

# Barrett's esophagus and the increasing role of endoluminal therapy

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Therapeutic Advances in Gastroenterology

(2008) 1(2) 121–142

DOI: 10.1177/  
1756283X08095883

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Los Angeles, London,  
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**Abstract:** Barrett's esophagus, or the presence of specialized intestinal mucosa in the esophagus that has a malignant potential, has experienced a rapid increase in diagnosis and prevalence over the past few decades. Once thought to progress to adenocarcinoma in an orderly sequence of increasing dysplasia, recent data suggest the process can be more random. In combination with targeted surveillance endoscopy, recent improvements in technology have aided endoluminal therapy in becoming a cost-effective adjunct to medication. When used in combination, in particular, these ablative therapies have become suitable, if not preferable, alternatives to surgery in many patients.

**Keywords:** Barrett's esophagus, esophageal cancer, gastro-esophageal reflux disease

## Introduction

Barrett's esophagus was first identified by N.R. Barrett in 1950, who described the replacement of the normal squamous mucosa of the distal esophagus by a columnar epithelium of both gastric and intestinal types [Barrett, 1950, 1957]. The definition of Barrett's esophagus has been modified over subsequent years to include only intestinal metaplasia within the tubular esophagus. While some pathologists require the presence of well-formed goblet cells interspersed between tall columnar cells, others prefer a broader definition which allows the columnar cells to lack goblet cell morphology, but still have acidic mucins seen with Alcian blue stains [Robert, 2003]. The staining pattern distinguishes what Trier characterized as specialized intestinal mucosa (SIM) [Trier, 1970] from gastric, small bowel or colonic mucosa, which have not shown the same malignant potential.

Morson and Belcher made the first association of esophageal columnar epithelium with adenocarcinoma in 1952 [Spechler and Goyal, 1985], and it is this connection that drives current interest in Barrett's esophagus. It is widely believed that Barrett's esophagus is the result of chronic injury to normal esophageal squamous mucosa caused by acid and perhaps bile reflux in genetically susceptible individuals [Lightdale, 1999].

In most patients with reflux esophagitis, the epithelium heals through regeneration of the normal squamous lining [Spechler, 2003]. Other patients, however, will develop Barrett's esophagus with the risk of ultimately progressing to esophageal adenocarcinoma [Spechler and Goyal, 1985].

This paper will discuss the epidemiology of Barrett's esophagus and its related conditions, as well as the metaplasia–dysplasia–carcinoma developmental sequence, to provide a context in which to address the role of endoscopic intervention for diagnosis, surveillance and possible treatment of dysplasia and early carcinoma.

## Epidemiology

Longstanding gastro-esophageal reflux and gastro-esophageal reflux disease (GERD) have been identified as the major risk factors for the development of Barrett's esophagus [Spechler, 2002; Lagergren *et al.* 1999]. As Barrett's does not produce any symptoms or health impairment other than those seen with GERD [Mashimo *et al.* 2005], it is important to consider aspects of the epidemiology of GERD as well as that of Barrett's. Approximately 10% of the US population suffers from daily heartburn, and 40% note occasional heartburn [Locke *et al.* 1997;

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Nebel *et al.* 1976]. Adding those patients who demonstrate only atypical GERD symptoms, the number of those with chronic reflux grows only larger [Castell, 2001]. Studies have shown that up to 20% of GERD patients develop more serious complications, including ulcerative esophagitis, peptic stricture or Barrett's esophagus, and as many as 10–12% of patients who undergo upper endoscopy for GERD symptoms are diagnosed with Barrett's [Falk, 2002].

Given that approximately 80% of those patients taking anti-acid medications will demonstrate a relapse of symptoms with a decrease in medication dose [Hetzel *et al.* 1988], and that more than 70% of patients and even healthy controls demonstrate nocturnal acid breakthrough with at least one hour of gastric pH < 4 overnight [Peghini *et al.* 1989], it is reasonable to assume that these patients are experiencing chronic acid exposure to the distal esophagus. It is not surprising then, that Barrett's esophagus is estimated to affect about 700,000 people in the US alone [Pera, 2000; Devesa *et al.* 1998]. As Barrett's can only be diagnosed with endoscopy and biopsy, the true incidence may be even higher than that [Cameron *et al.* 1990]. This hypothesis is supported by a recent study where 4.5% of otorhinolaryngology (ORL) clinic patients who presented with GERD symptoms alone were diagnosed with Barrett's esophagus, but 4.9% of those patients who presented only with GERD-related ORL symptoms were also diagnosed with Barrett's [Poelmans *et al.* 2004]. Similar data were found in Connor's study, where 264 patients presenting with dyspepsia but not reflux underwent endoscopy, and 6% were found to have Barrett's esophagus [Connor *et al.* 2004].

Ronkainen and colleagues [2005] used a population-based study to estimate the prevalence of Barrett's esophagus in Sweden. Of 19,000 Swedes within a target age range of 20–80, a random sample of 3,000 was surveyed via questionnaire. A random subsample of 1,000 people then underwent upper endoscopy, where an overall Barrett's prevalence of 1.6% was observed. However, if reflux symptoms were present, the prevalence rose to 2.3%. Underscoring the point that Barrett's esophagus generates no additional symptoms other than those seen with GERD, up to 44% of patients diagnosed with Barrett's did not report heartburn or regurgitation on their completed questionnaires.

Focusing on patients who presented for their initial endoscopy in the setting of suspected GERD, Westhoff *et al.* [2005] studied 378 consecutive patients who had biopsies taken of areas suspicious for Barrett's esophagus. The overall prevalence of Barrett's esophagus was found to be 13.2%. The majority of patients diagnosed had short-segment Barrett's esophagus (SSBE) (up to 3 cm in length), which agreed with previous data showing the prevalence of endoscopically recognizable SSBE at 5–7%, versus 1–3.4% for long-segment Barrett's esophagus (LSBE) [Mashimo *et al.* 2005].

Westhoff's study demonstrated multiple risk factors for the development of Barrett's besides reflux, including being Caucasian and/or male, having a history of smoking, and having a hiatal hernia. These associations also are supported by a myriad of other studies. One such study evaluated the complications of GERD (including Barrett's) and showed that 12.3% of whites are affected, compared to only 2.8% of blacks and 1.8% of Asians [Spechler *et al.* 2002]. To further explore differences between the sexes, Lin studied 543 patients with GERD symptoms, and showed that while male and female patients demonstrated an equal severity of erosive esophagitis, only 14% of female patients had Barrett's esophagus, compared to 23% of male patients ( $p < 0.05$ ) [Lin *et al.* 2004]. Banki, however, showed that there was an equal prevalence of Barrett's esophagus in men and women diagnosed with severe reflux by 24-hour pH monitoring [Banki *et al.* 2005]. A chart review of almost 22,000 first endoscopies identified 492 patients with Barrett's esophagus and suggested that there is a 20-year age shift between males and females in prevalence patterns, resulting in a male to female odds ratio of 4.15 (95% CI 2.99–5.77) [Van Blankenstein *et al.* 2005].

Other studies have demonstrated that increased age and obesity are also risk factors for developing Barrett's esophagus as well as esophageal adenocarcinoma (EAC) [Lagergren *et al.* 1999; Cameron, 1997]. In a retrospective case-control study, 129 patient cases with recent abdominal CT scan and upper endoscopy were reviewed, and a multivariable logistic regression model was created [El-Serag *et al.* 2005]. Visceral adipose tissue was found to be independently associated with the presence of Barrett's esophagus after adjustment for body mass index (BMI) (OR 1.077, 95% CI 1.007–1.151), suggesting

that this qualitative measurement of obesity may be an even stronger risk factor for Barrett's than BMI. Banki's study also demonstrated that patients with documented bile reflux were five to eleven times more likely to have Barrett's esophagus [Banki *et al.* 2005].

Recent results also suggest that there are additional diseases that may predispose patients to the development of Barrett's esophagus. Maieron *et al.* [2005] demonstrated a 26.6% prevalence of Barrett's in 60 Caucasian patients with celiac disease. Similarly, Wipff *et al.* [2005] found a 12.7% prevalence of Barrett's esophagus on esophageal biopsies of 110 patients with systemic sclerosis. These data suggest that altered intestinal motility may facilitate the chronic acid exposure required for intestinal metaplasia. It is not surprising then, that there is a negative association between the prevalence of *Helicobacter pylori* and the presence of Barrett's esophagus, as the decreased acid secretion seen with *H. pylori* infection may have a protective effect in the esophagus [Abe *et al.* 2004]. In line with the definition of Barrett's as a complication of long-term esophageal acid exposure, data also confirms that a longer duration of symptoms also increases the risk of finding Barrett's esophagus [Toruner *et al.* 2004].

Perhaps the most striking finding is the massive increase in the diagnosis of Barrett's esophagus during recent years. Irani *et al.* [2005] reviewed more than 18,000 endoscopy reports from 1991 to 2000, and showed an increase in the rate of suspected and confirmed Barrett's esophagus of 360% ( $p < 0.001$ ). The total number of endoscopies also increased by 135%, suggesting that increased vigilance did contribute to additional diagnosis. Similarly, the chart review mentioned above showed that for males between ages 20 and 59 and females from 20 to 79, the prevalence of Barrett's rose 7.36% per year [Van Blankenstein *et al.* 2005].

The increased prevalence of Barrett's esophagus is of particular importance because the majority of EAC cases arise from Barrett's epithelium [Kim *et al.* 1997]. Before the mid-1970s, more than 95% of esophageal malignancies were not adenocarcinomas, but EAC has shown a dramatic increase in incidence with a 600% increase in recent decades [Hesketh *et al.* 1989; Yang *et al.* 1988]. The incidence continues to rise with a reported increase in men ranging from 1.5% to

17% per year [Bollschweiler *et al.* 2001]. In the US, the reported annual increase is close to 10% for white males [Blot *et al.* 1991], while the greatest increase has been in white males over the age of 65 [Devesa *et al.* 1998]. Like Barrett's esophagus, EAC trends differ for males and females [Lagergren, 2005]. There are approximately 6,250 new cases of EAC in the US every year [Devesa *et al.* 1998]. Similarly, the rates of adenocarcinoma of the esophagogastric junction and gastric cardia have risen dramatically with a similar number of new cases annually [Pera, 2000]. This epidemic has been centred more in the US and Europe, but is not evident in Asia, where squamous cell cancer remains the predominant esophageal malignancy.

The presence of Barrett's esophagus continues to be the strongest risk condition for the formation of EAC, with larger-size studies calculating an increased risk of cancer at 30 to 60-fold above the baseline level for Barrett's patients [Van der Veen *et al.* 1989; Cameron *et al.* 1985]. The risk of developing EAC appears to be the same for SSBE and LSBE at approximately 0.5% per year, which is exponentially higher than that of the non-Barrett's population [Sharma *et al.* 2004; Falk, 2002]. Van Blankenstein *et al.* [2004] followed 386 institutionalized patients for 52,000 patient years, and noted an overall incidence of EAC of 2.5/1000 years, which increased to 6.3/1000 years in those patients who had confirmed Barrett's esophagus. A Swedish study showed that the presence and duration of symptoms both correlate with increased risk of EAC [Lagergren *et al.* 1999]. If reflux symptoms are present at least weekly, the relative risk is eight times greater and is even higher for more frequent or severe symptoms. Additionally, an odds ratio of 43.5 was found for EAC development in patients with longstanding reflux.

The data are mixed for prognosis of EAC in the setting of Barrett's esophagus. Mortality rates for Barrett's with EAC are similar to those of the general population [Anderson *et al.* 2003], and five-year survival of EAC is still only about 10% despite recent improvement [Farrow and Vaughn, 1996]. The median survival for EAC was 0.75 years between 1973 and 1977, and increased to only 0.9 years between 1993 and 1999 [Barr *et al.* 2005]. This improvement, however, could be due only to improved detection and reporting and not advances in therapeutics. Additionally, the lymphatic supply of the

esophagus extends into the lamina propria, and lymphatic spread is common even in early disease with nodal metastases reported in up to 5% of intramucosal cancers and 24% of tumours that have extended submucosally [Sabik *et al.* 1995]. However, there is a belief that EAC survival rates are better if the carcinoma arises from Barrett's esophagus, possibly due to earlier endoscopy and therapy caused by the presence of GERD symptoms [Thomas *et al.* 1997]. Therefore, diagnosis and management of Barrett's esophagus is focused around the prevention, early recognition and early treatment of EAC [Spechler, 2002]. Given the data on early cancer, attention must be paid to following and intervening in the earlier stages of Barrett's progression to invasive malignancy.

### Dysplastic Barrett's esophagus

The presence of specialized intestinal mucosa in the distal esophagus is believed to be only the first step in the generation of adenocarcinoma. It is believed that, for most patients, the neoplastic process passes from the presence of SIM to different stages of dysplasia, then ultimately to malignancy. To best understand this process, however, it is important to define the different stages of dysplasia.

Dysplasia in Barrett's esophagus is a histologic diagnosis suggesting that at least one cell clone has acquired sufficient genetic damage to render it neoplastic and predisposed to the formation of a malignancy [Spechler, 2001]. An accurate and full diagnosis of dysplastic Barrett's esophagus depends on both endoscopic and pathologic correlation [Attwood and Morris, 2001]. Unfortunately, due to the subjectivity involved in arriving at a histopathologic interpretation, categorization of the pathologic changes is very difficult [Robert, 2003]. Most studies consistently show that the histopathologic grade of a patient's Barrett's esophagus is the single most important predictor of future risk for development of invasive EAC [Montgomery *et al.* 2001; Cameron *et al.* 1985].

The degree of dysplasia in Barrett's esophagus is determined by evaluating four histologic elements: cytology, architecture, degree (or lack) of surface maturation, and the extent of background inflammation [Robert, 2003]. Inflammation is a most important consideration

as it injures epithelial cells, creating degenerative and regenerative changes such as increased nuclear size and increased mitotic activity, which is actually evidence of repair and not dysplasia. Therefore, when active inflammation is present, a diagnosis of dysplasia must be treated with scepticism.

Neoplasia in Barrett's esophagus is categorized as one of the following grades: indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal carcinoma (IMC), or invasive cancer. While 'indefinite for dysplasia' is seen as a 'wobble' category, it does serve an important purpose in that it alerts clinicians that one-year follow up biopsies are warranted without causing great alarm in either the physician or patient, as significant inflammation alone may lead to an indefinite diagnosis. It can be distinguished from LGD, however, as only low-grade biopsies demonstrate cytologic changes that must extend to the surface of the epithelium [Robert, 2003].

Perhaps the most important distinction lies between low-grade and high-grade dysplasia. The previously used term of 'carcinoma *in situ*' currently is classified as being the 'high end' of HGD [Robert, 2003]. Architectural changes in HGD include the branching and lateral budding of crypts, formation of a villiform mucosal surface, intraglandular bridging of the epithelium to form cribriform 'back-to-back' glands, and the absence or paucity of goblet and columnar cell mucus [Mashimo *et al.* 2005]. Nuclear abnormalities are often seen, such as loss of nuclear polarity and significant variation in the size, shape and staining of nuclei, consistent with increased DNA content [Haggitt, 1994]. While all of these mucosal changes can be seen, there is no evidence of invasion into the lamina propria. As we will discuss later, HGD must be confirmed by a second pathologist prior to initiation of any definitive therapy [Robert, 2003].

The most dysplastic categories of Barrett's esophagus demonstrate even greater changes. Intramucosal carcinoma is defined as a neoplastic process which invades the lamina propria but does not go deeper than the muscularis mucosa. It is diagnosed primarily because of massive architectural abnormalities, but diagnosis is difficult to make with confidence using mucosal biopsies given the limited depth of the tissue specimen

[Robert, 2003]. Therefore, pathologists often will report diagnoses as 'at least intramucosal carcinoma' if depth of invasion cannot be stated with assurance. Invasive EAC essentially involves a complete loss of normal architecture, and demonstrates the highest degree of agreement among pathologists when compared with other categories of dysplasia. However, it is important to note that it is not uncommon for invasive EAC to be well differentiated, and therefore special attention should be paid when dilated glands with necrotic debris are identified on biopsy, as these changes may be markers of malignancy.

Reid *et al.* [1988] first defined the pathologic criteria for dysplasia. However, even when splitting the dysplastic categories into two groups (non-dysplastic, indefinite and LGD *vs* HGD and IMC), there was poor intraobserver reproducibility with only 58–61% agreement between pathologists. Montgomery *et al.* [2001] studied intraobserver variability after modifying the Reid criteria, and while kappa scores were low when trying to differentiate between individual categories, there was an acceptable level of agreement (kappa = 0.8) when Reid's two groupings were used.

### Barrett's metaplasia-dysplasia-carcinoma sequence

In the past, it was widely assumed that Barrett's esophagus evolved through an orderly sequence of changes where the cells accumulated genetic mutations endowing them with certain growth advantages [Spechler, 2003]. Multiple studies have suggested that acid exposure is responsible for driving these changes. *In vitro* studies using biopsies of SIM from Barrett's patients have shown that pulses of acid exposure created greater proliferation with less differentiation of SIM than either continuous acid exposure or use of only neutral pH media [Fitzgerald *et al.* 1996]. *In vivo* studies using pH monitoring demonstrated greater evidence of proliferative activity with less differentiation of cells in biopsies of patients with ongoing reflux symptoms when compared to subjects with well-controlled GERD [Ouatou-Lascar *et al.* 1999].

The clinical importance of these stages is best understood when considering the likelihood of progression. While previous estimates of the

annual risk of developing EAC from Barrett's esophagus range from 0.2–2.9% per year, Sharma followed 1,376 Barrett's patients in a multicentre study and found a risk of developing EAC of 0.5% per year, with a mean time to EAC of about 5.3 years [2006]. Shaheen *et al.* found that publication bias erroneously increased previous estimations of EAC risk from Barrett's esophagus in 24 published studies, leading to a real risk more in line with 0.5% per year [Shaheen *et al.* 2000].

Efforts have been made to estimate the risk of progressing through each stage of the sequence to EAC. Non-dysplastic Barrett's and LGD have similar reported incidences of developing EAC with rates of 0.5–1% per year and 0.6–2% per year, respectively [Sampliner *et al.* 2002; Mashimo *et al.* 2005]. This estimate is in line with Weston *et al.*'s finding that 10% of LGD patients developed at least HGD within a mean of 41 months of follow up [Weston *et al.* 2001], and a study based in Seattle where 12% of LGD patients developed EAC after 5 years [Reid *et al.* 2000b]. In a study by Skacel *et al.* [2000], agreement among pathologists with the histopathologic diagnosis of LGD was a strong predictor of progression to HGD or EAC over a mean of 26 months of follow up. If two of three pathologists agreed with the LGD diagnosis, there was a 41% chance of progression, whereas 80% of patients with all three pathologists in agreement progressed from LGD to a more advanced dysplasia.

The risk of progressing from non-dysplastic Barrett's esophagus to HGD was estimated by Sharma to be about 0.8% per year, with a mean time to HGD of 3.8 years [Sharma *et al.* 2006]. Perhaps in light of its potential effect on medical decision-making, there are copious studies evaluating the risk of progressing from HGD to EAC. Sampliner describes a risk of EAC of 5–10% per year [Sampliner 2002], but Reid *et al.* [2000b] describes an even higher risk of 59% with EAC after 5 years. However, a majority of the cases of EAC progressed within the first year, suggestive of a synchronous lesion. If these cases are excluded from calculations, the rate of EAC progression from HGD drops to 3–5% per year [Mashimo *et al.* 2005]. Several studies have demonstrated that the extent of HGD correlates with an increased risk of EAC development. Buttar *et al.* [2001c] showed that, after 3 years, 14% of patients with focal HGD and 56% of

multifocal HGD patients progressed to EAC. Other studies have shown more than a 500% increase in risk of developing EAC with multifocal versus focal HGD. Similarly, HGD in flat mucosa progressed to EAC in only 13% of cases, while 63% of nodular mucosa demonstrated progression to cancer.

While the progressive development of dysplasia and ultimately carcinoma makes sense intuitively, it now appears that not all cases of Barrett's esophagus progress in a predictable manner. Carcinoma is surely not inevitable, and even regression of dysplasia is possible [Mashimo *et al.* 2005]. Several reports discuss finding EAC on biopsy when earlier specimens showed only non-dysplastic SIM or LGD [Schnell *et al.* 2001; Skacel *et al.* 2000]. It is unclear whether these aberrations are due to sampling error, rapid progression through the dysplastic sequence, or actual skipping of steps in the dysplastic pathway. Similarly, repeat biopsies in patients with LGD may show no dysplasia at all, which again could be due to either sampling bias or a true regression in condition [Montgomery *et al.* 2001; Schnell *et al.* 2000].

#### The role of screening and surveillance endoscopy

The goal of any Barrett's esophagus screening program is to detect the presence of Barrett's esophagus and enrol patients in a surveillance program to reduce EAC mortality [Mashimo *et al.* 2005]. As previously discussed, early recognition of the presence of Barrett's esophagus facilitates timely treatment. Barrett's esophagus is often unexpectedly diagnosed during an upper endoscopy performed for the evaluation of GERD symptoms. To minimize the effect of inflammation on diagnostic interpretation, biopsies are often repeated after one to three months of acid suppression therapy to obtain a more accurate grade of dysplasia. Repeat sampling not only decreases the effect of inflammation on biopsy grading, but also helps confirm that biopsies were taken from the correct location. There is poor reliability and reproducibility of endoscopic landmarks at the esophagogastric junction, especially in the setting of a hiatal hernia which is the case in a majority of Barrett's patients. Ensuring an esophageal biopsy is critical as intestinal metaplasia outside the esophagus is associated with a lower rate of adenocarcinoma. Unless an esophageal gland

duct is included in the specimen, there is no confidence that the biopsy comes from the esophagus and not the cardia or fundus [Shepherd, 2000].

The use of proper biopsy technique helps maximize the likelihood that Barrett's mucosa is sampled during the endoscopy. Most important in this process is obtaining sufficient tissue to feel confident in the diagnosis. The most aggressive approach is that of the 'Seattle protocol', which utilizes jumbo biopsy forceps inserted through a therapeutic endoscope to obtain biopsies from all visible abnormalities, plus random four-quadrant samples at every 1 cm level of potential Barrett's tissue from the gastro-esophageal junction to 1 cm above the proximal extent of the intestinal metaplasia. Studies have shown that this approach, when used for surveillance of HGD, can improve the detection rate of EAC by 50% when compared to taking biopsies at 2 cm intervals along the tubular esophagus [Reid *et al.* 2000a]. In this particular study, 82% of patients with EAC had evidence of malignancy at only a single 1 cm level, and 69% of patients showed cancer in only a single biopsy specimen. Even if these results are atypical, they underscore the importance of obtaining sufficient biopsies to sample for neoplasia. The method most frequently used today is a modified version of the 'Seattle protocol' with four-quadrant biopsies taken at least every 2 cm along the Barrett's esophagus segment. Just as obtaining a sufficient number of samples is crucial to proper screening and surveillance, so is obtaining biopsies of sufficient size and depth. This minimizes the crush artifact seen at biopsy edges, and ongoing studies are exploring the benefit of increasing biopsy forceps size to obtain larger samples. The 'turn-and-suction' biopsy technique, however, has been shown to maximize sample size when biopsying the tubular esophagus [Levine *et al.* 1991].

Several studies suggest a clear benefit for detecting early EAC during surveillance. Corley *et al.* [2002] demonstrated that 73% of patients with EAC diagnosed during surveillance endoscopy survived to follow up, whereas none of the patients with prevalent cancer did. The data also demonstrated that earlier-stage cancers were identified during surveillance. In a Hines VA study [Schnell *et al.* 2001], of the twelve patients who developed EAC during the surveillance period, eleven were potentially curable at the time of diagnosis [Reid *et al.* 2000b]. Similar conclusions in support of routine

surveillance are found in several retrospective surgical series, although a uniform surveillance protocol was not followed [Mashimo *et al.* 2005]. The popularity of surveillance programs has evolved over the past several years due to multiple factors. These include the association of Barrett's esophagus with EAC, slow progression for many patients through the escalating grades of dysplasia, EAC's dismal outcome and rapidly rising incidence, and increased public awareness of Barrett's esophagus and EAC as complications of GERD.

Present surveillance guidelines, published earlier this year [Wang and Sampliner, 2008], designate different protocols depending on the greatest degree of dysplasia identified on biopsy. For non-dysplastic Barrett's esophagus, the first surveillance endoscopy should be performed one year after the index procedure. If no dysplasia is seen, repeat endoscopies with biopsies should be performed every three years, whereas the patient jumps to the highest appropriate protocol if more dysplastic biopsies are obtained. While the guidelines suggest four-quadrant biopsies every 2 cm of Barrett's, several physicians will obtain samples at every 1 cm level unless there is particularly long Barrett's esophagus present. The timetable shortens somewhat for LGD, where a repeat procedure is performed six months after the index endoscopy, with yearly biopsies thereafter. It is recommended that the presence of dysplasia be confirmed by an expert pathologist. If two successive sets of biopsies all contain non-dysplastic tissue, the patient may 'drop down' to the non-dysplastic screening schedule of one procedure every three years. While several studies discuss the possibility of regression to non-dysplastic disease (up to two-thirds of patients without dysplasia after a mean of four years of follow up), in 2002 Sampliner argued that with similar incidence rates of EAC for patients with non-dysplastic Barrett's and LGD, both categories should undergo surveillance at one-year intervals. We tend to follow the current guidelines, which are more conservative with respect to non-dysplastic Barrett's esophagus. Continued endoscopic surveillance of confirmed HGD is more controversial. Current guidelines [Wang and Sampliner 2008] include a repeat endoscopy and biopsies three months after the index procedure, with expert pathologist confirmation of the dysplastic grade. At this point, the patient can either undergo treatment or continued endoscopic surveillance. If the observational route is

chosen, biopsies should be obtained every three months until three successive procedures produce no HGD on any samples. If IMC or invasive EAC is discovered, the patient is to proceed to treatment immediately. There is a dearth of published data directly supporting the safety and efficacy of this intensive surveillance program for HGD [Spechler 2003]. One series from Seattle of 32 patients with HGD who developed cancer showed that 97% of the patients were curable at the time of diagnosis [Reid *et al.* 2000b]. Additionally, there have been a number of asymptomatic patients with asymptomatic early EAC detected during surveillance [Van Sandick *et al.* 1998]. However, of 15 patients with unifocal HGD undergoing surveillance, four developed EAC during a mean of 36.8 months of surveillance, and one of these patients had developed metastases by the time of diagnosis [Weston *et al.* 2000]. This led the study's authors to discourage the observational approach to HGD.

Several studies have addressed the practicality of conducting surveillance programs in today's healthcare environment. One study of 155 newly diagnosed Barrett's patients demonstrated that only 55% of patients were actually compliant with the surveillance regimen [Conio *et al.* 2003]. This program, which also included patients with both dysplastic and non-dysplastic Barrett's, did not prevent cancer deaths, suggesting that performing surveillance only on patients with both sufficient risk and likelihood of compliance is required to obtain significant benefits. One such factor that may assist in risk stratification is family history. Chak *et al.* [2004] evaluated the role of family history in a screening program, and found that while 37% of patients with a first or second-degree relative with Barrett's esophagus or EAC had at least Barrett's on their biopsies, only 5% of those without such family history had any Barrett's. Clearly, family history may figure prominently in future algorithms for risk stratification prior to endoscopic screening and surveillance. Theoretical benefit must also be accompanied by cost effectiveness in order for any program to be adopted under present economic conditions. Inadomi *et al.* [2003] constructed a Markov decision analysis model to evaluate the cost utility of screening and surveillance. Three strategies were explored: (1) not performing any screening or surveillance, (2) offering screening and surveillance of only patients with dysplastic Barrett's, and

(3) performing screening and surveillance on all patients. The results demonstrated the cost effectiveness of following dysplastic patients with surveillance (\$10,440 per quality-adjusted life years (QALY) saved) but not the surveillance of all patients (\$596,000 per QALY saved). These studies are only the first wave in a series of analyses that will likely refine current guidelines, as will further advances in technologies for risk stratification (such as molecular markers), visualization and tissue sampling.

### Acid reduction therapy

Medical and surgical therapies to reduce exposure of the esophagus to acid remain a key component of Barrett's treatment. Laboratory studies have demonstrated that while esophageal acid perfusion activates MAPK (mitogen-activated protein kinase) pathways, including increased cell proliferation and decreased apoptosis [Souza *et al.* 2002], the proliferation marker PCNA (proliferating cell nuclear antigen) shows decreased expression after six months of proton pump inhibitor (PPI) therapy *vs* biopsies from patients with persistent reflux [Ouatu-Lascar *et al.* 1999]. The beneficial effect, however, appears to be limited to PPI therapy and does not include H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RA). In a study by Peters *et al.* [1999], biopsies were taken prior to and at the conclusion of 24 months of either omeprazole 40 mg twice daily or ranitidine 150 mg twice daily. Specimens from patients who had complete acid control on PPI showed significant regression of the Barrett's area compared with biopsies from H<sub>2</sub>RA patients. Similarly, a subsequent study by Peters *et al.* [2000] showed that while cells from patients treated with PPI for Barrett's did not show an increase in proliferative activity after two years, biopsies from patients on H<sub>2</sub>RA therapy did demonstrate increased proliferation. It is not surprising then, that studies have shown that PPI use after a diagnosis of Barrett's esophagus decreased the risk of developing dysplasia, with a hazard ratio of 0.25 (95% CI 0.13–0.47) in one study [El-Serag *et al.* 2004]. Spechler [2003] believes that aggressive anti-reflux therapy may even prevent EAC.

The data does not uniformly suggest that acid reduction therapy halts the progression of Barrett's esophagus. Sampliner [1997] showed that stopping acid reflux alone, with either medical or surgical therapy, has a minimal effect on

the development of either dysplasia or EAC in Barrett's patients. The critical distinction between symptomatic control and elimination of all acid reflux may explain this result. Studies using esophageal pH monitoring have shown that up to 80% of patients continue to have abnormal esophageal acid exposure, especially overnight, even after symptom relief has been achieved on PPI therapy [Katzka and Castell, 1994]. While the persistence of reflux on medical therapy might lead to a preference for surgical intervention, multiple studies have shown that fundoplication is no more successful than medication in the treatment of Barrett's esophagus. A review of 152 patients followed for over 100 months after anti-reflux surgery demonstrated a symptomatic failure rate of about 60% with multiple patients developing dysplasia and even EAC [Csendes *et al.* 1998]. Other surgical series have shown little evidence for regression of SIM. Two additional studies suggest that fundoplication does no more to prevent EAC than medical therapy [Spechler *et al.* 2001; Ye *et al.* 2001]. In fact, fundoplication may impede evaluation and treatment of Barrett's esophagus through its distortion of the normal anatomy of the distal esophagus, which prevents optimal visualization and the ability to take adequate surveillance biopsies.

While use of PPI therapy in Barrett's esophagus is generally accepted as standard of care, use of these medications does not come without at least theoretical risks, including a concern that PPI effects might even promote EAC [DeMeester and DeMeester, 2000]. The risk stems from the medication's effect of decreasing gastric acid secretion. Without significant acid suppression, there may be a resulting gastric colonization of bacteria. These organisms could then convert nitrites to nitrosamines and deconjugate bile acids, both of which could be carcinogenic [Thiesen *et al.* 2000; Verdu *et al.* 1994]. This topic deserves more attention in the laboratory and patient care setting before a consensus can be reached.

### Anti-inflammatory medical therapy

It is believed that nonsteroidal anti-inflammatory drugs (NSAIDs) may have a chemopreventive role in Barrett's esophagus [Spechler, 2003]. Studies have demonstrated that daily use of NSAIDs such as aspirin may protect patients from developing EAC [Farrow *et al.* 1996;

Funkhouser and Sharp 1995]. One study showed daily NSAID use was negatively associated with EAC development, with an odds ratio of 0.297 [Tsibouris *et al.* 2004]. Their benefit may lie in the ability to block the cyclo-oxygenase 2 (COX-2) inflammatory pathway. COX-2 is over-expressed in Barrett's esophagus [Wilson *et al.* 1998], and a high level of COX-2 expression in EAC is an independent prognostic factor for significantly reduced survival [Buskens *et al.* 2002]. However, the inhibition of COX-2 has antiproliferative and pro-apoptotic effects in Barrett's associated EAC cell lines [Souza *et al.* 2000]. COX-2 inhibitors have even blocked the development of EAC in a laboratory model [Buttar *et al.* 2002], and clinical trials are underway to further determine the role these medications may play in treating Barrett's esophagus.

### Surgical therapy for advanced dysplasia

The shortcomings of esophagectomy, which has been the standard of care for treatment of advanced dysplasia and carcinoma for many years, have been a driving force behind the search for less invasive but equally successful endoluminal therapies. Even with advancements in surgical instruments and techniques, esophagectomy still carries a complication rate of up to 57%, and morbidity and mortality rates of 30% and 1–5%, respectively [Headrick *et al.* 2002]. Given these findings, and in light of the technical difficulties in performing this procedure, esophagectomies should only be done in centres with high surgical volumes where the risk of morbidity and mortality can be substantially lower [Birkmeyer *et al.* 2002].

Despite its risks, esophagectomy remains the preferred approach to patients with invasive cancers. However, there is more debate regarding surgical intervention for treatment of HGD [Castell, 2001]. Some favour surgery for HGD as well, stressing that up to one-third of patients with HGD will also have an occult malignancy found on the resected esophageal specimen. Opponents will counter that up to 70% of resected specimens will not demonstrate any cancer, that EAC found on surveillance is most often curable, and that HGD may either persist or even regress without formation of a carcinoma. In light of these arguments, and in the setting of increasingly successful ablative options, the risks of initiating therapy with surgery appear to be outweighed by the benefits of selecting

an endoscopic-based therapy. This has created a shift in preference favouring endoluminal therapies as a preferred first option.

### The rationale for endoscopic therapy

The previously described drawbacks of medical and surgical treatment of Barrett's have led gastroenterologists to focus on endoluminal therapy as a viable alternative. Use of endoscopic techniques is predicated on the assumption that after destruction of the Barrett's mucosa, mucosal healing occurs with generation of a squamous epithelium in an acid-free environment [Gillen *et al.* 1988]. Endoscopic therapy is a minimally invasive, organ-sparing approach which avoids the morbidity and mortality associated with surgical intervention. While lymph nodes are not removed for evaluation during endoscopic therapy, the risk of lymph node metastases with HGD is zero, and the risk in the setting of intramucosal carcinoma is less than 5%, equivalent to or better than the perioperative mortality of esophagectomy. Therefore, an endoscopic approach must be actively considered when the benefits of such a minimally invasive procedure outweigh the risks.

### The principles of endoscopic therapy

Multiple factors play a role in choosing whether endoscopic therapy fits well with the needs of a particular Barrett's patient. First and foremost, the decision must be made as to whether the endoluminal therapy has the potential to be curative. In patients with invasive EAC (greater than stage pT1), 90% of patients have micrometastatic bone marrow disease which predicts early tumour recurrence [O'Sullivan *et al.* 1999]. Accurate staging remains a problem, especially at the esophagogastric junction [Holscher *et al.* 1997]. Technologies such as endoscopic ultrasound (EUS) may be helpful in classifying patients as good or poor candidates for endoscopic intervention. While we do not regularly use EUS to evaluate non-dysplastic Barrett's or LGD, we have found EUS to be 75–85% accurate in depth staging of HGD or focal EAC [Larghi *et al.* 2005], and in a separate study upgraded the staging of 26% of patients inaccurately staged by biopsy alone based on EUS findings [Lightdale *et al.* 2004]. However, others have shown an overall accuracy of EUS in differentiating early from advanced EAC of only about 60% [Scotiniotis *et al.* 2001]. The use of EUS to evaluate for lymphadenopathy also has considerable drawbacks, as enlarged mediastinal non-malignant nodes

are often found with Barrett's esophagus [Barr *et al.* 2005]. Even performing fine needle aspiration of the nodes is unreliable, with a false-negative rate of 20% in advanced cancers, and an even higher rate likely with early malignancies [Buttar *et al.* 2001a].

Another consideration must be whether the procedure type matches the required depth of invasion to treat the lesion. SIM has been measured to a depth of between 0.6 mm to about 1.5 mm, with dysplastic mucosa being even thicker [Ackroyd *et al.* 1999]. Any modality selected will need to be able to treat to the depth of the Barrett's mucosa. Data also has shown that the entire metaplastic area needs to be treated, not just any focal dysplastic lesions. A review of 41 patients who underwent esophagectomy for early EAC revealed that the surgical specimens yielded six nondiagnosed cancers and 28 patients with multifocal HGD [Holscher *et al.* 1997]. Another study showed that of 100 dysplastic Barrett's patients, two-thirds demonstrated diffuse disease and only one-third had focal dysplasia [Buttar *et al.* 2001c].

The ultimate goal of endoscopic therapy must be regeneration of a normal squamous epithelium. Therefore, the endpoint of therapy cannot be just a normal endoscopic appearance [Barr *et al.* 2005]. We know that neosquamous re-epithelialization is achieved through several mechanisms, including encroachment of adjacent squamous mucosa, squamous regeneration arising from pluripotential stem cells within the Barrett's mucosa itself, growth from squamous lined ducts of mucus glands, and from circulating stem cells [Biddlestone *et al.* 1998]. Regenerative squamous islands have been shown to be universally associated with esophageal gland duct epithelium [Coad *et al.* 2005]. Therefore, in the absence of acid secretion, any endoscopic therapy utilized must be able to remove any SIM present and allow for complete squamous regeneration.

The particular location and topography will also dictate the selection of an endoscopic approach, which should also vary depending on the length of the SIM segment and the presence or absence of dysplasia [Lightdale, 1999]. In particular, the angulation and presence of irregular folds within a hiatal hernia sac at the level of the esophago-gastric junction make ablation at this level particularly difficult. Large, macroscopically indistinct lesions should also be treated differently

than more focal findings [Mashimo *et al.* 2005]. However, 100% replacement of SIM with normal squamous epithelium must be the ultimate goal of any and all endoscopic interventions.

### Early thermal therapies

The earliest type of ablative therapy utilized in the treatment of Barrett's esophagus involves delivery of energy to esophageal tissues which is converted to heat, thereby causing tissue destruction. Multipolar electrocautery (MPEC) is dependent upon the heating effect of electric current passing between electrodes [Barr *et al.* 2005]. It has been used predominantly to treat nondysplastic circumferential Barrett's esophagus [Sampliner, 2003], and while it is generally well tolerated with rare pain or fever and less than 1% of patients experiencing stricture formation, residual Barrett's is found on average in about one in twelve patients.

Argon plasma coagulation (APC) provides an alternative to MPEC that involves the transfer of electric energy to esophageal tissue via an ionized electrically conducting plasma of argon gas [Barr *et al.* 2005]. APC has a theoretic safety advantage in that, in the setting of high temperatures, a zone of devitalization is formed with surrounding zones of coagulation, desiccation and tissue shrinkage [Franchimont *et al.* 2003]. These changes involve the loss of electrical conductivity, which force the plasma beam to change direction in order to maintain conduction. Thus, there is a low likelihood of full thickness necrosis and perforation in the setting of a limited depth of tissue effect [Barham *et al.* 1996]. However, when higher-power settings are used to reduce the chance of untreated or residual Barrett's esophagus, a far greater complication rate is seen, particularly with stricture formation (0–9%) [Schulz *et al.* 2000]. Fevers also can occur. APC has proven to be a laborious technique with multiple treatment sessions required in most patients [Martin *et al.* 1998]. A head-to-head trial between MPEC and APC found that MPEC required fewer treatment sessions and was more successful in helping patients achieve histologic ablation of Barrett's after up to four years of post-treatment surveillance [Dulai *et al.* 2004].

A similar approach to ablation is found in photothermal therapy. Theoretically, the potassium titanyl phosphate (KTP) laser, found at the

second harmonic of the Nd:YAG laser, has tissue penetration patterns that should permit safe and effective treatment of Barrett's esophagus [Barr *et al.* 2005]. The KTP laser is preferred over the Nd:YAG laser as it is extremely difficult for the KTP laser to generate high temperatures on the outer esophageal surface. Gossner *et al.* [1998a] showed that the KTP laser absorbed superficially with a high degree of safety (*vs* the Nd:YAG laser), with apparent improved penetration and depth control than APC. However, like the other thermal therapies, there is a risk of untreated Barrett's esophagus.

### Photodynamic therapy

Photodynamic therapy (PDT) is an alternate ablative therapy which is administered in two parts. First, a photosensitizing drug is administered and is allowed to accumulate in the target tissue. Light (usually from a laser) is then applied in the presence of oxygen, generating oxygen radicals through a photodynamic reaction. These radicals then cause a delayed cell death, usually visually apparent after 12–24 hours [Bergman, 2005]. PDT has multiple advantages over thermal therapies. The principal advantage of PDT is that the light energy is delivered by a light diffuser, which permits a more evenly treated surface as compared to the 'point-by-point' methods of thermal therapy [Barr *et al.* 2005]. The photosensitive agent is also retained with some selectivity in tissues that are rapidly proliferating, such as dysplastic or malignant cells. Therefore, PDT is a somewhat targeted therapy and selective necrosis of areas less than 2 mm in size is possible with preservation of adjacent structures [Barr, 2000]. A third benefit is that there is no possibility of full-thickness intestinal damage, because submucosal collagen is preserved and therefore the mechanical strength of the bowel wall is not reduced.

Photofrin<sup>®</sup> (porfimer sodium, Axcan Pharma Inc., Birmingham, AL) is the photosensitizing agent used most frequently in the US, and was approved for treatment of Barrett's esophagus with HGD in 2003. It accumulates in all wall layers of the esophagus, producing extensive necrosis that decreases the risk of residual Barrett's mucosa as treatment extends through the submucosa [Bergman, 2005]. The treatment depth can be up to 4–6 mm [Heier *et al.* 1995]. Overholt *et al.* [2007] reported a multicentre, randomized trial with HGD treated either with

omeprazole alone or omeprazole and PDT in combination, and found that two years after treatment, 76.8% of the PDT group remained without HGD on biopsies as compared with only 38.6% of the omeprazole alone group. While 28% of the omeprazole alone group developed EAC after two years, only 13% of the PDT group had progressed. After another 2 years of surveillance, 53% of the PDT group continued without HGD, but all of the patients receiving omeprazole only had relapsed.

Comparative trials have demonstrated clear advantages of PDT over other ablative therapies. Kapoor *et al.* [2002] studied the use of Photofrin PDT *vs* APC for eradication of dysplastic Barrett's esophagus, and found that APC, even after a mean of three treatments (one for PDT) eradicated dysplasia in only 69% of patients, compared with 77% of the PDT group. To evaluate PDT versus esophagectomy, Shaheen *et al.* [2004] constructed a Markov model for HGD patients which showed that PDT provided a longer quality-adjusted life expectancy than either surveillance or surgical intervention. Prasad *et al.* [2007] also evaluated PDT and esophagectomy in actual patients treated for HGD. While the PDT group had more comorbidities and a lower overall functional status than the surgical group, the overall mortality rate was 9% in the PDT group and 8.5% in the surgical group. Eighty-six per cent of the PDT group patients remained without any HGD after three years of follow up. However, morbidity was high with 27% of patients developing strictures and 60% demonstrating photosensitivity. These results are similar to the randomized trial reported by Overholt, where about one-third of patients had stricture formation and 68% had photosensitivity (which can last up to six weeks), in addition to common complaints of sunburn, nausea, chest pain and fever.

While Photofrin PDT treats deeper into the esophageal wall, it has not been shown to completely eradicate Barrett's esophagus. Subsquamous intestinal mucosa, or 'buried' Barrett's, was identified in about 5% of patients in Overholt's study, with 5% also developing buried EAC [2003]. Photofrin also can be administered only parenterally, and lacks any histopathologic correlation which can lead to undertreatment of the mucosa.

Outside the US and particularly in Europe, the photosensitizing agent 5-aminolevulinic acid (5-ALA) has been used with great frequency. It has several advantages over Photofrin, including the ability to be administered orally, limited photosensitivity of less than two days, and a low rate of esophageal stenosis owing to less muscular damage with more shallow penetration through the lamina propria but not the submucosa [Gossner *et al.* 1998b]. It produces necrosis to a depth of only 2 mm [Tan *et al.* 1999]. A prospective observational study of 66 patients with either HGD or early EAC who were treated with 5-ALA PDT demonstrated complete localized remission (as determined by negative biopsies on two endoscopies) in 97% of HGD and 100% of early EAC patients [Pech *et al.* 2005]. Severe nausea and vomiting are frequent adverse effects, and hypotension can occur, so most patients require treatment in hospital. After an average of 37 months of follow up, one patient's HGD returned, but ten EAC recurred ( $p < 0.005$ ), and at five years the survival rate was 97% for HGD and 80% for early EAC. Because of its more shallow penetration, 5-ALA PDT has a higher rate of residual Barrett's esophagus after treatment, along with a significant risk of hidden subsquamous Barrett's glands with reports of malignancies arising from this 'buried' tissue [Overholt *et al.* 2003].

While there are clear benefits to PDT, such as its ability to treat an entire segment of Barrett's esophagus in one session, there are multiple concerns regarding the tolerability and efficacy of this treatment modality. With the propensity to develop 'buried Barrett's', not only is treatment less successful, but also surveillance is made more difficult due to the depth of tissue that must be sampled for residual SIM [Lightdale, 1999]. There has been some progress in addressing this problem, as a blinded randomized trial using 510 nm wavelength green light for 5-ALA PDT showed an unexpected lack of buried SIM [Ackroyd *et al.* 2000]. However, the relatively high likelihood for stricture formation, photosensitivity, and other undesired effects of treatment have led PDT to fall out of favour among many gastroenterologists as other techniques have become available.

### Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) has been used as the primary alternative therapy to diffuse

ablative modalities for the treatment of Barrett's mucosa. With many techniques available, there are two that have been used extensively. One involves the use of submucosal saline or dilute epinephrine injection to lift the targeted mucosa, which is then sucked into a cap placed on the tip of the endoscope. Already deployed inside this cap is a hot snare, which is used with electrocautery to perform the resection. A second approach uses a system much like that used to band esophageal varices called the multiband ligator (MBL). In this case, once the mucosa is sucked inside the endoscopic cap, a rubber band is deployed over the cap to create a pseudo-polyp, which is removed by hot snare cautery. We have resected successfully using both techniques, though we frequently utilize the MBL as it facilitates performing multiple resections in a time-efficient manner. The two techniques produce essentially equivalent results. The deep resection margin is usually in the deep submucosa often extending to the muscularis propria [Abrams *et al.* 2008].

A large patient series that utilized only EMR comes from Wiesbaden, where 61 patients with early EAC and three with HGD were treated [Ell *et al.* 2000]. Patients were risk stratified, with lower risk lesions being less than 2 cm in diameter, stage I to IIc, histologic grade GI or G2, and limited to the mucosa. After EMR, complete remission was obtained in 97% of low-risk and 59% of high-risk patients. In a smaller series, Giovannini *et al.* [2004] reported on a retrospective cohort of 21 patients with either early EAC or HGD. After two sessions per patient, there were no strictures found and 86% of patients had a complete resection of the dysplastic mucosa. Seventy-five per cent of patients had their SIM replaced with squamous mucosa, but 18% of patients suffered complications and 11% of patients who had a complete resection developed a local recurrence.

While most endoscopists utilize EMR for treatment of focal lesions with advanced dysplasia (at least HGD), others have explored its use for complete removal of Barrett's esophagus. Seewald *et al.* [2003] studied the safety and efficacy of stepwise circumferential EMR using twelve patients with at least HGD and a median Barrett's mucosal length of 5 cm. An average of 3.8 cm<sup>2</sup> of Barrett's mucosa was removed over two to three sessions during treatment. While two patients developed strictures that were

treated successfully with esophageal dilation, after a median follow up of nine months, there was no evidence of recurrent Barrett's esophagus or malignancy. This and other studies suggest that, in experienced hands, EMR can be used to completely remove even long-segment circumferential Barrett's esophagus in a safe and feasible manner [Bergman, 2005].

Many gastroenterologists utilize EMR in combination with a more diffuse ablative therapy to achieve a high success rate in treatment of Barrett's esophagus. One study combined 5-ALA PDT with EMR for 28 patients with either HGD or early EAC, and 93% achieved complete local remission without any major complications after treatment [Peters *et al.* 2005]. During a median follow up of 19 months, five patients developed local recurrence and were retreated, with a 93% local remission rate at the conclusion of the follow up period. The five-year survival rate was greater than 90–95%. Similar results were achieved by Buttar *et al.* [2001b], where a combination of Photofrin PDT and EMR in 17 patients with superficial EAC allowed 94% to remain in remission after a 13-month follow up, though 30% of patients developed strictures. Other studies have included EMR as one of multiple treatment options to be used alone or in combination with other modalities. Using EMR and/or PDT, the Weisbaden group treated 115 HGD or early EAC patients and achieved a 98% local remission rate in 98% of patients after an average follow up of 34 months [May *et al.* 2002]. Of note, 30% of patients developed a metachronous lesion during this period.

Unlike the other therapies described above, EMR has the distinct advantage of providing a sample that can clearly demonstrate whether dysplastic tissue has been treated to sufficient depth. Additionally, the actual depth of invasion can be used to predict the risk of lymph node metastasis. In a Japanese multicentre study of 1,690 lesions, there was a 19% risk of metastasis if the tumour extended through the muscularis mucosa, but this risk rose to 44% if invasion was deeper than the most superficial third of the submucosa [Kodama and Kakagawa, 1998]. However, this technique also has its drawbacks. While few or no complications are seen if the lesion removed is less than 1 cm in diameter [Barr *et al.* 2005], a 5% overall risk of bleeding has been reported, and esophageal perforations are uncommon but still carry an

estimated 1% risk [Peters *et al.* 2006]. Many have worked to define the risk factors for complications, including Ell *et al.* [2000] who concluded that lower-risk lesions are less than 2 cm in diameter, lack ulcerations, are limited to the mucosa, show no evidence of venous or lymphatic invasion, and have no poorly differentiated histology.

### Radiofrequency ablation

Radiofrequency ablation (RFA) has quickly gained the favour of many gastroenterologists seeking to replace PDT with another ablative therapy that can effectively treat large areas of Barrett's esophagus in a single session. The currently available system (BARRX Medical, Sunnyvale, CA) treats Barrett's esophagus using a bipolar electrical array within a balloon-based electrode (HALO<sup>360</sup> System) for circumferential ablation or an endoscope-mounted electrode (HALO<sup>90</sup> System) for more focal ablative therapy.

RFA trials demonstrate an equivalent or improved efficacy in eradication of SIM compared to PDT. In early reports from a registry of 85 patients with HGD treated with either circumferential ablation ( $n=78$ ) or EMR followed by circumferential ablation ( $n=8$ ), 57 patients were followed for a mean of 9.5 months, and the median regression of Barrett's esophagus was 100% with no HGD or intramucosal carcinoma identified in 88% of patients [Ganz *et al.* 2007]. When 23 patients with HGD were treated with EMR (only when necessary) followed by circumferential then focal ablation, 91% had no SIM on any biopsy two months after the final ablation [Gondrie *et al.* 2007a]. After another six months of follow up, repeat biopsies showed there was no recurrence of either SIM or dysplasia in any of the successfully treated patients. Perhaps most important was the fact that none of the 521 biopsies obtained during surveillance demonstrated any evidence of the 'buried Barrett's' often seen in post-PDT biopsies. In a separate study, biopsies and cytology brushings were obtained from ten HGD patients both before and after RFA treatment, when there was visible eradication of all Barrett's mucosa [Gondrie *et al.* 2007b]. While all ten sets of biopsies showed abnormal Ki67 levels (marker of proliferative activity) or p53 accumulation activity prior to treatment, none of the biopsies were abnormal after ablation was performed. Similarly, all baseline cytology brushings were

abnormal on fluorescent *in-situ* hybridization (FISH), whereas all repeat studies displayed a normal diploid signal.

Ablation of LGD has shown similar promise. For ten patients treated with circumferential ablation (up to two treatments), 100% of dysplasia was eradicated, and eight patients had no SIM present on biopsies [Sharma *et al.* 2007a]. After as-needed focal ablation was performed, follow up biopsies at two years showed 100% eradication of any Barrett's mucosa without the presence of any buried IM or stricture formation. Mathematical modelling of the alternatives for following and treating LGD has shown that RFA is more cost effective than either surveillance or esophagectomy [Inadomi *et al.* 2007].

RFA of non-dysplastic Barrett's esophagus (NDBE) showed a 70% eradication rate following circumferential ablation at one year, with improvement to 83% for patients who participated in a trial extension permitting up to two focal ablations [Fleischer *et al.* 2007; Sharma *et al.* 2007b]. To evaluate cost-effectiveness of intervention, a Monte Carlo analysis was performed comparing three pathways: (1) the natural course of NDBE without surveillance or intervention, (2) surveillance per ACG guidelines, and (3) up to three ablations [Das *et al.* 2007]. The incremental cost-effectiveness ratio (ICER) was found to be less than \$50,000 if either ablations cost less than \$7450 or Barrett's mucosa could be eradicated in more than two-thirds of ablated patients. Given published total procedure costs of \$2000 per treatment and eradication rates of more than 70%, the authors concluded that RFA of NDBE is a cost-effective strategy when compared with both surveillance and no intervention.

Given the multiple common adverse effects seen following PDT, recent studies have suggested that RFA is a better-tolerated procedure. In the previously described study of 85 patients treated for HGD, only one stricture was noted and was cured following esophageal dilation [Ganz *et al.* 2007]. Only two RFA-associated adverse events were reported in the study where 23 patients underwent EMR, then circumferential and focal ablation, including two patients with fever and chest pain after treatment with HALO<sup>360</sup>. Of 182 cases using focal ablation, one patient reported esophageal spasm a day after treatment, but no perforations, lacerations, bleeding,

stricture formation or other adverse events were noted [Rothstein *et al.* 2007]. While it is still too early to evaluate long-term efficacy and tolerability of RFA, it appears that both metrics show improvement over other diffuse ablation techniques such as PDT.

### Cryo-ablative therapy

Another recent technique to emerge for ablation of Barrett's esophagus is cryotherapy, where exposure of the esophageal mucosa to super-cooled agents such as liquid nitrogen results in death of the mucosal layer, followed by squamous regeneration after the SIM sloughs off 24–48 hours after the procedure. The use of a liquid nitrogen spray for Barrett's ablation was tested as early as the late 1990s [Pasricha *et al.* 1998], and carries at least a theoretical benefit of being able to very effectively destroy a specified volume of tissue with minimal damage to the surrounding areas [Barr *et al.* 2005].

During a pilot study, eleven patients with Barrett's esophagus (ranging from non-dysplastic to multifocal HGD) were treated with multiple cryo-ablative treatment sessions [Johnston *et al.* 2005]. All patients demonstrated reversal of Barrett's, while nine (78%) showed complete histologic as well as endoscopic remission. As with early RFA trials, no buried SIM was seen in post-treatment biopsies. As in this study, our early experience with the technique suggests that it is a very well tolerated modality, with only minimal if any esophageal discomfort following the procedure. Patients do, however, require placement of a decompression tube into the upper GI tract for the procedure to vent the rapidly expanding gases produced. The overall high tolerability, plus the capability of the cryo-spray to evenly coat esophageal regions which are tortuous and lack the flat topography required for effective circumferential RFA ablation, suggest cryo-ablative therapy may have a role to play in future Barrett's treatment algorithms. However, larger studies with longer follow up periods are needed to demonstrate reproducibility of the positive early results.

### Conclusion

The rapidly rising incidence of Barrett's esophagus has focused attention on how best to follow and treat this condition in order to prevent the formation of EAC. Regardless of whether

Barrett's progresses in an orderly fashion to EAC, or instead advances in an unpredictable manner, current strategies have focused on routine surveillance to identify patients in need of therapeutic intervention. PPIs, as a means of reducing esophageal acid exposure, continue to be the mainstay of medical therapy and a key early therapeutic intervention gastroenterologists can make to minimize the risk of developing advanced dysplasia or carcinoma.

It is our belief that we have reached an inflection point with respect to the development and use of endoluminal ablative therapy for high-grade dysplasia and intramucosal carcinoma. Early options such as MPEC, APC and laser ablation proved to be less efficacious than PDT, but even in combination with EMR, the risks of stricture formation and residual or subsquamous Barrett's led to hesitation when considering endoscopic-based instead of surgical intervention. Early data from RFA trials suggest an exceptionally good rate of eradication in the setting of a generally well-tolerated procedure. While there is no doubt that surgical resection should be considered first for treatment of invasive carcinoma, RFA has become the preferred option for treatment of minimally or non-invasive lesions where, in the past, surgery would have been considered. For poor surgical candidates, endoluminal therapy has become an increasingly attractive alternative. Table 1 gives a comparison of endoluminal treatments for Barrett's esophagus.

An individualized approach to each patient's condition and anatomy remains crucial to developing a successful treatment plan. One must recognize, for example, that RFA is only a component (although a significant one) of a combinatorial approach to endoluminal therapy. EMR remains the preferred option for removal of any focal lesions, particularly those that disrupt the normally smooth contour of the wall surface. It is our belief that, prior to the use of any ablative therapy, targeted EMR should be performed to both accurately diagnose Barrett's (and possible malignancy) as well as create a level surface over which RFA or another ablative treatment can be applied. In some cases of very focal Barrett's, EMR alone may be adequate to successfully remove all of the dysplastic tissue. However, whenever there is multifocal disease, we believe combining targeted EMR of visible lesions with a therapy that ablates Barrett's across a field of treated mucosa is the preferred option. At this

time, the benefits of using RFA in combination with EMR far outweigh the risks of exposing the patient to two techniques.

Currently, many Barrett's patients are part of endoscopic surveillance programs. Our current knowledge deficit, though, prevents us from operating in a cost-efficient manner as we screen all Barrett's patients, not just those who are at a significant risk of progressing to advanced dysplasia or carcinoma. Hopefully, further studies and research will shed light on what factors can improve our risk stratification process. The identification of molecular markers for progression, as well as a better understanding of how family history and other exposures predispose patients to the development of advanced dysplasia and carcinoma, will greatly improve and streamline the screening and surveillance process. The efficiencies gained through this additional knowledge will play a major role in making the monitoring of Barrett's cost efficient.

As endoluminal options available for the treatment of Barrett's esophagus improve in number, efficacy and tolerability, there will only be greater interest in shifting from a more surveillance-based approach to Barrett's esophagus to one which is geared more toward early eradication. However, in light of the limited resources and high costs of healthcare, the ultimate arbiter of adoption may be the answer to a simple question. Can the use of acid suppression, combined with eradication of Barrett's metaplasia, decrease the risk of developing EAC to a level where further surveillance and expenditures of time and resources become unnecessary? Only time and more investigation will demonstrate which types of Barrett's and which patients will satisfy this criterion.

Continued evidence that endoluminal techniques are effective and well tolerated will only push gastroenterologists to incorporate these technologies into everyday practice. However, it is crucial to remember that the very positive results have come out of referral centres who see large numbers of Barrett's patients. Tools like EMR and RFA are not difficult to use, but we are wary that inconsistent and intermittent use will drive down the success rates in eradicating Barrett's and dysplasia. As with other invasive procedures, the risk of complications also clearly rises when the frequency of use declines. Gastroenterologists must consider this when pondering whether to

**Table 1.** Comparison of endoluminal treatments for Barrett's esophagus.

Treatment type	Treatment category	Method of action	Benefits	Drawbacks
MPEC	Thermal	Electric current passing between electrodes generates heat within Barrett's tissue	<ul style="list-style-type: none"> <li>• Easy to use</li> <li>• Well tolerated</li> </ul>	<ul style="list-style-type: none"> <li>• Labour intensive for all but very focal Barrett's</li> <li>• Multiple sessions needed if used beyond focal area</li> <li>• Risk of residual Barrett's</li> </ul>
APC	Thermal	Ionized electrically conducting plasma of argon gas transfers electric energy to heat Barrett's tissue	<ul style="list-style-type: none"> <li>• Easy to use</li> <li>• Theoretically safer – loss of electrical conductivity prior to perforation (lower power settings)</li> </ul>	<ul style="list-style-type: none"> <li>• Labour intensive for all but very focal Barrett's</li> <li>• Multiple sessions needed for larger areas</li> <li>• Lower power settings have high risk of residual Barrett's</li> <li>• Higher power settings have high risk of stricture or perforation</li> </ul>
Laser (KTP/Nd:YAG)	Thermal	Absorption of laser light generates heat within Barrett's tissue	<ul style="list-style-type: none"> <li>• Relatively safe</li> <li>• KTP has relatively good control of depth of treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Labour intensive for all but very focal Barrett's</li> <li>• Risk of residual Barrett's</li> </ul>
PDT with Photofrin®	Photodynamic, free radicals	Laser light activates photosensitizing drug within Barrett's tissue, generating oxygen radicals	<ul style="list-style-type: none"> <li>• Extensive necrosis of mucosa and extension into submucosa decreases risk of residual Barrett's</li> <li>• Entire Barrett's segment treated in single session</li> </ul>	<ul style="list-style-type: none"> <li>• Two-part treatment time consuming</li> <li>• Photofrin must be administered IV</li> <li>• Despite treatment extent, risk of residual and 'buried' Barrett's remains</li> <li>• High morbidity with frequent complications including stricture formation and photosensitivity (lasting up to 6 weeks)</li> </ul>
PDT with 5-ALA	Photodynamic, free radicals	Laser light activates photosensitizing drug within Barrett's tissue, generating oxygen radicals	<ul style="list-style-type: none"> <li>• Oral administration of photosensitizer</li> <li>• Photosensitivity limited to 2 days</li> <li>• Shallow penetration decreases stricture and perforation risk</li> <li>• Entire Barrett's segment treated in single session</li> <li>• Achieves greatest tissue depth for proper diagnosis</li> <li>• Sparing of normal tissues</li> </ul>	<ul style="list-style-type: none"> <li>• Frequent nausea and vomiting, along with occasional hypotension, lead to inpatient treatment for most patients</li> <li>• Higher risk of residual and 'buried' Barrett's</li> <li>• Post-treatment surveillance more difficult with need to sample deeper tissue levels</li> <li>• Photosensitivity can still occur</li> </ul>
EMR	Mechanical	Mucosa (and often deeper levels) removed with use of endoscopic cap and snare cautery of target tissue		<ul style="list-style-type: none"> <li>• Bleeding are small but real</li> <li>• Labour intensive if larger area requires treatment</li> <li>• Risk of stricture formation if larger area is treated</li> </ul>
RFA	Thermal	Bipolar electrical array generates heat energy within Barrett's tissue	<ul style="list-style-type: none"> <li>• Devices available to treat both focal and diffuse Barrett's</li> <li>• Well tolerated</li> <li>• Highly efficacious</li> <li>• No 'buried' Barrett's</li> </ul>	<ul style="list-style-type: none"> <li>• Requires multiple sessions to achieve full treatment</li> <li>• Requires flat surface to achieve successful ablation</li> <li>• Lack of long-term remission data</li> </ul>
Cryo-ablation	Thermal	Super-cooled liquid nitrogen spray freezes tissue to cause cell death	<ul style="list-style-type: none"> <li>• Does not require flat surface to treat</li> <li>• Well tolerated</li> <li>• Treats focal and diffuse Barrett's</li> </ul>	<ul style="list-style-type: none"> <li>• Requires multiple sessions to achieve full treatment</li> <li>• Requires venting of gases via decompression tube during treatment</li> <li>• Only limited, early clinical trial data is available</li> </ul>

5-ALA, 5-aminolevulinic acid; APC, argon plasma coagulation; EMR, endoscopic mucosal resection; KTP, potassium titanyl phosphate; MPEC, multipolar electrocautery; PDT, photodynamic therapy; RFA, radiofrequency ablation.

bring the technology into their own practice, or continue to refer to centres of excellence.

The future remains bright for further advancements in endoluminal therapy of Barrett's. Broader and more long-term follow up studies of RFA and cryo-ablation, combined with improvements in the devices themselves, will lead to fine-tuning of treatment algorithms and only greater rates of successful treatment. While these two approaches are poised to lead the field of ablative therapies, research may identify other options which deserve investment of time and attention. It appears, though, that endoluminal treatment of Barrett's esophagus has made great strides in catching up to other advances in the minimally invasive procedure era.

### Conflict of interest statement

CL has received small amounts of remuneration from various sources (AstraZeneca, Barrx, Boston Scientific, Cook, CSA, Ethicon, Olympus, Takeda). MS has nothing to declare.

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