Current issues in Barrett’s oesophagus and the oesophago-gastric junction

Professor Neil A Shepherd
Gloucester & Cheltenham, UK

Histopathology Regional Teaching
Bristol
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The changing role of the pathologist in the management of Barrett’s oesophagus

Suzanne A Hopcroft & Neil A Shepherd

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Published October 2014
Nomenclature and definitions of Barrett’s oesophagus and OGJ diseases

• What do we call it?

USA: Barrett’s esophagus (BE)
Europe: Columnar epithelium-lined lower oesophagus (CELLO)
UK: not BO but columnar-lined oesophagus (CLO)

• Definitions:

Traditional/classical CLO (CLO) arbitrary 3 cms (sometimes 2)
Short segment CLO (SSCLO) from short tongues to < 3 cms
Ultrashort segment CLO (USSCLO) IM in the cardia, cardia IM (CIM)
## Prevalence of reflux and CLO in the West

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult heartburn</td>
<td>22-39%</td>
</tr>
<tr>
<td>GORD (reflux disease)</td>
<td>10-12%</td>
</tr>
<tr>
<td>CLO at endoscopy</td>
<td>0.5-2%</td>
</tr>
<tr>
<td>SSCLO at endoscopy</td>
<td>8-17%</td>
</tr>
<tr>
<td>USSCLO at endoscopy</td>
<td>15-32%</td>
</tr>
<tr>
<td>CLO at autopsy</td>
<td>5%</td>
</tr>
</tbody>
</table>
- How many pizzas do you want?

- How many pizzas do you have??
The OGJ and the gastric cardia – controversy personified
The gastric cardia: does it exist?

- studies of perinatal and paediatric subjects
- no history of GORD/Barrett's oesophagus
- these papers showed that the cardia is a normal structure (although it is small)

*Kilgore et al, Am J Gastroenterol 2000*
*de Hertogh et al, Gut 2003*
The gastric cardia - for definite

- it exists as a normal structure
- it's very short (mm, not cm)
- often a transitional mucosa with admixture of cardiac and fundic glands
- is it gastric or is it oesophageal?
What is carditis?

- acute inflammatory cells
- chronic inflammatory cells
- regenerative epithelial changes

**Definition:**
An expansion of the lamina propria by chronic inflammatory cells with or without acute inflammatory cells and regenerative epithelial changes
Carditis: roles of GORD & *H pylori*

<table>
<thead>
<tr>
<th></th>
<th>GORD</th>
<th>HP</th>
</tr>
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<tbody>
<tr>
<td>Öberg</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Genta</td>
<td>N/A</td>
<td>+</td>
</tr>
<tr>
<td>Goldblum</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Wang</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hackelsberger</td>
<td>N/A</td>
<td>+</td>
</tr>
</tbody>
</table>
Time to speculate......
The gastric cardia and carditis – definite and less definite

- the cardia exists as a normal structure
- it's very short (mm, not cm)
- often a transitional mucosa with admixture of cardiac and fundic glands
- carditis in the upper stomach is strongly related to HP infection
- the cardia is a gastric anatomic structure but may also be metaplastic in the lower oesophagus
- here it is usually inflamed (96% in Oberg’s study)
- GORD and HP infection may both have a role in its genesis and that of carditis here
IM at the cardia/cardia IM/ultrashort segment
Barrett’s oesophagus

Do not let them biopsy the endoscopically normal OGJ. In 16-32% of cases, you will show cardia IM and we have no idea of its significance or management

RCPath guidelines, 2002
Riddell & Odze, 2009
Cancers close to or at the GOJ
Cardia IM/ IM at the cardia/CIM

- This is a gastric disease: IM in the cardia

- It is not Barrett’s oesophagus (although pathologists will say it is if clinicians/endoscopists don’t give them the right information)

- The evidence is now weighted towards the thesis that this is primarily related to gastric HP infection

- It remains uncertain how important GORD is in its genesis

- It is much commoner than classical and short segment Barrett’s oesophagus: 16-30% of an endoscopic population in the West

- It is by definition a pathological diagnosis: the demonstration of IM (with or without inflammation) in cardiac mucosa below a normally positioned SCJ/OGJ
Cardia IM/ IM at the cardia/CIM

- we have no idea, currently, of its significance and neoplastic potential

- it is now a national and international recommendation that this disease is NOT diagnosed outside the research setting

- please don’t let them biopsy the endoscopically normal OGJ (unless for research)........
The changing role of pathology in the management of Barrett’s oesophagus

- diagnosis

- the effects of treatment

- the management of neoplasia
The changing role of pathology in the management of Barrett’s oesophagus

- diagnosis: a short history
- the effects of treatment
- the management of neoplasia
Norman ‘Pasty’ Barrett
Consultant Surgeon
St Thomas Hospital
London, UK

Barrett NR.
Chronic peptic ulcer of the oesophagus and “oesophagitis”.
*Br J Surg* 1950; **38**: 175-182.
1950  congenitally short oesophagus

1970s  true glandular metaplasia due to reflux of gastric contents:
       ACID and OTHER PEPTIC CONTENTS

1990s  reflux of duodenal contents:
       BILE and ALKALI
recognition of intestinal metaplasia in CLO

*Bosher LH, Taylor FH; 1951*

first description of association of Barrett’s oesophagus with adenocarcinoma

*Morson BC, Belcher JR; 1952*
• recognition of the three phenotypes of Barrett’s oesophagus

• cardiac, fundic & intestinal

Paull et al, 1976
The history of the goblet cell story........
Some time in the late 1980s

- intestinal metaplasia/goblet cells became enshrined in the definition of CLO and its/their demonstration was required for the diagnosis

- ?? introduced by US physicians who did not understand the subtleties of pathological assessment, sampling and correlation with endoscopy

• The goblet cell question

• should Barrett’s be defined/diagnosed by showing intestinal metaplasia/goblet cells on biopsy?
although CLO may be diagnosed with reasonable accuracy either by endoscopic appearance, histological corroboration of endoscopically visible columnarisation results in highest diagnostic accuracy.

no requirement for the demonstration of goblet cells/IM

Watson, Heading & Shepherd, 2005
why no requirement for the demonstration of goblet cells/IM?

- all long segment CLO shows intestinalisation somewhere

- a lack of IM in biopsies merely represents a sampling issue

Watson, Heading & Shepherd, 2005
<table>
<thead>
<tr>
<th>Terminology and diagnostic criteria of Barrett's oesophagus as recommended by various societies.</th>
</tr>
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<tbody>
<tr>
<td><strong>Endoscopy shows columnar lined oesophagus</strong></td>
</tr>
<tr>
<td>AGA — ACG</td>
</tr>
<tr>
<td>SFED</td>
</tr>
<tr>
<td>GSP</td>
</tr>
<tr>
<td>Amsterdam IG</td>
</tr>
<tr>
<td>Montreal IG</td>
</tr>
<tr>
<td>BSG</td>
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</tbody>
</table>

AGA: American Gastroenterological Association; ACG: American College of Gastroenterology; BO: Barrett’s oesophagus; SFED: Société Française d’Endoscopie Digestive; GSP: German Society of Pathology; IG: International Group; ESEM: endoscopically suspected oesophageal metaplasia; BSG: British Society of Gastroenterology; CLO: columnar lined oesophagus.

Flejou, 2008
You don’t need to see IM to get cancer


Intestinal metaplasia in Barrett’s oesophagus may be an epiphenomenon rather than a preneoplastic condition, and CDX2-positive cardiac-type epithelium is associated with minute Barrett’s tumour*

Gen Watanabe, Yoichi Ajioka, Manabu Takeuchi,¹ Alexey Annenkov, Takashi Kato, Kaori Watanabe, Yusuke Tani, Kikuo Ikegami, Yoko Yokota & Mutsumi Fukuda
Division of Molecular and Diagnostic Pathology, and ¹Division of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
The influence of the number of biopsies on the demonstration of IM in classical CLO

Harrison et al, 2007
The influence of the number of biopsies on the demonstration of IM in classical CLO

UK Barrett’s Oesophagus Registry (UKBOR) study – diagnostic biopsies of 200 patients

Mandalia & Shepherd, 2016 (in Lowes, Somarathna & Shepherd, 2017)
But.......

- goblet cells/IM still required by the AGA for the definition/diagnosis of CLO (in North America)

- “change in the distal esophageal epithelium of any length that can be recognized as columnar-type mucosa at endoscopy and confirmed to have intestinal metaplasia by biopsy of the tubular esophagus”


  **AGA Position Statement, 2011**

  **Spechler, 2012**
Then......

Riddell RH, Odze RD.  
Definition of Barrett's esophagus: time for a rethink  
- is intestinal metaplasia dead?  
- goblet cells are uncommon in pediatric patients with BE
- small percentage of adults have CLO without goblet cells
- the chances of detecting goblet cells proportional to the length of CLO
- sampling error common
- interpretation & differentiation of goblet cells vs. pseudogoblet cells difficult
- goblet cells have been shown to wax and wane over the natural history of BE
- background non-goblet epithelium in BE is biologically intestinalised
- background non-goblet epithelium in BE shows molecular abnormalities similar to the goblet cell-containing epithelium
- well-defined risk of neoplasia in patients with esophageal columnar metaplasia without goblet cells

- a diagnosis of BE should not require demonstration of goblet cells in mucosal biopsies
- don’t biopsy the normal OGJ: cardia IM is common and we don’t have any idea of its surveillance

Riddell & Odze, 2009
Intestinal differentiation in metaplastic, non-goblet columnar epithelium in the esophagus

- 89 patients with CLO

- Immunohistochemistry for markers of intestinal differentiation: MUC2, DAS-1, villin and cdx2

- Metaplastic esophageal columnar epithelium without goblet cells shows phenotypic evidence of intestinal differentiation

- Supports the theory that squamous epithelium converts initially to non-goblet columnar epithelium before goblet cell metaplasia

*Hahn HP et al. Am J Surg Pathol, 2009*
And we ain’t no good at detecting goblet cells......

- goblet cells
- pseudo-goblet cells
- blue cells


PUBLISHED ONLY IN ABSTRACT FORM
## Oesophageal/OGJ biopsies

### Inter-observer variability

<table>
<thead>
<tr>
<th>Features</th>
<th>Kappa Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goblet cells</td>
<td>0.35</td>
</tr>
<tr>
<td>Pseudo-goblet cells</td>
<td>0.10</td>
</tr>
<tr>
<td>Gland type</td>
<td>0.54</td>
</tr>
<tr>
<td>&quot;Barrett’s&quot;</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Is this intestinalisation?

H & E

ABPAS
Is this intestinalisation?

H & E

ABPAS

Gloucestershire Cellular Pathology Laboratory
AGA

American Gastroenterological Association Medical Position Statement on the Management of Barrett’s Esophagus

Definition of Barrett’s Esophagus

For the purposes of this statement, the definition of Barrett’s esophagus is 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.
ALIMENTARY TRACT

Effects of Dropping the Requirement for Goblet Cells From the Diagnosis of Barrett’s Esophagus

MARIA WESTERHOFF,* LINDSEY HOVAN,† CHRISTINE LEE,‡ and JOHN HART‡

*Department of Anatomic Pathology, University of Washington Medical Center, Seattle, Washington; and ‡Department of Pathology, University of Chicago Medical Center, Chicago, Illinois

... developed adenocarcinoma. CONCLUSIONS: Decreasing the requirement for goblet cells would increase the diagnosis of BE by 147%. Among patients with short columnar segments, subsequent endoscopy generally does not reveal goblet cells, so the columnar mucosa might represent proximal stomach. Decreasing the requirement for goblet cells would cause many patients to be inaccurately labeled as BE.
Call me cynical.......
What about the new BSG Barrett’s oesophagus management guidelines?

- In the event the new guidelines are disappointing, to the senior author of this review at least, in some of the pathology aspects.

- despite the major reservations about the usefulness of the pathological demonstration of IM, its pathological demonstration has been reintroduced in the new guidelines in defining pathological diagnostic terms, despite the sampling issues, the very poor levels of agreement in the demonstration of goblet cells/IM, even by experts, and the fact that apparently non-intestinalised epithelium is actually intestinalised anyway in immunohistochemical and molecular studies

_Fitzgerald et al, 2014_  
_Hopcroft & Shepherd, 2014_
Barrett’s oesophagus: pathological conundrum

If goblet cells are not specific, are there any specific pathological features of Barrett’s oesophagus and, if there are, which are they?
Juxtaposition of glandular mucosa to native oesophageal structures

- seen in about 10-15% of biopsy sets
- diagnostic of CLO

*Takubo et al, 1995*
Multilayered epithelium

• said to be specific to CLO and a suggestion that it is a precursor of CLO

  Glickman et al, 2001;
  Srivastava et al, 2007

• no doubt that it is seen at the ‘normal’ OGJ

  Takubo et al, 2008
Pancreatic phenotype

- more recently recognised as the fourth phenotype of CLO

- no doubt that it is also seen at the ‘normal’ OGJ

*Takubo et al, 2008*
Hybrid glands

- said to be specific to CLO

Srivastava et al, 2007
Hybrid glands
Hybrid glands in the gastric antrum
recent evidence that glands with a pyloric-type phenotype are the initial CLO metaplasia (as Riddell and Odze suggested)

and that ‘hybrid glands’ represent the evolution of intestinalisation from these gastric-type glands

proliferation in the middle of Barrett’s glands, diminishing to the surface & base
IdU dynamics demonstrate bidirectional migration, similar to gastric glands
distribution of MUC5AC, TFF1, MUC6 and TFF2 in Barrett’s mirrors pyloric glands
LGR5 mRNA is detected in the middle of Barrett’s glands suggesting a stem cell niche in this locale, similar to that in the gastric pylorus
both gastric and intestinal cell lineages within Barrett’s glands are clonal, indicating derivation from a single stem cell

The ‘cardia feet’ of CLO

Jansen et al, 2015
The Barrett’s tree

*Jansen et al, 2015*

**Left:** H&E stained section of Barrett mucosa. This is the standard 2D appearance. Note the small mucous glands at the base.

**Middle:** 3D model of this same Barrett gland. In the 3D model it becomes clear (1) that Barrett’s glands are highly branched structures and (2) that every ‘terminal’ leg/branch of the gland has a (small) cardia-type mucous base at its end (in red). These mucous bases are characteristically short.

**Right:** Based on this 3D model I created a ‘roadmap’ for this gland (like a phylogenetic tree). The y-axis is section number and the length of the branches thus corresponds to the length of every duct branch. It’s clear that, again, Barrett’s glands are highly branched and their branching increases towards the base. The red measure is shown for comparison and corresponds to the mean height of the mucous glands base.
Cardia feet or basal buds in CLO
This week’s case
Specific to CLO?

• ‘hybrid glands’, multilayered epithelium, pancreatic phenotype

• none of these are specific but they are relatively more common in CLO compared to the stomach/OGJ

• ‘specialised’ intestinal metaplasia tends to infer that the IM of CLO is specific, and perhaps pathognomonic, to that condition.

• is there any feature, whether identified by morphological, histochemical, immunohistochemical or any other methodology, that is exclusive for CLO and not seen, for instance, in IM (especially incomplete) in the stomach?
Special techniques and ‘specialised’ intestinal metaplasia

- complete IM unusual: Paneth cells rare
  Takubo et al 1995

- electron microscopy – intermediate cells, etc
  Levine et al 1989

- immunohistochemistry: villin, colonic-type phenotype
  Das et al 1994, MacLennan et al 1999

- cytokeratin immunohistochemistry
  Ormsby et al 1999 & (many) others
Cytokeratin immunohistochemistry in CLO

cytokeratin 7

cytokeratin 20
Are cytokeratin subsets useful for distinguishing CLO from IM in the stomach?

- Antonioli DA
- Das KM
- El Zimaity H
- Falk GW
- Flejou J-F
- Goldblum JR
- Goyal RK
- Graham DH
- Jankowski JAZ
- Odze RD
- Richter JE
- Riddell RH
- Spechler SJ
Specificity of ‘specialised’ epithelium of CLO

There is no phenotype, however elucidated, that demonstrates that the epithelium of Barrett’s oesophagus is specific to CLO and different to IM in the gastric mucosa.

Barrett’s mucosa is therefore identical, in phenotype, to incomplete intestinal metaplasia in the stomach.

*Jass, 2002*
The role of histology in the diagnosis of CLO: the index endoscopy

- cardia IM/USSCLO but we should not seek this

- when there is endoscopic doubt:
  - endoscopic inexperience
  - stricturing
  - ulceration
  - hiatus hernia

- if we are not requiring the demonstration of IM, if there are no entirely specific histological features of CLO (excepting juxtaposition to native structures in 10-15% of biopsies) and if the diagnosis is essentially an endoscopic one..............................

*RCPath, 2002; Riddell & Odze, 2009*
WHY BIOPSY CLASSICAL BARRETT’S OESOPHAGUS AT THE INDEX ENDOSCOPY?
The role of histology in the diagnosis of CLO: the index endoscopy

- you do see dysplasia
- one day, there will be a biomarker..
- we won’t stop them......

HGD at index endoscopy
Pathological diagnosis of CLO

- is critically dependent on the amount of information from endoscopy

- demands adequate size and number of biopsies

- should not be reliant on the demonstration of IM, not because it isn’t important but because many cases of CLO will be excluded if biopsy numbers are low

- demands a reporting strategy

*BSG Management Guidelines for Barrett’s oesophagus, 2005*  
www.bsg.org.uk
Reporting CLO

- diagnostic for CLO
- corroborative of an endoscopic diagnosis of CLO
- biopsies in keeping with, but not specific for, CLO
- no evidence of CLO

BSG Management Guidelines for Barrett’s oesophagus, 2005
www.bsg.org.uk
These biopsies show a combination of oesophageal-type squamous mucosa and glandular mucosa featuring cardiac and intestinal phenotypes. The histological features serve to corroborate the endoscopic diagnosis of Barrett's oesophagus. There is no evidence of dysplasia or malignancy.
The changing role of pathology in the management of Barrett’s oesophagus

- diagnosis

- the effects of treatment

- the management of neoplasia
CLO: assessing response to ‘treatment’

Ablation methodology: KTP laser, argon beam coagulation, photodynamic therapy, radiofrequency ablation

- all require concomitant acid suppression with PPIs
- cause squamous re-epithelialisation
- which may conceal underlying CLO mucosa - ? neoplastic risk

Biddlestone et al, 1998
CLO: assessing response to ‘treatment’

Ablation methodology: KTP laser, argon beam coagulation, photodynamic therapy, radiofrequency ablation

- may cause mimicry of dysplasia and malignancy
The changing role of pathology in the management of Barrett’s oesophagus

- diagnosis
- the effects of treatment
- the management of neoplasia
Neoplasia in Barrett’s oesophagus

- indefinite for dysplasia
- low grade dysplasia
- high grade dysplasia
- intramucosal carcinoma
- invasive adenocarcinoma

_after Riddell et al 1983_
_Reid et al 1988_
The problems of dysplasia in CLO

- often endoscopically normal
- and yet multifocal
- demands Levine/Seattle biopsy protocols
- current imaging techniques poor at diagnosing early malignancy
Long segment CLO surveillance with Seattle biopsies:
Two biopsies from each quadrant every 2 cms

40 biopsy pots
352 individual sections
Dysplasia in CLO

- HGD was associated with co-existent adenocarcinoma in 30-55% of cases (now lower – 25% quoted in 2008)

- has been an indication for oesophagectomy in management guidelines in Europe & North America

- inter-observer agreement good (amongst experts) for HGD (kappa 0.65) but LGD and indefinite have lower levels of I-O agreement

  *Reid et al 1988; Montgomery et al, 2001; Treanor et al, 2007*

- HGD diagnosis to be confirmed by two experienced pathologists

  *Loft, Alderson & Heading, 2005; Treanor et al, 2007*

- management of dysplasia should always be discussed in the Upper GI MDTM
Traditional management of CLO dysplasia

Indefinite for dysplasia
- early re-evaluation with extensive biopsies following a course of PPI.

Low grade dysplasia
- extensive biopsies after intensive acid suppression for 8-12 weeks. 6-monthly surveillance as long as disease is stable.

High grade dysplasia
- if changes persist after intensive acid suppression and HGD is confirmed by two pathologists, oesophagectomy in specialised unit recommended
- (ablative therapy for patients unfit for surgery)
- BUT THIS IS CHANGING
Recently recognised dysplasia variants in CLO

- crypt dysplasia with surface maturation
- foveolar dysplasia
- serrated dysplasia
Crypt Dysplasia With Surface Maturation
A Clinical, Pathologic, and Molecular Study of a Barrett’s Esophagus Cohort

Leslie C. Lomo, MD,* Patricia L. Blount, MD,†‡ Carissa A. Sanchez, BA,†
X. Li,† Patricia C. Galipeau, BS,† David S. Cowan, BS,† Kamran Ayub, MD,§
Peter S. Rabinovitch, MD, PhD,⊥ Brian J. Reid, MD, PhD,†‡¶
and Robert D. Odze, MD*

- 7% prevalence basal crypt dysplasia-like atypia (BCDA)

3 year surveillance period:
87% BCDA had previous or concurrent HGD/Ca
v 59% controls developed HGD/Ca
Basal crypt dysplasia in Barrett’s oesophagus

- we need more data

- some GI pathologists in the UK have evidence to support the Odze data

- in the UK, we recommend a designation of ‘mucosa indefinite for dysplasia’ and await events

- with excellent endoscopy, EMR and good ablation, you won’t go far wrong
Foveolar dysplasia

- assessment of grade of dysplasia difficult as main criteria (eg loss of nuclear polarity) are absent

- can be associated with ‘conventional’ dysplasia elsewhere

- the conventional dysplasia is usually high grade

- foveolar dysplasia is biologically high grade
What about biomarkers?

All biomarkers are currently regarded as experimental

*Riddell, 1996*

Until randomised controlled evidence is available, biomarker panels cannot yet be recommended as routine of care

*BSG management guidelines, 2014*
Newer techniques for the in-situ detection of neoplastic change in CLO

- magnification and high resolution endoscopy
- chromo-endoscopy
- auto-fluorescence endoscopy
- narrow band imaging
- microscopic tools: confocal microscopy; multiphoton microscopy
- in situ molecular analysis: FISH
- spectroscopic analysis: fluorescence spectroscopy; light scattering spectroscopy; optical coherence spectroscopy; Raman (inelastic) spectroscopy
Standard endoscopic view of CLO with HGD: no lesion identified

Gloucestershire Cellular Pathology Laboratory
Chromo-endoscopy with indigo carmine dye-spray: HGD on histology
Endoscopic mucosal resection (EMR or ER) in CLO
How is the management of neoplasia complicating CLO changing?

- more conservative about surgery (30 day mortality 5-10%)

- increasing evidence that HGD only predicts concurrent carcinoma in about 20% of cases and is no longer a definitive indication for surgery

- better endoscopy: chromo-endoscopy, auto-fluorescence endoscopy and narrow band imaging: trimodal endoscopy localises and identifies dysplastic lesions, even if flat

- EMR, ESD and much better ablative therapy

- there is a lot less surgery.....
The management of low and high grade dysplasia (and even intramucosal carcinoma) is very similar now......

Hopcroft & Shepherd, 2014
Management of neoplasia in CLO: the present and the future

- less major surgery

- trimodal endoscopy means the endoscopist spends the time and not the pathologist!!

- directed biopsies after such endoscopy and not random Seattle

- simpler pathological classifications

- fun EMRs (or ERs) for pathologists to look at

- more sensible patient-directed management
Barrett’s oesophagus and the OGJ: take home messages

- there’s more of it about & there’s a lot more cancer
- definitions are changing and the diagnosis requires pathology less
- don’t accept biopsies from the normal OGJ
- surveillance is recommended but is unproven and costly in endoscopic and pathological time
- the management of dysplasia has required laborious biopsy protocols, pathological sense, two (? expert) pathologists and MDTM discussion
- we now have the advent of smart endoscopes & clever techniques for the accurate diagnosis of CLO neoplasia
- and we have EMR to stop unnecessary surgery
REVIEW

The changing role of the pathologist in the management of Barrett’s oesophagus

Suzanne A Hopcroft & Neil A Shepherd
Gloucestershire Cellular Pathology Laboratory, Cheltenham General Hospital, Cheltenham, UK
Definition, derivation & diagnosis of Barrett’s oesophagus: pathological perspectives

H Lowes, T Somarathna & Neil A Shepherd

A chapter for ‘Stem Cells, Pre-Neoplasia & Early Cancer of the Upper GI Tract’ edited by Sir Nicholas A Wright & Marnix Jansen