Barrett’s Oesophagus: An Evolving Challenge for the Gastroenterologist

Dermot O’Toole on behalf of the National Barrett’s Registry Project and the National Centre for Early Mucosal Neoplasia

St James’s Hospital, Dublin
Background & challenges

• GORD and Barrett’s oesophagus are major risk factors for oesophageal adenocarcinoma
• Represents a substantial “potential” problem
  – 5.6% of adults in US
• Screening & surveillance programmes
  – Endoscopy-based
    • Cost-effectiveness?
  – Identification of “at-risk” populations
    • Stratify
      – Patient and Barrett’s factors
• Where we do make a difference
  – Detecting neoplasia (endoscopist/pathology interface)
    • Low grade dysplasia, indefinite for dysplasia
    • Staging EMRs
  – Therapy
    • Dysplasia
    • All Barrett’s patients?
<table>
<thead>
<tr>
<th>Factor</th>
<th>Risk Factor for Barrett’s Esophagus</th>
<th>Risk Factor for Esophageal Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>White race</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Male sex</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic heartburn</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Age &lt;30 yr at onset of GERD symptoms</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity with intraabdominal fat distribution</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Family history of GERD, Barrett’s esophagus, or esophageal adenocarcinoma</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Low birth weight for gestational age</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Consumption of red meat and processed meat</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Human papillomavirus infection</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Risk of oesophageal cancer in Barrett’s?

• **Definite**
  - Intestinal metaplasia → adenocarcinoma: 0.1-0.3% / year
    - 2 times higher in men
    - >> in long segment Barrett’s and familial forms
  - LGD → adenocarcinoma: 6% / per patient / year
  - HGD → adenocarcinoma: >50% over 3 years

• **Detection of early HGD**
  - Surgery or endoscopic therapy
  - Surgery
    - Oesophagectomy
      - Invasive procedure
        » Substantial morbidity & mortality
Screening & surveillance

- **Endoscopy if GORD (detect curable neoplasia)**
  - Not proven
    - RCT (if risk is 0.1-0.3%/year) daunting

- **Theory: surveillance endoscopy**
  - Earlier-stage tumours and higher survival rates (Grade B)
  - Biases
    - Computer-modelling studies suggested screening and surveillance can be cost-effective under certain circumstances ...

Index OGD

<table>
<thead>
<tr>
<th>Negative for Barrett’s</th>
<th>Positive for Barrett’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop screening</td>
<td>OGD every 3 to 5 years</td>
</tr>
</tbody>
</table>

AGA Position Statement *Gastroenterology* 2011:1084
Spechler & Souza *NEJM*;371:9:836-845
Screening & surveillance (problems)

1. Prerequisite of GORD symptoms is limited
   • Patients with short-segment Barrett’s have no GORD
   • Up to 40% of patients with oesophageal adenocarcinoma report no history of GORD

2. < 10% of patients with oesophageal adenocarcinoma
   • Prior diagnosis of Barrett’s oesophagus
     – Suggesting that current screening practices are highly ineffective

3. High cost, potential complications, ...
   • Negative impact on patients (stress)

4. Biomarker panels not yet ready ...

AGA Position Statement Gastroenterology 2011:1084
Spechler & Souza NEJM;371:9:836-845
Screening & surveillance

• Societies recommend screening OGD
  – Chronic GORD symptoms and 1-3 other cancer risk factors
    • Age > 50 years
    • Male sex
    • White race
    • High BMI (intra-abdominal body-fat distribution)
    • +/- tobacco use

British Society of Gastroenterology
American College of Gastroenterology
French Society of Gastroenterology
American Society of Gastrointestinal Endoscopy
Others …
OVERALL OBJECTIVE: To target oesophageal cancer prevention and early diagnosis through registration of at risk patients with Barrett’s Oesophagus

SPECIFIC AIMS
1. To establish the first Barrett’s Registry in Republic of Ireland
2. To establish a biobank of biopsy and blood material in collaboration with Molecular Medicine Ireland (DCCR)

Personnel
• 5 data- & 3 biobank managers

Registry & Biobank
• 3000 patients
• Over 500 tissue samples
• Over 500 bloods for DNA
• Tissue microarrays: non progressors/progressors
National Barrett’s Registry

<table>
<thead>
<tr>
<th>Total patients</th>
<th>2955</th>
</tr>
</thead>
<tbody>
<tr>
<td>In database</td>
<td>2814</td>
</tr>
<tr>
<td>St James’s Hospital</td>
<td>1,451 (52%)</td>
</tr>
<tr>
<td>Mercy Hospital Cork</td>
<td>615 (22%)</td>
</tr>
<tr>
<td>Beaumont Hospital</td>
<td>396 (14%)</td>
</tr>
<tr>
<td>St. Vincent’s Hospital</td>
<td>269 (9%)</td>
</tr>
<tr>
<td>Mater Hospital</td>
<td>83 (3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vienna grade</th>
<th>2955</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIM</td>
<td>2,369</td>
<td>80</td>
</tr>
<tr>
<td>Indefinite for dysplasia</td>
<td>207</td>
<td>7</td>
</tr>
<tr>
<td>LGD</td>
<td>201</td>
<td>7</td>
</tr>
<tr>
<td>HGD / IMC</td>
<td>173</td>
<td>6</td>
</tr>
<tr>
<td>Unsuitable / unknown</td>
<td>5</td>
<td>0.2</td>
</tr>
</tbody>
</table>


A Barrett’s esophagus registry of over 1000 patients from a specialist center highlights greater risk of progression than population-based registries and high risk of low grade dysplasia.


• 1093 patients
  – Male, 67% (p<0.05)
  – 65% current or former smokers
  – 73% overweight or obese
  – Long segment BO: 34%
• **Progression risk**
  – 11 progressed to oesophageal adenocarcinoma (OAC)
    • 3 in 1st year
  – Incidence
    • OAC/HGD: 1.33 per year
      – 0.85 if exclude 1st year
    • Long segment higher risk (p< 0.001)
  – LGD at index endoscopy
    • 6.5% / year progression risk
    • 3.1% when tertiary referrals excluded
A Barrett’s esophagus registry of over 1000 patients from a specialist center highlights greater risk of progression than population-based registries and high risk of low grade dysplasia

Incidence of Adenocarcinoma among Patients with Barrett’s Esophagus

Frederik Hvid-Jensen, M.D., Lars Pedersen, Ph.D., Asbjørn Mohr Drewes, M.D., Dr. Med. Sci., Henrik Toft Sørensen, M.D., Dr. Med. Sci., and Peter Funch-Jensen, M.D., Dr. Med. Sci.
National Barretts Registry & Biobank

Progression rate to date: 3550 patients

<table>
<thead>
<tr>
<th>Neoplasia progression rate, %*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SIM</td>
<td>0.68</td>
</tr>
<tr>
<td>Indefinite for dysplasia</td>
<td>1.53</td>
</tr>
<tr>
<td>LGD</td>
<td>3.74</td>
</tr>
</tbody>
</table>

* Excluding 1st year
Building a bioresource for esophageal research: lessons from the early experience of an academic medical center

D. P. Ennis, G. P. Fidgeon, N. Millar, N. Ravi, J. V. Reynolds

Department of Surgery, Trinity Centre for Health Sciences, St James’s Hospital, Trinity College Dublin, Ireland

Dis Esophagus 2010: 23: 1-7

Courtesy JV Reynolds
The esophagitis to adenocarcinoma sequence; the role of inflammation

M.E. Kavanagh¹, K.E. O’Sullivan¹, C. O’Hanlon, J.N. O’Sullivan, J. Lysaght, J.V. Reynolds

Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett’s esophagus

The Esophageal Adenocarcinoma Genetics Consortium¹,² and the Wellcome Trust Case Control Consortium ²

Barrett's Esophagus Translational Research Network (BETRNet): The Pivotal Role of Multi-institutional Collaboration in Esophageal Adenocarcinoma Research
Barrett’s oesophagus is an imperfect model

• Despite that, surveillance for detecting neoplasia increasing
  – Barrett’s surveillance leads to earlier staged cancers
    • How do we improve detection?
    • Neoplasia easier to treat?
A, Schematic representation of the biopsy sites needed to carry out a Seattle protocol in a segment of Barrett mucosa of average length, indicated in blue. B, Detail of the 2-cm segments. Each segment has an average mucosal area of ~14 cm². Because the total mucosal surface obtained by the 4 biopsies adds up to ~0.5 cm², each set samples only 3.5% of the surface of that segment. The margin of error in the absence of visible lesions is, therefore, huge.
Limitations

- Endoscopic detection of dysplasia is difficult
  - Quality of endoscopists
  - Less a question of biopsying what you see …
    … but what you recognise!
  - Poor instruments
  - Random biopsies
    - Sampling errors
- Histology - interobserver variation
- Dysplasia vs inflammatory changes
  - Adequate PPI Rx
Improved imaging

Conventional WLE

Lugol’s

Conventional WLE

Methylene blue
Fluorescence imaging - real-time fluorescence imaging prototypes

Autofluorescence imaging of Barrett’s oesophagus with Xillix LIFE-GI fiberendoscopic system - sites of HGD (brick red fluorescence (A)) seen amidst a green/cyan background of non-dysplastic Barrett’s (B)
Confocal endomicroscopy: confocal miniprobes

Endomicroscopic characteristics of intestinal metaplasia (without dysplasia) & fundic glands
Regular glands & goblet cells

Boyер, Michalak, O’Toole - CHU Angers (France)
Mauna Kea Technologies
Flexible spectral Imaging Colour Enhancement (FICE)

Narrow Band Imaging

... Reconstruct spectral images decomposed from ordinary endoscopic images with free selection of three wavelengths, and can provide non-magnified images with high light intensity ...
Imaging (3 rules)

1. Use best endoscope

2. « You do not detect what you see; you detect what you recognise »
   - Up to 80% sent for work-up with HGD/IMC will have visible lesions by experts

3. Perform a systematic inspection
   “LOOK more and biopsy less”
Endotherapy for Barrett’s-related neoplasia

- **Endoscopic resection**
  - **Sequential endoscopic mucosal resection (EMR)**
    - High morbidity $^1$
      - 88% stenoses
      - 23% bleeds
      - 4% perforations
    - Endoscopic submucosal dissection

- **Thermal ablative techniques**
  - APC
  - Radiofrequency ablation

- **Photodynamic therapy**
  - 50% eradication rates and high morbidity $^2$

- **Cryoablation**

1 Van Vilsteren Gut 2011
2 Overholt Gastrointest Endosc 2005:488
Two situations with dysplasia

Smooth HGD

HGD with nodules
Visible lesions in Barrett’s

• Visible lesions harbour more advanced changes
  – Resection of focal abnormalities
  • Alters management in 49% of patients
  • Rules out submucosal cancers (requiring surgery)
• EMR recommended
  – All visible dysplastic lesions in Barrett’s
  – Staging and/or therapeutic

1 Peters Gastrointest Endosc 2008:604
2 AGA position statement 2011:1084
3 BSG Recommendations 2013
### Paris classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Lesion type</th>
<th>n</th>
<th>Sm, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-I</td>
<td>Protruding or polypoid</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>0-IIa</td>
<td>Slightly elevated</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>0-IIb</td>
<td>Flat</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>0-IIc</td>
<td>Slightly depressed</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>0-III</td>
<td>Ulcerated</td>
<td>0</td>
<td>-- *</td>
</tr>
<tr>
<td>Combinations 0-IIa/IIb 0-IIa/IIc</td>
<td>76</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

* Up to 80% sm involvement
Endoscopic mucosal resection - EMR

Diagnostic & therapeutic
Staging EMR changes therapy

17% of patients up-staged to surgery

Evolving changes in the management of early oesophageal adenocarcinoma in a tertiary centre
Once remaining mucosa is featureless ...

How do we eradicate the smooth Barrett’s epithelium?
Ablation catheter (sizes 22, 25, 28, 31, 34 mm) used to deliver ablative energy to targeted portion of the esophagus (60 electrode rings encircling the balloon)
Barrett's

Post RFA

12 months

< 1 sec, circumferentially & standardized energy

Controlled depth
44 yo man, multifocal HGD & a visible nodule
Histopathology

- Moderately differentiated adenocarcinoma with prominent mucin production
- Mucosal only
- Margins clear, including submucosa
After one 360 RFA and HALO-90
Monocentre cohort (St James’s’s Hospital)

- 2009 – 2014
  - 106
    - Male: 82 (77%)
    - Female: 24 (23%)
  - Mean age at diagnosis: 61.72
- Median length of Barrett's oesophagus: 4 cm
Highest level of Vienna Grade prior to treatment of HALO

<table>
<thead>
<tr>
<th>Dysplasia grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade dysplasia / intramucosal cancer</td>
<td>88  (83.0%)</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>2   (1.9%)</td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>16  (15.1%)</td>
</tr>
</tbody>
</table>
EMRs for visible lesions

Total EMRs performed
- 73 patients / 80 EMRs
  - Pre treatment RFA: 52 patients (57 EMRs)
  - During endotherapy: 21 patients (23 EMRs)
Vienna grade of EMR specimens progressing to endotherapy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pre RFA N = 52</th>
<th>During and Post RFA N = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>No SIM</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>No Dysplasia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Indefinite for Dysplasia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Low Grade Dysplasia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>High Grade Dysplasia/IMC</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Invasive Carcinoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>23</td>
</tr>
</tbody>
</table>

Up to 20% of patients undergoing EMR are staged >Tsm1 and undergo surgery
Radiofrequency ablation

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>106</td>
</tr>
<tr>
<td>- male</td>
<td>82 (77%)</td>
</tr>
<tr>
<td>- female</td>
<td>24 (23%)</td>
</tr>
<tr>
<td>RFA sessions</td>
<td>280</td>
</tr>
<tr>
<td>HALO 360</td>
<td>83</td>
</tr>
<tr>
<td>HALO 90</td>
<td>197</td>
</tr>
<tr>
<td>Average number of sessions per patient</td>
<td>2.6</td>
</tr>
</tbody>
</table>

HALO-90 alone: 38 patients
Efficacy

• Patients with HGIN
  – Completed endoscopic therapy, 65
  – Failed therapy, 4
  – Ongoing, 21

• Patients with LGIN
  – Completed, 6
  – Ongoing, 8
  – Failures, 2

CR neoplasia: 94%
CR SIM: 90%
Complications

• Post EMR bleeding, n=3
  – Controlled by haemoclip
    • 1 required transfusion
    • 2 hospitalisations

• Post EMR/RFA stenosis, 2
  – Both requiring dilatation

• Post RFA stenosis, 1
  – Required single dilatation
## Failures - surgery

<table>
<thead>
<tr>
<th></th>
<th>RFA</th>
<th>At follow-up</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>No 1</td>
<td>3</td>
<td>pT1m3 at EMR</td>
<td>IMC (3 mm)</td>
</tr>
<tr>
<td>No 2</td>
<td>3</td>
<td>Focal invasive adenocarcinoma in ulcer</td>
<td>LGD and SIM</td>
</tr>
<tr>
<td>No 3</td>
<td>1</td>
<td>Staging EMR – pT1sm</td>
<td>pT1m3</td>
</tr>
<tr>
<td>No 4</td>
<td>4</td>
<td>Multifocal HGD (Oesophagitis +++</td>
<td>HGD</td>
</tr>
</tbody>
</table>

2 in LGD group (SURF trial) – rebellious oesophagus and persistent LGD
Treated with fundoplication - regressing
Prospective multicenter registry from 19 UK centers

- **575 patients**: 77% with HGD & 23% with intramucosal cancer
- **69 years with 81% male**
  - Ablations mean: 2.5
  - Barrett’s length: 5.8 cm (1-20)
- **CR-D: 81%; CR-BE 62%**
- **Factors influencing response**
  - Length of Barrett’s
  - Numbers of RFA sessions
- **Cancer progression: 3%**
- **Complication**
  - Perforation: 1 (> 850 ablations)
  - Symptomatic strictures: 9%
- **Durability**
  - 94% remaining free of disease at (median f/u 19months)
Evolving changes in the management of early oesophageal adenocarcinoma in a tertiary centre

N. J. O’Farrell · J. V. Reynolds · N. Ravi · J. O. Larkin · V. Malik · G. F. Wilson · C. Muldoon · D. O’Toole
Low grade dysplasia (SURF-trial)

Table 2. Primary and Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>Ablation Group (n = 68)</th>
<th>Control Group (n = 68)</th>
<th>Risk Difference, % (95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to high-grade dysplasia or cancer</td>
<td>1 (1.5)</td>
<td>18 (26.5)</td>
<td>25.0 (14.1-35.9)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Progression to cancer</td>
<td>1 (1.5)</td>
<td>6 (8.8)</td>
<td>7.4 (0.0-14.7)</td>
<td>.03*</td>
</tr>
<tr>
<td>Complete eradication of dysplasia at the end of endoscopic treatment</td>
<td>63/68 (92.6)%</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Complete eradication of IM at the end of endoscopic treatment</td>
<td>60/68 (88.2)%</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Complete eradication of dysplasia during follow-up, No. of events/total patients (%) ²</td>
<td>62/63 (98.4)%</td>
<td>19/68 (27.9)</td>
<td>70.5 (59.4-81.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Complete eradication of IM during follow-up, No. of events/total patients (%) ²</td>
<td>54/60 (90.0)%</td>
<td>0/68 (0.0)</td>
<td>90.0 (82.4-97.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Figure 3. Occurrence of Progression to High-Grade Dysplasia or Adenocarcinoma
NICE – UK 2014 *

LGD – confirmed at 2 endoscopies by 2 pathologists, patients offered ablation therapy after MDT review (Grade A)

* www.nice.org.uk
Sponge-TFF3 biomarkers from primary care

‘Cytosponge’ compressed inside a gelatin pill capsule on a string, which is swallowed and dissolved before the expanded sponge is pulled back up to retrieve a cell sample.

- Sensitivity of around 80% for diagnosing BE
- Sensitivity increases with BE segment length
- Not compromised in the presence of dysplasia
- Specificity of 92%
Cytosponge method of detecting Barrett’s in GORD suffers (50 yo males)
Summary ...

- Problems with screening & surveillance
  - Cancer prevention, errors, cost effectiveness …
- Predicting which lesions progress to cancer
  - Patient/tumour characteristics and biomarkers
- Improved therapy methods
  - Combining resections (EMRs and ESD) with RFA, is safe and durable
- Patients, physicians, & insurance companies
  - Intuitively logical to remove precursor?
    - CR maintained over time?
    - Quality of life and costs vs surveillance strategy?
    - Stratification index predicting disease progression or response to therapy?
Conclusions

• Experience in dedicated Barrett’s Centre
  – Establish a Barrett’s registry and data set
    • Improves understanding of local population
    • Contributing to International research collaboration's to “risk stratify”

• Endoscopic therapy for early cancer in an Irish cohort of patients
  – 70% require EMR as 1st-line
  – Eradication rates similar to published data
    • > 90% for dysplasia
    • Low failure rates
  – Prospective f/u over longer period necessary
    • Ensure maintained responses
Thanks ...

C Muldoon, N Ravi & JV Reynolds

Barrett’s

Clinical collaborators
- Endoscopy & Pathology
- Endoscopic staff
- UK collaborators
- AMC Amsterdam

Research groups
- J O’Sullivan
- G Pidgeon
- A Long

REGISTRY - MP O’Brien
All data managers & teams

C.R.O.S.S. Supporting Cancer Research at St. James’s Hospital