The Pathologist’s Role in the Diagnosis and Management of Neoplasia in Barrett’s Oesophagus

Cian Muldoon,
St. James’s Hospital, Dublin

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THE LOWER ESOPHAGUS LINED BY COLUMNAR EPITHELIUM
N. R. BARRETT, LONDON, ENGLAND

DEFINITIONS

The idea discussed here are not based on statistics but upon a large collection of specimens; they are the result of thinking about a few unusual cases of esophageal disease. One might have rejected or modified in the light of future experience, but because I have changed my opinion relating to certain points, the subject which does not yield outputs, studies are conducted.

This paper concerns certain observations which are denied by some, misunderstood by others, and interpreted as a state of surgery. It has been called a variety of names by many surgeons. It has been suggested that the incorrect etiology of esophageal disease, short esophagus, esophageal gastritis, and esophageal cancer (sympathetic) esophageal epithelium are but a few. At that time, a precise, accurate description is that it is a state in which the lower esophagus is lined by columnar epithelium. This does not carry certain implications which could be wrong, but it carries certain implications which be corrected.
The Role of the Pathologist in Excluding Barrett’s in the First Place
How common is this scenario in your practice?

Endoscopist says:  
“? Barrett’s”

Endoscopist does:  
“biopsies from oesophagogastric junction”

Pathologist says:  
“Blah, blah, blah”  
(i.e. a descriptive report without conclusion)

or worse still  
“features consistent with Barrett’s” when it is not

Lifelong surveillance anyone?
What is needed?

• A full endoscopic report

• Endoscopic impression as to the presence or absence of Barrett’s and its extent

• Biopsies from the native oesophagus - clearly designated

• A pathologist who is alert to the diagnostic possibilities

• Pathology report - useful to the clinician and therefore the patient

• [New BSG guidelines]
2004

Biopsy → HGD

Oesophagectomy
Oesophageal Mapping Biopsies
2015 – Radically Changed Model

- **Biopsies +++** (multiwell blocks)
- **EUS**
- **EMR**
- **ESD**
- **Ablation**
- **Oesophagectomy**
2015 – Radically Changed Model

- Central role in the multidisciplinary management
- Challenge our existing practices
- Improve the reproducibility of our analysis
- Provide clinically useful reports
Classification of Dysplasia/Neoplasia in Barrett’s

- No dysplasia
- Indefinite for dysplasia
- Low grade dysplasia
- High grade dysplasia
- Intramucosal adenocarcinoma (at least)
- Invasive adenocarcinoma
Examples of short and comprehensive proformas for reporting histopathology diagnosis and surveillance biopsy findings.

**BSG guidelines (Fitzgerald et al. Gut 2014; 63:7-42)**

<table>
<thead>
<tr>
<th>Barrett’s Endoscopic Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of levels</td>
</tr>
<tr>
<td>Total number of biopsies</td>
</tr>
<tr>
<td>Squamous mucosa (Y/N)</td>
</tr>
<tr>
<td>Native oesophageal structures (Y/N)</td>
</tr>
<tr>
<td>Glandular mucosa (Y/N)</td>
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**SUMMARY**

- Barrett’s oesophagus with gastric metaplasia only
- Barrett’s oesophagus with intestinal metaplasia (state degree of dysplasia) or No evidence of Barrett’s oesophagus

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<td>Level/cm</td>
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<tr>
<td>p53 Significant immuno staining pattern (Y/N/ equivocal / Not performed)</td>
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**SUMMARY**

- Highest grade of inflammation:
  - Acute (none, mild, moderate, severe)
  - Chronic (none, mild, moderate, severe)

- Highest grade of dysplasia:
  - Barrett’s oesophagus with gastric metaplasia only
  - Barrett’s oesophagus with intestinal metaplasia (state degree of dysplasia) or No evidence of Barrett’s oesophagus
Low Grade Dysplasia

- Nuclei enlarged, crowded, hyperchromatic, ovoid
- May have visible nucleoli
- Mitoses +
- Usually stratified
- Changes ‘reach’ the luminal surface
- Discernible demarcation useful when present
- Goblet cells usually “lost”

- Interobserver agreement “not great”
Other Patterns of Dysplasia in Barrett’s

Foveolar Dysplasia

• Little or no loss of nuclear polarity
• Easily missed!
• Should regard as high grade

Serrated Dysplasia

• Epithelial serration
• Elongated nuclei
• Prominent eosinophilic cytoplasm
• Should regard as high grade

GOOD NEWS!

Both patterns tend to occur in association with more conventional dysplasia
“Indefinite for dysplasia” – WHEN?

1) Inflammation

2) Basal glandular “atypia” /dysplasia/ basal crypt dysplasia-like atypia

3) Poor orientation (Tangential sections)/Loss of surface epithelium

EXPLAIN WHY
Indefinite for dysplasia due to inflammation

- May make interpretation almost impossible

- Occasionally the differential diagnosis includes florid reactive atypia and high grade dysplasia
Indefinite for dysplasia due to basal glandular atypia

“Basal Crypt Dysplasia-like Atypia” (BCDLA)

→ “Basal crypt dysplasia”

Surface maturation (+)
Indefinite for dysplasia

Loss of surface epithelium

Poor orientation/tangential cut
High Grade Dysplasia

- Nuclei more enlarged and rounded
- Greater hyperchromasia
- More pleomorphism
- Nucleoli more prominent
- Mitoses ++ (atypical)
- May be stratified but often more disorganised

- Interobserver agreement generally good
Intramucosal Adenocarcinoma

• Single cells in lamina propria

• Cribriform or lateral growth pattern

• Often little or no desmoplastic response

• Often report as “intramucosal carcinoma at least”
Invasive Adenocarcinoma

- Can be difficult diagnosis to make on mucosal biopsies!

- Other tumour types
Help......is at hand?

- Ki67

- Alpha-Methyl-CoA racemase (AMACR)

- p53 - aberrant expression (+/-)
  - adjunct to routine clinical diagnosis (BSG 2014)
  - p53 interpretation module → ‘significant’/’not significant’

- Levels

- Second opinion
What needs a second opinion?
(BSG 2014)

- All cases of suspected dysplasia are reviewed by a second GI pathologist

- Given the difficulties associated with the management of the ‘indefinite for dysplasia’ category, all such cases should also be reviewed by a second GI pathologist
Interobserver (and intraobserver) agreement 2015

**Agreement (+)**
- Non-dysplastic
- High grade dysplasia
- Carcinoma

**Agreement (-)**
- Indefinite for dysplasia
- Low grade dysplasia

(vs)

(International variation in thresholds of diagnosis)
Is there a solution?

- Not Sure
- Dysplasia
- Carcinoma
Endomucosal Resection (EMR)

- Pinned on cork/similar
- Deep margin inked
- Serially sectioned at 2-3mm (through closest edge if a lesion visible)
- 2 or 3 slices per cassette
- 3 levels each
Endomucosal Resections – the Good

Avoidance of oesophagectomy
Endomucosal Resections – the Bad

- Poor differentiation
- Submucosal invasion
- Incomplete excision
- Lymphovascular invasion
Endomucosal Resection – The Ugly
Pin...Cautery....Fragmentation.....Surface loss...Curling edges
Learn to recognise the submucosa

Beware the double muscularis mucosae
Local reporting template for endomucosal resection specimens (EMR’s) of oesophageal lesions

- **Macroscopy:**
  - Site of tumour:
  - Maximum tumour dimension (mm) (if known):
  - Number of specimens:
  - Size of each specimen (mm):

- **Microscopy:**
  - Tumour type: Adenocarcinoma / Squamous / Other...........(specify)
  - Lauren classification (if applicable): intestinal or diffuse / mixed
  - Differentiation by worst area: Well / Moderate / Poor

- **Substage:**
  - Not assessible
  - M1 - High grade dysplasia
  - M2 - Intramucosal carcinoma (invasion of lamina propria)
  - M3 - Infiltration of muscularis mucosae
  - SM - Submucosa – if so, distance of tumour beyond muscularis mucosae (mm):

- **Margins:**
  - Deep margin involved: Yes / No / Not assessible
  - If no, distance of tumour to deep margin (mm):
  - Peripheral margin: Carcinoma /High grade dysplasia /Low grade dysplasia /Intestinal metaplasia / Not assessible
  - Lymphatic or Vascular invasion: Yes / No, If yes, which

- **Pathological stage (TNM 7th edition):** pT.....

- **Comments:**
Subclassification of pT1a oesophageal adenocarcinoma

BSG Guidelines 2014

m1: Carcinoma in-situ or with questionable invasion beyond the basement membrane
m2: Invasion into the lamina propria
m3: Invasion into the muscularis mucosa

Vieth 2014

HGD: High grade dysplasia
M1: Invasion into lamina propria
M2: Invasion into inner duplicated muscularis mucosae
M3: Invasion into the space between the two layers of duplicated MM
M4: Invasion into the outer layer of the duplicated MM
EMR’s – use of immunohistochemistry
Post radiofrequency ablation – biopsies/EMRs
Beware of buried glands!

- Squamous re-epithelialisation
- Loss of glandular surface for evaluation
- Mimicry of glandular dysplasia
- Mimicry of invasive adenocarcinoma
- (Squamous re-epithelialisation over invasive adenocarcinoma)
Please

- Help exclude Barrett’s when appropriate

- Confine second opinion practice to LGD (for the moment)

- Consider change to mirror the altered management landscape

- Embrace the EMR!