Disclosure Statement
Dr. Montgomery reports no relevant financial relationships with commercial interests.

Barrett Esophagus - Epidemiology
5th and 6th decade
M:F - 2:1 - 4:1
White: African-American - 10:1 - 20:1
Risk of cancer – about 0.5%/year – pooled data mostly US

Study from Denmark
Annual risk of progression to adenocarcinoma – 0.12%
Therefore surveillance pointless (at least in Denmark)

Denmark
Life expectancy (WHO)
M 77y/ F 81y
Obese population estimate:
7%

United States
Life expectancy
M 76y/ F 81y
Obese population estimate:
33%
Barrett’s Esophagus

- Overall incidence of progression in BE patients is 0.1 to 0.3%/year in first five years but 9.9.5% at 20 years


Prevalence of BE – Swedish Study

Columnar lined esophagus in about 10.3% BE found in [1.6%] [with goblet cells]
Alcohol, smoking were risk factors [Gastroenterology 2005; 129: 1825]

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Complications of Barrett’s Esophagus - Then versus Now

Then - severe erosive esophagitis and strictures
Now - in proton pump inhibitor era, ulcers readily healed
Esophageal reflux now established as a pre-neoplastic process
Objective now - endoscopic surveillance

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CHRONIC PEPTIC ULCER OF OESOPHAGUS

CHRONIC PEPTIC ULCER OF THE OESOPHAGUS AND ‘OESOPHAGITIS’

By N. R. BARRETT, LONDON
American College of Gastroenterology Criteria for Barrett’s Esophagus 2008

Barrett’s mucosa is a change of the esophageal epithelium of any length that
1) can be recognized at endoscopy and
2) is confirmed to have intestinal metaplasia on biopsy

American College of Gastroenterology Criteria for Barrett’s Esophagus 2016

“BE should be diagnosed when there is extension of salmon colored mucosa into the tubular esophagus extending greater than or equal to 1 cm proximal to the GEJ with biopsy confirmation of intestinal metaplasia”
Shaheen et al Am J Gastroenterol 2016 111(1): 30-50

British Society of Gastroenterology Criteria for Barrett’s Esophagus 2014

Endoscopically abnormal segment of esophagus that is greater than or equal to 1 cm in length.

Fitzgerald R et al. Gut 2014 63(1); 7-42
This biopsy is from esophagus - Submucosal glands are present (very purple on Alcian blue)

Alcian Blue “Fakes” [Tall Blue Columnars] and Pancreatic Acinar Cell Heterotopia

Classic Barrett mucosa with “incomplete” intestinal metaplasia

Normal duodenal mucosa

Duodenal mucosa, PAS/AB stain
**US Will Stop Requiring Goblet Cells?**

Example: Takubo et al. Hum Pathol 2009;40:65-74 used German cases and found that intestinal metaplasia accompanied only 43% of early esophageal adenocarcinomas and believed that most cases arose in association with cardiac type mucosa.

Stay tuned!

ACC did not remove the requirement for goblet cells in 2008; AGA did not in position paper – 2010 but changed definition to leave the door open.

**AGA Barrett 2011:**

“The condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus. Presently, intestinal metaplasia is required for the diagnosis of Barrett’s esophagus because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy.”

**2012 Study from USC**

**ONLY FOUND DYSPLASIA OR CARCINOMA IN PATIENTS WITH INTESTINAL METAPLASIA**

BUT these patients were all biopsied using systematic protocols (“perfect world”) by highly experienced colleagues


**The Rules for Barrett Mucosa**

US studies are always boring but European ones are catchy

(Think about the TOGA trial for gastric cancer - ToGA (Trastuzumab for Gastric Cancer) – we would have said “Efficacy of Trastuzumab for Gastric Cancer”

Let’s catch a BOB CAT (*Benign Barrett’s and Cancer Taskforce*)

**What they did**

Essentially they voted on statements pertaining to Barrett esophagus until they had folks agreeing with them

Lots of British colleagues and US colleagues who have strong viewpoints

*Colleagues with opposing viewpoints not invited*
The Big Points

1. Use the “B” word even if no intestinal metaplasia:
   “BE is defined by the presence of columnar in the esophagus and it should be stated whether intestinal metaplasia is present above the gastroesophageal junction”

The paper caused a stir

I got lots of emails asking if colleagues needed to change reporting practice (All from US colleagues) SOOOOOOOO
I asked all my gastroenterology colleagues if they wanted us to change our reporting habits.

In unison they replied

no no no

However

That’s OUR population
It seems reasonable in other populations

“Multilayered epithelium” - controversial
Multilayered epithelium – PAS/AB

Dysplasia

Neoplastic Epithelium
Confined within the basement membrane of the gland within which it arose.

Diagnostic Categories

Negative for dysplasia
Indefinite for dysplasia
Dysplasia, low-grade
Dysplasia, high-grade
Intra-mucosal carcinoma

Grading Dysplasia in Barrett’s - Algorithm

SURFACE MATURATION
[COMPARSED TO UNDERLYING GLANDS]
ARCHITECTURE
CYTOLOGIC FEATURES
INFLAMMATION

BE - Negative for Dysplasia

Surface - More mature than glands
Architecture - Abundant lamina propria
Cytology - Normal with mitoses confined to deeper glands. Nuclei with smooth nuclear membranes. Normal nuclear polarity
Inflammation - Variable
BE - Negative for Dysplasia

Indefinite for dysplasia

Originally defined in IBD and diagnosed by answering the questions...
- a) Is this epithelium unequivocally benign or reactive?
- b) Is this epithelium unequivocally neoplastic/adenomatous

The answer “NO” to both questions = IFD

But.....

Montgomery 2001 – study on dysplasia in BE
Deliberately defined any epithelium that looked dysplastic in the bases of the pits but had surface maturation as IFD
i.e. impossible to have dysplasia with maturation
Rationale – maturation is a major feature of regenerating mucosa, so will exclude all reactive changes.

BE, Indefinite for Dysplasia

Surface – often more mature than glands
Architecture - slight glandular crowding
Cytology - hyperchromasia, nuclear membrane irregularities, increased mitoses in deep glands. Maintained nuclear polarity
Inflammation - Frequently a factor
Nice to see an abrupt transition to be sure something is dysplastic – and thus clonal
BE, IND - MATURATION

Indefinite - Neutrophils
No abrupt transition

BE, IND - INFLAMMATION

Low Grade Dysplasia
Clearly neoplastic
Minimal loss of nuclear polarity
Surface involved
Only mild architectural crowding.

LGD, adenoma-like
Where is the “Minimum”

Abrupt transition – appears divergent and clonal compared to adjacent epithelium
But without inflammation in the specific “abnormal” focus

Unclear, gradual demarcation between zone of monolayered nuclei and stratification

Sharp demarcation of zone of abnormal nuclei
Basal pattern dysplasia

High-Grade Dysplasia
Surface - No maturation
Architecture - Crowded glands overrunning lamina propria
Cytology - Nuclear membrane irregularities, extending to surface and loss of nuclear polarity
Inflammation - Typically not abundant
HGD – Inflammation

Inflamed HGD, p53 labeling can be reassuring
Be aware of the p53 null pattern with complete loss of labeling due to biallelic inactivation of the gene (high grade dysplasia).

Pay attention to this area.

High grade dysplasia, P53 null pattern – note surface loss of polarity and nuclear hyperchromasia.

P53 is DEAD negative – internal control is labeling of squamous basal cell nuclei.

HGD, "small cell pattern" "non-adenomatous dysplasia"
Intramucosal Carcinoma

Surface - No maturation
Architecture - Effacement of lamina propria and syncytial growth pattern of glands. Back-to-back microglands, "dirty necrosis" in glands, DESMOPLASIA not yet developed
Cytology - as in HG –but often with nucleoli
Inflammation - variable
Intramucosal carcinoma, lateral spread of atypical glands

Intramucosal carcinoma, Budding and lateral growth

Well developed desmoplasia – Invasion into at least submucosa

Finding Pagetoid extension of single cells ALWAYS means there is a cancer underneath

Additionally

There are variant forms of dysplasia – initial studies were all using criteria for intestinal type dysplasia but variant patterns are less well recognized and less well understood. In the future these may be shown to have different biology and inform treatment.
Intestinal type LGD

Intestinal type HGD

Foveolar type LGD

Pyloric type/cardiac type

Look! Kulchitsky cells!
Pyloric/cardiac type
LGD and HGD

Chief cell type
dysplasia

Chief cell pattern
dysplasia, BE
Alternate dysplasia patterns

All can have serrated zones similar to colorectal lesions
Significance of the serrations is unclear

Changing the game

New endoscopic treatments and ability to visualize the mucosa (even with molecular markers) might slowly reduce the mortality of esophagus cancer
....assuming we can figure out how to get the right patients screened in a better way
**“Modern” View**

Once you remove the people who already have cancer, the progression rate is closer to 20-30% in HGD. 

**OVERALL - Risk of progression to cancer about 6%/year in patients with high grade dysplasia**

**SEER Data**

Patients with early esophageal cancer (T0, T1) managed with endoscopic therapy have equivalent long-term survival compared to those treated with surgical resection. 


**Then and Now – Paradigm Shift**

In the past esophagectomy was recommended for HGD BUT there was really nothing better to offer people. 

Now we know that radiofrequency ablation (BARRX) is a fantastic option with little risk (about 6%) for strictures. 


We are developing better ways to target biopsies to detect neoplasia as well.

**Example case**

A 65 year old man shown to have HGD in Barrett’s mucosa was offered surgery in 2003 but preferred to under an endoscopic mucosal resection.

Subclassification of Depth of Invasion by Superficial Carcinoma Proposed by the Japan Esophageal Society

<table>
<thead>
<tr>
<th>Depth</th>
<th>% Lymph node metastases on resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>m1</td>
<td>0%</td>
</tr>
<tr>
<td>m2</td>
<td>0%</td>
</tr>
<tr>
<td>m3</td>
<td>8%</td>
</tr>
<tr>
<td>sm1</td>
<td>17%</td>
</tr>
<tr>
<td>sm2</td>
<td>28%</td>
</tr>
<tr>
<td>sm3</td>
<td>49%</td>
</tr>
</tbody>
</table>

### Reported Subclassification Schemes for Intramucosal Carcinomas (T1a)

<table>
<thead>
<tr>
<th>Description of Depth of Invasion</th>
<th>Designation, Weserterp et al</th>
<th>Designation, Vieth et al</th>
<th>Designation, Kaneshiro et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (Tis, high-grade dysplasia, HGD)</td>
<td>m1</td>
<td>m1</td>
<td>m1</td>
</tr>
<tr>
<td>Tumor cells invading beyond basement membrane into lamina propria</td>
<td>m2</td>
<td>m1</td>
<td>LP</td>
</tr>
<tr>
<td>Tumor cells invading (inner) duplicated muscularis mucosae</td>
<td>m2</td>
<td>m2</td>
<td>IMM</td>
</tr>
<tr>
<td>Tumor cells in the space between the duplicated muscularis mucosae and original muscularis mucosae</td>
<td>m2</td>
<td>m3</td>
<td>OMIM</td>
</tr>
<tr>
<td>Tumor cells into (outer) original muscularis mucosae</td>
<td>m3</td>
<td>m4</td>
<td>DMIM</td>
</tr>
</tbody>
</table>

**Submucosal glands**

**Muscularis mucosae**

**Deep (submucosal) margin**

**Lateral (mucosal) margin – green – remember that samples curl once resected**

**ADENOCARCINOMA A, T1a, INVADING MUSCULARIS MUCOSAE**

**Well formed glands**

**Muscularis mucosae**

**Submucosal glands**

**Poorly differentiated component with single cells**
Studies – Early Esophagus Adenocarcinomas

<table>
<thead>
<tr>
<th>Depth</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamina propria</td>
<td>No mets</td>
</tr>
<tr>
<td>MM or superficial SM</td>
<td>22% mets</td>
</tr>
<tr>
<td>M1-M3, SM1</td>
<td>1/79 LN mets, 83% 5 yr surv</td>
</tr>
<tr>
<td>SM2, SM3</td>
<td>44% LN mets; 42% 5 yr surv</td>
</tr>
<tr>
<td>M1-M3, SM1</td>
<td>0.7% LN mets; 8.6% LN mets</td>
</tr>
</tbody>
</table>

2014 Study of Endoscopic Resection and Radiofrequency Ablation


- Achieved complete eradication of IMC in 1000 with invasion of T1m1-4 (using the Vieth et al system)

- Authors believed endoscopic treatment fine for patients with sm1 to a depth of 500 microns
Patient

- Patient was followed with photodynamic therapy
- Free of columnar metaplasia as of summer 2016 (13 years)

- Treatments for early esophageal cancer continue to improve but we have a long way to go in refining screening.

Thank you!!!