

Barrett's Esophagus

Epidemiology, Pathophysiology and Treatment Options

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Disclosures



None pertinent to this topic

Objectives

- Discuss the epidemiology and screening strategies for Barrett's Esophagus and dysplasia
- Focus on the Barrett's patient with dysplasia
- Discuss treatment and follow-up in the patient with dysplasia
- Review endoscopic ablative therapies in the high risk patient who has dysplasia or early cancer

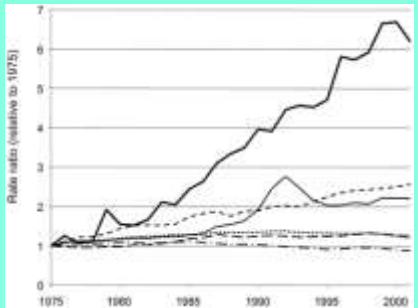
Barrett's Esophagus

A condition in which the lining of the esophagus is replaced by tissue similar to that of the intestine
(Intestinal Metaplasia or IM)

Dr Norman Barrett

Change in Incidence of Esophageal Cancer




Relative rates (relative to 1975):

- Esophagus
- Melanoma
- Prostate
- Lung/Breast
- Colorectal

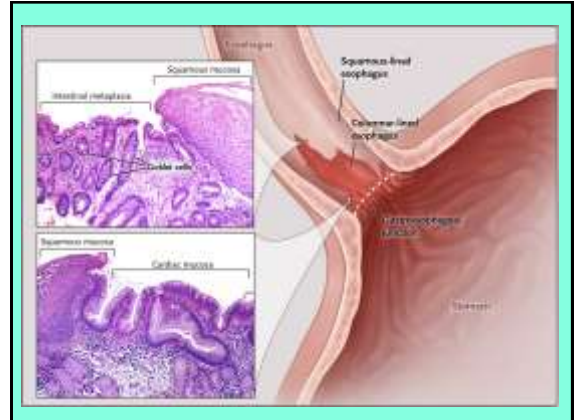
Pohl H. et al. J Natl Cancer Inst 2005; 97: 142-6

WHY ?



Diagnosis

- Endoscopy : Long segment > 3 cm
Short segment < 3 cm
- Histology : - intestinal metaplasia with goblet cells (USA)
- mucous-secreting columnar cells without GCs (UK)



Prevalence of Barrett's Esophagus

Autopsy studies : **0.4 %** (LSBE)

EGD for any indication	EGD for GERD
1 – 2 %	5 – 15 %

Cameron AJ et al. Gastroenterology 1990;99:918-22
Ronkainen J et al. Gastroenterology 2005;129:1825-31

Risk Factors for Barrett's Esophagus

- Older age
- White race (non-Hispanic)
- Male sex
- GERD (10-15 % will have BE)
- Age < 30 at onset of GERD symptoms
- Hiatal hernia
- Central Obesity with intra-abdominal fat distribution
- Metabolic syndrome
- Tobacco use
- Family history of GERD, BE, or esophageal adenocarcinoma
- Obstructive sleep apnea
- Low birth weight for gestational age
- Consumption of red meat and processed meat

Protective Factors for Barrett's Esophagus

- Use of NSAIDS
- Use of statins
- Helicobacter pylori infection
- Diet high in fruits and vegetables
- Tall height

Abnet CC et al. Eur J Cancer 2008;44:465-71

Screening for Barrett's Esophagus

- Observational studies : patients with BE associated cancers diagnosed by surveillance endoscopy have earlier stage tumors and higher survival rates than those who present with symptoms
- 40% of cancer patients report no GERD symptoms
- < 10% of patients with Ca have a prior diagnosis of BE
- Recent case-control study challenged the efficacy of surveillance for cancer prevention among patients with BE

Corley DA et al. Gastroenterology 2013;145:312-9

Screening for Barrett's Esophagus

- **Advanced Endoscopic Imaging Techniques for Screening**
 - Dye-based chromoendoscopy
 - Optical and digital chromoendoscopy
 - Autofluorescence endoscopy
 - Confocal laser endomicroscopy
 - Optical coherence tomography
 - Narrow band imaging
- **Biopsies:**
 - abnormalities in p53 expression
 - cellular DNA content (flow cytometry)
 - cytogenetic abnormalities (FISH)

Screening for Barrett's Esophagus

Minimally Invasive Screening Techniques

Video capsule endoscopy - currently not cost-effective

Transnasal endoscopy

Esophageal Capsule Cytology (Cytosponge)

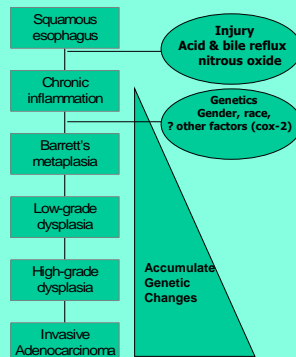
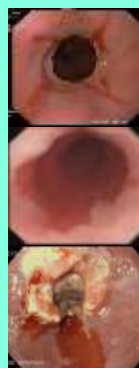


Risk of Cancer in Barrett's Esophagus

- True incidence of cancer in BE: 0.1 – 0.3%/year
- Life time risk for a patient with non-dysplastic BE is in the range of 5 – 8 %

Desai TK et al. GUT 2012;61:970-6
 Wani S et al. Clin Gastro Hepatol 2011;9:220-7
 Hvid-Jensen F et al. NEJM 2011;365:1375-83

Evolution of Barrett's



Dysplasia

- Epithelial cells have acquired genetic alterations that predispose them to the development of malignancy
- Often not identified endoscopically
- Patchy
- Seattle Protocol : 4 quadrant biopsies q 1 -2 cm + any focal abnormalities; jumbo forceps
- Inter-observer variability

Levine et al. Am J Gastro 2000
Weinstein et al. Gastro Endo Clin North Am 2000

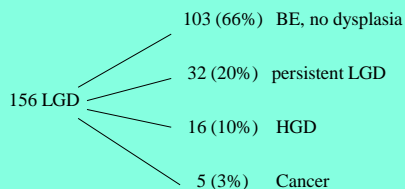
Dysplasia

Rates of progression :

- LGD to EAC : 0.5 – 3 % per year
- HGD to EAC : 2.3 – 10.3 % per year (5%)

Risk of Progression from LGD to EAC

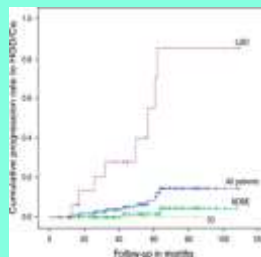
618 Barrett's patients with mean F/U 4.12 years



Sharma et al. Clin Gastro Hep 2006

How Benign is Low-Grade Dysplasia? Overdiagnosed but Underestimated

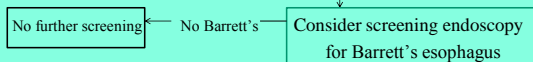
- 147 patients with diagnosis of LGD made in a community practice in Holland
- Path reviewed by 2 expert pathologists (disagreement resolved by consensus)
- 85 % of cases were down-graded
- In the 15 % who were not, the incidence rate of HGD or EAC was **13.4 % per patient per year** (mean f/u: 51 months)



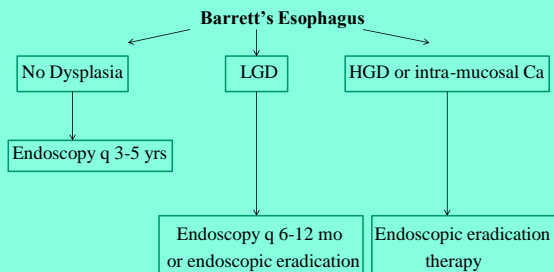
Curvers WL. Et al. Am J Gastroenterol 2010;105:1523

Algorithm for Screening and Surveillance

Chronic GERD symptoms and > 1 risk factor for esophageal adenocarcinoma: age > 50, male, caucasian, hiatal hernia, elevated BMI, intra-abdominal body-fat distribution or tobacco use



Algorithm for Screening and Surveillance

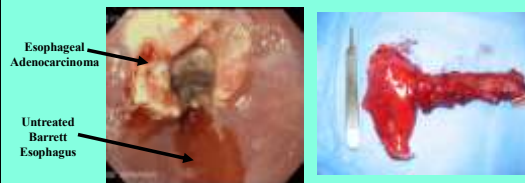


Guidelines for LGD

- Review biopsies with expert pathologists to confirm diagnosis
- Repeat endoscopy in 6 months
- EGD annually if LGD persists or in 3 years if there is no LGD on 2 consecutive endoscopies

Wang et al. AJG 2008

Risk of Watchful Waiting



ESOPHAGEAL ADENOCARCINOMA =
ESOPHAGECTOMY

Esophagectomy for HGD/early Adenocarcinoma

- Operative mortality : 2 - 10 %
- Early morbidity : 15 - 32 %
- Long-term morbidity : 75 %
- Recurrent intestinal metaplasia
- Average LOS : 20 days

Birkmeyer NEJM 2002
Viklund Eur J Cancer 2006
Chang et al. Ann Thor Surg 2008

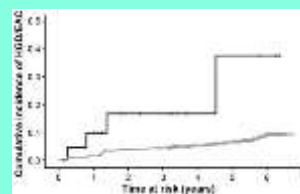


Acid Suppression in Barrett's Esophagus

- No long-term prospective clinical trials
- Refluxed acid can cause inflammation, ds DNA breaks, and increased cell proliferation
- PPIs relieve symptoms, heal inflammation and reduce proliferation, but may increase gastrin levels
- Observational studies suggest beneficial response

Acid Suppression in Barrett's Esophagus

- Multicenter prospective cohort study
- 540 patients with Barrett's
- Median follow-up of 5.2 years
- 7 % developed HGD or EAC
- PPIs reduced risk of neoplastic progression by 75 %



Kastelein F.
Clin Gastro Hepatol
2013;11:382-8

Anti-Reflux Surgery

- Bile acids can also cause ds DNA breaks and might contribute to carcinogenesis
- Anti-reflux surgery can prevent reflux of all gastric contents
- Surgery is not more effective than PPI therapy in preventing cancer

Spechler SJ. Dig Dis 2014;32:156-63

Barrett's Esophagus: Endoscopic Therapy

Endoscopic ablation of Barrett's epithelium

+

Suppression of acid reflux

=

Partial or complete healing with squamous mucosa

Risk Modifiers for Potential Metastasis

Factor	Increased Metastatic Potential	Decreased Metastatic Potential
Tumor Appearance	Ulcerated	Flat or Polypoid
Tumor Size	> 2 cm	< 2 cm
Depth of Invasion	Into Submucosa, > 500 um	Intramucosal, < 500 um
Differentiation	Poorly Differentiated	Well Differentiated
Angiolymphatic Invasion	Presence Increases	Absence Decreases

EMR



Endoscopic Eradication of Dysplasia Endomucosal Resection

- Therapy and most accurate means to delineate depth of invasion



EMR

- Recurrence of intra-mucosal CA or HGD is unacceptably high if EMR is the only therapy leaving intestinal metaplasia behind

Pech et al. GUT 2008;57:1200-6



Long-term Efficacy and Safety of Endoscopic Resection for Patients with Mucosal Adenocarcinoma of the Esophagus

- 1000 consecutive patients
- 481 SSBE; 519 LSBE
- All treated by EMR
- Excluded any submucosal extensions
- Follow-up period : 56.6 +/- 33.4 months

Pech O, et al Gastroenterology 2014;146:652-660

Long-term Efficacy and Safety of Endoscopic Resection for Patients with Mucosal Adenocarcinoma of the Esophagus

RESULTS

- 963 (96.3 %) complete remission
 - 12 (3.7 %) surgery for failed endo therapy
 - Tumor-related deaths 2 (0.2%)
- Recurrence of neoplasia: 140 patients (14.5 %) – endo reTx successful in 115
- Long-term complete Remission rate : 93.8 %
- Major complications in 15 pts. All treated endoscopically

Pech O, et al Gastroenterology 2014;146:652-660

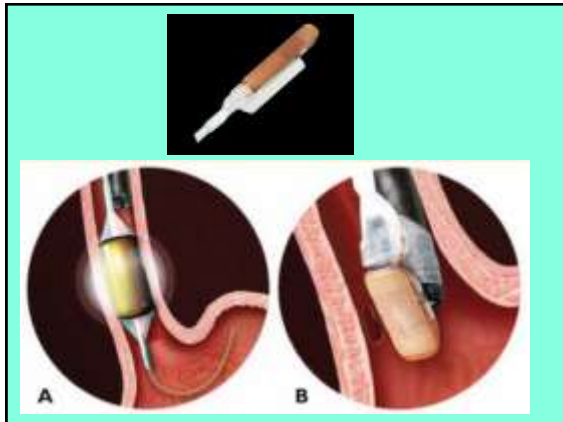
EMR

Limitations/Risks:

- Lesion should be small, <2cm
- Lesion must be liftable/polypoid
- Must be short segment Barrett's if complete removal is planned
- Increased incidence of strictures

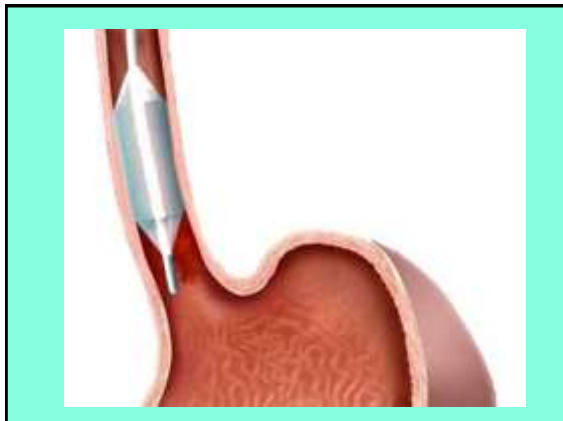
Radiofrequency Ablation

- Bipolar electrode array and a generator that delivers a fixed amount of thermal radiofrequency energy that results in uniform tissue dissipation to a depth of 0.5 mm.
- Devices: HALO 360; HALO 90; HALO Ultra 90
- Identify landmarks and length (Prague Classification)
- Sizing the balloon
- First ablation
- Cleaning the device and debride tissue (clear cap)
- Second ablation
- Post-procedure instructions
- Follow-up 2-3 months



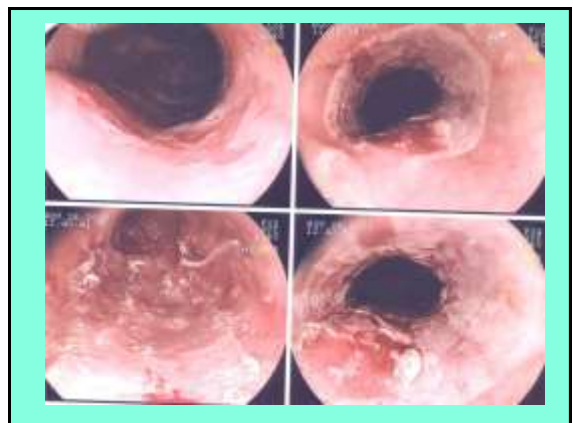
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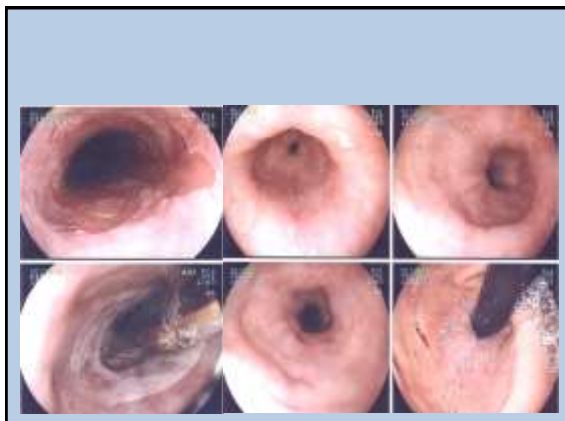
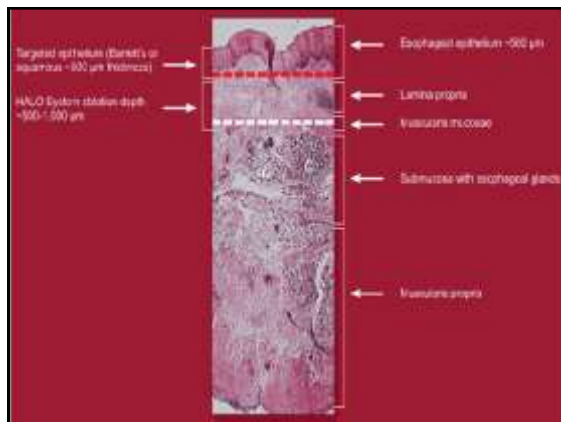
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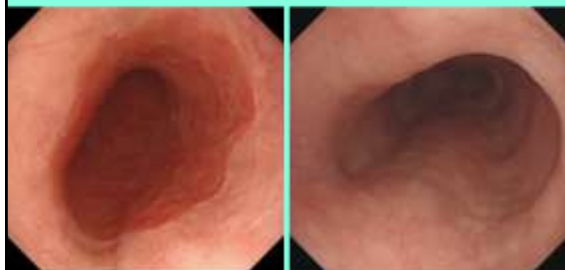


Systematic Review Comparing RFA and Complete EMR in the Treatment of Barrett's

- 22 studies; 1087 patients; 532 cEMR, 555 RFA
- Dysplasia was effectively eradicated at the end of treatment in 95 % after complete EMR and 92 % after RFA
- Over a median follow-up of 23 months it was maintained in 95 % after EMR and 94 % after RFA
- Adverse events : - 12 % in complete EMR (38% strictures)
- 2.5 % in RFA (4% strictures)

Chadwick B et al. Gastrointest Endoscopy 2014;79:718-31

Long-term Outcomes Halo RF Ablation



Baseline

Post-RFA: 2 years

RECURRENCE IN PATIENTS WITH CE-IM AFTER SUCCESSFUL RFA FOR DYSPLASTIC BE

Author	Year	# of Patients under surveillance	Median length of FU (months)	Recurrence Rate %/year
Pouw	2008	43	21	6.6
Gondrie	2008	11	14	7.8
Gondrie	2008	12	9.5	0.0
Pouw	2010	23	22	7.1
Herrero	2011	19	21	15.0
Van Vilsteren	2011	21	15	15.2
Vaccaro	2011	47	13.3	28.8
Shaheen	2011	108	36	4.3

Orman ES et al. Am J Gastro 2013;186-95

Durability and Predictors of Successful Radiofrequency Ablation for Barrett's

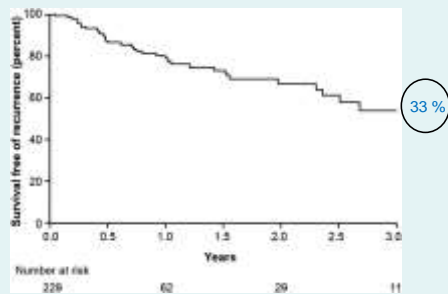
- US RFA registry: 5521 patients; 3728 had Bxs > 12 months
- 1634 (30 %) met inclusion criteria with FU of 2.4 years after CEIM

Results:

- 85 % achieved complete remission
- **IM recurred in 334 (20%)**
- 287/334 were non-dysplastic or indefinite for dysplasia
- Patients with recurrence were more likely to be older, have LSBE, non-Caucasians, have dysplastic BE before Tx and needed more Tx sessions

Pasricha S et al. Clin Gastro Hep 2014

Recurrence of Barrett's mucosa after EMR and RFA



Kaplan-Meier curve depicting the durability of CRIM over 3 years. All subjects with CRIM were analyzed from time 0 and followed forward until recurrence developed or until the end of the study. At 1 year 20 % of patients with CRIM had developed recurrence; and at 2 years 33 % had developed recurrence Gupta et al Gastroenterology 2013;145:79-86

Moncton Hospital Experience with RFA (HALO)

- 1st patient treated November 2009
- # of patients treated so far: 60
- Mean Age 63.8 years (Range: 43 – 82)
- 50 Males; 10 Females

Moncton Hospital Experience with RFA (HALO)

Pathology	# of Patients
Adenocarcinoma in situ	17
High Grade Dysplasia	36
Low Grade Dysplasia	7
Submucosal invasion	4
SSBE	21
LSBE	39
Prior EMR	36

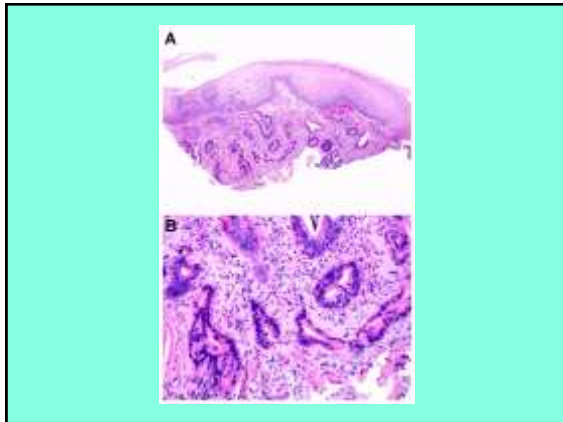
Moncton Hospital Experience with RFA (HALO) n = 60

- # of patients "eradicated" **36**
- Treatment not yet completed **19**
- Drop-outs **4**
- Recurrence: **Barrett 4**
- LGD 3**
- Indef. for dysplasia 1**
- Esophageal Carcinoma **0**

RFA for non-dysplastic Barrett's metaplasia

- Efficacy has not been established
- The problem with subsquamous intestinal metaplasia





Other Ablative Modalities

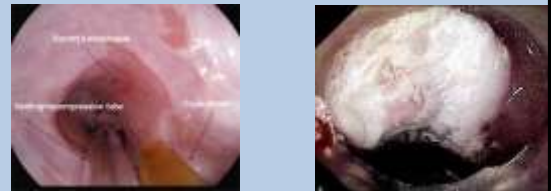
- ESD



Cryoablation

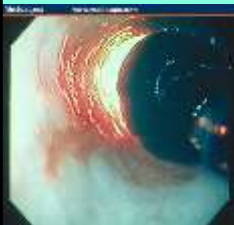
- Cycles of rapid freezing and thawing resulting in tissue destruction, fracturing of cell membranes and denaturation of proteins
- Non-contact
- Liquid nitrogen or CO₂ sprayed onto mucosa
- Cryospray Ablation System : liquid nitrogen (-196 C)
- Includes a 16 F orogastric decompression tube
- 20 sec cycle of deep freeze followed by thawing for 60 secs
- Typically 3 – 4 sessions
- Strictures 3 %; Chest pain 2 %

Cryo-ablation using liquid Nitrogen spray Temp – 196 C



Photodynamic Therapy

Argon Plasma Coagulation



Summary

- Barrett's esophagus is not rare and is a pre-malignant lesion for which we should screen
- Endoscopic surveillance seems reasonable once identified
- Patients with LGD need expert assessment and careful follow-up
- Ablation is effective and low risk for patients with HGD and LGD
- RFA is safe and effective but recurrence of disease mandates careful endoscopic follow-up
- RFA often needs to be combined with EMR
- The role for RFA in LGD remains controversial



Epidemiology

- Untreated patients with long-segment BE typically have severe GERD with erosive esophagitis
- Short segment BE is not associated with GERD symptoms or endoscopic esophagitis
- Patients with GERD symptoms : 7 x increased risk of EAC
- Patients with severe and longstanding GERD symptoms: 43 x increased risk of EAC

Lagergren J et al. NEJM 1999;340:825-31

