minimal morbidity
- No hidden Barrett’s underneath
- Decrease the rate of developing cancer
- Improve survival
- Cost effective

# **“Ideal” Ablation Technique for BE without Dysplasia**

	<b>Photodynamic therapy</b>	<b>Radiofrequency Ablation</b>
1. Eliminate BE and replace with normal epithelium	Yes	Yes
2. Minimal morbidity	No	Probably
3. No hidden Barrett’s underneath	Probably	Probably
4. Decrease the rate of developing cancer	<b>No</b>	<b>No</b>
5. Improve survival	<b>No</b>	<b>No</b>
6. Cost effective	<b>No</b>	<b>No</b>

# “Ideal” Ablation Technique for BE with LGD

	<b>Photodynamic therapy</b>	<b>Radiofrequency Ablation</b>
1. Eliminate BE and replace with normal epithelium	Yes	Yes
2. Minimal morbidity	No	Probably
3. No hidden Barrett’s underneath	Probably	Probably
4. Decrease the rate of developing cancer	<b>Unknown</b>	<b>Unknown</b>
5. Improve survival	<b>No</b>	<b>No</b>
6. Cost effective	<b>Unknown</b>	<b>Unknown</b>



# **“Ideal” Ablation Technique for BE with HGD**

	<b>Photodynamic therapy</b>	<b>Radiofrequency Ablation</b>
1. Eliminate BE and replace with normal epithelium	Yes	Yes
2. Minimal morbidity	No	Probably
3. No hidden Barrett’s underneath	Probably	Yes
4. Decrease the rate of developing cancer	<b>Yes</b>	<b>Probably</b>
5. Improve survival	<b>Unknown</b>	<b>Unknown</b>
6. Cost effective	<b>Probably</b>	<b>Probably</b>

# Summary

- Barrett's esophagus is common, fortunately, progression to adenocarcinoma is uncommon
  - “On average”, only 0.4% per patient-year
- Biopsy sampling error is a problem
- Expert pathologist is needed to diagnose HGD
- Endoscopic treatment of HGD and intramucosal cancer is improving and promising



# BE Research at UofL

## Investigators

- Shirish Barve, PhD
- Gerald Dryden, MD
- Yi Li, PhD
- Robert Martin, MD, PhD
- John Wo, MD

## Coordinators & Technicians

- Jennifer Eversmann, RN
- Susan Ellis, RN