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Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus

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Contents

These guidelines have been prepared by the British Society of Gastroenterology. They represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability.

Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus

A Watson, R C Heading, N A Shepherd

INTRODUCTION

Barrett's oesophagus, or columnar-lined oesophagus (CLO) as it is more appropriately known, owes its importance to being a precursor lesion of oesophageal adenocarcinoma, the incidence of which has increased threefold in the last decade and tenfold in the last three decades and currently has the most rapidly increasing incidence of any solid tumour in the western world. Major challenges include the identification of molecular markers of risk of adenocarcinoma development at an earlier stage than high grade dysplasia, the efficacy and cost-effectiveness of surveillance and the most appropriate management of CLO and high grade dysplasia. Furthermore, the fact that CLO complicates severe and long-standing gastro-oesophageal reflux disease (GORD) and the finding that GORD can predispose to adenocarcinoma, apparently without necessarily progressing through CLO, raise the question as to whether screening of patients with severe long-standing GORD is appropriate.

FORMULATION OF GUIDELINES

These guidelines were commissioned by the Clinical Services and Standards Committee of the British Society of Gastroenterology and have been produced by the Oesophageal and Pathology Sections and approved by the respective Section Committees.

A Guidelines Working Group was formed comprising members of the BSG Oesophageal Section Committee and A Watson was appointed Chairman, with RC Heading and NA Shepherd as co-editors. This working group determined the topics within the field of CLO which should be the subject of literature reviews and nominated one or two "experts" to review each area and make appropriate recommendations based on available evidence and expert opinion. Editing of successive drafts has incorporated comments from the Oesophageal and Pathology Section committees and the Clinical Services and Standards Committee

Literature searches were based on Medline, Embase, Pubmed and Cinahl searches either singly or in combination in the reviews. The strength of evidence was classified according to the North of England evidence based guidelines development project.

CATEGORIES OF EVIDENCE

Ia: Evidence obtained from meta-analysis of randomised controlled trials.

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well designed controlled study without randomisation.

IIb: Evidence obtained from at least one other type of well designed quasi-experimental study

III: Evidence obtained from well designed descriptive studies such as comparative studies, correlative studies and case studies.

IV: Evidence obtained from expert committee reports, or opinions or clinical experience of respected authorities.

GRADING OF RECOMMENDATIONS

Recommendations are based on the level of evidence presented in support and are graded accordingly.

Grade A requires at least one randomised controlled trial of good quality addressing the topic of recommendation.

Grade B requires the availability of clinical studies without randomisation on the topic of recommendation

Grade C requires evidence from category IV in the absence of directly applicable clinical studies.

BSG guidelines for the diagnosis and management of Barrett's Columnar-lined oesophagus (CLO)

Principal recommendations

DEFINITION

An appropriate definition of "Barrett's oesophagus" (more appropriately referred to as columnar-lined oesophagus[CLO]) is an oesophagus in which any portion of the normal squamous lining has been replaced by a metaplastic columnar epithelium which is visible macroscopically. In order to make a positive diagnosis of "Barrett's oesophagus", a segment of columnar metaplasia of any length must be visible endoscopically above the oesophago-gastric junction and confirmed or corroborated histologically. (Recommendation grade C).

DIAGNOSIS

Although CLO may be diagnosed with reasonable accuracy either by endoscopic appearance or histologically in the 10–15% of cases when native oesophageal structures are seen, **histological corroboration of endoscopically visible columnarisation results in highest diagnostic accuracy.** (Recommendation grade C.)

Chromoscopy does not give sufficiently accurate results consistently to justify its routine use in the diagnosis of CLO. (Recommendation grade C.)

It is vitally important for accurate diagnosis that the precise sites of biopsies taken are recorded by the endoscopist in terms of distance from the incisor teeth and relation to the oesophago-gastric junction. (Recommendation grade C.)

The following categories are appropriate for reporting diagnostic biopsies:

(i) Biopsies diagnostic for CLO.

Native oesophageal structures are present with juxtaposition to metaplastic glandular mucosa, whether intestinalised or not.

(ii) Biopsies corroborative of an endoscopic diagnosis of CLO

Intestinalised metaplastic glandular mucosa with or without non-organised arrangement, villous architecture, patchwork of different glandular types ect. This could potentially still represent incomplete intestinal metaplasia in the stomach, especially in a hiatus hernia or IM at the cardia.

(iii) Biopsies in keeping with, but not specific for CLO

Gastric type mucosa of either fundic or cardic type without IM. Patchwork appearance is still possible, as is a non-organised arrangement. Such appearances could, however, represent the OG junction or the stomach, with or without hiatal hernia**.**

(iv) Biopsies without evidence of CLO

Oesophageal type squamous mucosa with no evidence of glandular epithelium**.**

(Recommendation grade C**.**)

THE MALIGNANT RISK

Important clinical risk factors for progression to adenocarcinoma include male gender, age >45, "extended segment (>8cm) disease, duration of reflux history, early age of onset of GORD, duodeno-gastro-oesophageal reflux, mucosal damage (ulceration and stricture) and uncommonly, family history. (Recommendation grade A-C.)

Whilst in general terms, molecular markers such as expression of P53, P16 and APC and aneuploidy are not accurate predictors of malignant transformation**, they have been recommended in the confines of research studies as surrogates for adenocarcinoma risk but hard evidence is currently lacking. There are currently no verified markers of heritable risk of oesophageal adenocarcinoma.** (Recommendation grade C.)

MANAGEMENT OF NON-DYSPLASTIC CLO

CLO represents the extreme end of the pathophysiological spectrum of gastro-oesophageal reflux disease**.** There is evidence to show that the natural history of the columnarised segment, as demonstrated by stricture resolution and prevention, can be influenced by effective reflux control to justify treatment in the majority of patients. **In symptomatic patients, symptom control is an important objective of treatment but because many patients with CLO have few or no symptoms due to the relative insensitivity of columnar mucosa to acid, symptom control should not be interpreted as indicating suppression of gastro-oesophageal reflux.** (Recommendation grade B).

PPI therapy is an attractive form of treatment, particularly as CLO is largely a disease of the elderly. **However, several studies have shown that because of the extreme pathophysiological abnormalities in these patients, normalisation of acid exposure may not be achieved, even using doses of PPI up to four times the standard daily dose and when alleviation of symptoms, when present, has occurred. In the absence of a satisfactory symptomatic response and/or healing of any associated oesophagitis, dose escalation to maximal manufacturers' recommendations should be considered. If a satisfactory response is still not achieved, further assessment including pH and Bilitec monitoring (where appropriate) is recommended.** (Recommendation grade C).

The indications for fundoplication in patients with CLO are essentially the same as those in gastro-oesophageal reflux disease generally, although the high incidence of hiatal hernia, lower oesophageal sphincter failure and reflux of duodenal contents, together with the documented difficulty of normalising acid exposure even with high dose PPI therapy, results in these indications being fulfilled in a greater proportion of CLO patients than in those with mild disease. (Recommendation grade B).

Although there are suggestions in the literature that a competent fundoplication may reduce the incidence of adenocarcinoma, there is currently insufficient

evidence to recommend fundoplication on this basis. (Recommendation grade B).

Endoscopic ablation, performed in a reflux-free environment, can result in significant squamous re-epithelialization although rests of glandular metaplasia may remain beneath the neo-squamous epithelium in up to 60% of patients. The significance of these rests is unknown as is the optimal ablative technique. **Until these issues are resolved, endoscopic ablation remains experimental and should be performed only in the context of prospective randomised studies.** (Recommendation grade C).

SCREENING AND SURVEILLANCE

Chronic heartburn is a risk factor for oesophageal adenocarcinoma and the risk increases with increasing severity and duration of heartburn. However, the absolute risk in individual patients is less than 1 in 1000 per annum. **There is no evidence that endoscopic screening of heartburn patients to detect cancer is worthwhile and benefit is so unlikely that endoscopy with this intent cannot be recommended.** (Recommendation grade C).

Screening endoscopy has been advocated for chronic heartburn patients aged 50 years or more with the aim of detecting CLO, if present. However, this policy has not been shown to be of benefit. **Consequently, endoscopic screening of patients with chronic heartburn to detect CLO cannot be recommended.** (Recommendation grade C).

Neither of these recommendations about screening refutes the legitimacy of diagnostic endoscopy in the assessment of patients who have 'alarm features' such as dysphagia, weight loss or anaemia in association with chronic reflux.

Patients in whom CLO is newly diagnosed should ordinarily have the diagnosis made known to them and its implications discussed. In considering whether surveillance endoscopy should be initiated, the clinician should discuss with the patient the possible benefits of surveillance in detecting early stage tumours and improving cancer survival, explain that the efficacy of surveillance in these respects is unproven and make clear that for most patients the actual risk of death from oesophageal cancer is small. Disadvantages of endoscopic surveillance should also be discussed, including the physical and psychological morbidity, and the fact that surveillance cannot guarantee to detect every tumour that may develop. (Recommendation grade C).

Computer modelling has shown that for an adenocarcinoma incidence of 1% pa, as believed to be the case in the UK, the most effective and cost-effective surveillance interval is every 2 years. Therefore, **it is recommended that when surveillance is considered appropriate, it should be performed every 2 years.** (Recommendation grade C).

Where surveillance is practised, the emergence of endoscopic methods of treatment of high grade dysplasia, if proved effective, may negate the restriction of surveillance programmes to those patients fit to undergo oesophagectomy.

In surveillance endoscopy, quadrantic biopsies should be taken every 2cm in the columnar segment together with biopsies of any visible lesion. (Recommendation grade C). More frequent sampling might be expected to increase the yield of dysplasia when present but the most widely recommended biopsy protocol is for quadrantic biopsies at 2cm intervals. There is no evidence to support the superiority of intensive biopsy protocols using jumbo forceps.

A Markov model based on UK NHS costings estimate the cost of two yearly surveillance at £19,000 per life year saved. This appears comparable to that of other health care interventions, although some optimistic assumptions were made in the model. At present there is insufficient evidence to either promote or reject surveillance programmes in CLO on economic grounds alone. (Recommendation grade B.) It is possible that targeting surveillance to those at greatest risk of development of adenocarcinoma may be more effective and cost-effective, but studies are needed to test this hypothesis.

MANAGEMENT OF DYSPLASIA

A diagnosis of 'indefinite for dysplasia' is most often made where there are changes suggestive of dysplasia but inflammatory changes make the distinction impossible. **Such a pathological diagnosis should promote early re-evaluation with extensive biopsies following a course of PPI therapy. If this, together with a subsequent endoscopy and multiple biopsies at 6 months fail to reveal definite evidence of dysplasia, then the patient can return to routine surveillance.** (Recommendation grade C.)

Low-grade dysplasia should be managed firstly by extensive re-biopsy after intensive acid suppression for 8–12 weeks. If persisting, surveillance should be six monthly for as long as it remains stable. If apparent regression occurs on two consequent examinations, surveillance internals may be increased to 2–3 yearly. (Recommendation grade C).

High-grade dysplasia is associated with a focus of invasive adenocarcinoma in 30–40% of patients. For this reason, if the changes persist after intensive acid suppression and are confirmed by two expert pathologists, oesophagectomy in a specialised unit is currently recommended in patients considered fit for surgery (Recommendation grade C). **In those unfit for surgery, endoscopic ablation or mucosal resection should be considered** (Recommendation grade C).

The definition of "Barrett's" columnar-lined oesophagus

A Watson, N A Shepherd

EXECUTIVE SUMMARY

Current usage of the term "Barrett's oesophagus" is confusing and causes unnecessary anxiety when applied to conditions such as microscopic intestinal metaplasia at the squamo-columnar junction, with minimal risk of malignant change.

The insistence on identification of intestinal metaplasia to establish a diagnosis of "Barrett's oesophagus" or to signify malignant potential is not supported by UK pathological opinion which believes that intestinal metaplasia can always be identified in endoscopically-visible columnar metaplasia providing a sufficient number of biopsies are taken over an adequate time-scale.

An appropriate definition of "Barrett's oesophagus" (more appropriately referred to as columnar-lined oesophagus[CLO]) is an oesophagus in which any portion of the normal squamous lining has been replaced by a metaplastic columnar epithelium which is visible macroscopically. In order to make a positive diagnosis of "Barrett's oesophagus", a segment of columnar metaplasia of any length must be visible endoscopically above the oesophago-gastric junction and confirmed or corroborated histologically (Recommendation grade C). (O–G junction defined by the confluence of the proximal limit of longitudinal gastric folds, the distal limit of linear oesophageal vessels and the point of flaring of the stomach from the tubular oesophagus when the lumen is deflated).

Expert opinion believes that confusion would be avoided by replacing the eponym by a more descriptive term, such as "columnar-lined oesophagus" (CLO), and to qualify as to whether tongues or circumferential, and by length. It is believed that a distinction between "short-segment" and "traditional segment" columnarisation is arbitrary, although it is recognised that increasing length of the columnarised segments reflects increasing severity of gastro-oesophageal reflux disease and risk of malignant transformation.

INTRODUCTION

The lack of a universally accepted definition of Barrett's oesophagus has resulted in confusion and difficulties in comparing different studies on this condition. Furthermore, the application of Barrett's oesophagus to conditions such as intestinal metaplasia of the cardia with minimal risk of malignant change causes unnecessary anxiety. In order to fully understand the confusion which has arisen, it is important to be aware of historical milestones following the first description by Norman Barrett in 1950[1].

HISTORICAL PERSPECTIVE

Barrett's original description in 1950 related to two conditions, namely a congenital short oesophagus with intra-thoracic gastric columnar lining and congenital gastric heterotopia in the oesophagus, with ulceration. Three years later Allison provided sound anatomical reasons why columnar lining could occur in the distal oesophagus, as an acquired condition which appeared to be prevalent in patients with gastro-oesophageal reflux[2]. Subsequently, several authors confirmed the association of columnar lining of the oesophagus with clinical gastro-oesophageal reflux[3,4] and subsequent studies confirmed the development of a columnar lined oesophagus (CLO) as a response to gastro-oesophageal reflux in an animal model[5].

It became apparent from the histological standpoint that the columnar lined oesophagus embraced a spectrum of different cellular types, principally comprising a gastric fundic type epithelium, a junctional type epithelium, which had similarities to gastric mucosa but did not secrete digestive juices, although possessing the ability to withstand acid-peptic digestion, and a distinctive type of intestinal metaplasia, characterised by the presence of goblet cells[6]. The malignant potential of the columnar lined oesophagus was subsequently described[7,8], which conferred great importance on the condition and consequently on its accurate diagnosis. For this reason, and in order to eliminate any confusion between CLO and the normal junctional columnar epithelium, as well as difficulty in identifying the precise oesophago-gastric junction in cases of hiatal hernia, an arbitrary minimal length of 3cm of CLO from the oesophago-gastric junction was recommended before the diagnosis of CLO should be made[9]. Until the last few years, Barrett's oesophagus was defined as any histological type of columnar epithelium with a minimum length of 3cm above the oesophago-gastric junction.

RELEVANCE OF INTESTINAL METAPLASIA

If viewed from the standpoint of the risk of developing adenocarcinoma, it became apparent that this applied only to CLO with intestinal metaplasia (IM) and that CLO with fundic epithelium had no malignant potential[10,11]. However, endoscopic appearances did not distinguish between the various histological types and all comprised "Barrett's oesophagus" and were all included in the initial surveillance programmes, which resulted in a much lower incidence of adenocarcinoma than more recent series which have documented the risk in patients with intestinal metaplasia. The problem of definition has become more clouded with the realisation that short segments of columnar lined oesophagus with intestinal metaplasia, less than 3cm in length, can be associated with the development of adenocarcinoma and even in short, non-circumferential tongues of columnarisation[12]. These two entities have each been referred to as "short segment Barrett's" since the length of these segments, which have malignant potential, fall short of the 3cm required to fulfil the traditional definition. Subsequent studies have shown that such short and usually circumferential segments of columnar lined oesophagus with intestinal metaplasia are visible in 42% of adenocarcinoma of the cardia when detailed pathological examination is undertaken[13,14]. Furthermore, pathophysiological studies have shown that patients with these short segments of columnarisation have gastro-oesophageal reflux disease, the pathophysiological severity of which is

intermediate between that in patients with erosive oesophagitis and those with "traditional Barrett's CLO"[15].

The problem of definition has been further compounded by numerous reports of microscopic intestinal metaplasia around the oesophago-gastric junction, present in up to 36% of patients undergoing endoscopy for a variety of gastro-intestinal symptoms, and some have referred to this phenomenon also as "short-segment Barrett's or "ultra-short segment Barrett's"[11,16–18]. In Spechler's series[16], only patients with "traditional Barrett's oesophagus" and those with microscopic intestinal metaplasia at the cardia were studied, those patients with confluent or circumferential columnarisation seen endoscopically being excluded from the study. The bulk of evidence suggests that microscopic intestinal metaplasia at the cardia is not associated with gastro-oesophageal reflux disease, but associated principally with increasing age and Helicobacter infection. It is believed to have a different histogenesis from intestinal metaplasia in confluent and circumferential areas of columnarisation in the oesophagus, and its risk of malignant change appears to be extremely low[19]. In these circumstances, there is confusion in using the term "short segment Barrett's" interchangeably between endoscopically visible confluent or circumferential columnarisation with intestinal metaplasia and microscopic intestinal metaplasia around the cardia, and furthermore it would appear entirely inappropriate to apply the term "Barrett's oesophagus" at all to the latter group, in the absence of endoscopically visible columnarisation, gastro-oesophageal reflux disease and a significant malignant risk.

DEFINING THE MALIGNANT RISK

In view of these various factors, it seems appropriate to consider, when attempting to evolve a more rational definition of "Barrett's oesophagus", those factors which are relevant to malignant potential and those which are not, since this is the most important clinical consequence of the condition. What does not appear to be relevant to malignant potential is the endoscopic appearance per se, since a segment of fundic epithelium carries little or no malignant risk, nor histological identification of intestinal metaplasia per se, since that occurring at the cardia similarly carries little or no malignant risk. A combination of an endoscopically visible metaplastic segment with histological confirmation of columnarisation and intestinal metaplasia is certainly associated with malignant potential. British pathological opinion would not insist on the identification of intestinal metaplasia at first biopsy being a pre-requisite of malignant risk, since sampling error may be a problem, and it is believed that if a suffiucient number of biopsies are taken over an adequate period of time, intestinal metaplasia can usually be demonstrated in such cases[20].

Therefore, in making a confident diagnosis of "Barrett's oesophagus" or the reflux-induced columnarisation of the oesophagus which carries a malignant risk, both endoscopic and histopathological components are necessary. The endoscopist needs to confirm that there is visible columnar epithelium above the oesophago-gastric junction and that biopsies are taken from this as opposed to the gastric cardia and the histopathologist needs to confirm the presence of columnar metaplasia. Care is needed on the part of the endoscopist in identifying short segments of columnarisation as the precise oesophago-gastric junction can be difficult to identify, particularly in the presence of a hiatal hernia, and measurements and precise identification of the site of biopsy in relation to the O-G junction can be difficult in the living, moving oesophagus at endoscopy. The most widely accepted definition of the O-G junction is where the proximal limit of the longitudinal gastric mucosal folds, the distal limit of the longitudinal oesophageal vessels and the point of flaring from the tubular oesophagus into the more dilated stomach coexist in the absence of air insufflation.

DEFINITION AND CATEGORISATION OF BARRETT'S OESOPHAGUS

The definition of "Barrett's oesophagus" proposed by the American College of Gastroenterology[21] acknowledges these factors and states "Barrett's oesophagus is a change in the oesophageal epithelium of any length that can be recognised at endoscopy and is confirmed to have intestinal metaplasia by biopsy". This rather goes beyond the mere definition of "Barrett's oesophagus" and into the realms of criteria for diagnosis. The insistence on identification of intestinal metaplasia to establish a diagnosis of "Barrett's oesophagus" or to signify malignant potential is not supported by UK pathological opinion which believes that intestinal metaplasia can always be identified in endoscopically-visible columnar metaplasia providing a sufficient number of biopsies are taken over an adequate time-scale, and therefore a modified definition to encompass this is shown below. Such definitions appear eminently satisfactory in defining the reflux-induced columnar metaplasia that carries a risk of malignant transformation, but a major question is whether this condition should continue to be referred to as Barrett's oesophagus, since it is a different entity to that described by Barrett's in 1950, in which the relevance of intestinal metaplasia, of malignant risk and of short segments of columnar metaplasia were not recognised. If it is believed appropriate to retain the eponym for the condition defined as above, then another name should be found to describe those cases with no macroscopic change but with microscopic intestinal metaplasia at the cardia, both of which are currently referred to as "Barrett's oesophagus", resulting in considerable patient anxiety, and in the United States, difficulty in obtaining life insurance. Referring to this simply as IM of the cardia would suffice.

An alternative proposal is to replace the eponym by a more descriptive term such as "columnar-lined oesophagus", and to classify as to whether IM is present and by length, which would lend itself to a classification based on the modified Savary-Millar grading of oesphagitis[22], familiar to endoscopists viz:

Grade 0 – No CLO, no IM
Grade 1 – Non-circumferential CLO, no histological IM
Grade 2 – Non-circumferential CLO with IM
Grade 3 – Circumferential CLO without IM
Grade 4 – Circumferential CLO with IM

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REFERENCES

1 **Barrett NR**. Chronic peptic ulcer of the oesophagus and "oesophagitis". Br J Surg 1950; 38: 175–182. **IV**
2 **Allison PR**, Johnstone AS. The oesophagus lined with gastric mucous membrane. Thorax 1953; 8: 87–101. **III**
3 **Moersch R**, Ellis FH, McDonald JR. Pathologic changes occurring in severe reflux oesophagitis. Surg Gynecol Obstet 1959; 108: 476–484. **IV**
4 **Hayward J**. The lower end of the oesophagus. Thorax 1961; 16: 36–41. **IV**
5 **Bremner CG**, Lynch VP, Ellis FH. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. Surgery 1970; 68: 209–216. **IIb**
6 **Paull A**, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RP. The histological spectrum of Barrett's oesophagus. N Engl J Med 1976; 295: 476–480. **III**
7 **Naef AP**, Savary M. Ozzello L. Columnar-lined lower esophagus: an acquired lesion with malignant predisposition: report on 140 cases of Barrett's esophagus with 12 adenocarcinomas. J Thorac Cardiovasc Surgery 1975; 70: 826–834. **IIb**

8 **Haggitt RC**, Tryzelaar J, Ellis FH et al. Adenocarcinoma complicating columnar epithelium-lined (Barrett's) esophagus. Am J Clin Pathol 1978; 70: 1–5**. III**
9 **Skinner DB**, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR. Barrett's esophagus: comparison of benign and malignant cases. Ann Surg 1983; 198: 554–565. **III**
10 **Reid BJ**, Haggitt RC, Rubin LE, Rabinovitch PS. Barrett's esophagus: correlation between flow cytometry and histology in detection of patients at risk for adenocarcinoma. Gastroenterology 1987; 93: 1–11. **IIb**
11 **Spechler SJ** & Goyal RK. The columnar-lined esophagus, intestinal metaplasia and Norman Barrett. Gastroenterology 1996; 110: 614–621. **III**
12 **Schnell TG**, Sontage SJ, Chejfec G. Adenocarcinoma arising in tongues or short segments of Barrett's esophagus. Dig Dis Sci 1992; 37: 137–143**. III**
13 C**ameron AJ**, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. Gastroenterology 1995; 109: 1541–1546. **III**
14 **Clark GWB**, Smyrk TC, Burdiles P et al. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? Arch Surg 1994; 129: 609–614. **III**
15 **Clark GWB**, Ireland AP, Peters JH, Chandrasoma P, DeMeester TR, Bremner CG. Short-segment Barrett's esophagus: a prevalent complication of gastroesophageal reflux disease with malignant potential. J Gastrointest Surg 1997; 1: 113–122. **III**
16 **Spechler SJ**, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-oesophageal junction. Lancet 1994; 344: 1533–1536. **IIb**
17 **Trudgill NJ**, Suvarna SK, Kapur KC, Riley SA. Intestinal metaplasia at the squamocolumnar junction in patients attending for diagnostic gastroscopy. Gut 1997; 41: 585–589. **IIb**
18 **Nandurkar S**, Talley NJ, Martin CJ, Ng THK, Adams S. Short segment Barrett's oesophagus: prevalence, diagnosis and associations. Gut 1997; 40: 710–715. **IIb**
19 **Weston AP**, Krmpotich P, Makdisi WF et al. Short segments Barrett's esophagus; clinical and histological features associated endoscopic findings, and association with gastric intestinal metaplasia. Amer J Gastroenterol 1996; 91; 5: 981 –986. **IIb**
20 **Shepherd NA**, Biddlestone LR. The histopathology and cytopathology of Barrett's oesophagus. In CPD Bulletin Cellular Pathology (ed Manek S), Rila Publications, 1999; 1: 39–44. **III**
21 **Sampliner RE**. Practice guidelines on the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenerol 1988; 93: 1028–1031. **IV**
23 **Cameron AJ**, Zinsmeister AR, Ballard DJ, Carney JA. Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings. Gastroenterology 1990; 99: 918–22. **IIa**

Epidemiology of columnar-lined oesophagus

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EXECUTIVE SUMMARY

In considering the epidemiology of CLO, it is important to differentiate between **prevalence** which is the total number of existing cases as a proportion of the total population at one time and **incidence** which is the number of new cases found over a set time period as a proportion of the population risk, or in the case of CLO, the number of patients being endoscoped.

The median incidence of CLO in 10 studies is 1.17%. It occurs in approximately 12% of those endoscoped for symptoms of GORD and 36% of those with endoscopic oesophagitis. This equates to approximately 30 new cases of CLO per year in a catchment population of 250,000.

A meta-analysis shows that the incidence of CLO is increasing by 0.08% per annum, *pari passu* with the increase in GORD. In the United Kingdom, the rate of increase in incidence exceeds that of performance of endoscopy and parallels the increasing incidence of adenocarcinoma.

The mean age of endoscopically diagnosed CLO is 62 years. 65% of cases occur in males, the greatest incidence being between 50 and 70 years.

CLO is mostly a disease of Caucasian races although more recently has been reported in the Far East.

INTRODUCTION:

The cause of CLO is unclear but descriptive epidemiological data relating CLO in terms of *time, person,* and *place* may be helpful. We carried out a systematic review of the literature using Medline, Embase and Cinahl electronic databases (search strategy available on request). We included only English language articles that reported on the epidemiology of CLO. We identified 44 papers that provided descriptive epidemiological information on long segment CLO and these were divided into articles that addressed time, person and place.

MEASURING THE FREQUENCY OF CLO IN A POPULATION – INCIDENCE OR PREVALENCE?

The principal measures of disease frequency in public health are incidence and prevalence. There has been considerable confusion in the literature on the correct term to use when describing the frequency of CLO. Prevalence is the number of ***existing*** cases/total population at a set point in time and many articles use this term as the disease is likely to have been present for some time before the diagnosis is made at endoscopy. The definition implies that all ***existing*** cases are included in the calculations whilst authors usually discuss the number of ***new*** cases found over a set period of time. Incidence refers to the number of ***new*** cases/total population at risk over a given period of time and is therefore a more appropriate term to use. Measuring the true incidence of CLO however is virtually impossible as the condition is asymptomatic and the patient may have had the lesion for many years before it is diagnosed at endoscopy. There is therefore no ideal epidemiological term to describe the frequency of CLO. This article will use the term "incidence" to describe new cases of CLO diagnosed at endoscopy over a specified time period. The denominator in this definition is patients endoscoped rather than the total population at risk.

VARIATION IN INCIDENCE OF CLO OVER TIME

Studies which have evaluated the incidence of CLO over time have resulted in conflicting conclusions with one study suggesting that the incidence had remained stable[1], another a sharp rise in 1989 then a plateau[2] and a third suggested a linear increase in incidence[3]. The variation in incidence of CLO over time is therefore uncertain and we have addressed this in the systematic review. We included studies of unselected endoscopy patients and plotted the reported incidence of CLO against the median year of assessment. We excluded studies that did not evaluate predominantly Caucasian populations or did not define CLO as ≥ 3cm of macroscopically gastric like mucosa lining the oesophagus in an attempt to make the studies as comparable as possible. Ten studies[1,2,4–11] were eligible for inclusion and the median incidence of CLO was 1.17% with a strong positive linear relationship between the incidence of CLO and the median year of the study. The value for the slope of the line was 0.086 (95% CI = 0.043 to 0.128) with statistically significant correlation between the two variables (Pearson's correlation coefficient $r^2 = 0.73$; $p=0.002$).

These data suggest CLO has increased at a rate of 0.08% per year between 1980 and 1996. This is an ecological study and is evaluating groups rather than individuals. This type of study design is subject to the "ecological fallacy" and inferences about individual risk on the basis of group statistics should be made cautiously as data on individual behaviours has not been recorded[12]. There is however biological plausibility to the hypothesis that CLO is increasing given the association with adenocarcinoma of the oesophagus. Mortality from adenocarcinoma of the oesophagus is increasing more rapidly in the UK and US than any other cancer[13,14]. This 6 to 8 fold rise in incidence of oesophageal adenocarcinoma is mirrored by the 6–fold rise in Barrett's oesophagus in the last 15 years[15]. We therefore believe that CLO is increasing with time at approximately the rate suggested by our ecological analysis. Based on these data and a rate of upper gastro-intestinal endoscopy of 1% of a catchment population, it is estimated that approximately 30 new cases of CLO would be diagnosed annually in a catchment population of 250,000.

VARIATIONS IN INCIDENCE OF CLO WITH PATIENT CHARACTERISTICS

Age

We identified 15 studies[1,3,4,7,9,15–24] that reported mean age of diagnosis in unselected patients with CLO. The mean age of diagnosis was 62 years with all studies showing similar results. There was a marked increase in the diagnosis of CLO over the age of 40–50 years[3,5,8] with this finding being rare under this cut-off point. The reason for this is not clear and could reflect an age effect or a birth cohort effect. This has not

been adequately addressed in the literature although one study suggested an age effect is more likely[3]. Four case reports suggest that CLO develops relatively quickly[5]. Three studies have assessed the change of length of CLO over time and all report no statistically significant change over time[1,5,19].

Gender

There were 18 studies[1,3–5,7–9,11,15–24] that recorded the gender of unselected patients with CLO. All reported that the disorder was more common in men with a pooled estimate that 65% (95% CI = 63–67%) of CLO cases were male.

Race

Five studies suggest CLO is mainly found in Caucasians[7,9,11,15,18]. Three studies[7,15,18] did not state the ethnic mix of patients undergoing endoscopy adequately and in the remaining two studies the odds of a CLO case being Caucasian was 22 (95% CI = 3 to 155) with no statistically significant heterogeneity existing between studies (c^2 = 1.2, df = 1, p=0.27). This is based on only 56 cases of CLO and more data are needed before definite conclusions can be reached.

Gastro-oesophageal reflux disease

CLO is thought to arise as a consequence of mucosal damage secondary to gastro-oesophageal reflux and this is supported by epidemiological data. We identified 16 studies that evaluated the incidence of CLO in patients with reflux disease[7,8,11,16,17,25–35]. Almost all of these studies reported a higher incidence of CLO in gastro-oesophageal reflux disease (GORD) patients than would be expected from reports in unselected endoscopy patients.

There was no relationship seen between the median year of the study and the incidence of CLO in patients with GORD (value of slope = -0.29; 95% CI = -0.69 to 0.10; r^2 = 0.17, p=0.13). This suggests that the increasing incidence of CLO with time is due to an increase in the incidence of GORD in the population rather than an increased susceptibility to progress from GORD to CLO.

The risk of GORD patients developing CLO is difficult to determine from the studies identified from the systematic review. There were only six studies that gave the incidence of CLO in patients with an otherwise normal endoscopy compared with oesophagitis patients. A meta-analysis of these studies suggest the odds of having CLO in oesophagitis patients is 9.0 (95% CI = 5.7 to 14.1; p<0.001) compared to patients with a normal endoscopy. These data need to be interpreted with caution however as there was statistically significant heterogeneity between the studies (c^2 = 21.3, df = 5, p=0.001). Combining the studies to obtain a summary odds ratio may therefore not be appropriate. There is a need for more cross sectional studies assessing the incidence of in patients with and without oesophagitis.

Smoking, alcohol, coffee intake, body mass index and social class

Smoking, alcohol and coffee intake and obesity are thought to be risk factors for GORD. It is therefore surprising that we could identify only three case-control studies that investigated the association between lifestyle factors and CLO[23,36,37]. There was no association between CLO and smoking[23,36,37] and no convincing relationship between this disorder and alcohol intake[23,37] although one report did suggest alcohol consumption distinguished between patients with greater than 7 cm of CLO and those with shorter lengths[37]. One study evaluated body mass index and found no association with CLO[37]. We are not aware of any studies assessing the relationship between coffee intake or social class and CLO.

Smoking and alcohol have been suggested as risk factors for malignant progression of CLO but this is a separate question. We need more case-control and cohort studies investigating the influence of social class and lifestyle on the incidence of CLO.

Helicobacter pylori

A nested case-control study suggested *H pylori* infection was associated with a decreased risk of developing oesophageal adenocarcinoma and proximal gastric cancer[38]. A systematic review has suggested *H pylori* may also have a negative association with CLO[39]. The association between oesophageal adenocarcinoma, CLO and absence of *H pylori* may not be causal however, and may relate to an independent process (e.g. bile reflux) that both protects against *H pylori* and promotes carcinogenesis.

VARIATIONS IN INCIDENCE OF CLO WITH GEOGRAPHICAL REGION

CLO is said to be uncommon in countries that are not westernised and particularly rare in most of the Asian subcontinent. We found few reports however, of the incidence of CLO in these countries.

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REFERENCES

1 **Macdonald CE**, Wicks AC, Playford RJ. Ten years experience of screening patients with Barrett's oesophagus in a university teaching hospital. Gut 1997; 41: 303–307. **III**
2 **Prach AT**, MacDonald TA, Hopwood DA, Johnston DA. Increasing incidence of Barrett's oesophagus: education, enthusiasm or epidemiology? The Lancet 1997; 350: 933. **III**
3 **Caygill CPJ**, Reed PI, Johnson BJ, Hill MJ, Ali MH et al. A single centre's 20 years experience of columnar-lined (Barrett's) oesophagus diagnosis. European J of Gastroenterol & Hepatol 1999; 11: 12: 1355–1358. **III**
4 **Ovaska J**, Meittinen M, Kivilaakso E. Adenocarcinoma arising in Barrett's oesophagus. Digestive Disease & Sciences 1989; 34: 9: 1336–1339. **III**
5 **Cameron AJ**, Lomboy CT. Barrett's esophagus: age, prevalence and extent of columnar epthelium. Gastroenterology 1992; 103: 1241–1245. **III**
6 **Watson RGP**, Porter KG, Sloan JM. Incidence of adenocarcinoma in Barrett's oesophagus and an evaluation of endoscopic surveillance. European J of Gastroenterol & Hepatol 1991; 3: 2: 159–161. **III**
7 **Cooper BT**, Barbezat GO. Barrett's oesophagus: A clinical study of 52 patients. Quarterly Journal of Medicine, New Series 62 1987; 238: 97–108. **III**
8 **Bonelli L**, & GOSPE. Barrett's esophagus: Results of a multicentric survey. Endoscopy 1993; 25 (suppl) 652–654. **III**
9 **Spechler SJ**, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-oesophageal junction. The Lancet 1994; 344: 1533–1536. **III**
10 **Nandurkar S**, Talley NJ, Martin CJ, Ng THK, Adams S. Short segment Barrett's oesphagus: prevalence diagnosis and associations. Gut 1997; 40: 710–715. **III**
11 **Hirota WK**, Loughney TM, Lazas DJ, Maydonovitch CL, Rholl V et al. Specialized intestinal metaplasia, dysplasia and cancer of the esophagus and esophagogastric junction: Prevalence and clinical data. Gastroenterology 1999; 116: 277–285. **III**
12 **Morgenstern H**. Uses of ecological analysis in epidemiological research. Am J Pub Health 1982; 72: 1336–44. **IV**
13 **Blot WJ**, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265: 1287–1289. **IV**
14 **Powell J**, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer 1990; 62: 440–443. **III**
15 **Skinner DB**, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR. Barrett's esophagus. Comparison of benign and malignant cases. Annals of Surgery 1983; 198: 554–565. **III**
16 **Burbige EJ**, Radigan JJ. Characteristics of the columnar-cell lined (Barrett's) esophagus. Gastrointestinal Endoscopy 1979; 25: 4: 133–136. **III**
17 **Rothery GA**, Patterson JE, Stoddard CJ, Day DW. Histological and histochemical changes in the columnar lined (Barrett's) oesophagus. Gut 1986; 27: 1062–1068. **III**
18 **Spechler SJ**, Robbins AH, Bloomfield-Rubins H, Vincent ME, Heeren T et al. Adenocarcinoma and Barrett's esophagus. An overrated risk? Gastroenterol 1984; 87: 927–33. **III**

19 **Iftikhar SY**, James PD, Steele RJC, Hardcastle JD, Atkinson M. Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. Gut 1992; 33: 1155–1158. **Iib**
20 **O'Connor JB**, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus. American J Gastroenterol 1999; 94: 2038–2042. **III**
21 **Miros M**, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. Gut 1991; 32: 1441–1446. **III**
22 Van der Veen AH, Dees J, Blankensteijn JD, Van Blankenstein M. Adenocarcinoma in Barrett's oesophagus: an overrated risk. Gut 1989; 30: 14–18. **III**
23 **Robertson CS**, Mayberry JF, Nicholson DA, James PD, Atkinson M. Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus. Br J Surg 1988; 75: 760–763. **III**
24 **Hameeteman W**, Tytgat GNJ, Houthoff HJ, Van Den Tweel JG. Barrett's esophagus: Development of dysplasia and adenocarcinoma. Gastroenterology 1989; 96: 1250–1256. **III**
25 **Naef AP**, Savary M, Ozzello L, Pearson FG. Columnar-lined lower esophagus: An acquired lesion with malignant predisposition. Journal of Thoracic & Cardiovascular Surgery 1975; 70: 5: 826–835. **III**
26 S**arr MG**, Hamilton SR, Marrone GC, Cameron JL. American J Surg 1985; 149: 187–192. **III**
27 **Winters Jr. C**, Spurling TJ, Chobanian SJ, Curtis DJ, Esposito RL et al. Barrett esophagus. A prevalent occult complication of gastroesophageal relfux disease. Gastroenterol 1987; 92: 118–124. **III**
28 **Mann NS**, Tsai MF, Nair PK. Barrett's esophagus in patients with symptomatic reflux esophagitis. American J Gastroenterol 1989; 84: 12: 1494–1496. **III**
29 **Loof L**, Gotell P, Elfberg B. The incidence of reflux oesophagitis. A study of endoscopy reports from a defined catchment area in Sweden. Scan J Gastroenterol 1993; 28: 113–118. **III**
30 **Singh P**, Taylor RH, Colin-Jones DG. Esophageal motor dysfunction and acid exposure in reflux esophagitis are more severe if Barrett's metaplasia is present. American J Gastroenterol 1994; 89: 3: 349–356. **IIb**
31 **Yeh C**, Hsu C, Ho A, Sampliner R, Fass R. Erosive esophagitis and Barrett's esophagus in Taiwan. A higher frequency than expected. Digestive Diseases & Sciences 1997; 42: 4: 702–706. **III**
32 **Robinson M**, Earnest D, Rodriquez-Stanley S, Greenwood-van Meerveld B, Jaffe P, Silver MT et al. Heartburn requiring frequent antacid use may indicate significant illness. Arch Intern Med 1998; 158: 2373–2376. **IIb**
33 **Corder AP**, Jones RH, Millward-Sadler GH, Daniels P, Johnson CD. Heartburn, oesophagus and Barrett's oesophagus in self-medicating patients in general practice. Br J Clin Pract 1996; 50: 5: 245–248. **IIb**
34 **Csendes A**, Smok G, Burdiles P, Sagastume H, Rojas J et al. 'Carditis': an objective histological marker for pathologic gastroesophageal reflux disease. Disease of Esophagus 1998; 11: 101–105. **Iib**
35 **Voutilainen M**, Farkkila M, Mecklin JP, Juhola M, Sipponen P et al. Classical Barrett esophagus contrasted with Barrett-type epithelium at normal-appearing esophagogastric junction. Scand J Gastroenterol 2000; 1: 2–9. **III**
36 **Gray MR**, Donnelly RJ, Kingsnorth AN. The role of smoking and alcohol in metaplasia and cancer risk in Barrett's columnar lined oesophagus. Gut 1993; 34: 727–731. **Iib**
37 **Ritenbaugh C**, Sampliner R, Aickin M, Garewal H, Meyskens F. Risk factor for Barrett's oesophagus: a life history approach to behavioural assessment in the distant past. European J Cancer Prevention 1995; 4: 6: 459–468. **IIb**
38 **Chow W-H**, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, et al. An inverse relation between *cag*A$^+$ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. Cancer Research 1998; 58: 588–590. **IIb**
39 **Sharma VK**, Howden CW. Negative association of *H. pylori* infection with gastroesophageal reflux disease, Barrett's esophagus and esophageal adenocarcinoma: meta-analysis of studies examining prevalence (abstract). Gastroenterology 2002; 122: A291. **IIb**

Pathogenesis and pathophysiology of columnar-lined oesophagus

The late W J Owen, B R Warren

EXECUTIVE SUMMARY

CLO is a consequence of long-standing and severe gastro-oesophageal reflux disease. It represents the extreme end of the pathophysiological spectrum of GORD, with a high prevalence of associated hiatal hernia, lower oesophageal sphincter failure, peristaltic failure and high levels of acid exposure, compounded by impaired mucosal sensitivity.

There is a high prevalence of duodeno-gastro-oesophageal reflux, detected by abnormal levels of bilirubin exposure on Bilitec monitoring in patients with CLO, and particularly in those who develop complications such as ulcer, stricture and carcinoma.

The extent of the above pathophysiological abnormalities appears to be proportional to the extent of columnarisation, patients with short segments of columnarisation having a pathophysiological profile intermediate in severity between those with long segment disease and patients with erosive oesophagitis.

Columnar metaplasia occurs as a response by oesophageal stem cells to acute and chronic inflammatory processes consequent on mucosal injury with acid, pepsin and duodenal juice. The extent of metaplasia is variable, depending on the duration and severity of injury, the nature of the cytokine response and degree of epithelial resistance to these processes.

Heartburn affects 5–10% of the Western population daily; the vast majority of the sufferers self-medicate and only a small minority reach the hands of Gastroenterologists and undergo endoscopy. Longitudinal studies on those suffering from gastro-oesophageal reflux disease reveal that 90% still suffer from heartburn even ten years on but that complications are rare, strictures occurring in 2% and CLO in 1%[1].

It is accepted that CLO is initiated by chronic gastro-oesophageal reflux leading to oesophagitis and that the subsequent repair process is associated with development of columnar metaplasia with the presence of goblet cells. CLO is significantly more common in the white population and in cigarette smokers and its frequency increases with age[2,3]. There is also a possible correlation with alcohol consumption. Most of the interest has, however, focused on the severity of gastro-oesophageal reflux and also on the nature of the refluxate. CLO is considered by most to represent the extreme end of the gastro-oesophageal reflux disease spectrum characterised by poor oesophageal clearance and lower oesophageal sphincter hypotonia may either be secondary to chronic reflux or may even represent a primary deficiency.

GASTRO-OESOPHAGEAL REFLUX OF ACID

The relationship between acid reflux and the extent of oesophageal damage was investigated by Lascone et al[4] using ambulatory pH monitoring; they found significantly greater acid exposure (pH less than 4) in those patients with CLO when compared to controls with erosive oesophagitis. Many others have confirmed this finding and more recently Vaezi et al (1996) separated CLO patients into those who were classified as uncomplicated and another group which were complicated by stricture, ulcer, dysplasia or carcinoma. They found significantly greater oesophageal acid exposure in the complex CLO (22.8% exposure time to pH less than 4) when compared to the uncomplicated group (exposure time 14.7%)[5]. Sontag found a positive correlation between the amount of oesophageal acid exposure time and the length of the CLO segment[6].

Initially it was thought that CLO was associated with an increase in gastric acidity[7]. A more detailed study by Hirschowitz (looking at basal and Pentagastrin stimulated gastric acid production) found no difference in CLO patients when they were compared to controls carefully matched for sex and background gastrointestinal disease.[8] They also found no differences in the pepsin output both in the basal and stimulated state between CLO patients and their appropriate controls. In a previous study Hirschowitz confirmed the striking male predominance for CLO (28% in males as compared to 6.5% in females) although there was no sex difference in the stricture rate in those patients with reflux disease.[9] The relatively low prevalence of CLO in a series of 92 cases with Zollinger Ellison syndrome (3%) confirmed the absence of any correlation between CLO and gastric hypersecretion.[10]

RELATIONSHIP BETWEEN CLO AND H.PYLORI

Some authors report an increase in reflux symptoms after eradication of H.pylori and recent studies suggest that H.P. may indeed have a protective role on the oesophageal mucosa. Varanesei et al[11] found a significantly lower incidence of H.P infection in reflux patients with oesophagitis when compared with those without. Vickari et al[12] interestingly found that the prevalence of cagA H.pylori was 34% in reflux patients, 13.3% in CLO cases and 0% in CLO complicated with dysplasia or carcinoma. One explanation is that H.P causes a pangastritis leading to gastric atrophy and reduced gastric acidity, thereby reducing the likelihood and extent of gastro-oesophageal reflux disease.

MOTOR AND SENSORY FACTORS ASSOCIATED WITH CLO

An increase in prevalence and size of hiatal hernia has been found in those with CLO. Furthermore, when reflux inducing provocation manoeuvres were used the combination of a hiatal hernia and a low LOSp was particularly associated with a very high incidence of reflux[13]. Indeed a hypothesis was put forward by Mittal[14] to link some of the factors which are thought to be relevant in the genesis of progressive gastro-oesophageal reflux disease. The process probably starts with an increase in TLOSR's (transient relaxation of the lower oesophageal sphincter) leading to increased acid exposure in the lower oesophagus, oesophageal shortening and fibrosis. This would then have the effect of leading to the formation of a hiatal hernia with stretching of the diaphragmatic sling thereby weakening the contribution of the diaphragm and further impairing lower sphincter competence.

Paradoxically CLO seems to be relatively insensitive as judged by the high false negative Bernstein test and in one study 25% of patients with histologically proven Barrett's had never experienced any symptoms of GORD.[14]

THE NATURE OF THE TOXIC REFLUXATE

There are several reports of the occurrence of CLO in patients who have previously undergone total gastrectomy and oesophago-jejunostomy thus raising the question of whether factors other than acid are important in the genesis of CLO. Bile has been implicated either as a major contributor to oesophageal damage but also as a marker of the presence or absence of duodenal juice in the oesophagus. The mere presence of bile in the stomach or even in the oesophagus as seen at endoscopy is not considered reliable evidence for pathological duodeno-gastric reflux (DGR) or duodeno-gastro-oesophageal reflux (DGOR)[15].

The term alkaline reflux was originally used to describe the reflux of "alkaline duodenal contents" in to the stomach and oesophagus. The use of pH monitoring to determine DGR and DGOR has now been discredited and many other factors such as saliva, secretions from the oesophageal mucus glands, and pooling of luminal secretions may affect the oesophageal pH. Thus alkaline reflux should now be regarded as a misnomer[16]. Aspiration of both gastric and duodenal secretions at periodic intervals has been carried out to assess bile acids as a measure of duodenal reflux although this method is considered rather cumbersome and difficult to perform as an ambulatory test. Nevertheless, this work does allow confirmatory evidence to compare duodenal reflux with other methods of assessing DGR and DGOR[17]. Scintagraphy using HIDA to label bile has been used to estimate DGR and DGOR. It is an insensitive method and merely measures a small window in time. There are also technical problems because the left lobe of the liver overlaps the stomach and this makes it particularly difficult to assess DGR[18].

The "Bilitec 2000" probe was described by Bechi and essentially is a fibreoptic sensoring device measuring bile and relies on the optical properties of bile. The probe is passed nasally to lie 5 cm above the lower oesophageal sphincter; the luminal contents entering a small gap in the probe is examined by the absorbance of a beam of light shining across the gap. The methodology of the probe has been validated both measurement of light absorbence and bile salt concentrations[19].

There are some technical problems with the Bilitec probe which need to be considered. For instance coloured foodstuff in the diet may alter the absorbance values and solid food particles may also "clog" up the gap in the probe thereby invalidating the result. For this reason some centres recommend a "non coloured liquid diet" during the period of study and interpret the upright bile reflux data with caution. It should be regarded as a semi-quantative method of assessing duodeno-gastro-oesophageal reflux but undoubtedly is the best currently available.

Although measurement of bile acids by intubation and aspiration is cumbersome and difficult to carry out in the ambulatory setting, it have nevertheless provided some important information about the relationship between reflux disease and duodeno- gastric reflux. Thus Gillen et al[20] measured both fasting and post-prandial intra-gastric bile acids and found a positive correlation between the amount of bile acids in the post-prandial period with the presence of CLO. This association was more pronounced in cases with complex CLO. Vaezi and Richter[21] looked at fasting total gastric bile acid concentrations and found significantly higher levels in CLO patients when compared to non-CLO reflux controls. This difference was particularly marked in the complicated CLO cases. They went on to measure DGOR using Bilitec 2000 to measure bile absorbance in the oesophagus as an estimate of bilirubin concentration. They found a similar step-wise increase in bilirubin absorbance in the oesophagus comparing healthy controls, simple reflux disease, uncomplicated CLO and complicated CLO. They found no association between bile absorbance and oesophageal alkalinity further invalidating the concept that oesophagal pH might be a useful measure of duodeno-gastro-oesophageal reflux. This work was confirmed by Marshall et al[22] who found that supine bile reflux into the oesophagus correlated well with CLO when compared to non-CLO reflux controls. A further more detailed study by Vaezi and Richter found an association between the degree of oesophageal mucosal damage and oesophageal bile absorbance and the pattern of change was similar to the association seen with oesophageal acid exposure. Thus, the degree of duodeno-gastro-oesophageal reflux parallels that of gastro-oesophageal reflux of acid.

Marshall[23] investigated the temporal relationship between oesophageal bile reflux and pH in gastro-oesophageal reflux disease. Nocturnal oesophageal bile reflux occurred mostly between a pH of 4 and 7 and while acid reflux predominates during the first part of the night, bile reflux occurs virtually throughout the whole night.

Omeprazole has been shown to dramatically reduce the reflux of both acid and bile into the oesophagus in CLO patients. The mechanism of this reduction in oesophageal bile reflux is unclear and may be associated with a reduction in gastric volume and thus of the "tidal wave" which carries duodenal contents in to the oesophagus. Certainly, Omeprazole has not been shown to have any effect on duodeno-gastric reflux (DGR).

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REFERENCES

1 **McDougal N**l, Johnston BT, Kee F. National History of Reflux Easophagitis: A 10 Year Follow Up of its Effects on Patients Symptomatology and Quality of Life. Gut 1996; 38: 481–486 **IIb**
2 **Sonnenberg A**, El Serag HB. Epidemiology of Gastro-esophageal Reflux Disease in "Gastro-oesophageal Reflux Disease – Back to Surgery". PROG SURG BASEL KARGER (1997); 23: 20–36. **IV**
3 **Consensus Statement Management of Barrett's Oesophagus**. THE SSAT. AGA. ASGE Consensus Panel 17 May 1999. **IV**
4 **Iascone C**, DeMeester TR, Little AG et al. Barrett's Oesophageal Functional Assessment, Proposed Pathogenesis and Surgical Therapy. Arch Surg 1983; 118: 543–549. **III**
5 **Vaezi MF** and Richter JF. Role of Acid and Duodenogastro-oesophageal Reflux in Gastro-oesophageal Reflux Disease. Gastroenterology (1996); III: 1192–1199. **I1b**
6 **Sontag SI**, Schnell T et al. Length of Barrett's Epithelium Corresponds to Oesophageal Contact Time in Patients with Reflux. Gastroenterology (1996); 110–262. **IIa**
7 **Mulholland MW**, Road BJ, Levine DS et al. Elevated Gastric Acid Secretions in Patients with Barrett's Metaplastic Epithelium. Dig Dis Sci (1989); 34:1329–1335. **IIb**
8 **Hirschowitz BI**. Gastric Acid and Pepsin Secretion in Patients with Barrett's oesophagus and Appropriate Controls. Dig Dis Sci (1996); 41: 1384–1391. **IIb**
9 **Hirschowitz BI**. A Critical Analysis with Appropriate Controls of Gastric Juice and Pepsin Secretion in Clinical Oesophagitis. Gastroenterology (1991); 101: 1149–1158. **IIa**
10 **Strader DB**, Benjamin SB, Orbuch M. Oesophageal Functional and Occurrence of Barrett's Oesophagus in Zollinger Ellison Syndrome. Digestion (1995); 56: 347–356. **IIb**
11 **Varanesi RV**, Fantry GT, Wilson KT. Decreased Prevalence of H.Pylori Infection in Gastro-Oesophageal Reflux Disease. Helicobacter (1990); 3: 188–194. **IIb**
12 **Vicari JJ**, Pack RM, Falk GW et al. The Seroprevalence of cagA positive Helicobacter pylori Strains in the Spectrum of Gastro-Oesophageal Reflux Disease. Gastroenterology (1998); 115: 50–57. **11a**
13 **Nebel OT**, Fornes MF, Castell DO. Symptomatic Gastro-oesophageal Reflux: Incidence and Precipitating Factors. Am J Dig Dis (1976); 21: 953. **III**

14 **Sloan S**, Rademaker AV, Kahrilas PJ. Determinants of Gastro-Oesophageal Junction incompetence: Hiatus Hernia, Lower Oesophageal Sphincter or both? Ann Intern Med (1992); 117: 977 **IIb**
15 **Mittal RK**. Pathophysiology of Gastroesophageal Reflux Disease – Motility Factors in the Oesophagus, 3rd edition ed Castell DO and Richter JE (1999) page 405. **III**
16 **Kahrilas PJ** et al. Esophageal Peristaltic Dysfunction in Peptic Oesophagitis. Gastroenterology (1986); 91: 897 **IIa**
17 **Stein HJ**, Smyrk TC, DeMeester TR. Clinical Value of Endoscopy and Histology in the Diagnosis of Duodeno-gastric Reflux Disease. Surgery (1992); 112: 796–804. **IIb**
18 **Iftikhar SY**, Ledingham S, Evans DF. Alkaline Gastro-oesophageal Reflux. Dual Probe pH Monitoring. Gut (1995); 37: 465–470. **IIb**
19 **Vaezi, MF**, La Camera RG, Richter JE. Bilitec 2000 Ambulatory Duodenogastric Reflux Monitoring System: Studies of Validation and Limitations. Am J Physiol (1994); 267: G1050–G1057. **IIa**
20 **Thomas WEG**, Jackson PO, Cooper MJ, Davies ER. The Problems Associated with Scintigraphic Assessment of Duodenogastric Reflux. Scand J. Gastroenterol (1984); 19 suppl 36–40. **IIb**
21 **Bechi P**, Pucciani F, Baldini F. Long-Term Ambulatory Enterogastric Reflux Monitoring. Dig Dis Sci (1993): 38: 1297–1306. **IIa**
22 **Gillan P**, Keeling P, Byrne PJ. Implications of Duodenogastric Reflux in the Pathogenesis of Barrett's Oesophagus. Br J Surg (1988); 75: 540–543. **IIb**
23 **Vaezi MF**, Richter JE. Synergism of Acid and Duedenogastro-oesophageal reflux in Complicated Barrett's Oesophagus. Surgery (1995); 117: 699–704. **IIa**
24 **Marshall REK**, Anggiansah A, Owen WA, Owen WJ. The Relationship Between Acid and Bile Reflux and Symptoms in Gastro-Oesophageal Reflux Disease. Gut (1997); 40–182. **IIa**
25 **Marshall REK**, Anggiansah A, Owen WA, Owen WJ. The Temporal relationship Between Oesophageal Bile Reflux and pH in Gastro-oesophageal Reflux Disease. European Journal of Gastroenterology and Hepatology (1998).; 10: 385–392. **IIa**

Diagnosis of columnar-lined oesophagus

M D Hellier, N A Shepherd

EXECUTIVE SUMMARY

Although CLO may be diagnosed with reasonable accuracy either by endoscopic appearance or histologically in the 10–15% of cases when native oesophageal structures are seen **histological corroboration of endoscopically visible columnarisation results in highest diagnostic accuracy.** Recommendation grade C

Chromoscopy does not give sufficiently accurate results consistently to justify its routine use in the diagnosis of CLO. Recommendation grade C

It is vitally important for accurate diagnosis that the precise sites of biopsies taken are recorded by the endoscopist in terms of distance from the incisor teeth and relation to the oesophago-gastric junction (see definition) and the squamo-columnar junction. Recommendation grade C

The following categories are appropriate for reporting of diagnostic biopsies:

i) **Biopsies diagnostic for CLO**
Native oesophageal structures are present with juxtaposition to metaplasia glandular mucosa, whether intestinalised or not.

ii) **Biopsies corroborative of an endoscopic diagnosis of CLO**
Intestinalised metaplastic glandular mucosa with or without non-organised arrangement, villous architecture, patchwork of different glandular types etc. this could potentially still represent incomplete intestinal metaplasia in the stomach, especially in a hiatus hernia or IM at the cardia.

iii) **Biopsies in keeping with, but not specific for CLO**
Gastric type mucosa of either fundic or cardiac type without IM. Patchwork appearance is still possible, as is a non-organised arrangement. Such appearances could, however, represent the OG junction or the stomach, with or without hiatus hernia. Recommendation grade C

iv) **Biopsies without evidence of CLO**
Oesophageal type squamous mucosa with no evidence of glandular epithelium. Recommendation grade C

It should be noted that the identification of intestinal metaplasia in individual biopsies is not necessary to diagnose CLO. Furthermore, if present, application of the term "specialised" is unnecessary, since there are no specific features relating to morphology, histochemistry, immunohistochemistry or any other methodology which are different from those in intestinal metaplasia elsewhere.

INTRODUCTION

The diagnosis of CLO depends on endoscopic observation together with histology from endoscopic biopsies. Neither symptoms, signs nor radiological findings are of any real help in establishing the diagnosis. Symptoms may identify a section of the population more likely to suffer with CLO but in general are a poor predictor of the condition. A third of patients with CLO suffer no reflux symptoms. Furthermore, elderly people are more likely to present with long segment CLO and atypical features such as iron-deficiency or haemorrhage, due to associated ulceration[1]

ENDOSCOPY AND THE DIAGNOSIS OF CLO

Making the diagnosis depends on a clear understanding of the definition of CLO and here lies a major problem at present. When CLO was defined as more than 3cm of glandular metaplasia above the gastro-oesophageal junction, so-called long segment, or traditional, Barrett's oesophagus, endoscopic recognition of CLO was possible. With the recognition of short segment Barrett's oesophagus in which CLO is defined as intestinal metaplasia(IM) in the distal oesophagus irrespective of the length of the segment, endoscopic observation is no longer sufficient to make the diagnosis.[2,3] Short segment CLO may be missed purely on endoscopic observations whereas "ultrashort segment CLO" is effectively a histological diagnosis, requiring the absence of endoscopically demonstrable metaplasia in the oesophagus allied to histologically-defined IM in cardiac mucosa adjacent to the normally sited squamo-columnar junction.[2] More recently, the term ultra-short segment Barrett's has been discarded in favour of the more descriptive name of intestinal metaplasia at the cardia (CIM).

In a major endoscopic study of 2393 patients, endoscopic and histological findings at the time of first endoscopy have shown that endoscopists diagnosed CLO with a sensitivity of 82% and specificity of 81%. However the positive predictive value was only 34% compared to the negative predictive value of 97%. The length of the columnar segment was the strongest predictor of CLO at endoscopy. The conclusion was that alternative methods were needed to better identify CLO patients endoscopically, especially those with short segment disease.[4]

However, even long segment CLO depends on being able to identify the lower and upper limits of the columnar segment. Identifying the oesophago-gastric junction may be difficult. The European Society of Gastrointestinal Endoscopy has recently published Minimal Standard Terminology in Digestive Endoscopy.[5] The term oesophago-gastric junction is usually defined as the proximal limit of gastric folds seen at endoscopy with the endoscope retroflexed and the lumen deflated. The squamo-columnar junction or Z-line may be located well away from the junction between the oesophagus and stomach depending on the length of the columnarised segment. Likewise the lower oesophageal sphincter was felt to be difficult to identify endoscopically and therefore this criterion was not used. The length of CLO has been defined as the distance between the transition from oesophageal mucosa to gastric mucosa (Z-line) and the upper end of the gastric folds, the position of the Z-line being denoted in centimetres from the incisors.

Histological assessment is important in confirming or corroborating the endoscopic diagnosis but there is great variability among endoscopists in the size, number and location of biopsies that are taken. In a survey of British

Gastroenterologists in the Trent region, 74% of those who completed the questionnaire took biopsies at random and did not follow any set protocol.[6] Protocols recommending biopsies at each quadrant every 1 to 3cm throughout the length of the CLO segment and well into the normal squamous epithelium may improve diagnostic accuracy but there are no data to show they do so.[7] They greatly increase both the time taken to do the endoscopy (up to 20 minutes) and the workload for the Histopathologist. Even where such a protocol is followed and jumbo forceps are used to take large biopsies, unsuspected carcinoma in a CLO segment is still missed.[8]

A clear understanding of the definition of CLO is essential to avoid confusion caused by biopsies taken from the cardia, which may include IM, and true oesophageal biopsies. This may lead to an overdiagnosis of true CLO (as opposed to CIM). Confirmation of the true oesophageal derivation of biopsies may come only by demonstrating oesophageal components in the biopsy. This is demonstrated in a study comparing the precision of diagnostic sites with oesophageal manometry: in this study there were differences and inconsistencies, from one endoscopic examination to another, in the ability to detect specialised columnar epithelium, an area that might lead to substantial problems in establishing an accurate diagnosis of CLO.[9]

Routine endoscopy is particularly limited in its ability to identify dysplasia and sampling errors are likely to occur if insufficient biopsies are taken. Sometimes dysplasia may be seen as focal mucosal change with a granular or velvety appearance, together with isolated raised plaques or nodules.[10] In this situation the protocol describing quadrantic biopsies every 2cm might be more likely to detect dysplasia, particularly if focal areas of abnormality are targeted.[10,11] However, one study comparing histology with fluorescent technology found systematic 4–quadrant biopsies to be no better than multiple random biopsies in detecting dysplasia.[12]

At the Second European Endoscopic Forum looking at definitions and pathogenesis of CLO, the following conclusions were drawn.[13] Firstly it has not yet been clearly established which biopsy protocol is the optimal for the diagnosis of CLO. Secondly Jumbo biopsies were not recommended as necessary for the diagnosis of CLO. Thirdly routine biopsy of the endoscopically normal squamo-columnar junction, especially seeking evidence of intestinal metaplasia could not be justified, mainly because the management of this condition remains undefined. Fourthly it was recommended that biopsies are taken if there are tongues of columnar epithelium extending into the lower oesophagus, so-called short segment CLO.[13]

Is chromoscopy helpful in the endoscopic detection of CLO? Chromoendoscopy with toluidine blue has been used for mapping CLO and been found to reliably locate sites of dysplasia within the metaplastic segment.[14] Methylene blue staining is also an effective method for demonstrating intestinal metaplasia.[15;16] Lugol's iodine stains squamous epithelium but leaves metaplastic epithelium unstained and so improves delineation between the two. Indigo carmine is favoured by the Japanese in achieving better surface contrast. However there is considerable controversy about the use of chromoscopy and its value in CLO. These techniques remain to be evaluated and are not considered necessary for the diagnosis of CLO.[13] In summary, **chromoscopy does not give sufficiently accurate results consistently to justify its routine use in the diagnosis of CLO** (Recommendation grade C)

Endoscopic fluorescence has been used to detect dysplasia after 5–aminolevulinic acid-induced protoporphyrin IX sensitisation.[17] Acetic acid techniques similar to those used in uterine cervical histology have been used successfully to demonstrate islands of intestinal metaplasia not visible under normal endoscopy.[18] Newer optical biopsy techniques such as that using ELASTIC scattering spectroscopy to demonstrate dysplasia and cancer are in the developmental phase and may prove to be useful in the future. Interest has been shown in the role of endosonography in the diagnosis of CLO but as yet its value has not been established. Magnification chromoendoscopy and optical coherence tomography are also being assessed.

Regrettably, CLO is often diagnosed only when it presents with the complications of oesophageal carcinoma.[19] Indeed 95% of all CLO-associated adenocarcinomas present to the medical community, not with CLO, but with the adenocarcinoma complicating it.[20] This is likely to continue to be the case as long as gastro-oesophageal reflux is considered to be a benign condition diagnosed symptomatically and not requiring endoscopy. However gastro-oesophageal reflux is an exceedingly common symptom experienced intermittently by up to 25% of the general population and it would be impossible logistically to endoscope all patients with reflux symptoms.[21–23] In a prospective study of 742 patients referred for investigation of uncomplicated reflux, low rates of CLO were found and there were no cancers: treatment was not influenced by endoscopic findings.[24] Of patients presenting for endoscopy for any reason, 1–2% will have long segment CLO and between 4 and 10% short segment CLO. Less than 5% of cases of in the general population may be diagnosed endoscopically.[24]

Who then should be endoscoped? In a large well conducted study from Sweden, a strong association was demonstrated between symptoms of gastro-oesophageal reflux and oesophageal cancer, the risk increasing with frequency and severity of symptoms.[25] This study suggests that by endoscoping all those with frequent or severe symptoms of reflux and heartburn and especially those over the age of 45 would maximise the diagnostic yield of CLO: what is practised in terms of surveillance of these CLO patients remains controversial but is a subject dealt with elsewhere in these Guidelines.

PATHOLOGY AND THE DIAGNOSIS OF CLO

For pathologists, CLO remains a considerable problem and a potential diagnostic minefield. Few conditions require such close clinical, endoscopic and pathological correlation as CLO. This is because the pathological features, whilst often highly characteristic, are not necessarily pathognomonic of CLO in the majority of cases. Despite all this, few diseases suffer from such a paucity of useful data proffered to the pathologist at the time of consultation, as CLO. So many times pathologists are confronted with clinical data of "? Barrett's oesophagus" and are told that the specimens are "lower oesophageal biopsies". This is presumably because clinicians fail to realise that histology is not necessarily pathognomonic for CLO. In this situation the pathologist can undoubtedly provide misleading information. Accurate identification of the endoscopic appearances, especially the presence or absence of a hiatal hernia,[26] and detailed provision of the site of the biopsies are baseline requirements for the clinician to provide for the pathologist .In this regard, ideally the referring clinician should indicate the distance from the incisor teeth at which the biopsies are taken together with the distance of the squamo- columnar and gastro-oesophageal junctions.

So why is there such a problem with the pathological identification of CLO? Firstly it is important to emphasise the pathogenic mechanisms leading to the disease. The gut mucosa has only a limited repertoire of responses to noxious stimuli and one could argue that CLO is likely to represent a similar response to inflammatory insult as IM in the stomach in response to *Helicobacter pylori*. CLO is primarily a metaplasia of the lower oesophageal mucosa in response to gastro-oesophageal reflux, particularly acid, although other chemicals such as pepsin, bile and duodenal juice may also be important. The response is to convert the compromised

squamous mucosa into glandular mucosa. There is some evidence from immunohistochemical and ultrastructural data that the cell of origin is an oesophageal-derived stem cell with the ability to multipotential differentiation.[27,28] Thus CLO epithelium shows three subtypes: cardiac and fundic types, being identical in most respects to the mature mucosa of the stomach, and intestinal type.[29]

Intestinal-type mucosa in CLO has rather characteristic features, often being villiform and showing such profound immature (or incomplete) morphological and histochemical features that it has been termed "specialised intestinal metaplasia."[30] It is notable that mature (or complete) IM is unusual in CLO. Paneth cells are a distinctive feature of complete IM: they are seen in CLO but are usually only demonstrated sporadically.[31,32] The term specialised intestinal metaplasia tends to infer that the IM of CLO is specific, and perhaps pathognomonic, to that condition. We, and others,[33–35] have yet to be persuaded that there is any feature, whether identified by morphological, histochemical, immunohistochemical or any other methodology, that is exclusive for CLO.

Morphologically the incomplete intestinal metaplasia of CLO closely resembles that in the stomach and shows the same mucin phenotype.[33,34,36] Electron microscopy demonstrates characteristic features with intermediate cells, uncommitted to a specific lineage, being conspicuous.[27,37] Immunohistochemical studies have demonstrated the intestinal phenotype with the small intestinal-type protein, villin, readily demonstrable[38] and monoclonal antibodies suggesting a colonic phenotype.[39] More recently, cytokeratin immunohistochemistry has hinted at an oesophageal specificity.[28,40,41] However none of these studies, or indeed any other, has convincingly shown evidence that any of these phenotypes (or indeed their combination) are not seen in incomplete IM in the stomach.

CLO mucosa is characterised by a patchwork of the three mucosal types and this is often useful, pathologically, in corroborating a CLO diagnosis. Furthermore, the gastric-type mucosa often shows structural disorganisation and this 'non-organoid' pattern is also a diagnostic pointer. CLO mucosa is also often inflamed, especially when the patient is not treated with acid suppressing drugs. Other features, such as a villous architecture, double muscularis mucosae and Paneth cells, may also aid the recognition of CLO.[31,34,42] All of these morphological features can only be regarded as corroborating a diagnosis of CLO. So, can the pathologist ever make a definitive diagnosis of CLO, from biopsy material, in the absence of any other information? The answer is unequivocally in the affirmative but, sadly, only in the small minority of diagnostic biopsy procedures.

Biopsy material can contain native oesophageal structures, most notably the oesophageal gland duct.[43] The submucosal glands of the oesophagus can also be seen but these are often too deep for biopsies to contain them.[32] In one study of 49 'diagnostic' biopsies, such native oesophageal structures were demonstrated in just 10% of the biopsies.[32] The United Kingdom Barrett's Oesophagus Registry (UKBOR) has recently commissioned a multi-centre study of diagnostic biopsy material and a pilot study has demonstrated such native oesophageal structures in 15% of these biopsies.[20] Thus the pathologist can make a definitive diagnosis of CLO, when there is juxtaposition of these native structures to glandular mucosa in the same biopsy fragment, but this is only demonstrated in less than 1 in 6 diagnostic procedures. Although CLO may be diagnosed with reasonable accuracy either by endoscopic appearance or histologically in the 10–15% of cases when native oesophageal structures are seen, **histological corroboration of endoscopically visible columnarisation results in highest diagnostic accuracy.** (Recommendation grade C).

Once again the importance of differentiating traditional (>3 cms segment) and short segment CLO, on the one hand, and IM at the cardia cannot be emphasised too highly. The above comments only apply strictly to traditional and short segment disease. CIM at the cardia is, unavoidably a histological diagnosis and requires only the demonstration of intestinalisation, at the SCJ, in an otherwise endoscopically normal oesophagus.[2]

This review of the histopathology of CLO has shown that, in the majority of diagnostic biopsies from CLO patients, the histology can merely corroborate a diagnosis of CLO and cannot definitively and independently make such a diagnosis. The picture is particularly complicated by the presence of a hiatal hernia.[26] Such a hernia is lined, usually, by specialised gastric mucosa that can demonstrate IM. It is perhaps extraordinary that, to the authors' knowledge, that there has not been a rigorous structured histopathological study of the mucosa of the sliding hiatal hernia. The two conditions, sliding hiatal hernia and CLO, frequently co-exist[26] and the histopathology of mucosal biopsies can be similar and, often, identical.

HOW SHOULD PATHOLOGISTS REPORT CLO?

It is vitally important for accurate diagnosis that the histopathologist is made fully aware of the precise site of biopsies taken by the endoscopist in terms of distance from the incisor teeth and relation to the oesophago-gastric junction. (Recommendation grade C). An erroneous diagnosis can easily be made if the endoscopist biopsies the oesophago-gastric junction and infers to the pathologist that the oesophagus has been biopsied. Any demonstration of intestinalisation in this circumstance will suggest, to the pathologist, true CLO whereas the appropriate diagnosis may well be IM at the cardia. As traditional and short segment CLO on the one hand and IM on the other have such different aetiological, epidemiological, pathogenic and (probably) neoplastic implication, the distinction is clearly of much importance.

These authors believe that the following categories are appropriate for the reporting of "diagnostic" biopsies from presumed traditional and short segment CLO:

1. **Biopsies diagnostic for CLO**
   Native oesophageal structures are present with juxtaposition to metaplastic glandular mucosa, whether intestinalised or not. (10–15% of cases)
2. **Biopsies corroborative of an endoscopic diagnosis of CLO, if taken from the anatomical oesophagus**
   Intestinalised metaplastic glandular mucosa with or without non-organoid arrangement, villous architecture, patchwork of different glandular types, etc. This could potentially still represent incomplete intestinal metaplasia in the stomach, especially in a hiatal hernia or IM at the cardia.
3. **Biopsies in keeping with, but not specific for, CLO, if taken from the anatomical oesophagus.**
   Gastric-type mucosa of either fundic or cardiac type without IM. Patchwork appearance is still possible as is a non-organoid arrangement. Such appearances could, however, represent the oesophago-gastric junction or the stomach with or without a hiatal hernia.
4. **Biopsies without evidence of CLO.**
   Oesophageal-type squamous mucosa with no evidence of glandular epithelium.
   (Recommendation grade C).

Much has been made of the importance of demonstrating IM and it has been suggested that CLO should be classified according to its presence.[30] Some have gone further to suggest that only those cases of CLO with ("specialised") intestinalised mucosa should be regarded as CLO because of the important association between intestinalised mucosa and neoplasia in the oesophagus. This, however, fails to recognise

the inevitable sampling problem of diagnostic biopsies. There are many situations where initial diagnostic biopsies fail to show intestinalised mucosa and yet subsequent biopsies have demonstrated it. Furthermore, comprehensive studies of traditional CLO in which segmental and quadrantic biopsies throughout the CLO segment have been taken at multiple time points have shown that all patients with at least 3 cms of CLO will demonstrate intestinalised mucosa somewhere in the segment at some time.[44,45] Thus it may well be that the importance of demonstrating IM, in traditional CLO at least, has been overplayed.

If histological assessment of presumptive CLO causes pathologists such problems, is cytology of any further value? Initial reports suggested that cytology may provide a useful diagnostic adjunct to histology by its ability to demonstrate goblet cells.[46,47] However, the comments concerning histology are apposite here. Intestinalised mucosa is not specific to CLO and the consensus view is that cytology has such low sensitivity and specificity for a diagnosis of CLO that it should not be used, unless neoplasia is suspected.[48,49] Dysplasia and carcinoma can certainly be diagnosed by cytology and, with caution, can provide useful information.[47,50,51] Balloon abrasion cytology, as a non-endoscopic procedure, may have some merit for the detection of neoplasia in CLO[52] but it is no proven value for the routine diagnosis of CLO itself.[53]

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REFERENCES

1 **Murphy PP**, Ballinger PJ, Massey BT, Shaker R, Hogan WJ. Discrete ulcers in Barrett's esophagus: relationship to acute gastrointestinal bleeding. *Endoscopy* 1998;**30**:367–70**. III**
2 **Sharma P**, Morales TG, Sampliner RE. Short segment Barrett's esophagus—the need for standardization of the definition and of endoscopic criteria. *Am.J.Gastroenterol.* 1998;**93**:1033–6. **III**
3 **Sharma P**, Weston AP, Morales T, Topalovski M, Mayo MS, Sampliner RE. Relative risk of dysplasia for patients with intestinal metaplasia in the distal oesophagus and in the cardia. *Gut* 2000;**46**:9–13. **IIb**
4 **Eloubeidi MA**, Provenzale D. Does this patient have Barrett's esophagus? The utility of predicting Barrett's esophagus at the index endoscopy. *Am J Gastroenterol.* 1999;**94**:937–43. **IIb**
5 **Delvaux M**, Korman LY. Minimal standard terminology. *Endoscopy* 2000;**32**:159–88. **IV**
6 **Ackroyd R**, Wakefield SE, Williams JL, Stoddard CJ, Reed MW. Surveillance of Barrett's esophagus: a need for guidelines? *Dis Esophagus* 1997;**10**:185–9. **IV**
7 **Stein JH**, et al. Esophageal cancer: screening and surveillance. Results of a consensus conference held at the VIIth World Congress of the International Society for Diseases of the Esophagus. *Dis Esophagus* 1996;**9 suppl 1**:3–19. **IV**
8 **Falk GW**, Rice TW, Goldblum JR, Richter JE. Jumbo biopsy forceps protocol still misses unsuspected cancer in Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc* 1999;**49**:170–6. **IIb**
9 **Kim SL**, Waring JP, Spechler SJ, Sampliner RE, Doos WG, Krol WF *et al.* Diagnostic inconsistencies in Barrett's esophagus. Department of Veterans Affairs Gastroesophageal Reflux Study Group. *Gastroenterology* 1994;**107**:945–9. **IIb**
10 **Levine DS**. Management of dysplasia in the columnar-lined esophagus. *Gastroenterol Clin North Am* 1997;**26**:613–34. **IIb**
11 Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology* 1993;**105**:40–50. **IIb**
12 **Jornod P**, Stepinac T, Lange N, et al. Barrett's esophagus: high detection rate for dysplasia and early adenocarcinoma by combined screening with 4–quadrant biopsies and photodynamic detection. *Gastroenterology* 2000; 118 (supp 2) : A3763.
13 **Axon A**, Lambert R, Robaszkiewicz M, Rosch T, Sonnenberg A. The Second European Endoscopy Forum. Twenty questions on the esophagogastric junction. *Endoscopy* 2000;**32**:411–8. **IV**
14 **Eisen GM**, Montgomery EA, Azumi N, Hartmann DP, Bhargava P, Lippman M *et al.* Qualitative mapping of Barrett's metaplasia: a pre-requisite for intervention trials. *Gastrointest Endosc* 1999;**50**:814–8. **IIb**
15 **Canto MI**, Setrakian S, Petras RE, Blades E, Chak A, Sivak-MV J. Methylene blue selectively stains intestinal metaplasia in Barrett's esophagus. *Gastrointest Endosc* 1996;**44**:1–7. **IIb**
16 **Morales TG**, Bhattacharyya A, Camargo E, Johnson C, Sampliner RE. Methylene blue staining for intestinal metaplasia of the gastric cardia with follow-up for dysplasia. *Gastrointest Endosc* 1998;**48**:26–31. **IIb**
17 **Messmann H**, Knuchel R, Baumler W, Holstege A, Scholmerich J. Endoscopic fluorescence detection of dysplasia in patients with Barrett's esophagus, ulcerative colitis, or adenomatous polyps after 5–aminolevulinic acid-induced protoporphyrin IX sensitization. *Gastrointest Endosc* 1999;**49**:97–101. **IIb**
18 **Guelrud M**, Herrera I. Acetic acid improves identification of remnant islands of Barrett's epithelium after endoscopic therapy. *Gastrointest Endosc* 1998;**47**:512–5. **IIb**
19 **Cameron AJ**. Epidemiology of columnar-lined esophagus and adenocarcinoma. *Gastroenterol Clin North Am* 1997;**26**:487–94 **III.**
20 **Biddlestone LR**, Bailey TA, Whittles CE, Shepherd NA. The clinical and molecular pathology of Barrett's oesophagus. In Kirkham N, Lemoine NR, eds. *Progress in Pathology*. London: Greenwich Medical media, 2000, in press. **III**
21 **Atkinson M**, Iftikhar SY, James PD, Robertson CS, Steele RJ. The early diagnosis of oesophageal adenocarcinoma by endoscopic screening. *Eur J Cancer Prev.* 1992;**1**:327–30. **IV**
22 **Armstrong D**. Reflux disease and Barrett's oesophagus. *Endoscopy* 1994;**26**:9–19. **IV**
23 **Blustein PK**, Beck PL, Meddings JB, Van Rosendaal GM, Bailey RJ, Lalor E *et al.* The utility of endoscopy in the management of patients with gastroesophageal reflux symptoms. *Am J Gastroenterol* 1998;**93**:2508–12 **IV**
24 **Anonymous**. Surveillance of Barrett's oesophagus. Wessex Institute for Health Research and Development (102). 1999 **III**
25 **Lagergren J**, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;**340**:825–31 **IIb.**
26 **Cameron AJ**. Barrett's esophagus: prevalence and size of hiatal hernia. *Am J Gastroenterol* 1999; **94**:2054–9. **III**
27 **Shields HM**, Zwas F, Antonioli DA, Doos WG, Kim S, Spechler SJ. Detection by scanning electron microscopy of a distinctive esophageal surface cell at the junction of squamous and Barrett's epithelium. *Dig Dis Sci* 1993;**38**:97–108. **III**
28 **Salo JA**, Kivilaakso EO, Kiviluoto TA, Virtanen IO. Cytokeratin profile suggests metaplastic epithelial transformation in Barrett's oesophagus. *Ann Med* 1996;**28**:305–9. **III**
29 **Paull A**, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's esophagus. *N Engl J Med* 1976;**295**:476–80. **III**
30 **Spechler SJ**. The columnar-lined esophagus. History, terminology, and clinical issues. *Gastroenterol Clin North Am* 1997;**26**:455–66. **IV**
31 **Schreiber DS**, Apstein M, Hermos JA. Paneth cells in Barrett's esophagus. *Gastroenterology* 1978;**74**:1302–4. **III**
32 **Takubo K**, Nixon JM, Jass JR. Ducts of esophageal glands proper and paneth cells in Barrett's esophagus: frequency in biopsy specimens. *Pathology* 1995;**27**:315–7. **III**
33 **Hamilton SR**, Smith RR, Cameron JL. Prevalence and characteristics of Barrett esophagus in patients with adenocarcinoma of the esophagus or esophagogastric junction. *Hum Pathol* 1988;**19**:942–8. **III**
34 **Haggitt RC**. Barrett's esophagus, dysplasia, and adenocarcinoma. *Hum Pathol* 1994;**25**:982–93. **III**
35 **Spechler SJ**, Goyal RK. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. *Gastroenterology* 1996;**110**:614–21. **IV**
36 **Jass JR**. Mucin histochemistry of the columnar epithelium of the oesophagus: a retrospective study. *J Clin Pathol* 1981;**34**:866–70. **III**
37 **Levine DS**, Rubin CE, Reid BJ, Haggitt RC. Specialized metaplastic columnar epithelium in Barrett's esophagus. A comparative transmission electron microscopic study. *Lab Invest* 1989;**60**:418–32**. III**
38 **MacLennan AJ**, Orringer MB, Beer DG. Identification of intestinal-type Barrett's metaplasia by using the intestine-specific protein villin and esophageal brush cytology. *Mol Carcinog* 1999;**24**:137–43. **III**
39 **Das KM**, Prasad I, Garla S, Amenta PS. Detection of a shared colon epithelial epitope on Barrett epithelium by a novel monoclonal antibody. *Ann Intern Med* 1994;**120**:753–6. **III**
40 **Boch JA**, Shields HM, Antonioli DA, Zwas F, Sawhney RA, Trier JS. Distribution of cytokeratin markers in Barrett's specialized columnar epithelium. *Gastroenterology* 1997;**112**:760–5. **III**
41 **Ormsby AH**, Goldblum JR, Rice TW, Richter JE, Falk GW, Vaezi MF *et al.* Cytokeratin subsets can reliably distinguish Barrett's esophagus from intestinal metaplasia of the stomach. *Hum Pathol* 1999;**30**:288–94. **IIb**
42 **Takubo K**, Sasajima K, Yamashita K, Tanaka Y, Fujita K. Double muscularis mucosae in Barrett's esophagus. *Hum Pathol* 1991;**22**:1158–61. **III**
43 **Biddlestone LR**, Barham CP, Wilkinson SP, Barr H, Shepherd NA. The histopathology of treated Barrett's esophagus: squamous reepithelialization after acid suppression and laser and photodynamic therapy. *Am J Surg Pathol* 1998;**22**:239–45. **III**
44 **Gore S**, Healey CJ, Sutton R, Eyre B, I, Gear MW, Shepherd NA *et al.* Regression of columnar lined (Barrett's) oesophagus with continuous omeprazole therapy. *Aliment Pharmacol Ther* 1993;**7**:623–8. **IIa**
45 **Wilkinson SP**, Biddlestone L, Gore S, Shepherd NA. Regression of columnar-lined (Barrett's) oesophagus with omeprazole 40 mg daily: results of 5 years of continuous therapy. *Aliment Pharmacol Ther* 1999;**13**:1205–9. **IIa**

46 **Robey SS**, Hamilton SR, Gupta PK, Erozan YS. Diagnostic value of cytopathology in Barrett esophagus and associated carcinoma. *Am J Clin Pathol* 1988;**89**:493–8. **III**
47 **Riddell RH**. Early detection of neoplasia of the esophagus and gastroesophageal junction. *Am J Gastroenterol* 1996;**91**:853–63. **III**
48 **Alexander JA**, Jones SM, Smith CJ, Doull JA, Gietzen TH, Rathgaber SW. Usefulness of cytopathology and histology in the evaluation of Barrett's esophagus in a community hospital. *Gastrointest Endosc* 1997;**46**:318–20. **III**
49 **Antonioli DA**, Wang HH. Morphology of Barrett's esophagus and Barrett's-associated dysplasia and adenocarcinoma. *Gastroenterol Clin North Am* 1997;**26**:495–506. **III**
50 **Hardwick RH**, Morgan RJ, Warren BF, Lott M, Alderson D. Brush cytology in the diagnosis of neoplasia in Barrett's esophagus. *Dis Esophagus* 1997;**10**:233–*7* **III.**
51 **Hughes JH**, Cohen MB. Is the cytologic diagnosis of esophageal glandular dysplasia feasible? *Diagn Cytopathol* 1998;**18**:312–6. **III**
52 **Falk GW**, Chittajallu R, Goldblum JR, Biscotti CV, Geisinger KR, Petras RE *et al*. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. *Gastroenterology* 1997;**112**:1787–97. **III**
53 **Fennerty MB**, DiTomasso J, Morales TG, Peterson D, Karmakar A, Fernandez T *et al*. Screening for Barrett's esophagus by balloon cytology. *Am J Gastroenterol* 1995;**90**:1230–2. **III**

Natural history of columnar-lined oesophagus

R C Heading, S E A Attwood

EXECUTIVE SUMMARY

The length of the columnarised segment is related to the severity of underlying GORD which is typically present for up to 10 years before metaplasia to acid-resistant columnar epithelium develops. Once established, it appears that the length of the columnarised segment remains relatively static. However, progression has been described, but this is unlikely to exceed 2–3cm and may, in part, relate to inter-observer variation.

Squamous re-epithelialization may occur spontaneously as an intermittent process but more extensively and durably following PPI therapy or fundoplication. Macroscopic regression is unusual but may occur spontaneously in short segments of columnarisation. Partial regression has been described following intensive PPI therapy and fundoplication, although this occurs in only a small proportion of those treated and it is possible that, in part, these appearances may result from inter-observer variation and post-surgical changes.

Ulceration and stricture occur with a mean incidence of 30% in published series. These changes usually occur in those with the most severe pathophysiological abnormalities and are situated close to the site of maximum inflammatory response, usually the proximal part of the columnarised segment.

Dysplasia develops in around 5% of patients with CLO. In those developing low-grade dysplasia, 10–50% may progress to high-grade dysplasia and adenocarcinoma over 2–5 years. The remainder remain static if there is unequivocal low-grade dysplasia, but apparent regression can occur in cases where the diagnosis is not robust. In the presence of high-grade dysplasia, 40–50% will have a focus of invasive adenocarcinoma at the time of diagnosis. When followed prospectively 34% will develop adenocarcinoma within five years, the remainder remaining stable or regressing to low-grade dysplasia.

Adenocarcinoma occurs with an incidence of 1–1.5% per annum and has the most rapidly increasing incidence of any solid tumour in the West. The incidence and rate of change in incidence over the last three decades appear higher in the UK and Western Europe than the USA.

Notwithstanding the neoplastic risk in CLO, only 2–3% of Barrett's patients die from cancer and overall life expectancy is little different from those without CLO.

INTRODUCTION

There are no symptoms specific to CLO, symptoms being due to gastro-oesophageal reflux disease (GORD) or complications such as stricture or tumour[1]

Most CLO patients have reflux symptoms including regurgitation and heartburn. A review of studies examining the symptoms experienced by patients with Barrett's revealed that 72% had heartburn, up to 65% experienced dysphagia and 57% had regurgitation[1].

A long history of GORD correlates with the presence of CLO[2], but no specific symptom or combination of symptoms are predictive of CLO compared to oesophagitis.

Paradoxically patients with uncomplicated CLO have fewer symptoms than those with oesophagitis alone, despite having worse reflux on pH testing[3].

MECHANISM OF COLUMNARISATION & TIME COURSE OF CLO DEVELOPMENT

CLO is now generally believed to be an acquired condition due to its high prevalence in patients with severe GORD, its increasing prevalence with age[4] and the evidence from animal models of Bremner[5] and others. CLO occurs as a consequence of tissue injury due to GORD.

The current favoured hypothesis is the progressive theory of evolution where the changes begin at a microscopic level at the squamo-columnar junction (SCJ). This initially comprises a change from neutral to acid mucin production and eventually the formation of fully formed goblet cells. This may gradually increase to form a macroscopic columnar segment that lengthens until an adequate section of the oesophagus is protected from reflux injury. It is now generally held that the extent of the metaplastic segment correlates with the severity of reflux[6].

The time scale over which a long segment CLO develops is currently unknown but has been reported to occur within 10 years of initiation of GORD by resection of the gastro-oesophageal junction[7]. Once formed, the segment length appears to remain relatively static, with very little if any variation in length in the majority of patients[4,8]. This along with the lack of definite evidence for the progressive development of CLO provokes an alternative hypothesis, first proposed by Cameron and colleagues[4]. This instantaneous field change theory implies that in response to a specific reflux injury, the epithelium undergoes a metaplasia to form a long segment immediately, with the length of the segment depending on the severity of the insult and remaining constant thereafter. However, some authors have documented progressive increase in the length of the metaplastic segment over time[9,10].

There is good agreement in published reports that the average age of patients newly diagnosed with CLO is around 60–65 years, with females tending to be older than males. Cameron et al[4,48] have presented evidence that CLO probably develops on average some 20 years earlier and that in an overwhelming majority of individuals who have CLO, the condition is never detected.

BENIGN COMPLICATIONS

CLO is an inflammatory condition secondary to GORD, therefore it is not surprising that oesophagitis is also present in up to 80% of cases (see table).

The degree of inflammation within the columnarised segment is variable. Fitzgerald *et al* showed 68% of cases to have little macroscopic inflammation, but on microscopic examination most have evidence of inflammation with T cell, neutrophil and eosinophil infiltration which correlated with the degree of inflammation[11]. They further showed that the histopathological inflammation increased proximally in the

CLO segment and this was associated with elevated IL-8 pro-inflammatory cytokine levels[12]. This proximal part of the CLO segment is known to be the area with the greatest risk of inflammatory complications such as stricture formation.

Stricture

In early retrospective series, strictures were present in up to 100% of cases[13] but in prospective series, stricture rates of 15% to 40% are found. They may occur at any level within the distal oesophagus but are most frequent near the squamo-columnar junction[14].

Ulceration

The development of ulceration within the CLO segment is common, occurring in up to 60% of cases in reported series. They may be found incidentally or may present with complications such as bleeding (up to 50%)[15] or more rarely with perforation into the mediastinum[16] or fistula formation. Fistulation due to erosion through the oesophageal wall into adjacent structures has been reported into the aorta[17], pericardium[18] and respiratory tree[19].

Authors	Patients	Stricture (%)	Ulcer (%)
Borrie[13]	45	100	2
Herlihy[20]	20	40	10
Cooper[21]	52	19	44
McCallum[22]	312	34	60
Williamson[23]	212	–	14
Murphy[15]	78	–	46

MALIGNANT COMPLICATIONS:

Dysplasia

During the development of adenocarcinoma there is a gradual increase in dysplastic features of the epithelium through low-grade dysplasia and high-grade dysplasia culminating in invasive cancer[24]. The incidence of dysplasia varies greatly among reported series, but with figures generally around 5%[25–27].

In prospective series, low-grade dysplasia is most frequently seen. This can persist, regress or progress to HGD or adenocarcinoma in a longitudinal fashion[24,27]. Further evidence for adenocarcinoma developing within areas of HGD comes from observations of high-grade dysplasia frequently adjacent to invasive adenocarcinoma[30].

There appears to be great variation in the time taken for this progression with some patients developing HGD and adenocarcinoma rapidly, some having longstanding or intermittent LGD for long periods[22] and some oscillating between LGD and HGD[24,27]. The majority of patients with LGD however do not progress to invasive cancer in the short term[25,27].

The natural history of HGD between patients is also variable. Regression from HGD to LGD is well documented as is rapid progression to cancer[24]. However most patients have persistent HGD, some for up to 4 years prior to development of invasive cancer[27].

Specimens removed from patients undergoing oesophagectomy for HGD demonstrate invasive cancer in up to 50% of cases[31]. It is important to remember while reviewing these studies that dysplastic/neoplastic changes are frequently localised within the segment, not a field change[30]. Therefore areas of higher grade dysplasia or cancer may be missed on initial biopsy, being detected on follow up biopsy, leading to the appearance of rapid progression.

Levine et al studied 70 patients undergoing prospective surveillance[32]. 12 were found to have invasive cancer on early follow up (mean 2 months). 15 progressed to cancer over a mean of 27 months, while 43 remained stable or regressed during a mean of 30months follow-up.

Adenocarcinoma

Adenocarcinoma of the oesophagus and gastro-oesophageal junction is the fastest growing cancer in the western world[33]. Latest figures from the NW of England show the incidence exceeding 7 per 100,000 in men[34].

The risk of adenocarcinoma in CLO has been investigated by a number of groups in recent years. Their results are outlined below:

American Series

Author	Year	Pts	Ys f/u	Cancers	Ca/pt ys
Spechler[35]	1984	105	3	2	1:175
Sprung	1984	84	4	4	1:81
Cameron[36]	1985	104	8	2	1:441
Achkar[37]	1988	62	3	1	1:166
Williamson[38]	1991	176	3	5	1:99
Drewitz[39]	1997	170	5	4	1:208
Streitz[40]	1998	149	3	7	1:73
Katz[25]	1998	102	5	4	1:140
Weston[29]	1999	108	3.3	5	1:72

European & Others Series

Author	Year	Pts	Ys f/u	Cancers	Ca/pt ys
Robertson[41]	1988	56	3	3	1:56
Van der Veen[42]	1989	155	4	4	1:170
Hameeteman[43]	1989	50	5	5	1:52
Miros[27]	1991	81	3.6	3	1:96
Iftikar[43]	1992	102	4	4	1:100
Sanchez[45]	1995	46	3.6	2	1:104
Wright[46]	1996	166	3	6	1:83
Ferraris[28]	1997	88	3	3	1:88
Bujanda-fernandez-de-pierola[47]	1999	46	3.5	2	1:82

Combined this gives an overall risk of 1:108 patient years from worldwide studies. If split by country of study – USA studies give risk of 1:128, Europe 1:88. Interestingly when 1980's and 1990's USA studies are considered separately there is a tendency towards increasing risk from (1:185) to (1:108). However, recent analyses of published reports suggest that the risk of adenocarcinoma has been overestimated, particularly as a consequence of publication bias, and that the true risk is of the order of 1 in 200[49,50]. Accurate risk estimation is critically important to the economics of surveillance and other interventions to prevent carcinoma in CLO[51] and thus to the specification of optimal clinical management policies. Nevertheless, it remains possible that the risk differs in European and American populations and it is premature to accept the validity for the UK of a single estimate of cancer risk derived from combining all published reports.

OUTCOMES FOR CLO PATIENTS

It has been recognised for some time that survival rates of patients with CLO are virtually identical to those of age and sex matched control populations[36] and it is important to appreciate that notwithstanding the increased risk of developing oesophageal adenocarcinoma, the absolute risk of death

Author	Patients	Dysplasia at diagnosis	Pt Ys F/u	New LGD	New HGD	New dysplasia incidence (%)
Katz[25]	102	5	563	19	4	4.1
Miros[27]	81	13	290	10	1	7.5
Ferraris[28]	187	5	562	5	2	2.1
O'Connor[26]	136	excluded	570	24	4	4.9
Weston[29]	108	excluded	362	–	5	–

from this tumour is small. In a cohort study of 166 CLO patients in the Netherlands with 1440 patient-years of follow-up, 79 patients died but only 2 of the deaths were due to oesophageal carcinoma[52]. Most patients with CLO die from causes unrelated to their oesophageal disease and reducing the risk of adenocarcinoma can produce no more than a small effect on overall life expectancy.

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REFERENCES

1 **Phillips RW**, Wong RK. Barrett's esophagus. Natural history, incidence, etiology, and complications. *Gastroenterol Clin North Am*, 1991. **20**(4): p. 791–816. **III**
2 **Lieberman DA**, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. *Am J Gastroenterol*, 1997. **92**(8): p. 1293–1297. **IIb**
3 **Stein HJ**, Hoeft S, DeMeester TR. Functional foregut abnormalities in Barrett's esophagus. *J Thorac Cardiovasc Surg*, 1993. **105**(1): p. 107–111. **IIb**
4 **Cameron AJ**, Lomboy CT. Barrett's esophagus: age, prevalence, and extent of columnar epithelium. *Gastroenterology*, 1992. **103**(4): p. 1241–1245. **III**
5 **Bremner CG**, Lynch VP, Ellis FH, Jr. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. *Surgery*, 1970. **68**(1): p. 209–216. **IIa**
6 **Oberg S**, DeMeester TR, Peters JH *et al.* The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. *J Thorac Cardiovasc Surg*, 1999. **117**(3): p. 572–580. **III**
7 **Hamilton S**, Yardley J. Regeneration of cardiac type mucosa and acquisition of Barrett mucosa after esophagogastrostomy. *Gastroenterology*, 1977. **72**: p. 669–675. **III**
8 **Sampliner RE**, Garewal HS, Fennerty MB *et al.* Lack of impact of therapy on extent of Barrett's esophagus in 67 patients. *Dig Dis Sci*, 1990. **35**(1): p. 93–96. **III**
9 **Iftikhar SY**, James PD, Steele RJC et al. Length of Barrett's oesophagus; an important factor in the development of dysplasia and adenocarcinoma. *Gut* 1992 **33**: 155–58. **III**
10 **Ortiz A**, Martinez de Haro LF, Parilla P et al. Conservtive treatment versus anti-reflux surgery in Barrett's oesophagus; long term results of a prospective study. *Br J Surg* 1996, **78**: 274–78. **Ib**
11 **Fitzgerald R**, Onwuegbusi B, Saaed I *et al.* Characterisation of the inflammatory response in Barrett's oesophagus: implications for the disease pathogenesis and complications. *Gastroenterology*, 1999. **116**(4): p. A158. **III**
12 **Fitzgerald R**, Onwuegbusi B, Saaed I *et al.* Differential degree of inflammation and cytokine expression in distal compared with proximal Barrett's oesophagus may explain site specific complications. *Gastroenterology*, 1999. **116**(4): p. A402. **III**
13 **Borrie J**, Goldwater L. Columnar lined esophagus: Assessment of aetiology and treatment: A 22 year experience. *J Thorac Cardiovasc Surg*, 1976. **71**: p. 825–834. **III**
14 **Sjogren R**, Johnson L. Barrett's oesophagus: A review. *Am J Med*, 1983. **74**: p. 313–321. IV
15 **Murphy PP**, Ballinger PJ, Massey BT *et al.* Discrete ulcers in Barrett's esophagus: relationship to acute gastrointestinal bleeding. *Endoscopy*, 1998. **30**(4): p. 367–370. **III**
16 **Limburg AJ**, Hesselink EJ, Kleibeuker JH. Barrett's ulcer: cause of spontaneous oesophageal perforation. *Gut*, 1989. **30**(3): p. 404–405. **III**
17 **Katyal D**, Jewell LD, Yakimets WW. Aorto-esophageal fistula secondary to benign Barrett's ulcer: a rare cause of massive gastrointestinal hemorrhage [see comments]. *Can J Surg*, 1993. **36**(5): p. 480–482. **III**
18 **Shah S**, Saum K, Greenwald BD *et al.* Esophagopericardial fistula arising from Barrett's esophagus. *Am J Gastroenterol*, 1998. **93**(3): p. 465–467. **III**
19 **Diehl JT**, Thomas L, Bloom MB *et al.* Tracheoesophageal fistula associated with Barrett's ulcer: the importance of reflux control. *Ann Thorac Surg*, 1988. **45**(4): p. 449–450. **III**
20 **Herlihy KJ**, Orlando RC, Bryson JC *et al.* Barrett's esophagus: clinical, endoscopic, histologic, manometric, and electrical potential difference characteristics. *Gastroenterology*, 1984. **86**(3): p. 436–443. **IIb**
21 **Cooper BT**, Barbezat GO. Barrett's oesophagus: a clinical study of 52 patients. *Q J Med*, 1987. **62**(238): p. 97–108. **III**
22 **McCallum R**, Polepalle S, Davenport K. Progress report on ACG Barrett's Esophagus Study. *Am J Gastroenterol*, 1990. **85**: p. A51. **IV**
23 **Williamson WA**, Ellis FH, Jr., Gibb SP *et al.* Barrett's ulcer: a surgical disease? *J Thorac Cardiovasc Surg*, 1992. **103**(1): p. 2–6. **IV**
24 **Reid BJ**, Blount PL, Rubin CE *et al.* Flow-cytometric and histological progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. *Gastroenterology*, 1992. **102**(4 Pt 1): p. 1212–1219. **III**
25 **Katz D**, Rothstein R, Schned A *et al.* The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. *Am J Gastroenterol*, 1998. **93**(4): p. 536–541. **III**
26 **O'Connor J**, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. *Am J Gastroenterol*, 1999. **94**(8): p. 2037–2042. **III**
27 **Miros M**, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. *Gut*, 1991. **32**(12): p. 1441–1446. **III**
28 **Ferraris R**, Bonelli L, Conio M *et al.* Incidence of Barrett's adenocarcinoma in an Italian population: an endoscopic surveillance programme. Gruppo Operativo per lo Studio delle Precancerosi Esofagee (GOSPE). *Eur-J-Gastroenterol-Hepatol*, 1997. **9**(9): p. 881–885. **III**
29 **Weston AP**, Badr AS, Hassanein RS. Prospective multivariate analysis of clinical, endoscopic, and histological factors predictive of the development of Barrett's multifocal high-grade dysplasia or adenocarcinoma . *Am J Gastroenterol*, 1999. **94**(12): p. 3413–3419. **III**
30 **Menke Pluymers MB**, Mulder AH, Hop WC *et al.* Dysplasia and aneuploidy as markers of malignant degeneration in Barrett's oesophagus. The Rotterdam Oesophageal Tumour Study Group. *Gut*, 1994. **35**(10): p. 1348–1351. **IIb**
31 **Altorki N**, Sungawa M, Little A *et al.* High-grade dysplasia in the columnar lined esophagus. *Am J Surg*, 1991. **161**: p. 97. **III**
32 **Levine D**, Haggitt R, Irvine S *et al.* Natural history of high grade dysplasia in Barrett's esophagus. *Gastroenterol*, 1996. **110**: p. A550. **III**
33 **Blot WJ**, Devesa SS, Kneller RW *et al.* Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *Jama*, 1991. **265**(10): p. 1287–1289. **III**
34 **Byrne JP**, Parry JM, Woodman CJB *et al.*, The epidemiology of adenocarcinoma of the oesophagus and gasric cardia in the North West of England., in *O.E.S.O. The esophagogastric junction: 420 Questions.*, R Giuli, Editor. 1998, John Libbey Eurotext: Paris. p. 1140–1144. **III**
35 **Spechler SJ**, Robbins AH, Rubins HB *et al.* Adenocarcinoma and Barrett's esophagus. An overrated risk? *Gastroenterology*, 1984. **87**(4): p. 927–933. **IV**
36 **Cameron AJ**, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. *N Engl J Med*, 1985. **313**(14): p. 857–859. **III**
37 **Achkar E**, Carey W. The cost of surveillance for adenocarcinoma complicating Barrett's esophagus. *Am J Gastroenterol*, 1988. **83**(3): p. 291–294. IV
38 **Williamson WA**, Ellis FH, Jr., Gibb SP *et al.* Barrett's esophagus. Prevalence and incidence of adenocarcinoma. *Arch Intern Med*, 1991. **151**(11): p. 2212–2216. **III**
39 **Drewitz DJ**, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol*, 1997. **92**(2): p. 212–215. **III**
40 **Streitz JM**, Jr., Ellis FH, Jr., Tilden RL *et al.* Endoscopic surveillance of Barrett's esophagus: a cost-effectiveness comparison with mammographic surveillance for breast cancer. *Am J Gastroenterol*, 1998. **93**(6): p. 911–915. **III**
41 **Robertson CS**, Mayberry JF, Nicholson DA *et al.* Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus. *Br J Surg*, 1988. **75**(8): p. 760–763. III
42 **Van der Veen AH**, Dees J, Blankensteijn JD *et al.* Adenocarcinoma in Barrett's oesophagus: an overrated risk. *Gut*, 1989. **30**(1): p. 14–18. **IV**
43 **Hameeteman W**, Tytgat GN, Houthoff HJ *et al.* Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology*, 1989. **96**(5 Pt 1): p. 1249–1256. **III**
44 **Iftikhar SY**, James PD, Steele RJ *et al.* Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. *Gut*, 1992. **33**(9): p. 1155–1158. **III**
45 **Sanchez Robles C**, Santalla Pecina F, Retamero Orta MD. Barrett esophagus. An epidemiological study in an area of Spain. *Rev Esp Enferm Dig*, 1995. **87**(5): p. 353–355. **III**
46 **Wright TA**, Gray MR, Morris AI *et al.* Cost effectiveness of detecting Barrett's cancer. *Gut*, 1996. **39**(4): p. 574–579. **III**
47 **Bujanda Fernandez de Pierola L**, Munoz Villafranca C, Sanchez Martinez A *et al.* Adenocarcinoma in Barrett's esophagus. A retrospective study of 46 patients followed during 3.5 years. *An Med Interna*, 1999. **16**(4): p. 178–180. **III**
48 **Cameron AJ**, Zinsmeister AR, Ballard DJ, Carney JA. Prevalence of columnar-lined (Barrett's) .esophagus. *Gastroenterology* 1990. **99**: p.918–922. **III**
49 **Shaheen NJ**, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology,* 2000**. 119**. p.333–338. **IV**
50 P**rovenzale D**, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. *Am J Gastroenterol* 1999. **94** p. 2043–2053. **IV**
51 **Spechler SJ**. Barrett's esophagus: an overrated cancer risk factor. *Gastroenterology* 2000. **119**. p.587–589. **IV**
52 V**an der Burgh A**, Dees J, Hop WCJ, Van Blankenstein M. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. *Gut* 1996 **39** p.5–8. **III**

Progression to cancer and risk factors

J A Jankowski

EXECUTIVE SUMMARY

Important clinical risk factors for progression to adenocarcinoma include male gender, age >45, "extended segment" (>8cm) disease, duration of reflux history, early age of onset of GORD, duodeno-gastro-oesophageal reflux, mucosal damage (ulceration and stricture) and uncommonly, family history. Recommendation grade – see Table 1.

Progression of CLO to cancer occurs as a consequence of locally produced cytokines and bile acids in the refluxate creating a microenvironment which directly affects metaplastic stem cells resulting in a stepwise progression, involving a series of molecular events through metaplasia, dysplasia and finally adenocarcinoma.

Whilst in general terms molecular markers such as expression of P53, P16 and APC and aneuploidy are not accurate predictors of malignant transformation, **they have been recommended in the confines of research studies as surrogates for adenocarcinoma risk but hard evidence is currently lacking. There are currently no verified markers of heritable risk of oesophageal adenocarcinoma** Recommendation grade C.

Demonstration of the importance of COX-2 and cytokines such as TNF alpha in the process of neoplastic progression and the ability to inhibit these pharmacologically offers the opportunity to study the potential for chemo-prevention of neoplastic progression.

INTRODUCTION

The age-adjusted mortality rates for oesophageal and gastro-oesophageal junction cancer have increased steadily since the early 1970's to >6/100,000 and >3/100,000 population respectively[1]. Despite improvements in multi-modality therapy and surgical techniques, survival has not improved significantly suggesting that alternative strategies for identification and treatment are needed.

PREDISPOSING FACTORS TO CANCER RISK

The incidence of intestinal metaplasia (IM) of both the oesophagus and the gastric cardia, termed columnar-lined oesophagus (CLO) and intestinal metaplasia of the cardia(CIM)respectively, are also increasing. This metaplastic tissue is believed to have a pre-malignant potential and in the case of CLO is related to significant bile and acid reflux disease[2]. It is estimated that 8% of patients undergoing routine endoscopy and 3% of the adult population have CLO of at least 1 cm[3]. Furthermore 17% of patients undergoing routine endoscopy and 6% of the adult population may have CIM[3,4]. These metaplastic lesions are characterised by goblet cell-containing mucin-secreting epithelium, which replaces the native stratified squamous or transitional zone epithelium. It has been suggested that metaplastic changes progress through a sequence from metaplasia through dysplasia to frank adenocarcinoma (2) with 5–15% of individuals with CLO and 2–5% with CIM demonstrating dysplasia. The exact risk of progressing to adenocarcinoma is difficult to assess but estimates for the progression in CLO range from a 30 to 150 fold increase in risk of developing cancer compared with the normal population. Conventional clinical risk factors include male gender, age greater than 40 years, a metaplastic segment over 8 cm, evidence of duodeno-gastric-oesophageal reflux, previous gastric surgery, history of reflux over 10 years duration, symptoms of reflux greater than twice per week, obesity and family history of gastro-oesophageal cancer. Other factors including cigarette smoking, early age of reflux initiation and severity of oesophageal reflux including stricture formation have proven more controversial as independent risk factors.

In summary, **important clinical risk factors for progression to adenocarcinoma include male gender, age >45, "extended segment (>8cm) disease", duration of**

Table 1 Clinical risk factors predisposing to Barrett's adenocarcinoma

	Highest Risk	Lowest Risk	Categories of evidence for recommendations for surveillance
Gender	Male	Female	B
Age	> 45 years	< 40 years	B
Length of BM	> 8cm	< 3 cm	B
Severity of reflux symptoms	Severe and Frequent (>3 times /week)	Mild and Infrequent (< 1 time/week)	B
Chronicity	> 10 years	< 1 year	B
Race	White	Black	B
Body Mass Index	Obesity	Normal weight	B
Family history	Gastric cancer	None	B
Drug therapy	Nitrates, benzodiazines, Anticholinergics, theophyllines	Non-steroidal anti-inflammatory drugs	C
Helicobacter	absent	present	C
Cigarette smoking	Heavy smokers	Non-smoker	C
Mucosal damage	Ulceration or stricture in Barrett's metaplasia	Intact mucosa	B
Duodeno-gastro-oesophageal reflux	Markedly present(high Bilitec levels)	Mild or absent	B

reflux history, early age of onset of GORD, duodeno-gastro-oesophageal reflux, mucosal damage (ulceration and stricture) and uncommonly, family history.(Recommendation grade B–C).

The increased cancer risk associated with BO has led many centres to establish surveillance programmes in an attempt to identify dysplastic changes or early adenocarcinoma when lesions may still be curable[5]. While the available evidence does indicate that cancers detected in surveillance programmes are at an earlier and frequently curable stage, there is considerable controversy about the cost-effectiveness of this intervention[6,7]. As a consequence, interest has been rekindled in primary prevention strategies aimed at reducing the intitiation of CLO or CIM or detecting additional risk factors which more accurately detect the subgroups which will progress to malignancy.

MOLECULAR CHANGES IN THE METAPLASIA-DYSPLASIA-CARCINOMA SEQUENCE

Molecular changes in dysplastic epithelium which have been utilised as surrogate markers of impending cancer risk include p53 mutations, p16 mutations, cyclin D1 over expression, decreased E-cadherin expression and loss of heterozygosity of adenomatosis polyposis coli gene. Identification of these alterations, however, has not spread to the vast majority of centres and therefore remains in the realm of clinical research rather than proven evidence based clinical practice[2,13].

GENETIC FACTORS

Inherited colorectal cancer syndromes have given valuable information about the mechanisms of colorectal tumour initiation and progression. Familial gastro-oesophageal cancer syndromes are relatively uncommon and heterogeneous and probably account for only 1–5% of cases, although analysis of the diffuse gastro-oesophageal cancer syndrome has recently been reported[8]. Kindred studies of familial diffuse gastric cancer have demonstrated that a germline mutation of the cell adhesion E-cadherin gene is present in some families, which results in the loss of E-cadherin expression[8]. Furthermore, analysis of sporadic gastric cancer has shown that gastric tumour stage and invasiveness are also associated with reduced expression of E-cadherin and this is in accordance with findings in breast, lung and colorectal malignancies. E-cadherin is a cell adhesion molecule and tumour suppressor protein, which is known to associate with the multifunctional cytosolic protein β-catenin in the adhesion complex[9]. Free, non-complexed, β-catenin is degraded with any minute residual protein being able to translocate to the nucleus and bind a nuclear transcription factors of the LEF-TCF family. This β-catenin/TCF complex has been shown to promote transcription of oncogenic target genes which induce proliferation such as COX-2, c-myc and Cyclin D1[9]. The level of β-catenin/TCF complexes in the nucleus may be dramatically increased in situations where adhesion complexes break down and overwhelm the degradation process. Examination of oesophageal tissue demonstrates a reduction of E-cadherin and increased nuclear localisation of β-catenin during the progression from CLO to adenocarcinoma[10].

A second inherited predisposition to gastric cancer has also been reported following work exploring the association between H.pylori and gastric cancer. Infection of the gastric corpus with H.Pylori is clearly related to the development of hypochlorhydria, atrophy and malignancy whereas infection of the antrum is related to the development of peptic ulcer disease. This divergent response cannot be fully accounted for by bacterial virulence factors alone and evidence now suggests that this is related to the host response. Recent data have demonstrated that enhancing polymorphism of IL-1B gene cluster is associated with an increased risk of developing gastric cancer[11]. Patients possessing such a polymorphism have an augmented IL-1B secretory response to H.pylori infection and it has been proposed that increased IL-1B, a known suppressor of gastric acid production, predisposes to progression along the sequence of atrophy and malignancy. Furthermore and perhaps more significantly, IL-1B and other pro-inflammatory cytokines such as TNFα, can decrease E-cadherin expression and increase catenin regulated transcription further accentuating neoplastic propensity[12]. Therefore the presence of enhancing polymorphisms of IL-1B in gastric cancer may have numerous pathological roles in the development of gastro-oesophageal malignancy. None of these genetic predispositions have strong associations in oesophageal adenocarcinoma.

Whilst in general terms, molecular markers such as expression of P53, P16 and APC and aneuploidy are not accurate predictors of malignant transformation, they have been recommended in the confines of research studies as surrogates for adenocarcinoma risk but hard evidence is currently lacking. There are currently no verified markers of heritable risk of oesophageal adenocarcinoma. (Recommendation grade C).

THERAPEUTIC IMPLICATIONS

Gastro-oesophageal metaplasia can be likened to a bubbling cauldron where the epithelial changes resulting in neoplastic behaviour may be induced or potentiated as a consequence of intestinal inflammation. A greater understanding of the molecular changes involved in this process may ultimately lead to changes in clinical management and the identification of those who are likely to progress to malignancy. Initially, identification of E-cadherin mutations and IL-IB polymorphisms found in association with gastric cancer raise the prospect of similar discoveries in oesophageal adenocarcinoma which may provide an objective basis to offer screening to high risk individuals with conventional risk factors including strong family history, presence of metaplasia or dysplasia. Secondly, we now realise that there is a scientific basis to implicate chronic inflammation in cancer development. As a consequence, the role of anti-inflammatory drugs such as non-steroidals or aspirin which have a broad range of inhibitory effects are perfect agents for chemoprevention[2]. In this regard we have already started the largest chemoprevention trial in europe called AspECT (Aspirin, Esomeprazole, Chemoprevention Trial) which will recruit between 5,000–9,000 patients with Barrett's oesophagus for chemoprevention (see Digestive Disease Centre and aspect web site, University of Leicester or CRUK clinical trials web site).

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REFERENCES

1 **Powell J**, McConkey CC, The rising trend in oesophageal adenocarcinoma and gastric cardia. Eur J Cancer Prev 1992; 1:265–9 **(IIb)**
2 **Jankowski J**, Wright NA, Meltzer S, Triadafilopoulos G, Geboes K, Casson A, Kerr D, Young LS. Molecular evolution of the metaplasia dysplasia adenocarcinoma sequence in the esophagus (MCS). Am J Pathol 1999;154:965–974. **(IV)**
3 **Spechler SJ**. The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. Gastroenterology 1999;117:218–28. **(III)**
4 **Voutilainen M**, Farkkila M, Meckilin JP, Juhola M, Sipponen P. Chronic inflammation of the gastroesophageal junction (carditis) appears to be a specific finding related to Helicobacter pylori infection and gastroesophage\al reflux. Am J Gastroenterol 1999;94:3175–80 **(III)**
5 **Morales TG** Sampliner RE. Barrett's esophagus: an update on screening, surveillance and treatment. Arch Intern Med 1999:159:1411–6. **(IV)**

6 **Bytzer P**, Christensen PB, Damkier P, Vinding K, Seersholm N. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. Am J Gastroneterol 1999;94:86–91. **(IIb)**
7 **Whittington R**. Controversies in the management of adenocarcinoma of the esophagus and esophagogastric junction. Semin Radiat Oncol 1994;4:170–178. **(IV)**
8 **Richards FM**, McKee SA, Rajpar MH, Cole TRP, Evans GR, Jankowski J, McKeown C, Sanders DSA, Maher ER. Germ-line E-cadherin gene (CDH1) mutations predispose to familial gastric and colorectal cancer. Hum Mol Genet 199;4:607–610. **(IIb)**
9 **Eastman Q**, Grosschedl R. Regulation of LEF-1?TCF transcription factors by Wnt and other signals. Curr O~pin Cell Biology 1999;11:233–240. **(III)**
10 **Bailey T**, Biddlestone L, Shepherd N, Barr H, Warner P, Jankowski J. Altered cadherin and caternin complexes in the Barrett's esophagus-dysplasia-adenocarcinoma sequence: correlation with disease progression. Am J Pathjol 1998;152:135–44. **(III)**
11 **Interleukin-1** polymorphisms associated with increased risk of gastric cancer. EM El-Omar, M Carrington, W Chow, KEL McColl, JH Bream, HA Young, J Herrera, J Lissowska, C Yauan, N Rothman, G Lanyon, M Martin, JF Fraumeni, CS Rakin, Nature 2000 23;404(6776):398–402.nature. **(IIa).**
12 **Perry I**, Tselepis C, Sanders S, Iqbal T, Cooper B, Jankowski J. The phenotype of coeliac disease can be reproduced *in vitro* by cytokine stimulation. Lab Invest 1999;79:1489–1499. **(III)**
13 **Jankowski J**, Harrison RF, Perry I, Balkwill F, Tselepis C. Seminar: Barrett's metaplasia. Lancet 2000;356:2079–85. **(IV)**

Management of non-dysplastic columnar-lined oesophagus

N A Krasner, A Watson

EXECUTIVE SUMMARY

CLO represents the extreme end of the pathophysiological spectrum of gastro-oesophageal reflux disease. There is evidence to show that the natural history of the columnarised segment, as demonstrated by stricture resolution and prevention, can be influenced by effective reflux control to justify treatment in the majority of patients. **In symptomatic patients, symptom control is an important objective of treatment but because many patients with CLO have few or no symptoms due to the relative insensitivity of columnar mucosa to acid, symptom control should not be interpreted as indicating suppression of gastro-oesophageal reflux.** (Recommendation grade B)

PPI therapy is an attractive form of treatment, particularly as CLO is largely a disease of the elderly. **However, several studies have shown that because of the extreme pathophysiological abnormalities in these patients, normalisation of acid exposure may not be achieved, even using doses of PPI up to four times the standard daily dose and when alleviation of symptoms, when present, has occurred. In the absence of a satisfactory symptomatic response and/or healing of any associated oesophagitis, dose escalation to maximal manufacturers' recommendations should be considered. If a satisfactory response is still not achieved, further assessment including pH and Bilitec monitoring (where appropriate) is recommended.** (Recommendation grade C)

The indications for fundoplication in patients with CLO are essentially the same as those in gastro-oesophageal reflux disease generally, although the high incidence of hiatal hernia, lower oesophageal sphincter failure and reflux of duodenal contents, together with the documented difficulty of normalising acid exposure even with high dose PPI therapy, results in these indications being fulfilled in a greater proportion of CLO patients than in those with mild disease. (Recommendation grade B)

Although there are suggestions in the literature that a competent fundoplication may reduce the incidence of adenocarcinoma, there is currently insufficient evidence to recommend fundoplication on this basis. (Recommendation grade B)

Endoscopic ablation, performed in a reflux-free environment, can result in significant squamous re-epithelialization although rests of glandular metaplasia may remain beneath the neo-squamous epithelium in up to 60% of patients. The significance of these rests is unknown as is the optimal ablative technique. **Until these issues are resolved, endoscopic ablation remains experimental and should be performed only in the context of prospective randomised studies.** (Recommendation grade C)

INTRODUCTION

There is strong epidemiological evidence of a genuine increase in incidence of carcinoma of the lower oesophagus and gastric cardia although the aetiology remains obscure[1,2]. A population-based study has demonstrated a odds ratio of adenocarcinoma development of 43 among those with severe, long-standing heartburn, which was not entirely associated with progression through CLO[3]. There has also been a progressive increase over time in the prevalence of both heartburn and CLO (see section on Epidemiology). Genetic factors almost certainly influence the cycle and these, together with the mechanisms of oesophageal inflammation, are considered elsewhere. Barrett's oesophagus, more correctly described as columnar-lined oesophagus (CLO), was thought to be a relatively unusual development originally but has now achieved major status as a pre-malignant precursor of oesophageal adenocarcinoma[4]. Its prevalence has altered attitudes to the symptoms of heartburn, previously considered an inconvenience[5] .

As long ago as 1976, Nebel et al[6] and more recently confirmed by Talley and colleagues[7], it was estimated that perhaps half of the American population experienced an episode of heartburn at least once a month, and while this may have been relatively trivial, the more significant number of 4 per 1000 persons was considered to have prominent gastro-oesophageal reflux disease[8]. CLO is apparent in 1% of GI endoscopies and the detection rate rises to 3–8% in patients with reflux symptoms[9]. The true incidence of adenocarcinoma arising from CLO is unknown, but the risk has been estimated at between 0.5 and 1% per year[10]. Since the potential for cure of cancer when diagnosed at an early stage is high, there is much recent debate as to whether endoscopy should be used as a screening tool in symptomatic but apparently uncomplicated gastro-oesophageal reflux disease.

Acid and bile are both thought to contribute to mucosal changes in GORD and 24hr pH monitoring combined with bilirubin estimation has confirmed that there is greater oesophageal exposure to both constituents in patients with Barrett's than in simple reflux oesophagitis[11] and particularly bile in the presence of complications. Furthermore, a high proportion of patients with Barrett's CLO have an associated hiatal hernia and manometric lower oesophageal sphincter failure and peristaltic dysfunction than patients with erosive oesophagitis[12].

MANAGEMENT

The pathophysiological features of CLO as outlined above, which indicate that CLO represents the extreme end of the pathophysiological spectrum of gastro-oesophageal reflux disease, have implications regarding management and its efficacy. **In symptomatic patients, symptom control is an important objective of treatment but because many patients with CLO have few or no symptoms due to the relative insensitivity of columnar mucosa to acid[13], symptom control should not be interpreted as indicating**

suppression of gastro-oesophageal reflux. (Recommendation grade B).

Many authorities advocate no treatment for CLO other than symptom control, but this is controversial as stated in the American College of Gastroenterology Guidelines[14]. Those who believe that the objectives of management of CLO include attempting to influence the natural history of the condition advocate such modalities as pharmacological acid suppression, endoscopic ablation or anti-reflux surgery. At the present time, the optimal management of CLO is unknown and these modalities are applied largely on the basis of personal preference, although a large multi-centre randomised study to address this issue is proposed.

PHARMACOLOGICAL ACID SUPPRESSION

This clearly has theoretical advantages, being the least invasive form of long-term therapy, particularly as CLO is predominantly a disease of the elderly, the mean age being around 63. Although the development of squamous islands following PPI therapy is well recognised, circumferential regression of the columnarised segment is rare and has only been reported in one series[15], a meta-analysis of six subsequent series showing no evidence of regression[16]. Several studies have shown that because of the extreme pathophysiological abnormalities in these patients normalisation of acid exposure may not be achieved in 30–40% , even using doses of PPI up to four times the standard daily dose and when alleviation of symptoms, if present, has occurred[17–19]. The consequences of incomplete acid suppression is a matter of concern in this group of patients, since it has been shown that CLO cells in culture exhibit a greater degree of proliferation and de-differentiation when exposed to intermittent pulse acid exposure compared to no acid exposure and even continuous acid exposure[20]. It is, therefore, possible that inadequate levels of acid suppression may have contributed to the rising incidence of adenocarcinoma of the oesophagus and gastric cardia[21,22]. It has been recommended to try to overcome the problem of inadequate acid suppression that an H2 receptor antagonist should be added at night, possibly combined with a prokinetic agent and that the dose of proton pump inhibitor should be titrated against the level of oesophageal acid exposure on 24hr pH monitoring in order to optimise the effect of acid suppression therapy[17]. There remains, however, the problem of abnormal duodenal juice exposure, which although reduced as measured by Biltec monitoring on PPI therapy, presumably due to a volume-reduction effect, such exposure is normalised in less than 50% of patients[23]. **In the absence of a satisfactory clinical and/or endoscopic response to PPI therapy, dose escalation to maximal manufacturers' recommendations should be considered. If a satisfactory response is still not achieved, further assessment including pH monitoring and Bilitec monitoring (where appropriate) is recommended.** (Recommendation grade C).

ENDOSCOPIC ABLATION

While endoscopy is considered to offer a relatively poor return in assessing uncomplicated symptomatic GORD and in altering medical treatment[24], it offers a useful therapeutic option for mucosal ablation of metaplastic epithelium and putative regeneration of squamous lining[25–27]. It could be argued that ablative techniques should be reserved for areas of dysplastic change only and certainly further studies are needed to define the indications, efficacy and relative safety of the various modalities of treatment.

Ablative modalities can be divided into thermal and non-thermal. Thermal methods involve coagulation and vaporisation of epithelium using an Nd-YAG or GaAIAs semiconductor diode laser. A more recent and less expensive option involves the use of the Argon plasma coagulator (APC). While the learning curve is shorter for the use of APC, care must be taken to limit the depth of thermal injury to prevent undue stricture formation and perforation by penetrating through the deeper layers with all forms of thermal therapy. Photodynamic therapy (PDT) produces a cytotoxic action via the release of singlet oxygen when light of a specific wavelength is directed onto the tissue sensitised by the uptake of a photosensitising drug. The pro-drug, 5 aminolaevulinic acid, which converts to protoporphyin IX, the last step in the haem biosynthetic pathway, is selectively taken up by the mucosa and has yielded promising results as an agent for PDT in the treatment of CLO and dysplasia[26,28]. Since ALA is confined to the mucosa, stricture formation does not occur but this complication has been found in excess of 30% of cases treated by PDT where mTHPC or Photofrin have been used as photosensitisers[29]. Development in the light delivery systems and new generations of photosensitisers are likely to improve the uptake of OPT. Endoscopic ablation techniques, performed in a reflux-free environment using either high dose PPI therapy or fundoplication result in squamous re-epithelialization in 50–80% of patients, although residual islands of columnar metaplasia remain in 20–60% depending on the depth of injury[30].

Endoscopic ablation, performed in a reflux-free environment, can result in significant squamous re-epithelialization although rests of glandular metaplasia may remain beneath the neo-squamous epithelium in up to 60% of patients. The significance of these rests is unknown as is the optimal ablative technique. **Until these issues are resolved, endoscopic ablation remains experimental and should be performed only in the context of prospective randomised studies.** (Recommendation grade C).

ANTI-REFLUX SURGERY

Fundoplication has the theoretical advantage of being able to correct lower oesophageal sphincter failure and the frequently associated hiatal hernia and producing complete and continuous control of abnormal acid and duodenal juice exposure in 80–90% of patients. Three studies have demonstrated a greater degree of symptom control and healing of associated strictures and a lower incidence of new strictures after fundoplication compared to acid suppression therapy[31,32,39]. However, in two of these, acid suppression was by H2 receptor antagonists only. In the randomised controlled trial by Parrilla et al[39], although omeprazole was used in the last 8 years of the study, unfortunately the analysis does not clearly discriminate between the H2RA and PPI treated patients. There are considerably more reports of regression following anti-reflux surgery, although regression is rarely complete and occurs in only 10–44% of patients[31–36]. However, it is perhaps of greater importance what is happening at cellular level rather than whether or not macroscopic regression occurs.

The effect of fundoplication on the incidence of adenocarcinoma is unknown. The issue is highly controversial and the subject of conflicting reports. In a study from the Mayo Clinic in which 113 patients with CLO were followed for up to 18 years after fundoplication, 3 patients developed adenocarcinoma within 3 years of surgery, with no incidence of adenocarcinoma thereafter, an overall incidence of 1 in 274 patient years of follow up[37]. The clustering of adenocarcinoma in the early years following fundoplication and the absence of random distribution throughout the follow up period suggests firstly that these procedures may have been performed too late in the metaplasia-dysplasia-cancer sequence and accounts for the reported finding of adenocarcinoma developing after successful fundoplication. Secondly, it suggests that fundoplication may have altered the natural history of the disease in the remaining patients. A longitudinal study of CLO patients in the registry of the American College of Gastroenterology showed that of 161 patients undergoing

annual endoscopic surveillance, 119 received acid suppression therapy and 42 underwent fundoplication. The incidence of subsequent dysplasia in these groups was 19.7% and 3.4% respectively, again suggesting an influence in the natural history of those undergoing fundoplication[38]. In a prospective randomised trial involving 101 patients with CLO, 43 of whom received acid suppression therapy and 58 underwent fundoplication, adenocarcinoma developed in 5% in the former group and 3% in the latter, although in none of the 49 patients in whom fundoplication was documented as successful ($P<0.05$)[39], emphasising the importance of a high standard of care. A long-term follow up of a randomised controlled trial of medical versus surgical therapy in severe gastro-oesophageal reflux disease contained 85 patients with non-dysplastic CLO.[40] In addition to the findings in the whole group that fundoplication patients had lower symptom scores and required significantly less symptomatic treatment, in the CLO patients adenocarcinoma developed in 4 patients undergoing medical treatment and 1 undergoing fundoplication. However, these differences did not reach statistical significance

On the other hand, a population based study by Ye et al[41] concluded that the risk of adenocarcinoma remains increased after anti-reflux surgery. However, the authors state "we may have overlooked a small, long-term protective affect of anti-reflux surgery; the excess risk of esophageal adenocarcinoma remained relatively stable after the surgery but increased substantially with time among patients who did not undergo surgery. The small number of cases necessitates caution in the interpretation of these results".

In order to try to resolve this issue, two meta-analyses have been performed[42,43], but unfortunately they yielded conflicting results. A meta-analysis of 38 series from the Mayo Clinic found the incidence of adenocarcinoma to be 1 in 145 patient years in the medically treated patients and 1 in 294 years in those treated surgically.[42]. Corey et al in a meta-analysis of 34 studies found an incidence of adenocarcinoma of 5.3 per 1000 patient years of follow up in medically treated patients and 3.8 per 1000 patient years in the surgically treated patients but deemed this difference not to have reached statistical significance[43].

The indications for fundoplication in patients with CLO are essentially the same as those in gastro-oesophageal reflux disease generally, although the high incidence of hiatal hernia, lower oesophageal sphincter failure and reflux of duodenal contents, together with the documented difficulty of normalising acid exposure even with high dose PPI therapy, results in these indications being fulfilled in a greater proportion of CLO patients than in those with mild disease. (Recommendation grade B).

While there are suggestions in the literature that a competent fundoplication may reduce the incidence of adenocarcinoma, large prospective randomised studies with prolonged follow up are necessary before fundoplication can be recommended on this basis. (Recommendation grade B).

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REFERENCES

1 **Hanson S**, Wüg JN, Giercksky KE, Tretli S. Oesophageal gastric cancer in Norway, 1958–1992: incidence, time trend variability according to morphological stubtypes and organ subsites. Int J Cancer, 1997; 71: 340–4. **III**
2 **Powell J**, McConkey CC. The rising trend on esophageal adenocarcinoma and gastric cardia. Eur J. Cancer Prev, 1992; 1: 265–9. **III**
3 Spechler SJ, Goyal RK. Barrett's esophagus. N Engl J Med 1986; 315: 362–71. **III**
4 **Cohen S**, Hartman HP. Editorial: heartburn – a serious problem. N Engl J Med, 1999; 340: 878–9. **IV**
5 **Lagergren J**. Bergström R, Lindgren A, Nyren O. Symptomatic gastro-oesophageal reflux as a risk factor for esophageal adenocarcinoma. 1999, N Engl J Med; 340: 825–831**. IIa**
6 **Nebel OJ**, Fornes MF, Castell DO. Symptomatic gastro-oesophageal reflux: incidence and precipitating factors. Am J Dig Dis, 1976; 21: 953–6**. III**
7. **Talley NJ**, Zinsmeister AR, Schlek CD et al. Dyspepsia and dyspepsia subgroups: A population- based study. Gastroenterology, 1992; 102 1259–1264. **11a**
8 **DeMeesterTR**, Fuchs KH. Pre-operative evaluation of gastro-esophageal reflux. In: Grillo HC, Austen WG, Wilkins ER Jr et al, eds Current therapy in cardiothoracic surgery. Toronto: BC Decker, 1989: 217–20. **III**
9 **Lambert R**. The role of endoscopy in the prevention of esophago-gastric cancer. Endoscopy, 1999; 31: 180–199. **IV**
10 **Cameron AJ**, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophago-gastric junction and Barrett's esophagus. Gastroenterology, 1995; 109: 1541–6**. III**
11 **Vaezi MF**, Richter JE. Synergism of acid and duodeno-gastro-esophageal reflux in complicated Barrett's esophagus. Surgery, 1995; 117: 699–704. IIb
12 **Stein HJ**, Hoeft S, DeMeester TR. Reflux and motility pattern in Barrett's esophagus. Dis Esophagus 1992; 5: 21–28. **IIb**
13 **Ball CS**, Watson A. Acid sensitivity in reflux oesophagitis with and without complication. Gut 1998; 29: 729. IIb
14. Sampliner RE. Updated guidelines for the diagnosis, surveillanceand therapy of Barrett's esophagus. Am J Gastroenterol 2002; 97: 1888–95. **IIa**
15 **Gore S**, Healey CJ, Sutton R et al. Regression of columnar lined (Barrett's) oesophagus with continuous omeprazole therapy. Ailment Pharmacol Therap 1993; 7: 623–628. **IIb**
16 **Howden CW**, Horing CA. Do proton pump inhibitors induce regression of Barrett's oesophagus? A systematic review. Gastroenterology 1997; 112: A152. **IIb**
17 **Katzka DA**, Castell DO. Successful elimination of reflux symptoms does not ensure adequate control of acid reflux in patients with Barrett's esophagus. Amer J Gastroenterol 1994; 89:989–991. **III**
18 **Sampliner RE**. Effect of up to 3 years of high-dose Lanzoprazole. Amer J Gastroenterol 1994; 89: 1844–1848. **IIb**
19 **Ouatu-Lascar R**, Triadafilopoulos G. Complete elimination of reflux symptoms does not guarantee normalisation of intraesophageal acid reflux in patients with Barrett's esohagus. Amer J. Gastroenterol 1998; 93: 711–716. **IIb**
20 **Fitzgerald RC**, Omary MB, Triadofilopo**ulos G.** Dynamic effects of acid on Barrett's esophagus. J Clin Invest 1996; 98: 2120–8**. IIb**
21 **Blot WJ**, DeVesa SS, Fraumeni JF. Continuing climb in rates of esophageal carcinoma: an update. JAMA 1993; 270: 1320. **III**
22 **Pera A**, Cameron AJ, Trastek VJ et al. Increasing incidence of adenocarcinoma of the esophagus and esophago-gastric junction. Gastroenterology, 193; 104: 510–3. **IIb**
23 **Champion G**, Richter JE, Vaezi M et al. Dudodenogastroesophageal reflux: relationship of pH and importance in Barrett's esophagus. Gastroenterology 1994; 107: 747–754. **IIb**
24 **Blusten PK**, Bck PL, Meddings JB et al. The utility of endoscopy in the management of patients with gastro-oesophageal reflux symptoms. Am J Gastrol 1998; 93; 2508–12. **III**
25 **Barham CP**, Jones RZ, Biddlestone LR et al. Photothermal laser ablation of Barrett's oesophagus: endoscopic and histological evidence of squamous re-epithelialisation. Gut 197; 41: 281–4. **IIb**
26 **Barr H**, Shepherd NA, Dix A et al. Eradication of high-grade dysplasia in columnar-lined (Barrett's) oesophagus using photodynamic therapy with endogenously generated protoporphyrin IX. Lancet 1996; 348: 585–5. **IIb**
27 **Bryne JP**, Armstrong GR, Attwood SEA. Restoration of the normal squamous lining in Barrett's esophagus by Argon Bean Coagulation. Am J Gastroenterol, 1998; 93: 1810–15. **IIb**
28 **Gossner L**, Stolte M, Stroke R et al. Photodynamic therapy of high-grade dysplasia and early stage carcinomas by means of 5–aminolaevulinic acid. Gastroenterology 1998; 114: 448–55 **IIb**
29 O**verholt BF**, Banjepour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow up in 100 patients. Gastrointestinal Endosc 1999; 49: 1–7. **IIb**
30 V**an den Boogert J**, van Hillegersberg R, Siersena PD et al. Endoscopic ablation therapy for Barrett's esophagus: a review. Am J Gastroenterol 1999; 94: 1153–1159. **III**
31 **Attwood SEA**, Barlow AP, Norris TL, Watson A. Barrett's oesophagus; effect of anti-reflux surgery on symptoms control and development of complications. Br J Surg 1992; 79: 1050–1053. **IIb**
32 **Ortiz A**, Martinez De Haro LF, Parilla P, et al. Conservative treatment versus anti-reflux surgery in Barrett's oesophagus: long-term results of a prospective randomised study. Br J Surg 1991; 78: 274–278. **Ib**
33 **Skinner DB**, Walther BC, Riddell RH et al. Barrett's oesophagus. Arch Surg 1977; 112: 486–491. **III**
34 **Brand DL**, Ylvisader JT, Gelfand M, Pope CE II. Regression of columnar-lined oesophagus (Barrett's) epithelium after anti-reflux surgery. N Engl J Med 1980; 302: 844–848. **IIb**

35 **Williamson WA**, Ellis FH, Gibbs SP et al. Effect of anti-reflux operations on Barrett's mucosa. Ann Thorac Surg 1990; 49: 537–542. **IIb**
36 Sagar PM, Ackroyd R, Hosie KB et al. Regression and progression of Barrett's oesophagus after anti-reflux surgery. Br J Surg 1995; 82: 806–810. **IIb**
37 **McDonald ML**, Trastek VF, Allen MS et al. Barrett's esophagus; does an anti-reflux procedure reduce the need for endoscopic surveillance? J Thoraco Cardiovasc Surg 1996; 111: 1135–1140. **IIb**
38 **Katz D**, Rothstein R, Schned A, et al. The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. Am J Gastroenterol, 1998;93:536–541 **11a**
39 **Parrilla P**, Martinez de Haro L, Ortiz et al. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. Ann Surg, 2003; 237:291–298 **1b**
40 **Spechler SJ**, Lee E, Ahnen D et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease. Follow up of a randomized controlled trial. JAMA, 2001; 285: 2331–2338 **1b**
41 Y**e W, Chow**, WH, Lagergren J et al. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology, 2001; 121:1286–93.**11a**
42 **Bammer T**, Hinder RA, Klaus A et. Rationale for surgical therapy of Barrett's esophagus. Mayo Clinic Proc. 2001; 76:335–342. **11a**
43 **Corey KE**, Schmitz SM, Shaheen NJ. Does a surgical antireflux procedure decrease the incidence of esophageal adenocarcinoma in Barrett's esophagus? A meta-analysis. Amer J Gastroenterol,2003;98:2390–2395. **11a**

Screening and surveillance in columnar-lined oesophagus

D E Loft, D Alderson, R C Heading

EXECUTIVE SUMMARY

Chronic heartburn is a risk factor for oesophageal adenocarcinoma and the risk increases with increasing severity and duration of heartburn. However, the absolute risk in individual patients is less than 1 in 1000 per annum. **There is no evidence that endoscopic screening of heartburn patients to detect cancer is worthwhile and benefit is so unlikely that endoscopy with this intent cannot be recommended.** (Recommendation grade C).

Screening endoscopy has been advocated for chronic heartburn patients aged 50 years or more with the aim of detecting CLO, if present. However, this policy has not been shown to be of benefit. **Consequently, endoscopic screening of patients with chronic heartburn to detect CLO cannot be recommended.** (Recommendation grade C).

Neither of these recommendations about screening refutes the legitimacy of diagnostic endoscopy in the assessment of patients who have 'alarm features' such as dysphagia, weight loss or anaemia in association with chronic reflux.

Endoscopic surveillance of CLO with the aim of detecting cancer or pre-cancer at a stage when intervention may be successful is widely practised by European and North American gastroenterologists. No randomised controlled trial has been conducted to establish the efficacy of such surveillance and doubts have been expressed about the acceptability and even the ethics of conducting such a trial. In non-randomised studies, adenocarcinomas detected in CLO endoscopic surveillance programmes have been at an earlier stage and have been associated with longer survival than adenocarcinomas presenting outwith surveillance programmes. However, such data are not proof that surveillance is beneficial: only a fully randomised controlled study can provide such proof. Despite the fact that its efficacy remains unproven, the majority of GI units in the UK undertake endoscopic surveillance of at least some of their patients with non-dysplastic CLO.

Patients in whom CLO is newly diagnosed should ordinarily have the diagnosis made known to them and its implications discussed. In considering whether surveillance endoscopy should be initiated, the clinician should discuss with the patient the possible benefits of surveillance in detecting early stage tumours and improving cancer survival, explain that the efficacy of surveillance in these respects is unproven and make clear that for most patients with CLO the actual risk of death from oesophageal cancer is small. Disadvantages of endoscopic surveillance should also be discussed, including the physical and psychological morbidity, and the fact that surveillance cannot guarantee to detect every tumour that may develop. (Recommendation grade C).

Computer modelling has shown that for an adenocarcinoma risk of 1% pa, as is believed to be the case in the UK, the most effective and cost-effective surveillance interval is 2 years. Therefore, **it is recommended that when surveillance of a patient with non-dysplastic CLO is considered appropriate, it should be performed every 2 years.** (Recommendation grade C)

Where surveillance is practised, the emergence of endoscopic methods of treatment of high-grade dysplasia and early carcinoma, if proved effective, may negate restriction of surveillance programmes to those patients fit enough to undergo oesophageal resection.

In surveillance endoscopy, quadrantic biopsies should be taken every 2cm in the columnar segment together with biopsies of any visible lesion. (Recommendation grade C).More frequent sampling might be expected to increase the yield of dysplasia when present but the most widely recommended biopsy protocol is for quadrantic biopsies at 2cm intervals. There is no evidence to support the superiority of intensive biopsy protocols using jumbo forceps.

The cost-effectiveness of endoscopic surveillance is discussed in Chapter 10.

INTRODUCTION

The development and validation of screening and surveillance programmes in GORD and CLO have been constrained by a variety of factors, most notably uncertainty about the magnitude of the cancer risk and acknowledgement that in very many individuals who have GORD and/or CLO, the condition goes unrecognised because symptoms are so mild that medical attention for them has not been thought necessary. A further barrier to the evaluation of screening and surveillance has been a feeling on the part of many clinicians that even if the cancer risk is small, the development of adenocarcinoma in a patient with GORD/CLO is so serious that good clinical practice requires that some sort of action is taken to try to prevent it. Despite the absence of proof that screening or surveillance is effective, many clinicians and many of their patients therefore hold the view that they will support any reasonable programme of screening or surveillance that offers a chance of reducing the cancer risk: a 'do nothing' option is not acceptable to them. Such views have a bearing on the feasibility of any randomised trial to evaluate endoscopic surveillance of CLO. Patients who have been told they have an increased risk of oesophageal cancer may choose not to participate in a trial of a procedure with potential to enhance their life expectancy if participation means they may be randomised to a 'do nothing' option.

SCREENING ENDOSCOPY

Chronic heartburn is associated with a risk of developing oesophageal adenocarcinoma[1,2]. The risk appears to increase with duration and severity of symptoms: Swedish data suggest a 44–fold greater risk in individuals with severe heartburn of 20+ years duration compared with the general population[1]. Nonetheless, the enhanced risk still represents a relatively small absolute risk of oesophageal adenocarcinoma development in the individual patient with chronic heart-

burn. An incidence of less than 1 cancer in 1000 patients annually is a credible estimate[3]. Although the association between chronic heartburn and oesophageal adenocarcinoma is now clear, it is equally clear that many patients developing adenocarcinoma have not experienced troublesome heartburn, or at least have no recollection of experiencing such heartburn. About 40% of the cancer patients in Lagergren's study denied frequent heartburn[1]. Consequently, any endoscopic screening of patients with troublesome heartburn intended to detect oesophageal cancer will not only be unrewarding in terms of a low rate of cancer diagnoses but will necessarily be excluding many patients at risk of cancer development. No formal prospective or randomised trial has been undertaken and there is, therefore, no case on present evidence to support endoscopic screening for oesophageal cancer in patients with chronic heartburn, other than computer modelling studies, which have suggested possible benefit. Moreover, it is perhaps reasonable to conclude that because endoscopic screening is so unlikely to be worthwhile, a formal trial to examine the issue is not appropriate. Of course, there is a wide consensus among clinicians that endoscopic examination is warranted if a patient with heartburn (or dyspepsia) also has 'alarm features' such as dysphagia, recurrent vomiting, weight loss or anaemia. The appropriate management of patients with alarm features is beyond the scope of this review but diagnostic endoscopy performed in these circumstances should not be confused with screening endoscopy in chronic heartburn.

CLO is of course itself a risk factor for oesophageal adenocarcinoma. Although it has been known for many years that reflux symptoms may be minimal or absent in patients with CLO and abnormal gastro-oesophageal reflux[4–6], it is not clear whether it is this 'silent reflux' that underlies the development of adenocarcinoma in patients who have little or no heartburn. In patients who do have reflux symptoms, the possibility of CLO being present in 5–15% of cases[4,7,8] has prompted advocacy of endoscopic screening of patients with longstanding reflux, especially those aged over 50 years, so that CLO can be identified if it is present and endoscopic surveillance initiated (9,10). Although there is some logic in this idea, there is no direct evidence that reflux patients benefit from this type of screening. The uncertainties surrounding surveillance of patients with CLO are discussed below.

There is no evidence that endoscopic screening of heartburn patients to detect cancer is worthwhile and benefit is so unlikely that endoscopy with this intent cannot be recommended. (Recommendation grade C).

This judgement does not, however, refute the legitimacy of endoscopy in the assessment of patients who have 'alarm features' such as dysphagia, weight loss or anaemia in association with chronic reflux.

The merit of endoscopic screening of patients with chronic reflux symptoms to detect CLO has not been established. **Consequently, endoscopic screening of patients with chronic heartburn to detect CLO cannot be recommended.** (Recommendation grade C).

SURVEILLANCE ENDOSCOPY

Several reports are in agreement showing that adenocarcinomas diagnosed by CLO endoscopic surveillance programmes are, on average, at an earlier stage than adenocarcinomas diagnosed in CLO patients not in surveillance programmes. Because the prognosis of oesophageal adenocarcinoma is crucially dependent on stage, earlier stage should be associated with better survival. Nevertheless, the crucial question is 'Is endoscopic surveillance effective?'

Is surveillance effective?

In the UK, endoscopic surveillance of CLO detects adenocarcinoma with a frequency of about 1/100 patient years of follow-up, which is approximately twice the frequency found in the USA[11]. The magnitude of the cancer risk is potentially important to the cost-effectiveness of surveillance but does not affect the aim of CLO endoscopic surveillance, which is to identify cancer or pre-cancer in the oesophagus at a stage when intervention is likely to prolong life. There are no prospective randomised trials examining attainment of this objective in non-dysplastic CLO and consequently judgements have to be made at present on evidence of lesser strength. However, a demonstration that surveillance (when compared with non-surveillance) genuinely detects earlier stage cancers should be a reasonable predictor of longer survival, notwithstanding the fact that improved survival rates themselves will remain the most desirable indices of effectiveness.

In studies comparing surveillance with non-surveillance cancers, early stage disease has been found more often in surveillance cases than non-surveillance cases[12–19]. Additionally, survival rates have been better with surveillance-detected cancers than with non-surveillance cases[12,13,15,18,19]. Unfortunately, the lead-time bias and length bias inherent in surveillance may give rise to apparent longer survival and a greater proportion of early stage tumours when surveillance detected cancers are compared with non-surveillance cancers in non-randomised comparisons[20]. Survival may also be affected by selection bias**.** Whether bias can account for all the benefit seemingly derived from surveillance in the non-randomised studies is not known and only a properly randomised trial designed to take account of bias can resolve this uncertainty.

Other considerations are also of importance in evaluating endoscopic surveillance: not all published studies report on surveillance positively. Relevant observations made include the low (0.5–1%) risk of cancer development, failure to find any benefit from a surveillance programme and quantitatively important 'drop-out' of patients within a few years of entering the programme[21–24].

Nowadays, many patients with CLO are informed about their condition and expect to participate fully in decision-making regarding their management. **Those in whom CLO is newly diagnosed should ordinarily have the diagnosis made known to them and its implications discussed. In considering whether surveillance endoscopy should be initiated, the clinician should discuss with the patient the possible benefits of surveillance in detecting early stage tumours and improving cancer survival, explain that the efficacy of surveillance in these respects is unproven and make clear that for most patients with CLO the actual risk of death from oesophageal cancer is small. Disadvantages of endoscopic surveillance should also be discussed, including the physical and psychological morbidity, and the fact that surveillance cannot guarantee to detect every tumour that may develop.** (Recommendation grade C).

Who should be considered for surveillance?

As stated above, the purpose of endoscopic surveillance of CLO is to identify cancer or pre-cancer at a stage when intervention is likely to prolong life. At present, intervention usually means oesophageal resection but a variety of local therapies including endoscopic ablation and endoscopic mucosal resection are currently being evaluated. If they prove effective, it may be inappropriate to restrict surveillance to patients who are fit and willing to undergo oesophagectomy, but for the moment this remains the most generally accepted policy.

The length of the CLO segment has been linked to an increased risk of developing dysplasia or carcinoma development[25–27] but the relationship seems weak[28]. Consequently,

modifying clinical management according to CLO segment length is not warranted at present.

In the absence of dysplasia, the risk of adenocarcinoma development in CLO is twofold greater when intestinal metaplasia has been demonstrated compared with when it has not (1/88 patient-years compared with 1/187)[29]. The reasons for this difference are not certain. At present there is no basis to alter clinical management according to the presence or absence of intestinal metaplasia, provided the endoscopic finding of CLO and the biopsy sites are not in doubt.

Intestinal metaplasia may be found in biopsies taken from the cardia in some patients whose distal oesophagus appears normal.The natural history of this abnormality is uncertain and in reality it may be impossible to distinguish intestinal metaplasia in 'short segment' CLO from intestinal metaplasia in gastric cardiac epithelium[30]. The latter is thought to carry a lesser risk of adenocarcinoma[31]. Although surveillance endoscopy has been advocated for patients with intestinal metaplasia at the cardia, because of the possibility they may actually have unrecognised short segment CLO[30], there is no direct evidence that suggests such surveillance may be beneficial.

The development of dysplasia is usually considered a marker of malignant potential, offering the possibility of curative treatment at a stage before invasive carcinoma occurs. The evidence for a sequence of gastro-oesophageal reflux disease to CLO to low grade dysplasia (LGD) to high grade dysplasia (HGD) to carcinoma is based on the frequent finding of HGD in the mucosa surrounding adenocarcinomas, the progression of HGD to carcinoma in prospective series and on genetic studies.[32–35]

How Often?

Internationally published recommendations for surveillance intervals in non-dysplastic CLO have ranged from one to five years [9,10,36–38] but any sound recommendation for the UK must be founded on the adenocarcinoma risk in the UK – approximately 1% per annum. On the basis of a mathematical model[38], this risk would point to a surveillance interval of about 2 years. Therefore, **it is recommended that when surveillance of a patient with non-dysplastic CLO is considered appropriate, it should be performed every 2 years.** (Recommendation grade C).

In the UK, estimates of cost per cancer detected range from £15,000 in men to £42,000 in women[16] and the cost-effectiveness of surveillance every two years is estimated at £19.000 per year of life saved. (See section 'Economic considerations'). In a managed care setting in the USA, the cost of endoscopy is about one third of the total cost of medical care for a patient with CLO: the total cost ($1,241 annually) is similar to that of a patient with insulin dependent diabetes[39].

Shorter surveillance intervals (3–12 months) are usually considered appropriate if dysplasia has been found. (See section "Management of Dysplasia").

OTHER CONSIDERATIONS

The number of biopsies needed to detect dysplasia reliably is unknown. The usual recommendation is quadrantic biopsies every 2cm together with biopsy of any visible lesion: there is no convincing evidence to support the superiority of more intensive biopsy protocols, the use of "jumbo" forceps or chromoendoscopy in the identification of dysplasia. (See Section 'Diagnosis of Columnar–Lined Oesophagus'). **In surveillance endoscopy, quadrantic biopsies should be taken every 2cm in the columnar segment together with biopsies of any visible lesion.** (Recommendation grade C).

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REFERENCES

1 **Lagergren J**, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999,340, 825–31. (IIa)
2 **Farrow DC**, Vaughan TL, Sweeney C et al. Gastroesophagea reflux disease, use of H2 receptor antagonists and risk of esophageal and gastric cancer. Cancer Causes Control. 2000, 11, 231–8. (IIa)
3 **Shaheen N**, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus and esophageal cancer. JAMA. 2002, 287, 1972–81. (III)
4 **Winters C**, Spurling TJ, Chobanian SJ et al. Barrett's esophagus: a prevalent, occult complication of gastroesophageal reflux disease. Gastroenterology 1987, 92, 118–24. (III)
5 **Niemansverdriet EC**, Timmer R, Breumelhof R, Smout AJPM. The roles of excessive gastro-oesophageal reflux, disordered oesophageal motility and decreased mucosal sensitivity in the pathogenesis of Barrett's oesophagus. Eur J Gastroenterol Hepatol 1997, 9, 515–9. (IIb)
6 **Gerson LB**, Shetler K, Triadafilopoulos G. Prevalence of Barrett's oesophagus in asymptomatic individuals. Gastroenterology 2002;123:461–7. (IIb)
7 **Corder AP**, Jones RH, Sadler GH, Daniels P, Johnson CD. Heartburn, oesophagitis and Barrett's oesophagus in self-medicating patients in general practice. Br J Clin Pract 1996, 50, 245–8. (IIb)
8 **Csendes A**, Smok G, Burdiles P et al. Prevalence of Barrett's esophagus by endoscopy and histologic studies: a prospective evaluation of 306 control subjects and 376 patients with symptoms of gastroesophageal reflux. Dis Esophagus 2000, 13, 5–11. (IIa)
9 **Sampliner RE**. Practice guidelines on the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 1998, 93, 1028–32. (IV)
10 **Sampliner RE**. Updated guidelines for the diagnosis, surveillance and therapy of Barrett's oesophagus. Am J Gastroenterol 2002; 97:1888–95. (IV)
11 **Jankowski J**, Provenzale D, Moayyedi P. Oesophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the West. Gastroenterology 2002; 122: 588–590. (IIa)
12 **Streitz JM**, Andrews CW, Ellis FH. Endoscopic surveillance of Barrett's esophagus. Does it help? J Thorac Cardiovasc Surg 1993, 105, 383–8. (IIa)
13 **Peters JH**, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. J Thorac Cardiovasc Surg 1994, 108, 813–21. (IIa)
14 **Wright TA**, Gray MR, Morris AI, Gilmore IT, Ellis A, Smart HL, Myskow M, Nash J, Donnelly RJ, Kingsnorth AN. Cost-effectiveness of detecting Barrett's cancer. Gut 1996; 39:574–579. (IIa)
15 **Van Sandick JW**, van Lanschot JJB, Kuiken BW, Tytgat GNJ, Offerhaus GJA, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut 1998,43, 216–22. (IIa)
16 **Bani-Hani K**, Sue-Ling H, Johnston D, Axon ATR, Martin IG. Barrett's oesophagus: results from a 13 year surveillance programme. Eur J Gastroenterol Hepatol 2000, 12, 649–54. (III)
17 **Fitzgerald RC**, Saeed IT, Khoo D, Farthing MJ, Burnham WR. Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's oesophagus. Dig Dis Sci 2001; 46:1892–8. (IIb)
18 C**orley DA**, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: a population based study. Gastroenterology 2002, 122, 633–40. (IIa)
19 **Fountoulakis A**, Zafirellis KD, Dolan K et al. Effect of surveillance of Barrett's oesophagus on the clinical outcome of oesophageal cancer. Br J Surg 2004, 91, 997–1003.(IIa)
20 **Shaheen NJ**, Provenzale D, Sandler RS. Upper endoscopy as a screening and surveillance tool in esophageal adenocarcinoma. Am J Gastroenterol 2002, 97, 1319–27. (III)
21 **Nilsson J**, Skobe V, Johansson J, Willen R, Johnsson F. Screening for oesophageal adenocarcinoma: an evaluation of a surveillance program for columnar metaplasia of the oesophagus. Scand.J.Gastroenterol.2000, 35,10–16. (III)
22 **Macdonald CE**, Wicks AC, Playford RJ. Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study. Br med J 2000, 321, 1252–5. (III)
23 **Conio M**, Blanchi s, Lapertosa G et al. Long-term endoscopic surveillance of patients with Barrett's esophagus. Incidence of dysplasia and adenocarcinoma: a prospective study. Am J Gastroenterol 2003, 98, 1931–9. (IIb)
24 **Basu KK**, Pick B, de Caestecker JS. Audit of a Barrett's epithelium surveillance database. Eur J Gastroenterol Hepatol 2004, 16, 171–5. (III)
25 **Menke-Pluymers MB**, Hop WC, Dees J, van Blankenstein M,Tilanus HW. Risk factors for the development of an adenocarcinoma in columnar-lined

(Barrett) esophagus. The Rotterdam Esophageal Tumour Study Group. Cancer 1993, 15, 1155–8. (III)
26 **Avidan B**, Sonnenberg A, Schnell,TG, Chejfec G, Metz A, Sontag SJ. Hiatal hernia size, Barrett's length and severity of acid reflux are all risk factors for esophageal adenocarcinoma. Am J Gastroenterol 2002, 97, 1930–6. (IIa)
27 **Gopal DV**, Lieberman DA, Magaret N et al. Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. Dig Dis Sci 2003, 48, 1537–41. (III)
28 **Rudolph RE**, Vaughan TL, Storer BE, et al. Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. Ann.Intern.Med.2000,132, 612–620. (IIb)
29 **Ferraris R**, Luigina B, Conio M et al. Incidence of Barrett's adenocarcinoma in an Italian population: an endoscopic surveillance programme. Eur J Gastroenterol Hepatol 1997, 9, 881–885. (III)
30 **Spechler SJ**. Intestinal metaplasia at the gastroesophageal junction. Gastroenterology 2004, 126, 567–75 (IV)
31 **Spechler SJ** The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. Gastroenterology 1999, 117, 218 –28 (IV)
32 S**kacel M**, Petras RE, Gramlich TL, Sigel JE, Richter JE, Goldblum JR. The diagnosis of low-grade dysplasia in Barrett's oesophagus and its implication for disease progression. Am J Gastroenterol 2000, 95, 3383–7. (III)
33 **Weston AP**, Badr AS, Hassanein RS. Prospective multivariate analysis of clinical, endoscopic and histological factors predictive of the development of Barrett's multifocal high- grade dysplasia or adenocarcinoma. Am J Gastroenterol 1999, 94, 3413–9. (IIb)
34 **Reid BJ**, Prevo LJ, Galipeau PC et al. Predictors of progression in Barrett's esophagus II: baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk of neoplastic progression. Am J Gastroenterol 2001, 96, 2839–48. (IIb)
35 **Buttar NS**, Wang KK, Serbo TJ et al. Extent of high grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology 2001, 120, 1630–9. (III)
36 **Stein HJ**. Oesophageal cancer: screening and surveillance. Results of a consensus conference held at the 6th world congress of the international society of diseases of the oesophagus. Diseases of the Esophagus 1996, 9, 53–9. (IV)
37 **Provenzale D**, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am.J.Gastroenterol. 1999, 94, 2043–2053. (III)
38 **Boyer J**, Robaszkiewicz M. Guidelines of the French Society of Digestive Endoscopy: monitoring of Barrett's esophagus. The Council of the French Society of Digestive Endoscopy. Endoscopy 2000, 32, 498–9. (IV)
39 **Eloubeidi MA**, Homan RK, Martz MD, Theobald KE, Provenzale D. A cost analysis of outpatient care for patients with Barrett's esophagus in a managed care setting. Am.J.Gastroenterol. 1999, 94, 2033–6. (III)

The management of dysplasia

H Barr, N A Shepherd

EXECUTIVE SUMMARY

Dysplasia is defined as an unequivocal neoplastic alteration of epithelium which has the potential to progress to invasive malignancy but remains confined within the basement membrane of the epithelium within which it arose.[1] Dysplastic change is classified as indefinite for dysplasia, low-grade dysplasia and high-grade dysplasia.

Dysplasia is diagnosed with greatest accuracy when confirmed by two experienced gastrointestinal pathologists, after inflammatory changes have been minimised by PPI therapy. Optical methods of diagnosis are currently being evaluated but at present histology remains the gold standard.

A diagnosis of 'indefinite for dysplasia' is most often made when there are changes suggestive of dysplasia but inflammatory changes make the distinction impossible. **Such a pathological diagnosis should prompt early re-evaluation with extensive biopsies following a course of PPI therapy. If this, together with a subsequent endoscopy and multiple biopsies at 6 months fail to reveal definite evidence of dysplasia, then the patient can return to routine surveillance.** (Recommendation grade C.)

Low-grade dysplasia should be managed firstly by extensive re-biopsy after intensive acid suppression for 8–12 weeks. If persistent, surveillance should be six monthly for as long as it remains stable. If apparent regression occurs on two consequent examinations, surveillance intervals may be increased to 2–3 yearly. (Recommendation grade C.)

High-grade dysplasia is associated with a focus of invasive adenocarcinoma in 30–40% of patients. For this reason, if the changes persist after intensive acid suppression and are confirmed by two expert pathologists, oesophagectomy in a specialised unit is currently recommended in patients considered fit for surgery (Recommendation grade C). **In those unfit for surgery, endoscopic ablation or mucosal resection should be considered** (Recommendation grade C). These techniques, together with continued surveillance after intensive efforts to exclude incident cancers are being evaluated as to their utility as first-line therapy.

INTRODUCTION

Clinicians and pathologists accept that the term dysplasia equates with malignant potential. The term should be restricted to use only when there is convincing pathological evidence that a neoplastic process is present in a columnar-lined oesophagus (CLO).

In CLO, the detection of dysplasia is primarily pathological. Routine endoscopic methods may not detect neoplastic change, including high grade dysplasia (HGD) and/or adenocarcinoma, and biopsies from macroscopically unremarkable CLO are necessary.[2] There is great potential for sampling error: dysplasia may be missed if insufficient biopsies are taken. Protocols for surveillance patients recommend four quadrant biopsies at 2cm levels within the columnarised segment segment as well as biopsies of any macroscopic abnormality.[3] Although dysplasia may appear macroscopically normal, it can manifest with endoscopic abnormality: a subtle granularity or velvety appearance to the salmon pink mucosa of CLO, isolated plaques, polyps, nodules or erosions may indicate dysplasia[2,4] Any larger mass lesion, especially with ulceration, should raise suspicions of invasive malignancy.

THE DIAGNOSIS OF DYSPLASIA

There is now general agreement that the classification of neoplastic change in CLO should conform to that given in Table 1.[5,6,7] The restriction to two grades of definite dysplasia, low and high, is more helpful for individual patient management.[6] Inter-observer and intra-observer studies have demonstrated that pathologists can demonstrate acceptable levels of agreement for high grade dysplasia in CLO. There are poorer levels of agreement for the categories of low grade dysplasia and indefinite for dysplasia.[5] This underpins the importance of surgical conservatism (but enhanced surveillance by endoscopy and biopsies) for the lower grades of dysplasia.[4,6]

Table 1 The classification of neoplastic change in CLO

Negative for dysplasia
Indefinite for dysplasia
Low grade dysplasia
High grade dysplasia
Intramucosal carcinoma
Invasive adenocarcinoma

The principal diagnostic problem is the pathologist overcalling reactive/inflammatory states as dysplasia.[4,6] This may occur when there is juxtaposition of 'bland' gastric cardiac-type epithelium to much more active appearing intestinal-type epithelium(IM) with its much more prominent proliferative zone, a typical pathological feature in the patchwork of different epithelial types that occur in CLO.[4] This feature, also observed in IM in the stomach, is perhaps one of the commoner indications for use of the 'indefinite for dysplasia' category. Pathologists should make full use of this category. Such a diagnosis does not mean that the pathologist is uncertain but rather that it is not possible, with confidence, to exclude low grade dysplasia in inflamed material. In the future, it is likely that similar dysplasia classifications to that recently proposed for the stomach (the Padova classification)[8] may be used for CLO.

There is a lack of definitive criteria upon which to diagnose dysplasia, and to separate the various categories. Most learned articles on CLO dysplasia identify cytological changes such as nuclear enlargement, nuclear pleomorphism, nuclear hyperchromatism, nuclear stratification, increased mitotic activity and atypical mitotic figures as the most important diagnostic features. However, the more useful morphological features are architectural. Villous configuration is a characteristic and

relatively common, although not a specific, accompaniment of dysplasia. Nevertheless the most useful diagnostic feature, for both low and high grade dysplasia, is a lack of the normal maturation and differentiation, so-called dysmaturation or loss of basal-luminal proliferative axis, as one ascends the crypt.[4,6] Thus the nuclear and cytological features, in dysplasia, are similar in the surface epithelium to those at the crypt base.

The diagnosis of dysplasia in short segment disease and IM at the cardia(CIM) is beset by similar problems, for the pathologist, as dysplasia in classical CLO. Whilst dysplasia appears to have a significantly lower prevalence in short segment disease than traditional CLO,[9] it may well contribute equally or possibly more to the incidence of adenocarcinoma, because short segment disease is appreciably more common than long segment disease.[10] At present we know little about the potential for dysplasia, and malignancy, in CIM. Pathologists frequently demonstrate adenocarcinoma at the oesophago-gastric junction or in the cardia without evidence of an accompanying CLO segment: these cases could well represent dysplasia and cancer arising in CIM but evidence for this is currently lacking.

Given the inter-observer variations in the diagnosis of dysplasia, especially low-grade disease, are there other modalities that may aid pathologists in the demonstration of significant dysplasia? The use of cytology for the assessment of neoplasia in CLO patients remains controversial. As the difference between HGD and invasive carcinoma is essentially an architectural one, one would not expect to be able to distinguish these using cytology alone. Most studies support the view that cytology should be regarded as a corroboration of histological diagnosis but that cytology alone is not a useful method for the diagnosis of dysplasia and particularly for grading dysplasia or differentiating it from adenocarcinoma.[4,11–14] It has been suggested that non-endoscopic balloon abrasion cytology might be a useful surveillance technique for neoplastic change in CLO (including dysplasia), as it compares favourably with endoscopy in terms of specificity of a neoplastic diagnosis and cost although it has a lower sensitivity.[15] Nevertheless its routine use in CLO surveillance cannot be currently recommended.

Although we are rapidly gaining knowledge about the molecular events that underpin the progression of the metaplasia-dysplasia-malignancy sequence of CLO, [16,17] at present no single molecular marker or combination of markers can be recommended for use in the routine diagnosis of dysplasia complicating CLO.[4,18] Optical methods of diagnosis of dysplasia by laser induced florescence, elastic scattering spectroscopy and optical coherence tomography are also being assessed. All of these techniques should be presently regarded as experimental and histological assessment remains the gold standard for the diagnosis of dysplasia in CLO.[18]

Many patients with CLO are receiving acid-suppressing drugs and pathologists are increasingly observing the effects of various treatment strategies on CLO.[19] Ablative techniques, notably laser, photodynamic therapy (PDT) and argon plasma coagulation therapy, have been used to treat both low and high grade dysplasia, especially in those patients unfit for surgery. These treatments can lead to difficulties for the pathologist. The squamous re-epithelialisation may actually conceal any remaining dysplastic mucosa making this more difficult to detect.[19,20] The surface squamous mucosa, overlying dysplastic epithelium, can lead the pathologist to erroneously diagnose invasive malignancy. This is because neoplastic glandular mucosa immediately beneath surface squamous mucosa may be misinterpreted as invasive adenocarcinoma infiltrating beneath native oesophageal squamous mucosa.[4]

In conclusion, the pathological diagnosis of the various grades of dysplasia in CLO works well in practice. The "indefinite for dysplasia" category is appropriate in difficult borderline cases with active inflammation. **Such a pathological diagnosis should promote early re-evaluation with extensive biopsies following a course of PPI therapy. If this, together with a subsequent endoscopy and multiple biopsies at 6 months fail to reveal definite evidence of dysplasia, then the patient can return to routine surveillance.** (Recommendation grade C).

The more clinically significant high grade dysplasia demands very accurate pathological diagnosis and is best substantiated either by a further endoscopy and multiple biopsies or by a second, preferably expert, pathological opinion following intensive acid suppression therapy.[6] (see below)

CLINICAL ASPECTS OF DYSPLASIA IN CLO

Low grade dysplasia in CLO represents a more stable phenotype than high grade dysplasia. Some series show no evidence of malignant transformation in 3– 84 months.[21,22] Evidence to suggest regression to non-neoplastic metaplasia has also been documented from 6–86 months.[21–23] On the contrary, patients with low grade dysplasia have been documented to progress to invasive cancer without areas of high-grade dysplasia being apparent in a time sequence of 52 and 56 months.[22,24] There is controversy concerning the efficacy of anti-reflux surgery in causing regression of the columnarised segment or halting progression of dysplasia. Whether there is regression or reduction of neoplastic transformation after anti-reflux surgery is controversial (see "Management of Non-Dysplastic Columnar-lined Oesophagus"), although the rate of progression may be reduced.[25,26]

An important influence on the management of high grade dysplasia has been the finding that many patients diagnosed with high-grade dysplasia have co-existent cancer found after surgical excision of the affected oesophagus.[3,27–42] These historical data collected over the past two decades suggest that co-existent cancer occurs in 30–40% of patients if the preliminary diagnosis was of high grade dysplasia. There are some longitudinal studies that give some indication of the time sequences involved in the progression or non-progression of high-grade dysplasia. The variability is large with some patients progressing rapidly to invasive cancer and others remaining with persistent dysplasia for prolonged periods. Longitudinal studies indicate that the average time for progression from high-grade dysplasia to cancer is approximately 24 months with a range of 6–43 months.[3,22,23,43–45] That high-grade dysplasia may remain as a stable phenotype is supported by some evidence that demonstrates no progression to cancer between 32 and 48 months.[3, 23] There are also data to suggest that in some patients high-grade dysplasia may regress to no dysplasia or low-grade dysplasia after follow up of periods between 1 and 12 months, especially in patients with short segment CLO. [21,46]

It has been sporadically documented that high-grade dysplasia has appeared to resolve, particularly when proton pump inhibitor therapy is effective at suppressing acid. [21,46] It appears that prolonged proton pump inhibitor therapy may improve certain histological parameters.[24,47–50] There is a decrease in the length of the CLO segment with an increase in the number of squamous islands.[50] There is also a reduction in the proportion of sulphomucin-rich intestinal metaplasia, a parameter representing unstable intestinal epithelium that is closely associated with dysplasia.[47,50] A randomised double blind study has confirmed that profound acid suppression with a proton pump inhibitor leading to elimination of acid reflux induces a partial regression of the CLO segment.[24] Similarly antireflux surgery may on occasion improve the histological appearance of CLO.[51–53]

We should remain cautious with regard to the potential for dysplasia, to regress. Whilst it remains possible that particularly low grade dysplasia may regress, what little evidence there is is often based on historical data. There should be concerns about the accuracy of the initial diagnosis and certainty

about subsequent apparent lack of dysplasia because of biopsy sampling errors[2,3]

MANAGEMENT OF LOW GRADE DYSPLASIA

Intensive medical therapy with a proton pump inhibitor is recommended for a period of 8–12 weeks. It may be necessary to confirm that adequate acid suppression is achieved and increase therapy to assure that there is full reflux control.[46] If there is histological improvement, then 6 monthly endoscopic surveillance with a comprehensive biopsy protocol[3] is necessary until at least two consecutive examinations reveal no dysplastic change. Surveillance can then be decreased to 2 yearly intervals. The patient should remain on a proton pump inhibitor. If the dysplasia persists, continued intensive control of reflux is necessary and should be confirmed with appropriate investigations. Endoscopic and biopsy surveillance should continue at 6 monthly intervals.[54,55]

All patients with confirmed dysplasia require full endoscopic assessment and biopsy by rigorous protocol. After detailed identification of all landmarks, the CLO segment is biopsied from its lowermost to above the squamo-columnar junction. Samples must be taken from all areas of mucosal abnormality and any areas where high-grade dysplasia had been identified previously. All four quadrants of the oesophagus are also biopsied at 2cm intervals. The number of samples removed may be greater than 50.[3]

The development of endoscopic mucosal ablation techniques means that consideration must given to mucosal ablation therapy if low-grade dysplasia persists.[56] Most experience has been obtained using photodynamic therapy (PDT) with exogenously administered Photofrin or endogenously generated protoporphyrin IX from orally administered 5 aminolaevulinic acid (ALA).[57,58] An alternative is thermal ablation, using electrocoagulation or the argon plasma coagulator (APC)[59–62] or photothermal ablation with lasers.[63–66] The only mortality has been reported following the use of the APC, related to early experience.[59] All methods must be combined with proton pump inhibitor therapy or surgical reflux control. Following ablation therapy continued surveillance with comprehensive biopsy protocols is imperative since metaplastic and dysplastic glands can survive under the neosquamous epithelium[19] and relapse can occur.[67]

Low grade dysplasia should be managed firstly by extensive re-biopsy after intensive acid suppression for 8–12 weeks. If persisting, surveillance should be six monthly for as long as it remains stable. If apparent regression occurs on two consecutive examinations, surveillance intervals may be increased to two yearly . (Recommendation grade C).

MANAGEMENT OF HIGH GRADE DYSPLASIA

The diagnosis of high grade dysplasia should be confirmed by a second, preferably expert, pathologist.[6] If any doubt remains then the endoscopy should be repeated immediately and the biopsy protocol must be rigorous.[3] Adequate time must be given to obtaining large and multiple specimens.

A. *Patients confirmed to have persistent, multifocal high-grade dysplasia*. These patients should be considered for surgical resection: all columnar-lined oesophagus should be resected. Extensive lymphadenectomy is not necessary, if there is no invasive cancer. Referral to a specialist oesophageal surgeon and centre is important: the mortality of the procedure must be less than 5%.[68–71]
B. *Patients confirmed to have persistent, multifocal high-grade dysplasia but in whom the operative mortality and morbidity is considered to be prohibitive.* These patients should receive endoscopic mucosal ablation with permanent acid reflux control with the aim of removing all the dysplastic and metaplastic epithelium.[57–59,72–75] They also require lifelong endoscopic surveillance with comprehensive biopsy protocol at 6 monthly intervals.[3]
C. *Patients with a focal area of high grade dysplasia after full and repeated endoscopic biopsy assessment*. Patients considered at low operative risk with a long life expectancy with other risk factors for the development of an adenocarcinoma[76] should be assessed by a specialist oesophageal team and be considered for oesophagectomy.[70,71,77,78]
D. *Patients with a focal area of high-grade dysplasia after full and repeated endoscopic biopsy assessment with high operative risk and without other risk factors for adenocarcinoma.* These patients should be treated with endoscopic mucosal resection allowing full histological assessment[79] and continued surveillance[3] with further mucosal resection as necessary. The complete area can be treated with endoscopic mucosal ablation with thermal,[59,80,81] photodynamic[57,72,73] or ultrasonic methods.[82]

High grade dysplasia is associated with a focus of invasive adenocarcinoma in 30–40% of patients. For this reason, if the changes persist after intensive acid suppression and are confirmed by two expert pathologists, oesophagectomy in a specialised unit is currently recommended in patients considered fit for surgery. (Recommendation grade C). **In those unfit for surgery, endoscopic ablation or mucosal resection should be considered.** (Recommendation grade C).

METHODS OF ENDOSCOPIC MUCOSAL ABLATION

There are important considerations in the choice of endoscopic mucosal ablation. The most important consideration is the depth of destruction that can be obtained to destroy both the metaplastic mucosa and neoplastic tissue and at the same time allow safe healing. The mean thickness of non-dysplastic Barrett's mucosa is about 0.6mm.[83] The various methods available are:

A. Exogenous photodynamic therapy with administered photosensitiser. This will destroy sufficient depth to eradicate early T1 and some T2 cancers.[57,84,85] Up to 30% of patients may develop oesophageal strictures[57] and cutaneous photosensitivity is a problem. The depth of necrosis will be approximately 6mm.[86–88]
B. Endogenous photodynamic therapy with orally administered 5 ALA is ideal if there is no morphological distortion. There is little risk of stricture or cutaneous photosensitivity. The depth of tissue necrosis is limited to 2mm.[72,73,88]
C. Thermal and photothermal methods often require repeated application but are cheaper, more readily available and as effective as PDT methodology.[59–66,73,74,78,89–90]

SURGICAL APPROACH FOR PATIENTS WITH HIGH GRADE DYSPLASIA

All patients with high grade dysplasia require full assessment and staging. In the next few years diagnostic methods, such as optical coherence tomography and optical biopsy, may become realistic options.[91,92] The morbidity of the surgical procedure is directly related to the extent of dissection. In patients with high grade dysplasia an extended en-bloc lymphadenectomy is usually unnecessary and lesser resections with a conservative lymphadenectomy or vagus-sparing technique still result in prolonged survival.[93,94] For invasive oesophageal adenocarcinoma overall survival is related to the stage of disease at diagnosis and the surgical experience.[95–98] The entire dysplastic and metaplastic segment must be resected. The surgical management should always be under the care of a dedicated oesophageal surgical team.

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REFERENCES

1 **Riddell RH**, Goldman H, Ransohoff D, et al. Dysplasia in inflammatory bowel disease. Standardised classification with provisional clinical application. Hum Pathol 1983; 14: 931–966. IV.
2 Levine DS. Management of dysplasia in the columnar-lined esophagus. Gastroenterol Clin North Am 1997; 26: 613–34. IV.
3 Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. Gastroenterology 1993; 105: 40–50. IIa.
4 Shepherd NA. Dysplasia in Barrett's oesophagus. Acta Endoscopica; 2000; 30: 123–132. press. IV.
5 Reid BJ, Haggitt RC, Rubin CE, Roth G, Surawicz CM, Van Belle G, Lewin K, Weinstein WM, Antonioli DA, Goldman H et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. Hum Pathol 1988; 19: 166–78. III.
6 Haggitt RC. Barrett's esophagus, dysplasia, and adenocarcinoma. Hum Pathol 1994; 25: 982–993.IV.
7 Antonioli DA, Wang HH. Morphology of Barrett's esophagus and Barrett's-associated dysplasia and adenocarcinoma. Gastroenterol Clin North Am 1997; 26: 495–506 IV.
8 Rugge M, Correa P, Dixon MF, Hattori T, Leandro G, Lewin K, Riddell RH, Sipponen P, Watanabe H. Gastric dysplasia. The Padova International Classification. Am J Surg Pathol 2000; 24: 167–176. **IV.**
9 Weston AP, Krmpotich PT, Cherian R, Dixon A, Topalosvki M. Prospective long-term endoscopic and histological follow up of short segment Barrett's esophagus: comparison with traditional long segment Barrett's esophagus. Am J Gastroenterol 1997; 92: 407–13. III.
10 Sharma P, Morales TG, Bhattacharyya A, Garewal HS, Sampliner RE. Dysplasia in short-segment Barrett's esophagus: a prospective 3–year follow-up. Am J Gastroenterol 1997; 92: 2012–6. III.
11 Geisinger KR, Teot LA, Rubin CE, et al. A comparative cytopathologic and histologic study of atypia, dysplasia and adenocarcinoma in Barrett's esophagus. Cancer 1992; 69: 8–16. III.
12 Wang HH, Doria MI, Purohit-Boch S, et al. Barrett's esophagus. The cytology of dysplasia in comparison to benign and malignant lesions. Acta Cytologica 1992; 36: 60–64. IV.
13 Alexander JA, Jones SM, Smith CJ, Doull JA, Gietzen TH, Rathgaber SW. Usefulness of cytopathology and histology in the evaluation of Barrett's esophagus in a community hospital. Gastrointestinal Endoscopy 1997; 46: 318–20. III.
14 Hardwick RH, Morgan RJ, Warren BF, Lott M, Alderson D. Brush cytology in the diagnosis of neoplasia in Barrett's oesophagus. Dis Esophagus 1997; 10: 233–7. III.
15 Falk GW, Chittajallu R, Goldblum JR, Biscotti CV, Geisinger KR, Petras RE, Birgisson S, Rice TW, Richter JE. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. Gastroenterology 1997; 112: 1787–97. III.
16 Fitzgerald RC, Triadafilopoulos G. Recent developments in the molecular characterization of Barrett's esophagus. Dig Dis 1998; 16: 63–80. IV.
17 Jankowski JA, Wright NA, Meltzer SJ, Triadafilopoulos G, Geboes K, Casson AG, Kerr D, Young LS. Molecular evolution of the metaplasia-dysplasia-adenocarcinoma sequence in the esophagus. Am J Pathol 1999; 154: 975–984. IV.
18 Riddell RH. Early detection of neoplasia of the esophagus and gastroesophageal junction. Am J Gastroenterol 1996; 91:853–863. IV.
19 Biddlestone LR, Barham CP, Wilkinson SP, Barr H, Shepherd NA. The histopathology of treated Barrett's oesophagus: squamous re-epithelialisation following acid suppression, laser and photodynamic therapy. Am J Surg Pathol 1998; 22: 239–245. III.
20 Sharma P, Morales TG, Bhattacharyya A, Garewal HS, Sampliner RE. Squamous islands in Barrett's esophagus: what lies underneath? Am J Gastroenterol 1998; 93: 332–335. III.
21 Sharma P, Weston AP, Morales T, Topalovski M, Mayo MS, Sampliner RE. Relative risk of dysplasia for patients with intestinal metaplasia in the distal oesophagus and in the gastric cardia. Gut 1999; 46: 9–13. IIb.
22 Miros M, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. Gut 1991; 32: 1441–1446. IIb.
23 Hameeteman W, Tytgat GN, Houthoff HF, Van Den Tweel JG. Barrett's oesophagus: development and adenocarcinoma. Gastroenterology 1989; 96:1249–1256. IIb.
24 Peters FTM, Ganesh S, Kuipers EJ, Sluiter WJ, Klinkenberg-Knol EC, Lamers CBHW, Kleibeuker JH. Endoscopic regression of Barrett's oesophagus during omeprazole treatment; a randomised double blind study. Gut 1999; 45: 489–494. Ib.
25 Sagar PM, Ackroyd R, Hosie KB, Patterson JE, Stoddard CJ, Kingsnorth AN. Regression and progression of Barrett's oesophagus after antireflux surgery. Br J Surg 1995; 82: 806–810. IIb.
26 Ortiz A, Martinez de Haro LF, Parrilla P, Moralers G, Molina J, Bermejo J, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. Br J Surg 1996; 83: 274–278. IIb.
27 Schmidt HG, Riddell RH, Walther B, et al. Dysplasia in Barrett's esophagus. J Cancer Res Clin Oncol 1985; 110: 145–152. III.
28 Womack C, Harvey L. Columnar epithelial oesophagus or Barrett's esophagus: mucin histochemistry, dysplasia, and invasive adenocarcinoma. J Clin Pathol 1985; 38: 477–478. III.
29 Lee RG. Dysplasia in Barrett's esophagus: a clinicopathologic study of six patients. Am J Surg Pathol 1985; 9: 845–852. III.
30 Reid BJ, Weinstein NM, Lewin KJ et al. Endoscopic biopsy can detect HGD or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. Gastroenterology 1988; 94: 81–90. IIa.
31 Hamilton SR, Smith RR. The relationship between columnar epithelial dysplasia and invasive adenocarcinoma arising in Barrett's esophagus. Am J Clin Pathol 1987; 85: 301–312. III.
32 Garewal HS, Sampliner RE, Steinbronn K. Increase in ornithine decarboxylase activity associated with development of dysplasia in Barrett's esophagus. Dig Dis Sci 1989; 34: 312–314. IIb.
33 Altorki NK, Sunagawa M, Little AG, Skinner DB. High-grade dysplasia in the columnar-lined esophagus. Am J Surg 1991; 161: 97–99. IIb.
34 Pera M, Trastek VF, Carpenter HA, Allen MS, Deschamps C, Pairolero PC. Barrett's esophagus with high-grade dysplasia: an indication for esophagectomy? Ann Thoracic Surg 1992; 54: 199–204. III.
35 Rice TW, Falk GW, Achkar E, Petras RE. Surgical management of high-grade dysplasia in Barrett's esophagus Am J Surg 1997;174:1832–1836. III.
36 Steitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's oesophagus. Does it help? J Thoracic Cardiovasc Surg 1993; 105: 383–388. III.
37 Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester T. Outcome of adenocarcinoma in Barrett's esophagus in endoscopically surveyed and non-surveyed patients. J Thorac Cardiovasc Surg 1994; 108: 813–821. III.
38 Edwards MJ, Gable DR, Lentsch AB, Richardson JD. The rationale for esophagectomy as the optimal therapy for Barrett's esophagus with high-grade dysplasia. Ann Surg 1996; 223: 585–589. III.
39 Collard JM, Romagnoli R, Hermans BP, Malaise J. Radical esophageal resection for adenocarcinoma arising in Barrett's esophagus Am J Surg 1997; 174: 307–311. III.
40 Heitmeller RF, Redmond M, Hamilton SR. Barrett's esophagus with high-grade dysplasia. An indication for prophylactic esophagectomy. Ann Surg 1996; 224: 66–71. III.
41 Ferguson MK, Naunheim KS. Resection for Barrett's mucosa with high-grade dysplasia: implications for prophylactic photodynamic therapy. J Thoracic Cardiovasc Surg 1997; 114: 824–829. III.
42 Cameron AJ, Carpenter HA. Barrett's esophagus, high-grade dysplasia, and early adenocarcinoma: a pathological study. Am J Gastroenterol 1997; 92: 586–591. Grade IIb.
43 Robertson CS, Mayberry JF, Nicholson DA, James PD, Atkinson M. Value of endoscopic surveillance in the detection of neoplastic Change in Barrett's oesophagus. Br J Surg 1988; 75: 760–763. Grade IIb.
44 Reid BJ, Blount PL, Rubin CE, Levine DS, Haggitt RC, Rabinovitch PS. Flow-cytometric and histological progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. Gastroenterology 1992; 102: 1212–1219. Grade IIb.
45 Pera M, Trastek VF, Carpenter HA, Allen MS, Deschamps C, Pairolero PC. Barrett's esophagus with high-grade dysplasia: an indication for esophagectomy? Ann Thorac Surg 1992; 54: 199–204. Grade IIb.
46 Ouata-Lascar R, Fitzgerald RC, Triadafilopoulos G Differentiation and proliferation in Barrett's esophagus and the effects of acid suppression. Gastroenterology 1999;117:327–335. Grade IIb.
47 Gore S, Healey CJ, Sutton R, Eyre-Brook IA, Gear MWL, Shepherd NA, Wilkinson SP. Regression of columnar lined (Barrett's) oesophagus with continuous omeprazole therapy. Aliment Pharmacol Ther 1993; 7: 623–628. Grade IIa.
48 Sampliner RE. Effect of up to 3 years of high dose lansoprazole on Barrett's esophagus. Am J Gastroenterol 1994; 89: 1844–1888. Grade IIb.
49 Malesci A, Savarino V, Zentilin P, Belicchi M, Mela GS, Lapertosa G, Bocchia P, Ronchi G, Franceschi M. Partial regression of Barrett's esophagus by long-term high dose omeprazole. Gastrointest Endoscopy 1996; 44: 700–705. Grade IIb.
50 Wilkinson SP, Biddlestone L, Gore S, Shepherd NA. Regression of columnar-lined (Barrett's) oesophagus with omeprazole 40mg daily – results of 5 years of continuous therapy. Aliment Pharmacol Ther 1999; 13: 1205–1209. IIb.
51 Csendes A, Braghetto I, Burdiles P, Diaz J-C, Maluenda F, Korn O. A new physiologic approach for the surgical treatment of patients with Barrett's esophagus. Technical considerations and results in 65 patients. Ann Surg 1997; 226: 123–133. IIb.
52 DeMeester SR, Campos GMR, DeMeester TR, Bremner CG, Hagen JA, Peters JH, Crookes PF. The impact of an anti-reflux procedure on intestinal metaplasia of the cardia. Ann Surg 1998; 228: 547–556. IIb.
53 Katzka DA. Gastro-oesophageal reflux disease. Clinical Evidence 1999; 1: 145–153. IV.
54 Dent J, Bremner CG, Collen MJ et al. Working party report to the World Congresses of Gastroenterology, Sydney 1990: Barrett's Oesophagus. J Gastroenterol Hepatol 1991; 6: 1–22. IV.
55 Spechler SJ. Esophageal columnar metaplasia (Barrett's esophagus). Gastrointest Endosc Clin North Am 1997; 7: 1–18. IV.

56 Overholt BF, Panjehpour M. Barrett's esophagus: photodynamic therapy for ablation of dysplasia, reduction of specialized mucosa and treatment of superficial esophageal cancer. Semin Surg Oncol 1995; 11: 372–376. IIb.
57 Overholt BF, Panjepour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow-up in 100 patients. Gastrointest Endoscopy 1999; 49: 1–7. IIa.
58 Ackroyd R, Brown NJ, Davis MF, Stephenson TJ, Stoddard CJ, Reed MWR. Aminolaevulinic acid-induced photodynamic therapy in the treatment of dysplastic Barrett's oesophagus and adenocarcinoma. Lasers Med Sci 1999; 14: 278–285. III.
59 Byrne JP, Armstrong GR, Attwood SEA. Restoration of the normal squamous lining in Barrett's esophagus by argon beam plasma coagulation Am J Gastroenterol 1998; 93: 1810–1815. IIb.
60 Maass S, Martin WR, Spietfff A, et al. Barrett's esophagus with severe dysplasia in argon beam therapy. Z Gastroenterol 1998; 36: 301–306. III.
61 McBride MA. Vanagunas AA, Breshnan JP, et al. Combined endoscopic thermal coagulation with high dose omeprazole therapy in complicated heterotopic gastric mucosa of the esophagus. Am J Gastroenterol 1995; 11: 2029–2031. III.
62 Sampliner RE, Fennerty MB, Garewal HS. Reversal of Barrett's esophagus with acid suppression and multipolar electrocoagulation: Preliminary results. Gastrointest Endoscopy 1996; 44: 532–535. III.
63 Berenson MM, Johnson TD, Markowitz NR, et al. Restoration of squamous mucosa after ablation of Barrett's esophageal epithelium. Gastroenterology 1993; 104: 1686–1691. III.
64 Brandt LJ, Kauver DR. Laser-induced transient regression of Barrett's epithelium. Gastrointest Endoscopy 1992; 38: 619–622. III.
65 Sampliner RE, Hixson LJ, Fennerty MB, et al. Regression of Barrett's esophagus by laser ablation in an antacid environment. Dig Dis Sci 1993; 38: 365–368. IIb.
66 Barham CP, Jones RL, Biddlestone LR, Hardwick RH, Shepherd NA, Barr H. Photothermal laser ablation of Barrett's oesophagus: endoscopic and histological evidence of squamous re-epithelialisation. Gut 1997; 41: 281–384.IIb.
67 Sharma P, Bhattacharyya A, Garewal HS, Sampliner RE. Durability of new squamous epithelium after endoscopic reversal of Barrett's esophagus. Gastrointest Endosc 1999; 50: 159–164. IIb.
68 Altorki NK, Sunagawa M, Little AG, Skinner DB. High-grade dysplasia in columnar-lined esophagus. Am J Surg 1991; 161: 97–100. IIb.
69 Rusch VW, Levine DS, Haggitt R, Reid BJ. The management of high grade dysplasia and early cancer in Barrett's esophagus. A multidisciplinary problem. Cancer 1994; 74: 1225–1229. III.
70 Clark GWB, Ireland GWB, DeMeester TR. Dysplasia in Barrett's esophagus: Diagnosis, surveillance and treatment. Dig Dis 1996; 14: 213–227. III.
71 Heitmiller RF, Redmond M, Hamilton SR. Barrett's esophagus with high-grade dysplasia. An indication for prophylactic esophagectomy. Ann Surg 1996; 224: 66–71. III.
72 Barr H, Shepherd NA, Dix A, Roberts DJH, Tan WC, Krasner N. Eradication of high grade dysplasia in columnar-lined (Barrett's) oesophagus using photodynamic therapy with endogenously generated protoporphyrin IX. Lancet 1996; 348: 584–585. IIb
73 Gossner L, May A, Stolte M, Seitz G, Hahn EG, Ell C. KTP laser destruction of dysplasia and early cancer in columnar-lined Barrett's esophagus. Gastrointest Endoscopy 1999; 49: 8–12. IIb.
74 van den Boogert J, Van Hillegersberg R, Siersema PD, de Bruin RWF, Tilanus HW. Endoscopic ablation therapy for Barrett's esophagus with high-grade dysplasia: a review. Am J Gastroenterol 1999; 94: 1153–1160. IV.
75 Laukka MA, Wang KK. Initial results using low-dose photodynamic therapy in the treatment of Barrett's oesophagus. Gastrointest Endoscopy 1995; 42: 96–98. IIb
76 Menke-Pluymers MBE, Hop WCJ, Dees J, van Blankenstein M, Tilanus HW. Risk factors for the development of an adenocarcinoma in columnar-lined (Barrett) esophagus. Cancer 1993; 72: 1151–1158. IIb.
77 DeMeester TR, Attwood SEA, Smyrk TC, Therkildsen DH, Hinder RA. Surgical therapy in Barrett's esophagus. Ann Surg 1990; 212: 528–542. IV.
78 Nava HR. Photodynamic therapy in Barrett's high-grade dysplasia: are we ready to abandon esophagectomy for a more conservative therapy? J Surg Oncol 1998; 68: 207–208. III.
79 Soehendra H, Binmoeller KF, Bohnacker S, et al. Endoscopic snare mucosectomy in the esophagus without any additional equipment: a simple technique for resection of flat early cancer. Endoscopy 1997; 29: 380–383. III.
80 Farin G, Grund KE. Technology of argon plasma coagulation with particular reference to endoscopic applications. Endosc Surg 1994; 2: 71–77. III
81 Gossner L, May A, Stolte M, Seitz G, Hahn EG, Ell C. KTP laser destruction of dysplasia and early cancer in columnar-lined Barrett's esophagus. Gastrointest Endosc 1999; 49: 8–12. IIb.
82 Bremner RM, Mason RJ, Bremner CG, et al. Ultrasonic epithelial ablation of the lower esophagus without stricture formation. A new technique for Barrett's ablation. Surg Endosc 1998; 12: 342–346. IV.
83 Ackroyd R, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW. Ablation treatment for Barrett oesophagus: what depth of tissue destruction is needed? J Clin Pathol 1999; 52: 509–512. III.
84 Sibille A, Lambert R, Souquet J-P, Sabben G, Descos F. Long-term survival after photodynamic therapy for esophageal cancer. Gastroenterology 1995; 108: 337–344. IIa.
85 Wang KK, Geller A. Photodynamic therapy for early esophageal cancers: light versus surgical might. Gastroenterology 1995; 108: 593–607. IIb.
86 Heier SK, Rothman KA, Heier LM, Rosenthal WS. Photodynamic therapy for obstructing esophageal cancer: light dosimetry and a randomized comparison with Nd:YAG laser therapy. Gastroenterology 1995; 109: 63–72. 1b.
87 Barr H, Krasner N, Boulos PB, Chatlani PT, Bown SG. Photodynamic therapy for colorectal cancer: a quantitative pilot study. Br J Surg 1990; 77: 93–96. III.
88 Tan WC, Fulljames C, Stone N, Dix AJ, Shepherd NA, Roberts DJH, Brown SB, Krasner N, Barr H. Photodynamic therapy using 5–aminolaevulinic acid for oesophageal adenocarcinoma associated with Barrett's metaplasia. J Photochem Photobiol B: Biology 1999; 53: 75–80. III.
89 Van Laethem J-L, Cremer M, Peny MO, Delhaye M, Deviere J. Eradication of Barrett's mucosa with argon plasma coagulation and acid suppression: immediate and mid term results. Gut 1998; 43: 747–751. IIb.
90 Michopoulos S, Tsibouris P, Bouyzakis H, Sotiropoulou M, Kralios N. Complete regression of Barrett's oesophagus with heat probe thermocoagulation: mid-term results. Gastrointest Endosc 1999; 50: 165–172. IIb.
91 Bamford K, James J, Barr H, Tatam R. Electromagnetic simulation of laser-induced fluorescence in bronchial tissue and predicted optical scattering behaviour. Optical and Imaging Techniques for Biomonitoring IV (SPIE Proceedings) 1998; 3567: 18–28. III.
92 Barr H, Dix AJ, Stone N. Optical spectroscopy for the early diagnosis of gastrointestinal malignancy. Lasers Med Sci 1998; 13: 3–13. IV.
93 Peters JH, Clark GWB, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients J Thoracic Cardiovasc Surg 1994; 108: 813–822. IIa.
94 Korst RJ, Altorki NK. Extent of resection and lymphadenectomy in early Barrett's cancer. Dis Esophagus 1997; 10: 172–178. III.
95 Farrow DC, Vaughan TL. Determinants of survival following the diagnosis of esophageal adenocarcinoma (United States). Cancer Causes and Control 1996; 7: 322–337.IIb.
96 Matthews HR, Powell DJ, McConkey CC. Effect of surgical experience on the results of resection for oesophageal carcinoma. Br J Surg 1986; 73: 621–623. III.
97 Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg 1990; 77: 845–857. III.
98 Somerville M, Milne R. Surveillance of Barrett's oesophagus. Wessex Institute Development & Evaluation Committee Report 1999; 102: 1–37. IV.

Economic aspects of surveillance

P Moayyedi

EXECUTIVE SUMMARY

European studies have estimated the cost of detecting a cancer in CLO surveillance programmes at between £15–20,000 in males and £27–42,000 in females, which are significantly lower than those in the United States series.

A Markov model based on UK NHS prices estimates that two yearly surveillance costs £19,000 per life year saved. This appears comparable to that of other health care interventions, although some optimistic assumptions were made in the model. At present there is insufficient evidence to either promote or reject surveillance programmes in CLO on economic grounds alone. (Recommendation grade B.)

It is possible that targeting surveillance to those at greatest risk of development of adenocarcinoma may be more effective and cost-effective, but studies are needed to test this hypothesis.

INTRODUCTION

Surveillance of patients with CLO has become increasingly popular in recent years with 70% of a randomly selected group of British Society of Gastroenterology members offering this service[1]. The remaining 30% cited prohibitive costs as one of the main reasons why a surveillance programme was not instituted. The resources available to the Health Service are limited and therefore the cost-effectiveness of CLO surveillance is an important consideration. This review presents the data available on the economics of CLO surveillance and outlines a Markov model evaluating the cost-effectiveness of this approach from a UK National Health Service perspective.

REVIEW OF THE LITERATURE ON THE HEALTH ECONOMICS OF CLO SURVEILLANCE

Three reports have estimated the cost of detecting cancer cases[2,3,4]. A UK study[2] suggested CLO surveillance cost £14,868 for men and £42,084 for women per cancer case detected, a Swedish study[3] reported a cost of £20,000 for men and £27,000 for women, whilst a US study[4] estimated CLO surveillance cost £39,000 per cancer case discovered. These studies treat "cancer case detected" as an outcome whereas the amount of life surveillance saves is the important outcome to patients as not all cases found are curable. One study reported the cost of CLO surveillance at £2,600/life year saved which compares very favourably with breast cancer screening[5] using the authors clinical experience.

The problem with using survey data is that the data are based on only a few cancer cases and therefore there is considerable uncertainty surrounding the estimate of cost-effectiveness. There is also no control group with which to compare survival. An alternative approach is to construct an economic model based on data obtained from a literature review to establish whether CLO surveillance is likely to be cost-effective. Provenzale et al.[6] reported a Markov model evaluating the cost effectiveness of CLO surveillance and this has recently been updated[7]. This was a well constructed model from a health care perspective which used quality adjusted life years gained as an outcome. The authors assessed quality adjusted life years (QALY) gained from interviewing health care workers[6] or patients[7] after oesophagectomy using time trade off techniques. CLO surveillance performed at five yearly intervals cost £61,000/QALY gained[7]. Surveillance at shorter intervals was less attractive than the five-year option as less QALYs were saved and the programme was more expensive. The author concluded that CLO surveillance was cost-effective as the cost/QALY gained was similar to some other health care interventions but that it should only be offered at five yearly intervals.

This model was thorough and well researched but was devised from a US perspective. The cost of endoscopy is cheaper in the UK but the threshold at which an intervention is deemed cost effective is also lower. It would appear useful, therefore, to construct a model from a UK perspective. The extension of surveillance to once every five years is interesting but is not based on any data. Most reports of early cancer detection are based on endoscopy performed every one or two years and therefore it is more appropriate to establish the cost-effectiveness of CLO surveillance within this range. A review of the literature has been conducted to establish likely impact CLO surveillance will have on survival from oesophageal adenocarcinoma and these have been incorporated into a Markov model.

THE IMPACT OF CLO SURVEILLANCE ON MORTALITY FROM OESOPHAGEAL ADENOCARCINOMA

The incidence of oesophageal adenocarcinoma and the proportion of those benefiting from early detection are the two most important factors in determining the effectiveness of a CLO surveillance programme. There have been a number of reviews which have suggested approximately a 1% incidence of adenocarcinoma arising from CLO. A US review suggested that the incidence may be closer to 0.5% and previous estimates were due to publication bias (8). We have conducted a review of the literature and found a pooled incidence of 1/119 patient years (95% CI = 1/98 to 1/152) with no evidence of publication bias in UK studies (9).

The detection of oesophageal adenocarcinoma does not necessarily translate into improved survival. The cancer may be detected too late, patients may be unfit for surgery and oesophagectomy is associated with post-operative mortality. The overall success of CLO surveillance was therefore estimated from the literature. Eighteen surveys[3–5,10–24] were identified which reported the outcome of patients with oesophageal adenocarcinoma detected by surveillance. Success was defined as a patient alive two years after surgery and/or adjuvant therapy. Post-operative deaths, patients unfit for any intervention and those dying within two years of surgery (even if the death was not related to cancer) were classified as surveillance failures. The pooled mean success rate was 55% (95% CI = 43% to 67%). This is likely to be an overestimate as poor outcomes are less likely to be reported

and only one study[22] critically evaluated how the cancer cases were detected. Two out of the three cancers detected in this series were by endoscopy for symptoms rather than as part of the surveillance programme[22]. The majority of reports offered yearly endoscopy with only two studies lengthening the screening interval to two years.

MODELLING THE COST-EFFECTIVENESS OF CLO SURVEILLANCE

A Markov model (Data version[3.5], TreeAge software incorporated, Williamstown, US) was constructed to evaluate the cost-effectiveness of a CLO surveillance programme compared with no intervention from a UK National Health Service perspective. The baseline scenario assumed patients would enter the programme aged 50 and be endoscoped annually for the next 20 years with 90% attending for endoscopy each year. Patients with low grade dysplasia would be investigated every six months and subjects with high grade dysplasia every three months. There is controversy as to whether patients with high grade dysplasia should have oesophagectomy rather than increased surveillance[25]. The model addresses this by assuming 50% of patients with high grade dysplasia develop adenocarcinoma and that this is always detected at an early stage by increased surveillance. The model assumes that a third of the oesophageal cancers detected arise de novo, a third from low grade dysplasia and a third from high grade dysplasia[26]. The costs of the programme were obtained from UK National sources where possible. The cost of proton pump inhibitors was not included as it was assumed that both groups would be prescribed these drugs.

The outcome was measured in life years saved and the model assumes the incidence of oesophageal adenocarcinoma is 1%, which represent the lower limit of the confidence intervals of the review. The 5–year survival was assumed to be 50%, which is similar to the two-year survival seen in the review. All costs and benefits were discounted at 5% and the robustness of the model was evaluated by one-way sensitivity analyses.

The model suggested that 34 years of life would be saved for every 100 CLO cases undergoing surveillance at a cost of £649,600. This gives an incremental cost effectiveness ratio of £19,100 / life year saved. A one way sensitivity analysis suggested this value was altered very little be variations in attendance rate, percentage of low and high grade dysplasia progressing to cancer and the cost of surgery. The cost-effectiveness of CLO surveillance was altered to a moderate extent by the cost of endoscopy, cost of biopsy and the discount rate applied. Survival after surgery influenced the cost –effectiveness of CLO surveillance (£57,000/ life year saved if 20% survival, £9,000 / life year saved if 100% survival). Cost-effectiveness was also very sensitive to the incidence of adenocarcinoma arising from CLO (£80,000/life year saved if incidence is 1/500, £11,000/life year saved if incidence is 1/50).

The impact of extending endoscopy surveillance to once every two years was also evaluated. There are very few data to determine the impact this would have on survival. It was therefore conservatively assumed that cancers arising in the year patients were not screened would become incurable. A two year programme would save 17 years of life at a cost of £319,000 for 100 CLO cases undergoing surveillance. This gives an incremental cost-effectiveness ratio compared with a "do nothing" strategy of approximately £19,000. The incremental cost of increasing endoscopy from every two years to annually is also £19,000. This is based on the assumption that oesophageal adenocarcinoma progresses to incurable disease within one year. If this is not the case a two-year programme would be more cost-effective but this needs evaluation in further trials.

DISCUSSION

The model estimates the cost of CLO surveillance to be approximately £19,000/life year saved. This is expensive compared to many screening strategies with breast cancer estimated to cost £9,000/life year saved[27]. The upper limit that it is acceptable to pay in the UK to save a life year is uncertain. Five hundred and eighty seven life saving interventions have been evaluated in the United States and the median cost is approximately £26,000/life year saved[28].

This model does, however, make several assumptions that may overestimate the cost-effectiveness of surveillance. The decision analysis model was constructed from a health service perspective. A societal perspective may have given higher cost estimates as travel costs, leisure time costs and time off work of subjects attending for surveillance was not considered.

The model did not incorporate any extra medical costs other than those relating to dyspepsia in individuals surviving longer as a result of screening. The inclusion of these costs is controversial.

The cost-effectiveness calculations were expressed in terms of years of life saved and therefore implicitly all years of life are valued equally. This is a common perspective to take, but it could be argued that many of the life years saved would be in the elderly some of whom would be frail. This problem could be overcome by incorporating health-related quality of life measures such as Quality Adjusted Life Years (QALY) as an outcome in the model. This is the approach taken by Provenzale et al.[7] and will give a more conservative estimate of cost-effectiveness. The accuracy of QALYs in measuring quality of life has however been questioned[29].

It is assumed that oesophageal cancer cases have no extra co-morbidity. Subjects that are prevented from developing oesophageal cancer therefore have an age standardised life expectancy that is the same as the general population. If subjects developing oesophageal adenocarcinoma are less healthy than the normal population then this model will over-estimate the cost-effectiveness of surveillance.

A Markov model based on UK NHS prices estimates that two yearly surveillance costs £19,000 per life year saved. This appears comparable to that of other health care interventions, although some optimistic assumptions were made in the model. At present there is insufficient evidence to either promote or reject surveillance programmes in CLO on economic grounds alone. (Recommendation grade B.) It is possible that targeting surveillance to those at greatest risk of development of adenocarcinoma may be more effective and cost-effective, but studies are needed to test this hypothesis.

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REFERENCES

1 Smith A.M, Maxwell-Armstrong, C.A, Welch N.T, Scholefield J.H. Surveillance of Barrett's oesphagus in the UK. British J of Surg 1999; 86: 276–280. **III**
2 Wright T.A, Gray M.R, Morris A,I, Gilmore I.T, Ellis A, et al. Cost effectiveness of detecting Barrett's cancer. Gut 1996; 39: 574–579. **III**
3 Nilsson J, Skobe V, Johansson J, Wllen R, Johnsson F. an evaluation of a surveillance program for columnar metaplasia of the oesophagus. Scand J Gastroenterol 2000; 35:10–16. **III**
4 Achkar E, Carey W. The cost of surveillance for adenocarcinoma complicating Barrett's esophagus. American J Gastroenterol 1988; 83: 291–194. **III**
5 Streitz J.M, Ellis F.H, Tilden R.L, Erickson R.V. Endoscopic surveillance of Barrett's esophagus: A cost effectiveness comparison with mammographic surveillance for breast cancer. American J Gastroenterol 1998; 93: 911–915. **III**

6 Provenzale D, Kemp J.A, Arora S, Wong J.B. A guide for surveillance of pateints with Barrett's esophagus. American J Gastroenterol 1994; 89: 670–680. **III**

7 Provenzale D, Schmitt C, Wong J.B. Barrett's esophagus: A new look at surveillance based on emerging estimates of cancer risk. American J Gastroenterol 1999; 94: 2043–2053. **III**

8 Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there a publication bias in the reporting of cancer risk in Barrett's oesophagus? Gastroenterology 2000; 119: 333–8. **III**

9 Jankowski J, Provenzale D, Moayyedi P. Oesophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the West. Gastroenterology 2002; 122: 588–590. **III**

10 Spechler S.J, Robbins A.H, Bloomfield-Rubins H, Vincent M.E, Heeren T, Doos W.G, Colton T, Schimmel E.M. Adenocarcinoma and Barrett's esophagus. An overrated risk? Gastroenterology 1984; 87: 927–33. **III**

11 Cooper B.T, Barbezat G.O. Barrett's oesophagus: A clinical study of 52 patients. Quarterly J Med 1987; 238: 97–108. **III**

12 Williamson W.A, Ellis F.H.Jr., Gibb S.P, Shahian D.M, Aretz H.T, Heatley G.J, et al. Barrett's esophagus. Prevalence and incidence of adenocarcinoma. Archives of Internal Medicine 1991; 151 (11): 2212–2216. **III**

13 Hameeteman W, Tytgat G.N.J, Houthoff H.J, van den Tweel J.G. Barrett's esophagus: Development of dysplasia and adenocarcinoma. Gastroenterol 1989; 96: 1249–1256. **III**

14 O'Connor J.B, Falk G.W, Richter J.E. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus. American J Gastroenterol 1999; 94: 2037–2042. **III**

15 Miros M, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. Gut 1991; 32: 1441–1446. **III**

16 Iftikhar S.Y, James P.D, Steele R.J.C, Hardcastle J.D, Atkinson M. Length of Barrett's oesophagus: an important factor in the development of dyplasia and adenocarcinoma. Gut 1992; 33: 115–1158. **III**

17 Robertson C.S, Mayberry J.F, Nicholson D.A, James P.D, Atkinson M. Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus. Br J Surg 1988; 75: 760–763. **III**

18 Ferraris R, Bonelli L, Conio M, Fracchia M, Lapertosa G et al. Incidence of Barrett's adenocarcinoma in an Italian population: an endoscopic surveillance programme. Europ J Gastroenterol & Hepat 1997; 9: 881–885. **III**

19 Watson R.G.P, Porter K.G, Sloan J.M. Incidence of adenocarcinoma in Barrett's oesophagus and an evaluation of endoscopic surveillance. Europ J Gastroenterol & Hepat 1991; 3: 159–162. **III**

20 Katz D, Rothstein R, Schned A, Dunn J, Seaver K, Antonioli D. The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. Am J Gastroenterol 1998; 93: 536–541. **III**

21 Drewitz D.J, Sampliner R.E, Garewal H.S. The incidence of adenocarcinoma in Barrett's esophagus: A prospective study of 170 patients followed 4.8 years. Am J Gastroenterol 1997; 92: 212–215. **III**

22 Macdonald C.E, Wicks A.C, Playford R.J. Ten years' experience of screening patients with Barrett's oesophagus in a university teaching hospital. Gut 1997; 41: 303–307. **III**

23 Van Sandick J.W, van Lanschot J.J.B, Kuiken B.W, Tytgat G.N.J, Offerhaus G.J.A, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut 1998; 43: 216–222. **III**

24 Peters J.H, Clark G.W.B, Ireland A.P, Chandrasoma P, Smyrk T.C, DeMeester T.R. Outcome of adenocarcinoma arising in Barrett's oesophagus in endoscopically surveyed and nonsurveyed patients. J Thorac Cardiovasc Surg 1994; 108: 813–822. **IIb**

25 Wright T.A. High-grade dysplasia in Barrett's oesophagus. Br J Surg 1997; 84: 760–766. **III**

26 Rusch V.W, Levine D.S, Haggitt R, Reid B.J. The management of high grade dysplasia and early cancer in Barrett's esophagus. A multidisciplinary problem. Cancer 1994; 74: 1225–1229. **IV**

27 Department of Health and Social Security (1986) Breast cancer screening. Report to the Minister of England, Wales, Scotland and Northern Ireland by a Working Group Chaired by Professor Sir Patrick Forrest. London: HMSO. **IV**

28 Tengs, T. O., Adams, M. E., Pliskin, J. S., Safran, D. G., Siegel, J. E., Weinstein, M. C., and Graham, J. D. Five-hundred life-saving interventions and their cost-effectiveness. Risk Analysis 15, 369–390. 1995. **III**

29 Mason J. Drummond M. Torrance G. Some guidelines on the use of cost effectiveness league tables. BMJ 1993; 306:570–2. **IV**

30 Department of Health (1989) General practice in the NHS: a new contract. London: Department of Health. (estimates of the cost of invitation for cervical screening). **IV**

31 Department of Health reference costs: F16 day case stomach or duodenum – diagnostic procedures (http: and www.doh.gov.uk/nhsexec/refcosts.htm, 1999) **IV**

32 Local estimates of cost of Barrett's surveillance quadrantic biopsies every two centimetres (Leeds General Infirmary). **IV**

33 Bodger, K., Daly, M.J., Heatley, R.V. and Williams, D.R. Clinical economics review: gastroenterology. Alimentary Pharmacology & Therapeutics 1996; 10: 55–60. **IV**

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