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Barrett's Oesophagus
Optimal Strategies for Prevention and Treatment

Ronnie Fass and *Richard E. Sampliner*

Department of Internal Medicine, Section of Gastroenterology, Southern Arizona VA Health Care System and University of Arizona Health Sciences Center, Tucson, Arizona, USA

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Abstract

Barrett's oesophagus is a change in the lining of the distal oesophagus recognised at endoscopy and documented to have intestinal metaplasia by biopsy. It is thought that it is an acquired condition resulting from chronic gastro-oesophageal reflux disease (GORD). Barrett's oesophagus has the potential to progress to adenocarcinoma of the oesophagus.

Evidence to support the association between Barrett's oesophagus and GORD appears to be strong but circumstantial. The intermediate steps that lead from GORD to Barrett's oesophagus are speculative and the timeline for the development of this condition remains obscure. It has yet to be demonstrated that erosive oesophagitis is a necessary intermediate step for the development of Barrett's oesophagus.

In spite of effective therapy, documentation that medical or surgical therapy prevents Barrett's oesophagus is lacking. The goal of screening for Barrett's oesophagus is ultimately to improve the survival of patients with adenocarcinoma of the oesophagus. This goal has not been achieved and the evidence-based criteria for screening remain to be defined. Medical and surgical therapy of Barrett's oesophagus is effective in controlling reflux, although not proven to prevent neoplastic progression of the at risk mucosa. Endoscopic techniques of mucosal injury have been applied as alternatives to oesophagectomy in efforts to prevent progression to cancer. Surveillance endoscopy and biopsy is the currently accepted method aimed at early intervention and improved survival for oesophageal adenocarcinoma. A working surveillance protocol to accomplish this is proposed based on dysplasia grade. If no dysplasia is found and confirmed with subsequent endoscopy and biopsy, a 3-year interval is recommended. If only low grade dysplasia is confirmed, then annual endoscopy until no dysplasia is recognised is recommended. On the basis of defined risk factors, high grade dysplasia can lead to intense surveillance every 3 months or an intervention.

Future developments in understanding the biology of Barrett's oesophagus and in therapeutic interventions will provide an opportunity for more effective screening, surveillance and prevention of neoplastic progression.

Barrett's oesophagus is a change in the lining of the distal oesophagus recognised at endoscopy and documented to have intestinal metaplasia by biopsy.[1] Barrett's oesophagus is thought to be an acquired condition resulting from chronic gastro-oesophageal reflux disease (GORD). The importance of Barrett's oesophagus is its potential to progress to adenocarcinoma of the oesophagus, the most rapidly rising incidence cancer in the US[2,3] and Western Europe.[4] This review examines the relationship of GORD and Barrett's oesophagus, whether the treatment of GORD prevents the development of Barrett's oesophagus, the goals of therapy and screening for Barrett's oesophagus, the medical and surgical therapy available for Barrett's oesophagus and the prevention of progression to adenocarcinoma of the oesophagus. A comprehensive review of the Medline and HealthStar computerised bibliographic databases from 1970–2002 was performed to address these issues.

1. Gastroesophageal Reflux Disease (GORD) and Barrett's Oesophagus

It is widely accepted by many authorities and investigators that Barrett's oesophagus is a complication of chronic GORD.[5,6] Surprisingly, the currently available evidence to support this concept is merely circumstantial. There is a lack of reports demonstrating the development of Barrett's oesophagus in patients known to have GORD, who have been followed by sequential upper endoscopies regardless of treatment. Barrett's oesophagus appears to be almost always diagnosed on the first endoscopy.

The reported prevalence of Barrett's oesophagus in patients undergoing an upper endoscopy for any reason is 0.5–4% and 12–15% in patients who present for endoscopy with GORD symptoms.[7-13] However, many patients with Barrett's oesophagus lack classic symptoms of GORD. The extent of this phenomenon is unknown because most of these patients are diagnosed incidentally when undergoing upper endoscopy for non-GORD related reasons or when presenting for the first time with oesophageal adenocarcinoma. Approximately 40% of the patients with Barrett's oesophagus in one study[10] and 40% of patients with adenocarcinoma of the oesophagus in another denied having classic symptoms of GORD during their lifetime.[14,15] Reduced oesophageal chemosensitivity to acid due to the Barrett's tissue itself or due to aging have been suggested to explain the absence of symptoms in some patients with Barrett's oesophagus.[16,17] However, if the Barrett's tissue or age were important factors for lack of symptoms then one would expect classic GORD symptoms prior to Barrett's mucosa development or in younger patients. Alteration in pain perception in some patients with GORD, probably not specific to Barrett's oesophagus only, allows repeated acid-reflux events and even tissue injury that are not perceived ('silent reflux').

When compared with patients with erosive oesophagitis and non-erosive reflux disease, patients with Barrett's oesophagus have the highest acid exposure profile as measured by ambulatory 24-hour oesophageal pH monitoring. In a recent study, Martinez et al. demonstrated that Barrett's oesophagus patients had the highest mean percent total time pH <4 in the distal oesophagus – 18.8% as compared to 11% and 6% in patients with erosive esophagitis and non-erosive reflux disease, respectively.[18] Furthermore, patients with Barrett's mucosa were least likely to have a negative pH test (7%) as compared with those with erosive oesophagitis (25%) or non-erosive reflux disease (50%). It appears that the greater the duration of abnormal oesophageal acid exposure in the distal oesophagus the higher the likelihood that the pH probe will record an acid reflux event. Although several authors have suggested that patients with Barrett's oesophagus have an elevated basal gastric output and thus gastric hypersecretion, others could not demonstrate such a correlation when appropriate controls were used.[19-22]

Recent studies have demonstrated a close correlation between the duration of acid exposure in the distal oesophagus and the length of Barrett's mucosa.[23,24] Using a commercially available four sensors pH probe, Tharalson and his colleagues showed a significant relationship between the intensity of acid

exposure as measured by rate of the change in acid exposure along the oesophagus and the length of Barrett's mucosa.[25]

This highly abnormal oesophageal acid exposure has been related to severe oesophageal motor dysfunction as well as oesophagogastric anatomic abnormalities that are prevalent in patients with Barrett's oesophagus. Compared with patients with erosive oesophagitis, patients with Barrett's oesophagus had lower mean lower oesophageal sphincter (LOS) pressure and longer supine transit time.[26] Of the patients with Barrett's oesophagus, 83% were found to have abnormal oesophageal manometry compared with 41.7% of the patients with erosive esophagitis. In another study, patients with Barrett's oesophagus were more likely to have a defective LOS, defined by the presence of either a LOS resting pressure <6mm Hg, overall sphincter length of <2cm or abdominal sphincter length of <1cm, than patients with erosive oesophagitis and non-erosive reflux disease.[27] Öberg et al. have demonstrated that the extent of Barrett's oesophagus is inversely correlated with LOS pressure and length.[24]

Anatomical factors that further worsen acid reflux have been found to commonly affect patients with Barrett's oesophagus. They include a short LOS, reduced intra-abdominal LOS length and the presence of hiatal hernia. Hiatal hernia promotes acid reflux by trapping gastric acid, abolishing the flap-valve mechanism and widening the oesophageal hiatus.[28,29] The frequency of transient LOS relaxations has been recently shown to be directly proportional to the size of the hernial sac.[30] Hiatal hernia has been documented in 90–96% of the patients with long segment (>3cm) and 65–72% of those with short segment (<3cm) Barrett's.[31] For comparison, 71% of the patients with erosive oesophagitis were found to have hiatal hernia and 29% of those with non-erosive reflux disease.[31] There is a close correlation between the length of hiatal hernia and the extent of Barrett's mucosa.[32]

In addition to physiological data, further support for the close relationship between GORD and Barrett's oesophagus originate from the clinical arena. In an observational, prospective, community-based study, Lieberman and colleagues demonstrated that compared with patients with GORD symptoms <1 year, the odds ratio for Barrett's oesophagus in patients with GORD symptoms for 1–5 years was 3.0, which increased to 6.4 in patients with symptoms for >10 years.[33] In another study, the authors concluded that there is a strong and probably a causal relationship between gastroesophageal reflux and oesophageal adenocarcinoma.[15] This conclusion was supported by the findings that increased frequency, severity and duration of GORD symptoms was strongly associated with higher risk for adenocarcinoma of the oesophagus.

Despite the plethora of articles emphasising the potential link between GORD and Barrett's oesophagus, it is well known that most patients with GORD do not harbour Barrett's mucosa. It is yet to be determined what factors are necessary for the emergence of Barrett's oesophagus in patients with GORD. The current hypothesis is that refluxate from the stomach leads to injury and denudation of the oesophageal squamous epithelium (erosive oesophagitis).[34] In the setting of an abnormal reflux milieu, the injured epithelium is replaced with intestinal metaplasia, the hallmark of Barrett's oesophagus. The problem with this hypothesis is that no one has been able to observe these histological changes develop during endoscopic follow-up of patients with GORD. Consequently, Cameron and Lomboy concluded that Barrett's oesophagus evolves rapidly to its full length with little subsequent change.[9]

Genetic predisposition to the development of reflux in families of patients with Barrett's oesophagus and oesophageal adenocarcinoma has been suggested by a recent study.[35] Other reports described families with various presentations of GORD in which several members were found to have Barrett's oesophagus or even adenocarcinoma of the oesophagus.[36-38] Although these studies further support the relationship between Barrett's oesophagus and GORD, the genetic make-up that predisposes GORD patients to the development of Barrett's mucosa remains unknown.

An animal model that clearly demonstrates the development of Barrett's oesophagus in response to repeated exposure to acid reflux only is not available. In a dog model, investigators have excised oesophageal mucosa, induced reflux and left behind squamous bridges to prevent gastric cell migration upwards.[39] Only the areas denuded of normal squamous epithelium were later re-epithelialized with columnar mucosa. However, the columnar epithelium that appeared *de novo* had distinct morphological differences from human Barrett's epithelium.[40]

Many investigators believe that acid reflux may not be the only essential factor for the evolution of Barrett's mucosa. Several studies pointed to the potential role of bile, especially the conjugated bile acids, as co-promoter with acid of oesophageal mucosal injury.[41-43] Most of these studies include assessment of bilirubin pigment spectrophotometrically, which is an indirect measurement of bile acid. A rat model of intestinal metaplasia and adenocarcinoma has been demonstrated after esophagojejunostomy resulting in oesophageal exposure to bile and pancreatic secretions.[44]

As summarised at the beginning of the section the evidence to support true association between GORD and Barrett's oesophagus appears to be strong but circumstantial. The intermediate steps that lead from GORD to the appearance of Barrett's oesophagus are speculative. The time line for the development of Barrett's oesophagus remains obscure. Finally, it is yet to be demonstrated that erosive esophagitis is a necessary intermediate step for the development of Barrett's appearance.

2. GORD Treatment and the Prevention of Barrett's Oesophagus

Studies that evaluate the effect of GORD treatment on Barrett's oesophagus development are not available. These types of studies require long-term follow-up of patients, as well as repeated endoscopies at pre-determined intervals. However, even such longitudinal studies may not provide the answer to the role of GORD treatment in preventing Barrett's oesophagus. The therapeutic interventions that will prevent Barrett's evolution are not defined. This is compounded by the difficulties of ensuring compliance with treatment over a long duration. Thus, the answer to the role of GORD therapy in preventing Barrett's oesophagus remains elusive.

Interestingly, studies assessing the natural history of patients with GORD reveal very little if any progress to Barrett's oesophagus.[45-47] Many of these studies are hard to interpret because of flaws in study design and a plethora of confounding factors. Nevertheless, patients with non-erosive reflux disease appear to have very little risk of developing erosive oesophagitis over the years let alone Barrett's oesophagus, regardless of treatment. Surprisingly, the data are not different when the literature is scrutinised for evidence to support progression of erosive oesophagitis to Barrett's oesophagus in patients that lack concomitant Barrett's mucosa underneath the inflammation. However, the absence of substantial data did not deter experts from including the prevention of progression to Barrett's oesophagus as part of the rationale for maintenance treatment of erosive oesophagitis.[48]

Evidence to support that Barrett's oesophagus is an acquired disorder has been primarily anecdotal.[49-52] There is sufficient information from the paediatric literature to suggest that Barrett's oesophagus is not a congenital anomaly.[53,54] Furthermore, the prevalence of the disease increases with age, which also points to an acquired rather than a congenital lesion.[9] Thus, prevention of Barrett's mucosa evolution by medical treatment of GORD may be a legitimate goal albeit not documentable in the near future. Several studies have actually speculated that medical treatment may increase the risk for the development of Barrett's and adenocarcinoma of the oesophagus.[15,53] Finally, the role of surgery in preventing the progression of GORD to Barrett's oesophagus has not been rigourously evaluated, although studies have suggested that Barrett's oesophagus is an uncommon finding in patients after anti-reflux surgery.[54-56]

3. Screening for Barrett's Oesophagus

The impetus for screening patients with GORD is to identify those that have Barrett's oesophagus. The hope is to provide a surveillance programme for patients with Barrett's oesophagus and thus to reduce mortality through early detection. The urgency in developing a screening programme for detecting Barrett's oesophagus is further enhanced by the fact that 94–98% of patients diagnosed with oesophageal adenocarcinoma have no known history of Barrett's oesophagus.[57,58] Thus, the rising incidence of adenocarcinoma of the oesophagus, the high death rate from this tumour and the diagnosis of cancer in patients without a known history of Barrett's oesophagus are sufficient reasons to support a screening program.[2,3]

A screening programme for Barrett's oesophagus should be simple, acceptable for patients, highly sensitive and specific, widely applicable and cost effective.[59] The Practice Parameters Committee of the American College of Gastroenterology concluded that one time endoscopy to exclude Barrett's oesophagus during a symptomatic patient's lifetime is sufficient.[1] If patients have no evidence of intes-

tinal metaplasia then future screening endoscopies are not needed unless clinical circumstances change. This recommendation is based on the observation that patients with GORD who lack Barrett's tissue on endoscopy appear to be at minimal risk of developing Barrett's mucosa during their lifetime.

Knowing the high prevalence of GORD in the general population, screening with the current endoscopic technique is not feasible or cost effective. One solution for this dilemma is to focus on patients with the highest risk for Barrett's oesophagus. This would be White men, 50 years and older with at least 5 years duration of classic GORD symptoms.[1] The other solution is to develop an endoscopic technique that can be easily performed in the office setting, preferably unsedated with equal reliability to the traditional endoscopic procedure. This type of approach would allow large-scale, population-based screening programmes. A promising tool is the unsedated, transnasal, ultrathin endoscope, which is performed in adults seated in the upright or left lateral decubitus position.[60] This type of endoscopic technique demonstrated a higher completion rate and shorter procedure duration when compared with traditional upper endoscopy.[61] In addition, the elimination of conscious sedation may result in significant cost savings.

Developing a screening programme for patients with GORD symptoms only may prove to be ineffective in markedly reducing the number of patients that present with adenocarcinoma of the oesophagus. Many of the patients with Barrett's oesophagus or those presenting with adenocarcinoma of the oesophagus lack previous symptoms of GORD. Most patients with Barrett's oesophagus will never know that they have a pre-malignant lesion. This large core of asymptomatic patients may point to the need to consider even larger screening programmes that include the general adult population. The practicality and economic viability of such programmes will need to be seriously considered.

In a study reporting 10 years' experience of screening patients in a university teaching hospital, the percentage of new patients identified with Barrett's oesophagus in relation to the number of endoscopies performed remained stable (1.4%).[62] Other studies are needed to determine the yield of screening programmes, primarily their impact in reducing the mortality from adenocarcinoma of the oesophagus. Studies evaluating the cost effectiveness of a screening programme in patients with GORD are scarce. Provenzale and Horman stated that given the low cancer risk in patients with Barrett's oesophagus, screening GORD patients to reduce mortality from oesophageal adenocarcinoma is expensive compared with screening for colorectal cancer.[63] However, Soni et al. used an incremental cost-effectiveness ratio as an outcome measure and determined that under favourable conditions, general screening by endoscopy of all patients with GORD symptoms to prevent death from oesophageal adenocarcinoma may represent a cost-effective strategy.[64] Unfortunately, the favourable conditions are difficult to meet as they include a high sensitivity and specificity of the endoscopic procedure for high grade dysplasia, little or no reduction in health-related quality of life by the subsequent therapy (surgery), and focus screening on patients with *a priori* high risk for Barrett's oesophagus.

4. Treatment Goals for Barrett's Oesophagus

The aim of treatment of Barrett's oesophagus is to control the symptoms of gastroesophageal reflux, to heal mucosal inflammation and ultimately to prevent the progression of Barrett's oesophagus to adenocarcinoma. The first two goals are the same as for any patient with gastroesophageal reflux disease. The treatment goal unique to Barrett's oesophagus is the attempt to prevent the progression of Barrett's to dysplasia and malignant transformation.

4.1 Medical Therapy

The mainstay of medical therapy of Barrett's oesophagus is treatment with proton pump inhibitors (table I).[1] The controversy is whether the endpoint of therapy should be gastroesophageal reflux symptom control or oesophageal pH control. Barrett's oesophagus represents the severe end of the spectrum of gastroesophageal reflux disease. This is manifested by a lower mean of the LOS pressure and a greater duration of time that pH is <4 in the oesophagus.[65] Although the symptom of heartburn can usually be controlled in patients with Barrett's

Table I. Treatment strategies for Barrett's oesophagus

Proton pump inhibitor
Antireflux surgery
Endoscopic reversal therapy – experimental
Oesophagectomy – for high grade dysplasia/adenocarcinoma

oesophagus, regurgitation may remain a persistent problem and the metaplastic epithelium remains.[66] This can be manifested by regurgitation of gastric contents that do not cause heartburn and that may not have a bad taste. It has been well documented that symptom control in patients with Barrett's oesophagus does not necessarily reflect normalisation of intraesophageal acid exposure.[67-69] In select patients with Barrett's oesophagus, oesophageal pH control is possible.[70] Twenty-six patients with Barrett's oesophagus were treated with omeprazole 40mg twice daily resulting in a mean 24-hour oesophageal pH <4 of 0.1%. However, patients were excluded who required more acid suppression than 'ranitidine 150mg twice daily or its equivalent for symptom relief' or the same dose of ranitidine in combination with cisapride >10mg once daily. Other studies have documented much more oesophageal acid exposure on the same dose of omeprazole or rabeprazole 20mg twice daily.[71,72]

4.2 Surgical Therapy

Antireflux surgery is another modality of therapy for patients with Barrett's oesophagus. The effect of antireflux surgery in the setting of Barrett's oesophagus is controversial. Experience in 81 patients from Australia suggested that 'the outcome of laparoscopic antireflux surgery is similar for patients with Barrett's oesophagus compared with other patients with gastroesophageal reflux disease'.[73] In a series of 74 patients from Atlanta, Georgia, USA, with Barrett's oesophagus, the procedure failure rate was 6.3% in patients with Barrett's oesophagus versus 2.5% in patients lacking intestinal metaplasia ($p = 0.061$).[74] In a series of 152 patients with Barrett's oesophagus from Chile, 54% with 'non-complicated' Barrett's oesophagus and 64% with 'complicated' Barrett's oesophagus demonstrated failure after a follow-up of 100 months.[75] In the first two of the above series, most of the patients had laparoscopic surgery, and the last series the majority had a Hill procedure (a posterior gastropexy with calibration of the cardia).

In summary, there is a suggestion that patients with Barrett's oesophagus may have a higher surgical failure rate than patients with GORD lacking Barrett's mucosa.

5. Prevention of Progression to Adenocarcinoma

With the goal of preventing intestinal metaplasia from progressing to dysplasia and adenocarcinoma, recommendations have been made to achieve total oesophageal acid control. It is unlikely that this can be achieved in unselected patients with Barrett's oesophagus. However, there have been physiological studies demonstrating that treatment with a proton pump inhibitor twice daily plus a nocturnal histamine H_2 receptor antagonist does result in better intragastric pH control.[76] This approach remains controversial and without documentation in the clinical arena. A theoretical rationale for aggressive acid control is demonstrated in the decreased proliferating cell nuclear antigen and decreased villin expression in patients with normalised intraoesophageal acid suggesting decreased proliferation and increased differentiation.[77] More recently, many of the patients in the prospective cohort series evaluating the incidence of adenocarcinoma of the oesophagus have been treated with proton pump inhibitor therapy.[78-80] However, the specific therapy and duration of therapy is not well documented in these studies.

If eliminating gastroesophageal refluxate – i.e. all components including acid, bile acids and pancreatic enzymes – would prevent neoplastic progression, then antireflux surgery would be a model therapy. Successful antireflux surgery should normalise the antireflux barrier and normalise oesophageal pH exposure. There are many surgical series which document the progression to adenocarcinoma in spite of antireflux surgery.[70,81-85] In some cases, the progression to neoplasia has occurred in patients documented to have effective antireflux surgery.[86] Even in the hands of enthusiasts, antireflux surgery is not 100% successful. All patients who have gone on to cancer have not had 24-hour oesophageal pH studies to determine if, in fact, they had a failed procedure.

It is plausible to hypothesise that the pathophysiology that leads to intestinal metaplasia may not be the same pathophysiology that leads to dysplasia. The oesophageal environment that leads to the development of metaplastic epithelium may not be necessary for the development of dysplasia. A series of molecular events may be initiated in a subgroup of patients that is independent of the earlier environmental exposures.

The apparent lack of efficacy of our current clinical therapy in preventing the development of adenocarcinoma has led to attempts to eliminate intestinal metaplasia with a combination of endoscopic therapy and proton pump inhibitor therapy or antireflux surgery. In an effort to reverse the intestinal metaplasia, the oesophageal milieu has been altered with either antireflux surgery or high-dose proton pump inhibitor therapy. The precise proton pump inhibitor dose to enable reversal has not been determined. Patients have had Barrett's reversal in spite of abnormal 24-hour oesophageal acid exposure.[87,88] Many different forms of energy have then been applied in an attempt to destroy the intestinal metaplasia. The most commonly applied forms have included multipolar electrocautery, argon plasma coagulation and photodynamic therapy.[89] It has proven difficult to eliminate all intestinal metaplasia and there has even been a case report of a nondysplastic Barrett's going on to adenocarcinoma after apparent reversal.[90] Endoscopic reversal therapy is still considered experimental and will not be ready to apply until more effective criteria to risk stratify patients are defined. With a panel including demographic information and biological markers, individuals at highest risk of developing cancer should ultimately be identifiable. Then endoscopic reversal therapy would be applicable in the clinical arena to reduce the likelihood of progression to adenocarcinoma.

6. Surveillance

In the absence of documented methods to prevent the progression of Barrett's oesophagus to adenocarcinoma, surveillance with endoscopy and biopsy remains the most widely practised method for the early detection of high grade dysplasia and/or adenocarcinoma. The assumption is that this early detection will lead to earlier intervention with improved outcome. Although this has never been prospectively documented, cost analyses suggest that it may well be cost effective if the price of endoscopy is low enough, the incidence of adenocarcinoma of the oesophagus high enough, the accuracy of endoscopy good enough, the quality of life after esophagectomy is adequate and the intervals of surveillance endoscopy are long enough.[91] The vast majority of endoscopists in the US perform surveillance endoscopy and biopsy.[92,93] Surveillance is less frequently practised in Europe.[94] Two cohorts of patients with Barrett's oesophagus were followed for 9–10 years with only 2.5–9% of deaths due to oesophageal cancer,[95,96] demonstrating that most patients with Barrett's oesophagus die from a cause other than oesophageal cancer.

The frequency of surveillance is a function of the grade of dysplasia. There has been recent expansion in the database of published literature on patients with dysplasia in Barrett's oesophagus, especially in those with high grade dysplasia. The progression of dysplasia is derived from prospective follow-up of patient cohorts, including series published in the last 2 years. With a follow-up ranging from 3 to 7 years, patients with no dysplasia have a <5% chance of going on to adenocarcinoma of the oesophagus. Patients with low grade dysplasia have less than a 10% chance. 170 patients with high grade dysplasia have been followed with <25% of these patients going on to adenocarcinoma of the oesophagus.[78,79,97-99] This percent results from assuming that any cancer found within the first year of recognising Barrett's represents a prevalence cancer. The surveillance interval is a function not only of the risk of progressing to cancer but of the time period over which the cancer develops.

From the published series it is often difficult to follow the specific time interval of a subgroup of patients. However, it is reasonable to project from the above database that patients lacking dysplasia on two endoscopies with systematic biopsy protocols need endoscopy no more than every 3 years (table II). If a patient has low grade dysplasia that has been documented to be the highest grade present with a follow-up biopsy protocol, than annual endoscopy should be sufficient. High grade dysplasia remains a great controversy. It is important to note that the regularity of the Barrett's epithelium is an important risk factor in relation to the likelihood of cancer. The presence of mucosal nodularity increases the likelihood of developing cancer over a short-term follow-up 2.5-fold.[100] If the high grade dysplasia is more than focal – i.e. involving more than 5 crypts in a

Table II. Surveillance endoscopy of Barrett's oesophagus

Dysplasia	Next step	Interval
None	Repeat	3 years for no dysplasia
Low grade	Repeat	Annual if only low grade dysplasia
High grade	High grade Cancer	3 month endoscopy[a] Resection

a Consider intervention if nodular mucosa.

biopsy specimen – then there is a 3.7-fold increased risk of developing cancer over a short-term follow-up. Given the above information, it may be appropriate to follow a patient with high grade dysplasia which is focal and which occurs in flat Barrett's epithelium with intensive surveillance endoscopy until more extensive high grade dysplasia or frank cancer is detected.

7. Conclusion

The focus on Barrett's oesophagus has increased because of the rapidly rising incidence of adenocarcinoma of the oesophagus. GORD is thought to be the underlying cause of Barrett's oesophagus with the majority of patients with Barrett's oesophagus having reflux symptoms and excessive oesophageal acid exposure as measured by pH studies. In spite of the use of proton pump inhibitor therapy and the increasing application of surgical fundoplication, effective therapy has not been documented to prevent the development of Barrett's oesophagus.

Screening patients with reflux disease for Barrett's oesophagus is reasonable. The criteria for selecting patients for screening are not evidence based and screening has not been documented to reduce the mortality of oesophageal adenocarcinoma.

Proton pump inhibitor therapy and surgical fundoplication are each effective in controlling the symptoms of reflux and healing the oesophageal mucosa in the majority of patients. However, preventing neoplastic progression has not been documented. This lack of prevention may be attributed to inadequate oesophageal acid control, imperfect anti-reflux surgery, under powered studies or inability to prevent progression after the development of Barrett's oesophagus.

Surveillance endoscopy and biopsy provides a potential mechanism for early intervention to improve survival from oesophageal adenocarcinoma. Although tissue sampling and interobserver variability of reading dysplasia remain problems, a surveillance strategy is proposed.

The future offers the opportunity for a better understanding of the natural history of reflux disease and Barrett's oesophagus. Further developments in pharmacological and surgical therapy are likely. Progress in the understanding of the biology of Barrett's oesophagus will provide the opportunity for more effective screening and surveillance with the ultimate goal of improving the survival of adenocarcinoma of the oesophagus.

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Correspondence and offprints: *Richard E. Sampliner*, Southern Arizona VA Health Care System (111G-1), 3601 S. 6th Avenue, Tucson, AZ 85723, USA.
E-mail: samplinr@u.arizona.edu