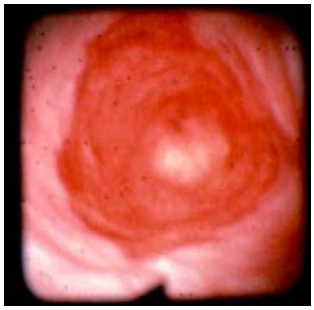
Barrett's Esophagus: Controversy and Management



History

- Norman Barrett (1950)
  "Chronic Peptic Ulcer of the Oesophagus and Oesophagitis"
- Allison and Johnstone (1953)
  "The Oesophagus Lined with Gastric Mucous Membrane"

Barrett's Esophagus
Columnar-lined Esophagus

"An esophagus in which any portion of the normal squamous lining has been replaced by a metaplastic columnar epithelium which is visible macroscopically and confirmed histologically to have intestinal metaplasia"

American College of Gastroenterology

Prevalence at Endoscopy

Naef et al (1975)	140/6368	2.2%
Burbige and Radigan (1979)	8/203	3.9%
Rothery et al (1986)	58/5534	1.0%
Cooper and Barbezat (1986)	52/4448	1.2%
Ovaska et al (1989)	32/12499	0.25%
Herlithy et al (1984)	18/906	2.0%

Prevalence at Endoscopy

- Phillips and Wong (1991)
  31133 endoscopy
  5285 GERD and endoscopy

1.7% all endoscopies showed Barrett's
9.6% GERD also had Barrett's

Prevalence and Reflux Sx

Heartburn, regurgitation, dysphagia at least once per week

Winters et al (1987)	6%
Mann et al (1989)	6.7%
Cameron et al (1997)	3.5%

Prevalence and Duration of Sx

Odds Ratio = 6.4 when symptoms > 10y

Population Prevalence

- 20% of adult population have weekly reflux
- 5% of reflux patients have Barrett's
- 1/100 General Population will be expected to have Barrett's

Barrett's and Cancer Risk

- Katz et al (1998 Am J Gastroenterol) 1/141 pt-y
- Van der Burgh et al (Gut 1996) 1/180 pt-y*
- Drewitz et al (1997 Am J Gastroenterol) 1/208 pt-y

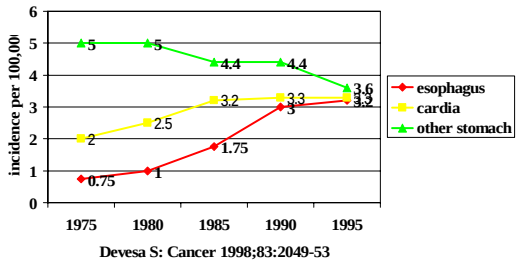
* 2/79 at 9.3 years follow-up died of esophageal cancer

Barrett's and Cancer

- Barrett's patients develop adenocarcinoma at a rate of ~ 0.4% per year or 1/175 person yrs

40 X increased incidence of cancer as compared to the general population

Age Adjusted Incidence of Esophagogastric Adenocarcinoma In White Males in USA 1974-1994



Devesa S: Cancer 1998;83:2049-53

Barrett's Esophagus

1. Risk factors to develop cancer
2. Natural history of Barrett's
3. Screening for cancer
4. Management of metaplasia
5. Management of dyplasia
6. Treatment Options

Reflux and the Risk of Cancer

Odds ratio	Esophageal adenocarcinoma	Cardia adenocarcinoma
Weekly GERD	8	2
Nocturnal GERD	20	2.8
Any GERD > 20yrs	16.3	3.3
Severe GERD > 20 yrs	43.5	4.4

Langergren et al N Engl J Med. 1999 Mar 18;340(11):825-31

Associated Risk factors

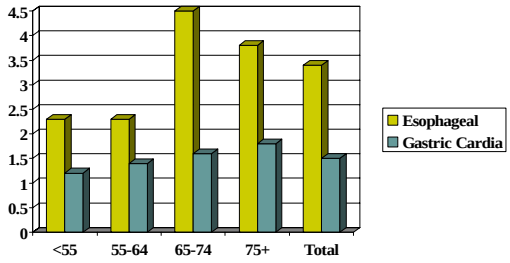
	Odds Ratio
Obesity	
Top BMI quartile	7.6
> 30 kg/m^2	16.2
Asthma drugs > 5 yrs	3.1
Tobacco	2.4
Dietary fat & calories	4.1
Well done red meat	3.2

N Engl J Med. 1999; 340:825-31
Ann Intern Med 1999;130:883-90.
J Natl Cancer Inst 1997;89:1277-84

Adenocarcinoma in Barrett's Esophagus

	Odds Ratio
H pylori infection	0.4
Beer	0.8
Wine	0.6
Dietary fibre	0.7
Vit A,C,B6, E	0.8

Age Adjusted Rates of Esophageal and Gastric Cardia Adenocarcinoma Among White Males (1988-1994)



Barrett's Esophagus: Genetic Factors?

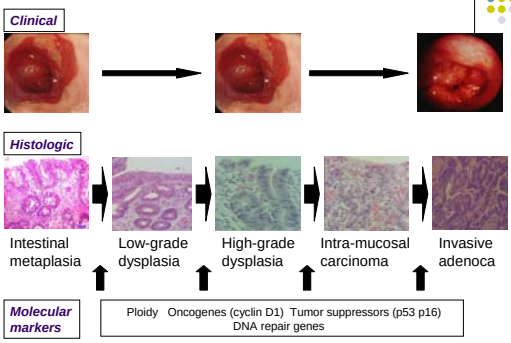
NCI SEER Database 1988-1990

Annual Incidence/100,000

White	2.5 M	0.3 F
Black	0.6 M	0.2 F

P53 mutation and Barrett's in twins

Metaplasia-Dysplasia Progression to Cancer

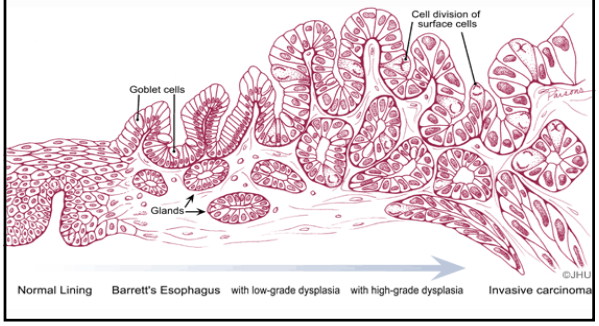


Grading Dysplasia in Barrett's Esophagus

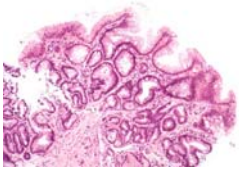
- 250 Barrett's esophagus cases with varying degrees of dysplasia
- Follow-up information on 138 patients.
- To evaluate both inter and intra-observer variability in diagnoses, the 250 slides were each circulated twice to each of the 12 pathologists, so 24 diagnoses were rendered on each case

Human Pathology 2001; 32:368-78
Human Pathology 2001; 32:379-88

Barrett's Esophagus: Histology



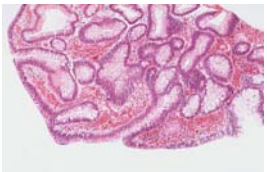
Columnar-lined Esophagus Metaplasia



- In 44 cases during 78 months
- 3 LGD
- 1 HG
- 0 Ca
- Endoscopic biopsy every two years

Human Pathology 2001; 32:379-88

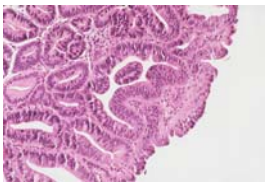
Columnar-lined Esophagus Low Grade Dysplasia



- In 26 patients
- 4 HGD (2-7 mo)
- 4 cancer (26 mo)
- Treat reflux
- Endoscopic biopsy in 1-3 mo.

Human Pathology 2001; 32:379-88

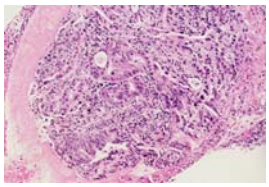
Columnar-lined Esophagus High Grade Dysplasia



- In 33 patients
- 20 cancers in 10 mos
- Management
  - Endoscopic biopsy in 1 month
  - Mucosectomy
  - Ablation
  - Esophagectomy

Human Pathology 2001; 32:379-88

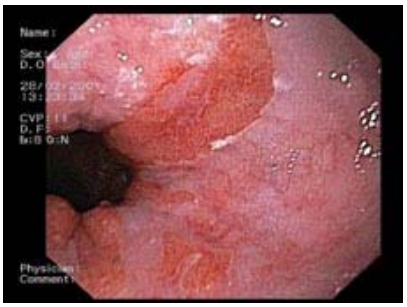
Columnar-lined Esophagus Intramucosal Cancer



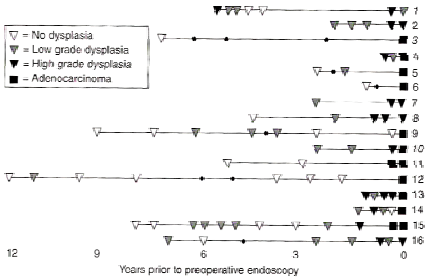
- In 13 patients
- 13 cancers in 4 mos
- Treatment
  - Mucosectomy - Ablation - Esophagectomy

Human Pathology 2001; 32:379-88

Barrett's Esophagus: Screening Strategy

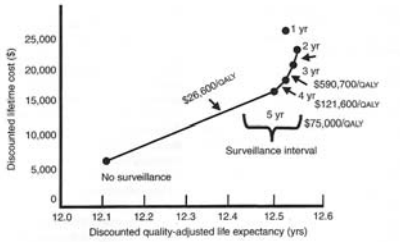


Variable Progression to Adenocarcinoma



Van Sandick et al. Gut (1998) 43:216

Surveillance and Incremental Cost



Comparison of Screening Costs

- Colon Cancer $20,000 LY
- Breast Cancer $22,000 LY
- Heart Transplant $160,000 LY
- Cervical Ca Screening $250,000 LY
- Barrett's q5y at 0.4% $98,000 QALY
- Barrett's q2y at 1% $590,700 QALY

Provenzale et al. Am J Gastroenterol 1999 94:2043

Columnar Lined Esophagus Screening

- 4 quadrant bx every 1 cm. and atypical areas
- Reviewed by two pathologists

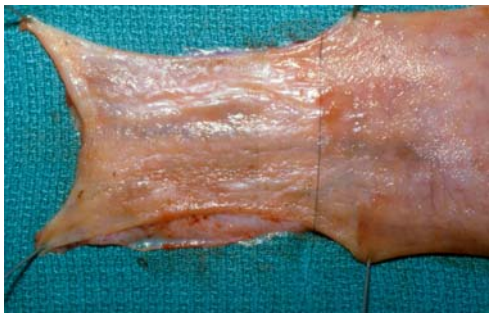
- Metaplasia - every two years
- Low grade dysplasia - treat reflux
  - re-biopsy in 1 mo.
- High Grade dysplasia - re-biopsy
  - endoscopic U/S

High Grade Dysplasia Early Adenocarcinoma

- 43% had an adenocarcinoma
- Lesion not visible on endoscopy
  - -Intramucosal (88%),Submucosal (12%)
  - -Lymph node involvement (10%)
  - -90 % 5 yr survival
- Lesion visible on endoscopy
  - -T1 (25%)
  - -Lymph node involvement (56%)
  - -5 yr survival (82%)

Blom,D,JAmCollSurg 195:241-250,2002.

High Grade Dysplasia Early Adenocarcinoma



Location of Adenocarcinoma

Cameron and Carpenter, Am J. Gastroenterol (1997) 92:586

Management of metaplasia

- Omeprazole 20 mg po bid or equivalent
- Prokinetics are not effective due to defective contractility of the lower esophagus or LES
- Ablation not proven to decrease the risk of cancer
- Anti-reflux surgery for ulceration,strictures and breakthrough symptoms

Endoscopic Ablation of Barrett's

- Thirty-five patients with ablation plus:
  - Nissen (n=5)
  - PPI (n=30)
- Biopsy shows neosquamous epithelium:
  - Normal Stroma (n=15)
  - Submucosal glands without metaplasia (n=9)
  - Submucosal glands with metaplasia (n=11)

Attwood, S. Can J Gast 12:45,1998

VA GERD STUDY: AdenoCa in Barrett's with Medicine vs. Surgery

- Patients with Barrett's develop Ca at 0.4%/y
- Patients without Barrett's developed Ca at 0.07%/y
- No significant difference in incidence of adenocarcinoma between medical and Nissen groups after 10 yrs followup

Medical and Surgical treatment of Barrett's esophagus (RCT)

5 yr followup	PPI n = 43	Fundoplication N = 58
Good clinical results	91%	91%
+ 24 hr ph	43/43	9/58
High grade dysplasia	2/43	2/58
Cancers/yr	1/111	1/319

Parilla P.Ann Surg. 2003 Mar;237(3):291-8.

Does antireflux surgery potentially reduce the risk of malignancy?

No since 10% continue to reflux after surgery which increases over time.

Probably if there is lifelong elimination of reflux.

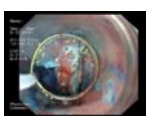
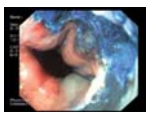
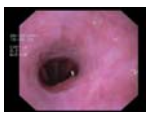
What is the best treatment for High Grade dysplasia?

1. Esophagectomy
2. Mucosectomy + PPI
3. Ablation + PPI

Esophagectomy for High Grade Dysplasia

	OR Mort	Cancer	%>T1	% ln	5yr
Collard	2%	50%	25%	6%	88%
Finley	2%	55%	28%	11%	90%
Lerut	3%	84%	26%	15%	92%

Endoscopic Mucosectomy for High Grade Dysplasia

6 months

Photos Courtesy: Prof. Horst Neuhaus, M.D.

Superficial Esophageal Cancer

- Endoscopic mucosectomy
  - 95% 5 year survival rate
  - 7% local recurrence rate
  - 3% perforation rate

Photodynamic therapy for ablation of high-grade dysplasia in Barrett's esophagus:RCT 30 centers, 485 pts

- RCT comparing PDT plus omeprazole with omeprazole only.
- Complete ablation of HGD in PDT 106/138 [77%]

Overholt,BF,Gastrointest Endosc. 2005 Oct;62(4):488

Photodynamic therapy for ablation of high-grade dysplasia in Barrett's esophagus

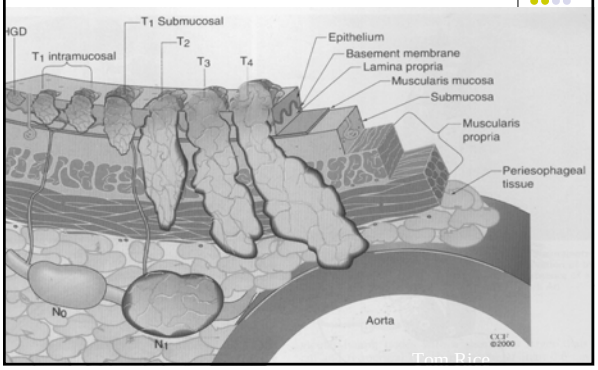
* P < .05	PDT/POR plus omeprazole	Omeprazole
HGD ablated	106/138 [77%]	27/70 [39%] *
Incidence of adenocarcinoma	13% (n=18)	20% (n=20) *
Adverse events	94%	13% *

Overholt,BF,Gastrointest Endosc. 2005 Oct;62(4):488-98.

Why is esophagectomy better than ablation or mucosal resection for high grade dysplasia?

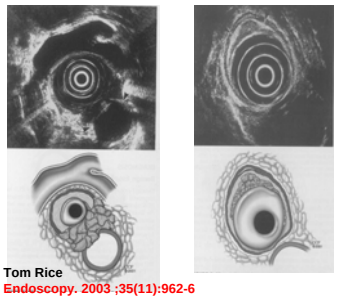
- Non-invasive staging with U/S or CAT scan is inadequqate
- 25% of patients have greater than T1 lesions so esophagectomy is the only curative Rx
- 10% of patients with cancer have lymph node involvement

T Stage



Endoscopic Ultrasound: Tumor Stage

T staging
= 89% accuracy



Tom Rice
Endoscopy. 2003 ;35(11):962-6

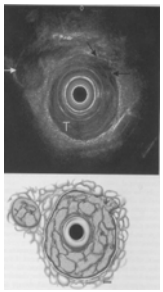
Endoscopic Ultrasound: Early Tumor Staging

Intramucosal	6/9
Submucosal	15/19

Am J Gastroenterol 2004 89:702

Endoscopic Ultrasound: Nodal Staging

T3N1



N staging
86% accuracy

Recommendations for Esophageal Cancer arising in Barrett's Mucosa

- Mucosal resection for superficial lesions in poor operative candidate
- Transhiatal esophagectomy (THE) for high grade dysplasia or early stage cancer
- Neoadjuvant chemoradiation and THE for Stage 3 cancer
- Palliative radiation
- Stent