Oesophagus and Stomach update
dysplasia and early cancer

Dr Tim Bracey  STR teaching 13/4/16
Please check pathkids.com for previous talks
Executive Summary

Patient experience, as defined by outcomes and satisfaction levels, is high at the Centre.

A total of 129 patients have undergone surgical resection in the last 12 months at the surgical centre. There were 94 oesophagectomy and 35 gastrectomy procedures performed, with in-hospital mortality rates of 1.1% and 5.7% respectively – 2.3% overall.

The National Oesophago-gastric Cancer Audit 2010 describes in detail the findings of the first national audit of oesophago-gastric cancer care in England and Wales, and provides useful benchmark data. The overall post-operative in-hospital mortality for 3,612 oesophageal and gastric resections from this audit was 5.1% in England and Wales. For the 2,200 oesophageal and 1,412 gastric resections nationally it was 4.5% and 6.0% respectively.

• One of the biggest units in the country (100 major resections per annum. 6 OG surgeons, 1 pathologist!)
• All biopsies of suspected OG cancers/HG dysplasia from 5 hospitals reviewed with radiology /clinical / endoscopic findings
Local OG workload

Last audit (2014-2015) showed 524 cases received from Outside PHNT, almost doubled since 2013, with >10% dysplasia cases for review (more difficult than cancer!)
Types of Barrett’s oesophagus

- Long segment
- Short segment
- Ultra short segment
Types of Barrett’s oesophagus

- Long segment
- Short segment
- Ultra short segment
- Intestinal metaplasia at the cardia

OGJ

3cm
1cm
The Development and Validation of an Endoscopic Grading System for Barrett’s Esophagus: The Prague C & M Criteria

Distance (cm) from GEJ

Maximal extent of metaplasia:
M = 5.0 cm

Circumferential extent of metaplasia:
C = 2.0 cm

True position of GEJ:
Origin = 0.0 cm

Figure 4. Video still of endoscopic Barrett’s esophagus showing an area classified as C2M5. C: extent of circumferential metaplasia; M: maximal extent of the metaplasia (C plus a distal “tongue” of 3 cm).
Definite Barrett’s (UK and USA!)
“A diagnosis of BE should not require demonstration of goblet cells in mucosal biopsies”
Barrett’s oesophagus is considered any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium (>1cm) above OGJ → No need for intestinal metaplasia.

Endoscopic report should include length of Barrett’s using the Prague criteria.

Short segments of columnar epithelium (<3cm) with no intestinal metaplasia and no native oesophageal structures should be regarded as equivocal for a diagnosis of Barrett’s oesophagus.

All cases of suspected dysplasia / indefinite for dysplasia should be reviewed by a second pathologist with a specialist GI interest.

p53 immunostaining to the histopathological assessment may improve the diagnostic reproducibility of a diagnosis of dysplasia.
Guidelines on the Diagnosis and Management of Barrett's Oesophagus

Fitzgerald RC, di Pietro M, Ragunath K et al.

Abstract

These guidelines provide a practical and evidence-based resource for the management of patients with Barrett's oesophagus and related early neoplasia. The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument was followed to provide a methodological strategy for the guideline development. A systematic review of the literature was performed for English language articles published up until December 2012.

Guidelines on the Diagnosis and Management of Barrett's Oesophagus - An Update

Tony Tham, Secretary BSG Clinical Services and Standards Committee

This is an update to the management of low grade dysplasia in the recent BSG guidelines on Barrett's oesophagus. The new recommendation is that patients with LGD should have a repeat endoscopy in 6 months time. If LGD is found in any of the follow up OGDs and is confirmed by an expert GI pathologist, the patient should be offered endoscopic ablation therapy after review by the specialist MDT. If ablation is not undertaken, 6-monthly surveillance is recommended. For the full text of the update, please go to the link below:

Guidelines on the Diagnosis and Management of Barrett's Oesophagus - 2015 Update
Barrett’s oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel

Lucas C Duits, K Nadine Phoa, Wouter L Curvers, Fiebo J W ten Kate, Gerrit A Meijer, Cees A Seldenrijk, G Johan Offerhaus, Mike Visser, Sybren L Meijer, Kausilia K Krishnadath, Jan G P Tijssen, Rosalie C Mallant-Hent, Jacques J G H M Bergman

ABSTRACT

Objective Reported malignant progression rates for low-grade dysplasia (LGD) in Barrett’s oesophagus (BO) vary widely. Expert histological review of LGD is advised, but limited data are available on its clinical value. This retrospective cohort study aimed to determine the value of an expert pathology panel organised in the Dutch Barrett’s Advisory Committee (BAC) by investigating the incidence rates of high-grade dysplasia (HGD) and oesophageal adenocarcinoma (OAC) after expert

• Only a quarter of LGD is confirmed at specialist center
• Confirmed cases have 9.1% risk of progression in 3yrs
• ND and IFD have 0.6% and 0.9% progression rate
Types of dysplasia in Barrett’s oesophagus

- Adenomatous type
- Gastric foveolar type.
- Crypt dysplasia.
- Mixed
- ?Gastric pyloric type

Grading of gastric foveolar-type dysplasia in Barrett's esophagus.

*Gastric/foveolar type dysplasia has no requirement for intestinal metaplasia!!*
Indefinite for dysplasia
PPI increased
Repeat biopsy 6/12
No dysplasia
Indefinite for dysplasia

- Doesn’t mean we are indecisive!
- It is a holding category and the reasons for using it should be stated in the report
- Favour reactive or suspect dysplasia?
- Inflammation or technical (eg. Small bx)
- “optimisation of acid suppression and repeat biopsy is recommended”
Figure 6 Barrett esophagus, indefinite for dysplasia. Notice some nuclear stratification, enlargement, and some prominent nucleoli in association with intraepithelial neutrophils. While some might report these as reactive changes, others would prefer a diagnosis of indefinite for dysplasia with repeat biopsy after inflammation has subsided.
<table>
<thead>
<tr>
<th>Path 1</th>
<th>A1</th>
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<th>B1</th>
<th>B2</th>
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Sharp cutoff / abrupt transition favours dysplasia
Specific areas of difficulty

- Small biopsies, poor quality H&Es (IFD,L’s)
- Acute inflammation
- Juxtaposition of intestinal and gastric type glands
- Squamo-columnar junction
- Stromal invasion
Acute inflammation
Juxtaposition of intestinalised and non-intestinalised glands.
Look for surface maturation
Stroma in non-dysplastic Barrett’s
Markers in the diagnosis of Barrett’s dysplasia

Are there any fancy stains that help?
Colitis-associated colon cancer

Sporadic adenoma

Barrett's
Colitis-associated colon cancer

Sporadic adenoma

Barrett's
p53

- Significant staining pattern
- Strong staining
- Absent staining pattern
- Significant p53 staining in area of interest correlates with likely disease progression

This is normal
This is normal
If only it were always this easy (LGD)
If only it were always this easy (LGD + p53)
Remember (complete) loss of p53 expression also correlates with neoplasia
Figure 7 Barrett esophagus with low-grade dysplasia. There is superficial mucin loss with nuclear stratification, enlargement, and hyperchromasia without significant acute inflammation. The tinctorial quality of superficial and basally-located epithelium is similar.
High grade dysplasia

- Easier to diagnose for the generalist but still some difficulties
- If there is a nodule then distinction from low grade dysplasia on a bx is academic
- Even flat HGD now ablated with RFA
- *I am particularly interested in features which reliably predict invasion on a subsequent excision specimen, and particularly those that may predict risk of (LN) metastasis*
Figure 8 Barrett esophagus with high-grade dysplasia. Nuclei are large and irregular with dark, smudged nuclear chromatin pattern. Some loss of nuclear polarity can be appreciated at this magnification (arrow). Glandular crowding is more striking than in low-grade dysplasia and some glands exhibit irregular shapes.
Name two “textbook worthy” histological features of invasive adenocarcinoma on a mucosal biopsy.
A Histologically Defined Subset of High-Grade Dysplasia in Barrett Mucosa Is Predictive of Associated Carcinoma

Weijian Zhu, MD,¹ Henry D. Appelman, MD,¹ Joel K. Greenson, MD,¹ Stephen R. Ramsburgh, MD,¹ Mark B. Orringer, MD,² Andrew C. Chang, MD,² and Barbara J. McKenna, MD¹

Key Words: Barrett esophagus; High-grade dysplasia; Esophageal adenocarcinoma; Dysplasia; Esophagectomy; Biopsy

Patients with Barrett esophagus whose biopsies reveal HGD with none of the additional high-risk histologic features have a low risk of concurrent unrecognized carcinoma (5%) and may be good candidates for conservative management, including continued surveillance. On the other hand, 1 or more high-risk histologic features indicate a high likelihood of concurrent carcinoma, and this risk should be considered in weighing the operative and endoscopic therapeutic options.

From the Departments of ¹Pathology and ²Surgery, Section of Cardiothoracic Surgery, University of Michigan, Ann Arbor.

Address reprint requests to Dr McKenna: Dept of Pathology, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0054.
Image 7: Invasive adenocarcinoma. Individual cells infiltrate the stroma adjacent to neoplastic tubules, indicating adenocarcinoma invading the lamina propria (H&E, x100).
Single cell / signet ring infiltration of lamina propria demonstrated with MNF116 immuno. Older pathologists will tell you mucin stain is best (but they are wrong)
Image 8: Invasive adenocarcinoma. Carcinomatous tubules are invested by a desmoplastic stromal reaction that appears pale owing to abundant extracellular ground substance (H&E, ×200).

*submucosal invasion (± arterioles)*
But note that dysplastic glands in submucosa doesn’t always signify invasion.
Do you know any “softer” histological features that might make you suspicious of invasion in HGD?
1. Surface ulceration*

* may not be reliable in exophytic lesions

Image 3: Barrett mucosa with high-grade dysplasia with features suggestive of carcinoma. Superficial ulcer marked by the presence of fibrinopurulent exudate adherent to the surface (H&E, ×200).
2. Extensive cribriform / solid pattern

**Image 2** Barrett mucosa with high-grade dysplasia with features suggestive of carcinoma. Cribriform architecture characterized by solid nests of dysplastic cells with multiple secondary lumens (H&E, ×200).
Image 4: Barrett mucosa with high-grade dysplasia with features suggestive of carcinoma. Dilated dysplastic tubules containing granular eosinophilic and nuclear debris (H&E, ×200).

3. At least 3 dilated dysplastic tubules per biopsy
4. Extensive neutrophils – not useful in my experience

- **Image 5** Barrett mucosa with high-grade dysplasia with features suggestive of carcinoma. Infiltration by numerous polymorphonuclear neutrophils (H&E, ×200).
5. Pagetoid infiltration of squamous epithelium – strongly predictive of invasion

**Image 6** Barrett mucosa with high-grade dysplasia with features suggestive of carcinoma. Dysplastic tubules appear to extend upward and be incorporated into benign squamous epithelium (H&E, ×200).
5. Pagetoid infiltration of squamous epithelium – strongly predictive of invasion
CK 5 (brown) &
CAM5.2 (red)
### Classification schemes for evaluating dysplasia and invasive adenocarcinoma in the upper gastrointestinal tract

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Vienna classification</th>
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<td>Negative for dysplasia</td>
<td>1. Negative for dysplasia</td>
</tr>
<tr>
<td>Indefinite for dysplasia</td>
<td>2. Indefinite for dysplasia</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>3. Non-invasive, low grade dysplasia</td>
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<tr>
<td>High-grade dysplasia</td>
<td>4. Non-invasive neoplasia</td>
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<tr>
<td></td>
<td>4.1 High-grade dysplasia</td>
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<td>4.2 Non-invasive carcinoma</td>
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<td></td>
<td>4.3 Suspicious for invasive carcinoma</td>
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<tr>
<td>Invasive adenocarcinoma*</td>
<td>5. Invasive neoplasia</td>
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<tr>
<td></td>
<td>5.1 Intramucosal carcinoma</td>
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<tr>
<td></td>
<td>5.2 At least submucosal carcinoma</td>
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</tbody>
</table>

High grade dysplasia (suspicious)  
At least intramucosal adenocarcinoma

* Includes intramucosal carcinoma.
EMR (endoscopic “mucosal” resection)
What is the implication of diagnosing submucosal invasion in EMR?
Submucosal (pT1b) invasion predicts LN metastasis
Significance of the Depth of Tumor Invasion and Lymph Node Metastasis in Superficially Invasive (T1) Esophageal Adenocarcinoma


T1a – lamina propria. T1b – muscularis mucosae. T1c – superficial submucosa. T1d – deep submucosa.
Endoscopic mucosal resection (EMR)

- Usually diathermy artefact – no need to ink.
- Often multiple with dysplasia at circumferential margins.
- Orientation and exact site usually lost.
- Diagnostic, therapeutic and “debulking” procedure!
Endoscopic mucosal resection (EMR) +
Endoscopic submucosal dissection (ESD)

- Ideally pin out on cork board
- Fix in >3x volume of formalin
Endoscopic mucosal resection (EMR)

- Resection not a biopsy.
- Treat like a cervical cone (do NOT bisect!).
- If received orientated – ink margins.

4 – 15mm
Endoscopic mucosal resection (EMR)

- Ends in one cassette
Ideally only 2 sections a cassette to optimise orientation
Endoscopic mucosal resection (EMR)

- Diagnosis of dysplasia/IMC/invasive.
- Stage lesion.
- Circumferential margins.
- Deep resection margin.
Sectioning/fixation artefact
Sectioning/fixation artefact
Where / if possible do not report pT staging and invasion on ends!
Intramucosal adenocarcinoma

- Poor agreement between histopathologists.
- Clinicians keen to separate HGD from IMA.
- Need for criteria for well/moderately differentiated lesions.
- Consensus - architectural change with horizontal rather than vertical orientation of glands.
Beware dilated bland glands – usually (at least) IMA!
Early oesophageal adenocarcinoma often lacks a desmoplastic stroma –
→ Pattern of infiltration / low power view important (Cytokeratin).
What staging systems do you know for measuring depth of invasion in early GI cancer?
Staging of submucosal disease

- Oesophagectomy specimens:
  - SM1 upper 1/3
  - SM2 middle 1/3
  - SM3 lower 1/3

- EMRs
  - SM1 < 500 um
  - SM2 > 500 - 1000 um
  - SM3 > 1000 um
Staging of EMRs

pT1a (Shimada 2006)

• M1 – Limited to the epithelial layer (HGD / IMC).
• M2 – Invades the lamina propria.
• M3 – Invades into but not through the muscularis mucosa.

pT1b (modified Kikuchi)

• SM1 – Infiltrates submucosa <500 microns.
• SM2 – Infiltrates submucosa <1000 microns.
• SM3 – Infiltrates submucosa ≥1000 microns.
Double muscularis mucosae in Barrett’s Esophagus

Double muscularis mucosae in 87.5% Barrett’s patients!!

What immunostains can make our life easier reporting EMRs?
Use of desmin staining in staging EMRs

- Stage lesion.
- Measure depth of invasion beyond muscularis mucosae.
- Desmin staining can be very helpful in delineating the lower border of the muscularis mucosae.
Desmin staining
0.8mm invasion beyond muscularis mucosae → pT1b, SM2
Simple proforma – RCPath dataset pending

OESOPHAGUS AND STOMACH ENDOSCOPIC RESECTIONS (eg. EMR)

CLINICAL / ENDOSCOPIC DETAILS PROVIDED:
<< . See also attached endoscopy form >>

GROSS DESCRIPTION:
Number of specimens: << >>
Dimensions: << >>
Pinned out?: <<yes/no>>

HISTOLOGY:
Dysplasia present?: <<IFD, low grade / high grade / no dysplasia or other pathology to explain endoscopic lesion>>
Carcinoma present: <<yes / no>> ;
Grade: <<differentiated / undifferentiated >>;
Submucosal invasion if yes give depth below deepest visible muscularis: <<yes / no .... note large vessels and submucosal glands >>
Lymphovascular space invasion: <<yes / no / equivocal>>
Distance in mm to deep margin: << >>mm
If carcinoma present, TNM7 pathological stage: <<pT1a / pT1b>>. <<SM1, SM2, SM3>>

COMMENTS/DESCRIPTION:
<< >>
If dysplasia/neoplasia present, diagnosis agreed with Dr << >>
Measuring depth and width of invasion: Japanese methodology

Assessment of depth of invasion (if completely excised)
- direct measurement from muscularis mucosae
  - depth > 2mm: 20% nodal +ve (vs. 5%)
  - width of invasive front > 4mm: 20% nodal +ve (vs 4%)

Simple?
This ppt will be on pathkids.com with all the others!

Please don’t re-publish my slides anywhere online as many of them belong to Marco Novelli at UCH but I have used them with his permission!
---Edelleenlähettely viesti---

Lähettely: Re: reprint request!
Päivitys: Tue, 19 Apr 2016 10:02:50 +0000
Vastaanottaja: Dr Tim Bracey <timbracey@doctors.net.uk>

Pekka Laurén is my grandfather. I forwarded this mail to my father who promised to ask Pekka about the matter, maybe he still has a copy somewhere. This could, however, take at least a few days.

From: timbracey@gmail.com <timbracey@gmail.com> on behalf of Dr Tim Bracey <timbracey@doctors.net.uk>
Sent: Tuesday, April 19, 2016 11:47 AM
To: [redacted]
Subject: reprint request!

Dear all,

Apologies for emailing you because you have similar names but I am desperately searching for the original Pekka Laurén 1965 publication about the two types of gastric cancer. I can only find this open access commentary which is not the original article. Even the UCH library does not have it so I wondered if someone in your library may be able to email me a pdf?

http://garfield.library.upenn.edu/classics1993/A1993LQ46500001.pdf

Many thanks in advance

Dr Tim Bracey
Consultant Pathologist
Derriford Hospital
[redacted] (office)
[redacted] (giffag mobile)

THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA

An Attempt at a Histoclinical Classification

By

PEKKA LAURÉN

Received 19.4.65

The Department of Pathological Anatomy, University of Turku, Turku, Finland,
(Head: Prof. Osmo Jarvi, M.D.)

THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA

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The histological classification of gastric carcinomas is difficult as these tumours appear to be very varying structurally. This has led to considerable confusion in the histological terminology of gastric cancer. Moreover, the descriptive histological types such as adenocarcinoma, papillary, solid, sessile and colloid carcinomas appear to show a fairly poor correlation with the other features of the disease. The significance of histological classification was denied completely by Stout (1953) and Ackerman & del Rey (1962) who advanced the view that the histological structure of gastric carcinoma shows arbitrary differences in the various parts of the tumour. But the necessity of defining the histological basic types associated with the other features of gastric carcinomas has also been emphasized (Schilling 1941, Hamperl 1956, conclusions of the Symposium on the Geographical Pathology of Gastro-intestinal Cancer 1961).

As gastric carcinomas obviously may be preceded by different pathological changes in the mucosa, and as the gastric mucosa is composed of many different cell types, there is reason to assume that the group of gastric carcinomas also includes forms with specific structural differences. In their study of this point Järvi & Laurén (1955) established that the histological structure of gastric carcinomas often displays features characteristic of intestinal mucosa and claimed that in at least 30 per cent of the cases gastric carcinomas arise from intestinal metaplasia in the stomach. On the basis of corresponding observations (Mulliegon & Rembin 1954, Morson 1955, 1956, Wattenberg 1959, Henschke 1960) the name "intestinal-type gastric carcinoma" has become increasingly used in the literature.

The present study—a preliminary report of the results has been