ANZ J. Surg. 2003; **73**: 234–246

REVIEW ARTICLE

ANTIREFLUX SURGERY FOR BARRETT'S OESOPHAGUS

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Barrett's oesophagus is usually the result of severe reflux disease. Relief of reflux symptoms is the primary aim of treatment in patients with Barrett's oesophagus who do not have high-grade dysplasia. Some studies with medium-term (2–5 years) follow up show that antireflux surgery can provide good or excellent symptom control, with normal oesophageal acid exposure, in more than 90% of patients with Barrett's oesophagus. Antireflux surgery, but not medical therapy, can also reduce duodenal nonacid reflux to normal levels. There is no conclusive evidence that antireflux surgery can prevent the development of dysplasia or cancer, or that it can reliably induce regression of dysplasia, and patients with Barrett's oesophagus should therefore remain in a surveillance programme after operation. Some data suggest that antireflux surgery can prevent the development of intestinal metaplasia (IM) in patients with reflux disease but no IM. The combination of antireflux surgery plus an endoscopic ablation procedure is a promising treatment for patients with Barrett's oesophagus with low-grade dysplasia.

Key words: anti-reflux surgery, Barrett's oesophagus, fundoplication, gastro-oesophageal reflux disease, oesophageal adenocarcinoma.

Abbreviations: APC, argon plasma coagulation; CI, confidence interval; CIM, cardiac mucosa with intestinal metaplasia; GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia; OR, odds ratio; PDT, photodynamic therapy; PPI, proton pump inhibitor; SIR, standardized incidence ratio.

CLINICAL AND BIOLOGIC FEATURES OF BARRETT'S OESOPHAGUS

A widely used definition of Barrett's oesophagus is any length of macroscopically visible columnar mucosa containing microscopic intestinal metaplasia (IM) above the gastro-oesophageal junction, with the junction defined as the proximal extent of the gastric rugal folds.[1] Thus a visible, intestinalized tongue, and a segment extending throughout the thoracic oesophagus are both Barrett's oesophagus. The term 'cardiac mucosa with intestinal metaplasia' (CIM)[2] refers to non-visible areas of IM. The term CIM is preferable to the alternative term 'ultra-short segment Barrett's oesophagus', which implies that patients with these lesions have Barrett's oesophagus, an interpretation that is not uniformly accepted. The prevalence of Barrett's oesophagus is uncertain. Barrett's oesophagus is found in 3–12% of patients who undergo upper gastrointestinal endoscopy for the investigation of chronic reflux symptoms.[3–6] The prevalence of Barrett's oesophagus in the general population has been estimated from autopsy studies to be 0.4–0.9%,[7,8] but in a recent study of individuals without reflux symptoms, most of whom were white men older than 50 (the highest risk group for this disease), the prevalence of Barrett's oesophagus was a remarkable 25%.[9]

Barrett's oesophagus is the precursor epithelium for oesophageal adenocarcinoma, although the approximate risk of cancer development is low, between 1 in 100 and in 200 patient-years.[10–19] Cancer arises via a multistep process in which IM is replaced by low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive adenocarcinoma.[20–22]

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Accepted for publication 22 November 2002.

Barrett's oesophagus is usually the result of severe gastro-oesophageal reflux disease (GORD).[23] The severity of the reflux disease is demonstrated by clinical, physiological, and basic biological findings. Reflux symptoms and complications of reflux, such as stricture and ulceration, are typically more severe in patients with Barrett's oesophagus compared to age- and sex-matched patients with GORD.[24] Most patients with Barrett's oesophagus have a hiatal hernia, and they have larger hernias than patients with reflux oesophagitis without Barrett's.[25] The reflux severity is worst in patients with long-segment Barrett's oesophagus,[26,27] in whom the Barrett's segment is >3 cm in length,[28] but even patients with short-segment Barrett's oesophagus have more severe reflux disease than patients with erosive oesophagitis alone.[29,30]

Most patients with Barrett's oesophagus have abnormally high oesophageal acid exposure,[31–35] a mechanically incompetent lower oesophageal sphincter,[31,32,34–37] and poor oesophageal body clearance.[31,34,37–39] Both the frequency and the duration of reflux episodes, and the proportion of patients with supine period reflux[37] or both upright and supine (bipositional) reflux[40] are increased in comparison to patients without Barrett's.[34,35] The oesophageal body dysmotility impairs clearance of refluxed material, enhancing the likelihood of mucosal damage.[37]

The constituents of the refluxate differ significantly in patients with Barrett's oesophagus compared to those with GORD without Barrett's. Direct measurement of aspirated bile or measurement of bilirubin in the distal oesophagus as a marker for duodenal juice has shown that duodeno-oesophageal reflux is significantly more frequent in those with Barrett's oesophagus than in those with GORD without Barrett's.[26,32,41–53] A study of 100 patients with GORD found a significant association between the degree of mucosal injury and the presence of duodenogastro-oesophageal reflux rather than gastro-oesophageal reflux.[51] The importance of pepsin concentrations in the refluxate of patients with Barrett's oesophagus was demonstrated by Gotley *et al*.[54] Animal studies of nitrosamine-stimulated oesophageal tumour development suggest that duodenal reflux, especially in the

absence of acid reflux, plays a role in the development of oesophageal adenocarcinoma,[42,55–60] although differing results were found in a large non-carcinogen animal study.[61]

Genetic analysis provides further evidence that Barrett's oesophagus is a significant disease.[62] Histopathological progression through the Barrett's sequence requires the evolution of a clone of cells along one of multiple complex pathways of increasing genetic and epigenetic abnormality.[62–65] Features of this process include cellular hyperproliferation,[66] evasion of apoptosis,[67] and abnormal DNA content and chromosomal alterations.[68,69] Growth signal abnormalities are mediated by growth factor and growth factor receptor alterations, activation of oncogenes,[70] and inactivation of critical tumour suppressor genes including the *APC*,[71] *p16*, and *p53*[72] genes. Telomerase activation[73,74] and an angiogenesis factor-stimulated neovasculature[75,76] are increasingly prevalent at later stages.

CONTROL OF SYMPTOMS AND NON-BARRETT'S COMPLICATIONS OF REFLUX DISEASE

Relief of reflux symptoms in patients with Barrett's oesophagus

Optimum therapy for reflux disease of the severity typically present in patients with Barrett's oesophagus requires complete control of the reflux. Complete reflux control can be difficult to achieve using medical therapy,[77] which is likely to require lifelong, continuous, high-dose[78] proton pump inhibitor (PPI) use.[79] Nocturnal gastric acid breakthrough, with a gastric pH <4 for >1 h and frequent oesophageal acid reflux, occurs in a majority of individuals taking standard twice daily PPI medication.[80–82] This nocturnal acid breakthrough period can be reduced by adding an evening histamine H_2-receptor antagonist, but short pulses of oesophageal acid exposure still occur in some patients.[83] *In vitro* data indicate that these short periods of acid exposure may be more deleterious for the Barrett's epithelium than continuous oesophageal acid exposure. Using a Barrett's mucosa organ culture system, Fitzgerald *et al*. found that continuous acid exposure did not induce cellular proliferation, but exposure to 1-h pulses of acid at pH 3.5 resulted in a dramatic increase in the proliferation rate.[84] Intestinal cell differentiation, as assessed by expression of the apical membrane cytoskeletal protein villin, was also higher after continuous 24-h exposure to acid in a pH range 3–5 compared to an exposure of only 6 h of acid at this pH.[84]

Relief of symptoms is a primary aim of treatment for Barrett's oesophagus. If questioned carefully, most or all patients with this disease have reflux symptoms,[35,85,85] although symptoms may improve after Barrett's develops in patients with GORD.[86] Abolition of reflux by antireflux surgery can relieve all reflux symptoms (including regurgitation and cough, which may not be adequately relieved by medical therapy).[87] Numerous studies have shown that antireflux surgery provides safe, effective, long-term control of reflux symptoms,[88–99] with improvements in quality of life after operation,[100–104] and a cost advantage[105–107] over medical therapy.[108] In the most complete study, Lafullarde *et al*. at the Royal Adelaide Hospital reported at least 5-year follow-up data for 99% of their patients who had undergone laparoscopic Nissen fundoplication, finding a 'good or excellent' outcome in 90% of patients.[89]

Three randomized trials,[99,109,110] and two other trials[111,112] have shown significant advantages for surgical treatment over medical treatment for GORD. An evaluation of the long-term follow-up results for one of these randomized trials (the US Veterans Affairs trial) initially reported that patients treated with fundoplication had significantly better symptom control and significantly less frequent use of antireflux medications than medically treated patients,[113] but in the final report there was no significant advantage for operative treatment for symptom control.[114] A large proportion of the surgery-arm patients took antireflux medications on a regular basis during follow up (46.9% in the initial report,[113] 62% in the later publication[114]), but another study has shown that most patients who take acid suppressant medications after antireflux surgery do not have abnormal oesophageal acid exposure.[115]

Many studies have shown that antireflux surgery provides adequate symptom control in patients with Barrett's oesophagus,[38,116–126] and, with the exception of the University Hospital, Santiago, Chile experience,[119,127] the few studies with at least medium-term follow up report good or excellent symptomatic results in >75% of patients.[38,92,120,121,125,126] Some studies that report on symptomatic outcome following laparoscopic antireflux surgery in patients with Barrett's oesophagus are listed in Table 1. In the study by Patti *et al.* relief of heartburn was reported in 95% of 72 patients with Barrett's, relief of regurgitation in 93%, and relief of cough in 100% of patients with Barrett's oesophagus at a mean follow up of 23 ± 14 months after fundoplication.[124] Farrell *et al*. reported that outcomes after fundoplication were very similar in patients with Barrett's oesophagus compared to controls without this disease.[122] At a mean of 3.2 years after operation, symptomatic improvement remained excellent in both groups, but reoperation rates were higher in the Barrett's patients. The authors postulated that this higher reoperation rate might be due to a higher prevalence of undetected oesophageal shortening, with consequent wrap herniation, in the Barrett's group.[122] Chen *et al*. reported control of all reflux symptoms, with reduction in 24-h oesophageal acid exposure from a mean of 10% to 1%, in 45 Barrett's oesophagus patients at a mean 35.9 months after (uncut) Collis–Nissen fundoplication.[123] Richardson and Richardson also reported good results using the

Table 1. Symptomatic outcome after laparoscopic antireflux surgery in patients with Barrett's oesophagus

First author	No. patients	Operation type	Successful outcome (%)	Follow up
Hofstetter[126]	85	Nissen 86%, Collis–Belsey 11%	97% cured (77%) or improved (22%)	Median 5 years
Yau[125]	75	Total fundoplication 78%, partial 22%	Significant improvement in symptom score in all patients	Median 2 years
Chen[123]	45	Collis–Nissen	100% free of reflux symptoms	Mean 35 months
Patti[124]	38	Nissen or partial (Guarner)	>93% symptom resolution	Mean 23 months
Farrell[122]	37	Fundoplication†	approx. 80% symptom-free†	Mean 37 months
Bell[128]	29	Partial (Toupet)	79% symptom-free without re-operation	Mean 30 months

†Operation details were not provided. A heartburn or regurgitation symptom score of 0 or 1 (range 0–4) was reported by approximately 90% of Barrett's oesophagus patients at 2–5 years after operation.

Collis–Nissen operation in a series of patients with oesophageal shortening, approximately one-quarter of whom also had Barrett's oesophagus.[129]

Relief of reflux symptoms and effect on the non-Barrett's reflux complications of oesophagitis and stricture in patients with Barrett's oesophagus

Several studies have compared the effectiveness of medical and surgical therapies for control of symptoms and non-Barrett's complications of GORD. Ortiz *et al*. conducted a prospective randomized comparison of medical and surgical therapy in 59 patients with Barrett's oesophagus.[120] Twenty-seven patients were treated medically, including with omeprazole, and 32 with antireflux surgery. Symptomatic improvement occurred in the majority of patients in both groups (85% of patients in the medical and 89% in the surgical group), but there was a marked difference in the prevalence of post-treatment persistent oesophagitis and stricture in the two groups. The medically treated group had persistent oesophagitis or stricture in 53% and 45% of patients, respectively, compared to 5% and 15% of patients in the operated group. The authors concluded that the 'systematic' non-surgical approach to Barrett's oesophagus should be questioned.[120]

Attwood *et al*. reported on 45 patients who were randomized to undergo either medical ($n = 26$) or surgical ($n = 19$) treatment of Barrett's oesophagus.[118] The groups were similar in age, length of Barrett's segment, 24-h oesophageal acid exposure, and length of follow up. Mean symptom scores improved dramatically following antireflux surgery. Symptoms of heartburn and/or dysphagia eventually recurred in 88% of patients treated with medical therapy alone, compared to 21% after antireflux surgery. During the 3-year follow-up period, an oesophageal stricture developed in 38% of those treated medically and in 16% of surgically treated patients ($P < 0.05$). The authors concluded that antireflux surgery was superior to medication therapy for both the control of symptoms and the prevention of reflux complications in patients with Barrett's oesophagus. McEntee *et al*. reported similar results in a non-randomized comparison of medical and surgical therapy.[130]

Good results for the aim of preventing or healing non-Barrett's complications of GORD were also reported by Chen *et al.* who found healing of mucosal injury in all Barrett's oesophagus patients after Collis–Nissen fundoplication,[123] and by Stein *et al.* who reported healing of erosive oesophagitis in 42 of 45 patients with Barrett's oesophagus after Nissen fundoplication, with incomplete reflux control in those without healing.[131] Most published data support the ability of both properly performed antireflux surgery[132] and adequate medical acid suppression to heal oesophagitis in patients with or without Barrett's oesophagus.[133,134] Although surgery may have an advantage for both healing and preventing reflux-induced strictures, compared to the combination of acid suppression medication and endoscopic dilatation,[135] it must also be acknowledged that the prevalence of reflux-induced stricture has declined substantially since the introduction of PPI medications.[136–139]

OBJECTIVE ASSESSMENT OF REFLUX CONTROL

Assessment of objective as well as symptomatic outcome criteria is important in research studies because continued reflux and progression to more advanced Barrett's stages may occur in treated asymptomatic individuals.[127,140] Few patients, especially if asymptomatic, will volunteer for postoperative 24-h pH or bilirubin measurement, however, and the reported number of patients with Barrett's oesophagus studied in this way is small. As shown in Table 2, the results vary considerably. High rates of reflux control were reported in studies from Lund University (normalization of oesophageal acid exposure in 95% of patients with Barrett's oesophagus)[141] and from the Royal Adelaide Hospital (90% normal pH studies).[125] In contrast, the long-term (median 9 years follow up) results for a series of patients who were mostly treated by performance of highly selective vagotomy and posterior gastropexy with calibration of the cardia were disappointing, with a normal pH study in only 34% of patients, according to my calculations.[127] Ninety-four per cent of the patients who developed dysplasia in this study had abnormal oesophageal acid exposure.[127]

Considering the role of duodenogastro-oesophageal reflux in the pathogenesis of Barrett's oesophagus, important results were reported by Stein *et al.* who showed that Nissen fundoplication provides normalization of bile exposure as well as acid exposure in almost all patients.[131] In contrast, acid suppressant medications do not normalize duodenogastro-oesophageal reflux: two studies reported significant reduction, but not normalization, in duodenogastro-oesophageal reflux with administration of omeprazole 20 mg twice daily.[47,131] Using simultaneous intraoesophageal impedance and pH measurement, Vela *et al*. further showed that the frequency of non-acid reflux was not altered by use of omeprazole at this dosage.[144] Omeprazole had no effect on antral duodenogastric reflux in patients with Barrett's oesophagus in another study.[145]

Table 2. Objective assessment of control of acid reflux after antireflux surgery in patients with Barrett's oesophagus: published results of 24-h distal oesophageal pH monitoring for the period 1995–2002

First author	Year	Operation	*n*	Length of follow up	Normal pH study
Sagar[142]	1995	Partial fundoplication (Lind) or Nissen	18	Median 7 years	11 (61%)
Ortiz[120]	1996	Nissen 30 patients, Collis–Nissen 2 patients	32	Mean 5 years	27 (84%)
Horvath[143]	1999	Partial (Toupet)	13	Mean 22 months	4 (13%)
Yau[125]	2000	Total fundoplication in 78%, partial in 22%	21	Median 2 years	19 (90%)
Hofstetter[126]	2001	Nissen in 86% of patients	21	Median 5 years	17 (83%)
Öberg[141]	2001	Nissen	20	Median 6 months	19 (95%)
Csendes[127]	2002	HSV and posterior gastropexy with cardia calibration (majority) or HSV and Nissen	68	Mean 9 years	23 (34%)

HSV, highly selective vagotomy.

EFFECT ON THE BIOLOGY OF BARRETT'S DISEASE

Prevention of progression to dysplasia and adenocarcinoma

The hypothesis that ongoing reflux-related injury to the Barrett's mucosa is important in the aetiology of dysplasia and cancer is supported by the observation that dysplasia and adenocarcinoma probably develop in most cases after IM has been present for many years.[17,146] According to this hypothesis, complete abolition of pathological reflux (as provided by successful antireflux surgery) should have a beneficial effect in preventing progression to more advanced Barrett's stages. Although this theory is an attractive one, it must be acknowledged that it is currently not substantiated by convincing evidence. Several studies indicate that medical acid suppression therapy alone is not effective in preventing disease progression. Hameeteman *et al.* reported on 50 patients with columnar mucosa followed for a mean 5.2 years (range: 1.5–14 years). Three patients developed new IM, four developed LGD, two developed HGD, and five developed adenocarcinoma.[17] Sharma *et al.* followed 32 patients with short-segment Barrett's oesophagus for a mean 36.9 ± 5.4 months. During this period five patients developed dysplasia (three with LGD and two with HGD, with cancer detected in one of the patients with HGD), giving an incidence of any dysplasia of 5.7% per year.[147] Only patients with abnormal acid exposure after operation developed dysplasia in a study of 45 patients treated by Collis–Nissen gastroplasty.[148]

There are reports of Barrett's adenocarcinomas in patients who have undergone antireflux surgery.[5,114,116,117,119,121,125,142,149–154] It is difficult to assess the significance of these reports because in some cases the antireflux surgery was noted to have been technically unsuccessful[120] or the technical adequacy of the operation was not mentioned. In the study by Yau *et al.* from the Royal Adelaide Hospital, however, HGD or adenocarcinoma developed after antireflux surgery in four (5%) of 81 patients with Barrett's oesophagus, all of whom were symptomatically reflux free and thus presumably had a technically satisfactory fundoplication.[125]

It is possible that cancers found within a few years after antireflux surgery were already present but undetected at the time of the operation, or the disease had reached a point at which malignant change was inevitable. This possibility is supported by an analysis of published cases that showed that the cancers were clustered in the early years following surgery rather than dispersed throughout the follow-up period: 58% of the reported cancers were detected within the first 3 years after antireflux surgery, and 79% were detected within 5 years of operation.[155] It has been argued that the relative infrequency of cancer development at 5 or more years after antireflux surgery in these studies suggests that antireflux surgery may be associated with prevention of the development of malignancy, but similar findings are reported in some studies of medically treated patients with Barrett's oesophagus,[17,147,156,157] and the decreasing number of patients at longer follow up may also explain the results, at least in part.

Institutional studies

No published single-institution studies have had sufficient numbers to conclusively determine whether antireflux surgery influences the likelihood of progression to dysplasia and cancer in patients with non-dysplastic Barrett's. Several studies support the possibility that antireflux surgery could have a protective effect, but most of these studies are underpowered. Two studies, however, despite the small number of patients studied, demonstrate a statistically significant advantage for surgical therapy compared with medical therapy.[120,158] In a prospective randomized study reported by Ortiz *et al.*, dysplasia developed in six of 27 (22%) patients while on medical treatment but in only one of 32 (3%) patients who were treated surgically.[120] The present author's analysis finds this difference to be statistically significant, with $P = 0.04$ and a relative risk for developing dysplasia for medical treatment compared to surgical treatment of 7.1 (95% confidence interval (CI) 0.91–55.5; all two-sided Fisher's exact test). A 24-h distal oesophageal pH monitoring study showed that the fundoplication was ineffective in the surgically treated patient who developed dysplasia.[120]

The second study reporting a significant advantage for surgical treatment for the prevention of disease progression was a retrospective analysis by Katz *et al.* of 102 patients with Barrett's oesophagus without HGD.[158] Sixteen patients were treated with antireflux surgery, the remainder were given acid suppressant medication therapy. Nineteen of the medically treated patients developed new-onset LGD and four developed HGD. Adenocarcinoma developed in four medically treated patients but none of the surgically treated patients developed dysplasia or cancer. The authors calculated an estimated hazard ratio for prior fundoplication of 0.20 (0.04–1.0), and a Kaplan–Meier estimate for dysplasia or adenocarcinoma-free survival at 9 years of 100% for those treated surgically versus only 50% for those treated medically ($P = 0.03$; log–rank test).[158] The importance of these results is limited, however, because most of the medically treated patients received H_2-receptor antagonist, rather than PPI, therapy. Other studies report no progression to either HGD or cancer after fundoplication in patients with Barrett's,[61,124,159] although in one of these reports (by DeMeester *et al.*) progression to LGD occurred in 11% of patients without preoperative dysplasia after antireflux surgery.[159]

In a comprehensive review, Bammer *et al.* calculated that the cancer risk for patients with Barrett's oesophagus treated by antireflux surgery (1 in 294.4 patient-years) was lower than the risk for Barrett's patients treated medically (1 in 114.7 patient-years).[162] The post-surgery risk is even lower (1 in 323.7 patient-years) if recent data from another series[126] are included, but recent studies also indicate that the risk for medical treatment is also lower (by half) than estimated by Bammer *et al.*[163] Furthermore, the surgery calculations do not take into account the mortality rate for laparoscopic antireflux surgery, which in the largest survey occurred in four of 2453 cases (0.16%).[164]

Another study reported in abstract form[165] on the annually surveyed patients with Barrett's oesophagus in the American College of Gastroenterology registry.[166] All patients had non-dysplastic Barrett's oesophagus at initial endoscopy. A high proportion of the medically treated patients (10 of 119 patients, 19.7%) developed dysplasia. In contrast, only two of the 42 patients (3.4%) who underwent an antireflux operation developed dysplasia. This study dates from the pre-PPI era, however, and the importance of these results, like those of Katz *et al.*,[158] is thus limited. Detailed long-term follow-up results on this surgically treated group would be interesting.[166]

Population studies

Considering that the lack of statistical power precludes definitive conclusions in the institutional studies reviewed here, the results of epidemiological studies on therapies for reflux disease and the incidence of oesophageal adenocarcinoma are particularly

important. Unfortunately, epidemiological studies have so far included large numbers of patients with GORD but not with Barrett's oesophagus, and the results of the studies have varied.

Adenocarcinoma and medical therapy

Some data suggest that there may an association between oesophageal adenocarcinoma and the use of either drugs that relax the lower oesophageal sphincter or acid-suppressant medications. These data are not conclusive but they are nevertheless disturbing in view of the fact that these drugs are among the most frequently prescribed medications worldwide and that continuous treatment with the acid suppressant drugs is the usual treatment for patients with GORD and with Barrett's oesophagus. A medical record-based study of the members of a large Southern California prepaid health plan reported a positive association between medication use and cancer risk.[167] Most notably, those who had been given four or more prescriptions or refills for H_2 antagonists had an increased risk for development of adenocarcinoma of the oesophagus or cardia, even after adjusting for a composite index that included the factors gastro-oesophageal reflux, hiatal hernia, oesophagitis or oesophageal ulcer, and difficulty swallowing (odds ratio (OR): 1.8; 95% CI: 0.5–6.7).[167]

An increased ratio of observed to expected oesophageal cancers was found in a prospective cohort study of 9928 patients who had been prescribed the H_2 antagonist Cimetidine.[168,169] There were more oesophagocardia adenocarcinomas than oesophageal squamous cell carcinomas detected, and there was a statisically significant excess number of oesophageal cancer deaths at 7 and 8 years after cimetidine use, an interval that excludes the possibility that the drug was being given for symptoms due to an undiagnosed cancer.[169] Another study reported a small but non-significant increased risk of oesophago-cardia adenocarcinoma, with the null value not excluded, for use of certain antacids (Rolaids and Tums).[170]

Other epidemiological findings oppose the likelihood that chronic acid suppressant medication use might contribute to the risk of disease progression in patients with Barrett's oesophagus. The prescribing patterns for acid suppressant drugs in the community are not consistent with the marked male predominance of Barrett's cancers. Furthermore, areas with incidence data for the period prior to 1977,[171,172] when the first H_2 antagonist was released, have shown that the incidence of oesophageal adenocarcinoma was already increasing at a rapid rate in the prehistamine H_2 receptor antagonist period.[173]

Antireflux surgery, medical therapy, and oesophageal adenocarcinoma

Two large Swedish studies have investigated the influence of antireflux therapy on the development of adenocarcinoma.[154,174] The first study was a population-based case-control study that included 451 cases of adenocarcinoma of the oesophagus or gastric cardia and 820 controls.[154] There was a significant positive association between medical therapy and adenocarcinoma development but no association with a history of antireflux surgery. Persons with symptoms of gastro-oesophageal reflux who had used medications for these symptoms at least 5 years before interview had an increased risk of oesophageal adenocarcinoma compared to those with symptoms who did not use such medications. This increased risk was present even after adjustment for severity of reflux symptoms (OR: 2.9; 95%CI: 1.9–4.6).[154] In the second study, the same group studied 66 965 patients with gastro-oesophageal reflux who did not undergo antireflux surgery, and 11 077 patients who had undergone antireflux surgery.[174] Cancers occurring within the first year of follow up were excluded. During 1–32 years of follow up of those who underwent antireflux surgery, 16 oesophageal adenocarcinoma cases were identified, compared with 1.1 expected cases based on incidence rates for the general Swedish population (standardized incidence ratio (SIR): 14.1; 95%CI: 8.0–22.8). Patients who underwent vagotomy in addition to an antireflux operation had a higher relative risk of oesophageal adenocarcinoma (SIR: 32.0; 95%CI: 10.4–74.8). Information on individual patients, such as whether they had pretreatment Barrett's oesophagus, was not available to the investigators. It may be speculated that the poor results for antireflux surgery are attributable to the tendency in Sweden to reserve surgery for patients with severe reflux disease. Nevertheless, this study, which includes a very much larger number of patients than any other, indicates strongly that antireflux surgery, at least as practised in the community, does not protect against the development of oesophageal adenocarcinoma.[174]

Regression of Barrett's intestinal metaplasia

Regression in the length and surface area of Barrett's intestinal metaplasia can occur after both medical[77,175] and surgical[28,117,118,142,159,160,178,179] treatment, but neither form of treatment consistently results in complete regression of Barrett's epithelium.[17,38,117,120,121,124,146,159,180–186] Complete regression of Barrett's oesophagus has been reported in only 11 patients after medical therapy alone.[89,177,187] The most encouraging data were published by Weston *et al.* who reported complete regression in seven of 99 patients (7.1%) treated with acid suppression medication. Five of these seven patients had short-segment Barrett's oesophagus.[177]

There are isolated reports of high regression rates after antireflux surgery.[178] Sagar *et al*. found regression of Barrett's oesophagus in 24 of 56 (43%) patients at a median follow up of 5.5 years after partial fundoplication, with complete regression in five patients (9%).[142] Baulieux *et al*. reported complete or partial regression after fundoplication in 7/26 (27%) patients, among them three patients with short-segment Barrett's and one patient preoperatively treated by argon laser ablation.[161] An advantage for surgical compared to medical treatment was reported by Ortiz *et al.* who found in a prospective study that regression of the length of the Barrett's segment occurred in eight of 32 (25%) patients randomized to antireflux surgery, but in only two of 27 (7%) patients randomized to medical treatment.[120]

Most studies have reported relatively low regression rates, however. A review of studies with at least 4 years follow up28,117,120,142,190,191 calculated that regression occurred in 37 of 190 (19%) patients after antireflux surgery.[184] Another review found that complete regression after antireflux surgery was documented in only 3.8% of patients, while partial regression had occurred in 12%.[155]

The importance of maintaining complete control of acid reflux for induction of regression is shown by the findings that a decrease in proliferation rate and an increase in a differentiation marker were present in 24 patients with Barrett's oesophagus in whom intraoesophageal pH could be normalized by acid suppression, but no changes in the proliferation or differentiation were present in 15 patients with persistently pathological acid reflux despite medical treatment.[192] The presence of a hiatal hernia is

also important: complete regression was significantly and independently associated only with absence of a hernia in a logistic regression analysis involving 99 medically treated patients.[177] One interpretation of this result is that complete regression should be more frequent after antireflux surgery than after medical therapy, because antireflux surgery reduces the hiatal hernia that is commonly present in patients with Barrett's oesophagus, whereas the anatomic problem of hiatal hernia is not affected by medical therapy.

Regression of dysplastic Barrett's oesophagus

Studies that have specifically addressed whether antireflux surgery can cause regression of dysplastic Barrett's are few, and interpreting their results is complicated by the observation that dysplasia can occasionally regress spontaneously or transiently, and by the problem of sampling error, which may lead to a false negative diagnosis for dysplasia. Regression of preoperative LGD to IM with no dysplasia after antireflux surgery has been reported in seven of 10 patients in one study,[159] and in four of four patients in another study.[160] Regression of dysplasia has also been reported after performance of the duodenal switch procedure combined with an antireflux operation, highly selective vagotomy, and a Roux-en-Y anastomosis.[193] In summary, there are insufficient data available to estimate the frequency with which antireflux surgery (or medical acid suppressant treatment[147,192]) results in regression of dysplastic to non-dysplastic Barrett's epithelium. There are reports of complete regression of even HGD occurring after medical acid suppression alone,[157,194–196] but other investigators consider that permanent reversal of HGD to either LGD or metaplasia without dysplasia is uncommon.[197]

Prevention of Barrett's oesophagus in patients with gastro-oesophageal reflux disease

The hypothesis that elimination of reflux by performance of a fundoplication should prevent the de novo development of Barrett's oesophagus has been tested in only a few studies. Two recent studies, however, have stimulated considerable interest in this subject.[141,198] In a well-designed serial endoscopy study, Öberg *et al*. analysed the development of IM in patients who had GORD but no IM on two consecutive endoscopies at entry into the study.[141] Patients treated with antireflux surgery were 10.3 times less likely to develop IM than patients treated with acid suppressant medication, 91.8% of whom receieved PPI (Fig. 1).[141] In the second study, Wetscher *et al*. prospectively compared medical and surgical therapies in a later study that included only patients whose reflux symptoms and oesophagitis were effectively controlled.[198] Endoscopies were performed at 6 months intervals during follow-up surveillance, and all patients were followed for at least 2 years. Surgical treatment consisted of either Nissen or partial fundoplication in approximately equal proportions. Barrett's oesophagus developed in 14.5% of medically treated patients, but no Barrett's was detected in those treated by antireflux surgery.[198] The same authors had earlier reported in a retrospective study that approximately one-third of 138 patients with GORD but no IM developed Barrett's oesophagus while on medical therapy.[199]

Luostarinen *et al*. investigated 21 patients at 20 years after antireflux surgery.[92] Barrett's oesophagus was present in five of six patients with an apparently defective fundoplication, whereas only two of 15 patients with an intact fundoplication developed

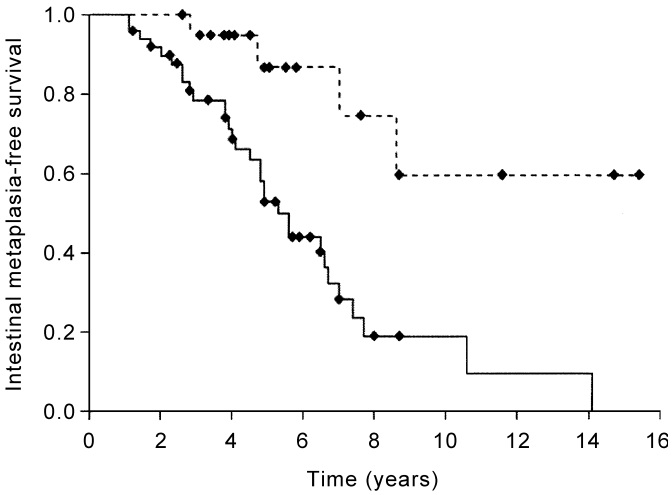

Fig. 1. Kaplan–Meier curve showing intestinal metaplasia (IM)-free survival during endoscopic surveillance of patients with GORD treated with either (—) acid suppressant medication ($n = 49$; PPI therapy in 91.8%) or (---) Nissen fundoplication ($n = 20$). All the patients had two consecutive endoscopies with no evidence of IM at the start of the study. Patients treated with antireflux surgery were 10.3 times less likely to develop IM ($P = 0.001$, log–rank test). GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor. From Oberg S *et al.* Endoscopic surveillance of columnar-lined esophagus. *Ann. Surg.* 2001; 234: 619–626.

Barrett's oesophagus. Furthermore, the two patients with newly diagnosed Barrett's did not have preoperative biopsies, so the possibility that the Barrett's oesophagus was present before surgery cannot be excluded.[92] In a separate article, Luostarinen *et al*. also reported that Barrett's oesophagus developed in four of 33 patients at a median 80 months after fundoplication. Two of these patients had recurrent reflux with wrap disruption, in one other case Barrett's oesophagus had been visualized but not biopsied preoperatively, and sampling error was considered possible for the fourth case. No regression was observed in five other patients with preoperative Barrett's metaplasia.[182] Further studies examining the potentially protective effect of antireflux treatments on the development of Barrett's oesophagus are needed.

CHOICE OF OPERATION

The importance of completely eliminating pathological reflux[84,176,192] suggests that the antireflux procedure of choice is Nissen fundoplication. The Nissen operation, or more commonly a variant of the original operation, is the most commonly performed fundoplication. It is performed laparoscopically in the great majority of cases and, although an increasing amount of randomized trial data suggest that many outcomes for the laparoscopic approach may be no better, or even worse, than for open surgery,[97,132,200–208] the laparoscopic operation will almost certainly remain the usual method because of the wound and patient acceptance advantages.

Some studies indicate that the circumferential Nissen fundoplication provides more complete control of reflux than any of the partial fundoplication operations (Toupet, Dor, Belsey, Watson, Lind, Guarner) or other antireflux operations (Hill, Angelchik),[119,128,143,209–215] and the Nissen operation remains the gold standard against which other operations are compared.[216]

When such a comparison has been made, however, there is little evidence to support the superiority of the Nissen fundoplication over partial fundoplication as performed by the posterior hemifundoplication (Toupet),[212,217–219] anterior hemifundoplication (Dor or variant),[212,219,220] 300° posterior fundoplication (Lind),[221] or the 'physiological repair'.[222] These comparison studies have not specifically included patients with Barrett's oesophagus, however, and the poor results by Horvath *et al*. using the Toupet operation in patients with Barrett's suggest that they may not apply in these patients.[143]

It was formerly advocated by some surgeons that the type of operation selected had to be tailored to the patient's preoperative oesophageal body motility findings, with Nissen fundoplication contraindicated in patients with low-amplitude or disordered motility.[29,223,224] This approach has been refuted in randomized trials[225,226] and in other studies.[227–231] Most patients with Barrett's oesophagus, particularly if young, are thus suitably treated by Nissen fundoplication. Selecting the operation on the basis of the preoperative manometry is still indicated for patients with an aperistaltic body. In these patients a partial fundoplication is generally preferred.

Relative contraindications to surgery are the presence of significant medical comorbidity or advanced age in patients with no factors suggestive of an increased risk of disease progression. These factors include the presence of dysplasia, a large hiatal hernia, a long Barrett's segment, and a manometrically incompetent lower oesophageal sphincter.[15,26,35,232–235]

Csendes *et al*. advocate that patients with complicated Barrett's oesophagus or long-segment Barrett's should be treated with vagotomy with antrectomy, an antireflux operation (by Nissen fundoplication or 'calibration' of the cardia), and a Roux-en-Y procedure as the first option for antireflux surgery.[236] The rationale for this operation is that the vagotomy and antrectomy reduces gastric acid production, while the Roux limb (50 cm) diverts bile to the small intestine, resulting in elimination of duodenal reflux in almost all cases.[237] These authors have also used the duodenal switch procedure instead of antrectomy with Roux-en-Y.[193] They report regression of LGD to non-dysplastic mucosa in more than half of all patients, with better results in patients with shorter lengths of IM.[237] These impressive results suggest that there may be a role for this extensive antireflux operation in some patients, particularly those with LGD.

Considering the lack of conclusive data indicating regression of Barrett's mucosa after standard medical or surgical treatments, the use of ablative therapies has become increasingly attractive. The most popular methods involve argon plasma coagulation (APC), multipolar (electro)coagulation, photodynamic therapy (PDT), and endoscopic mucosal resection.[238] Endoscopic mucosal resection has the advantage that the full histopathology specimen can theoretically be removed for examination. There are currently no manuscript publications indicating that any of the ablative therapies reduce cancer risk, and cancers have developed after both APC[239] and PDT (unpublished case). The main complications are stricture formation (in approximately 25% of patients after PDT). The Barrett's mucosa is fully eradicated in only approximately one-third of patients,[240] even after multiple treatments, and IM may persist under apparently healed squamous epithelium (subsquamous or 'buried' Barrett's).[241,242] Cost-effectiveness has not been evaluated. Despite these concerns, ablative therapies offer great promise for eliminating the Barrett's mucosa and associated cancer risk. Because maintainence of an anacid environment seems to promote re-epithelialization with squamous mucosa after ablation,[243,244] several centres have combined ablation with fundoplication.[245–249] The reported ablation plus surgery series include few patients but the early results are encouraging. In one study, squamous re-epithelialization was found throughout the tubular oesophagus in all 11 patients with Barrett's non-dysplastic IM who underwent antireflux surgery followed by endoscopic laser ablation. Intestinal metaplasia persisted, in contrast, in the control patients who were treated only with antireflux surgery, despite achieving normal oesophageal acid exposure in all patients.[248] It seems reasonable to enroll patients with Barrett's oesophagus with LGD in ablation research trials, but it can be argued that patients with non-dysplastic IM do not require ablation, and those with HGD should still preferentially be treated by oesophagectomy.

CONCLUSION

Barrett's oesophagus is an important health problem. It is usually the result of severe reflux disease and effective therapy requires optimum reflux control. Surgical therapy can provide adequate symptom control, with normal oesophageal acid exposure, in more than 90% of patients with Barrett's oesophagus, but patients still need endoscopic surveillance after surgery. Further clinical research should help identify the merits of different types of antireflux operations, including partial fundoplications, the ability of antireflux surgery to prevent the development of intestinal metaplasia, and the role of endoscopic ablative therapies after fundoplication. Basic research studies are being conducted with the aim of identifying reliable genetic markers associated with an increased risk of disease progression in patients with Barrett's oesophagus. The results of these studies should eventually provide additional information to help select appropriate therapies for patients with this disease.

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