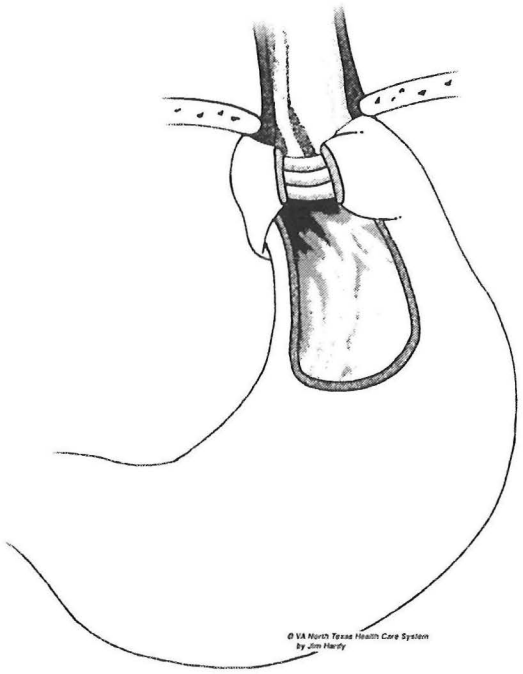
Medical or Invasive Therapy for GERD: An Acidulous Analysis



University of Texas Southwestern Medical Center at Dallas
Internal Medicine Grand Rounds
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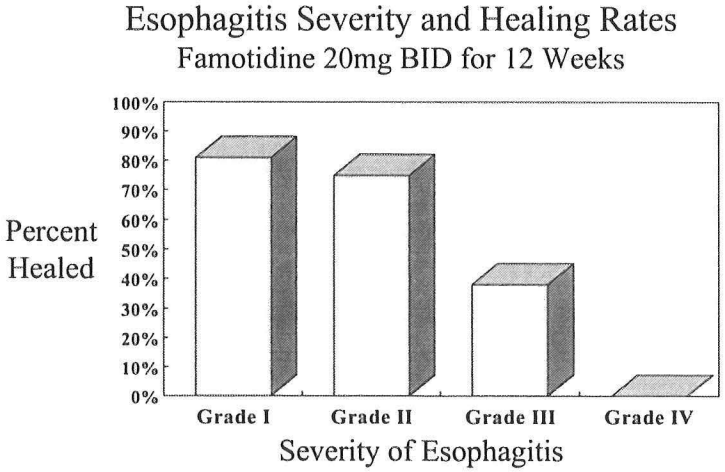
It has been estimated that Americans spend $9.3 billion each year for the evaluation and treatment of gastroesophageal reflux disease (GERD) (1), a disorder that responds well both to medical and invasive therapies. Medical antireflux therapy is directed primarily at controlling gastric acid secretion (2), whereas the invasive treatments (surgical fundoplication and endoscopic antireflux procedures) are designed to create a mechanical barrier to the reflux of gastric contents. There are vocal proponents for all of these therapies, and there is no clear consensus on how to choose among them (3). For a disease that can be treated medically or surgically, a rational therapeutic choice should be based on consideration of five key features of the alternative therapies: 1) Efficacy in healing, 2) Efficacy in preventing complications, 3) Safety and side effects, 4) Convenience, and 5) Cost. In this Grand Rounds, we will consider these features for medical and surgical antireflux therapies. Presently, insufficient data are available to evaluate these features for the endoscopic antireflux procedures.

Efficacy in Healing

Some historical perspective is needed to appreciate the current controversy regarding the efficacy of GERD therapies. In 1956, a Swiss surgeon named Rudolf Nissen described the antireflux procedure that now bears his name (Nissen fundoplication) (4). There was no effective medical treatment for GERD and its complications in 1956. Antacids were available, but there were no useful antisecretory medications. Thus, the Nissen fundoplication was born in an era when there was no effective non-invasive treatment for reflux esophagitis.

During the 1960s, surgeons like Nissen, Rossetti, Belsey, Dor, and Toupet described a number of refinements in antireflux operations (5), but there were no substantial advances in the medical treatment of GERD. The histamine H_2-receptor



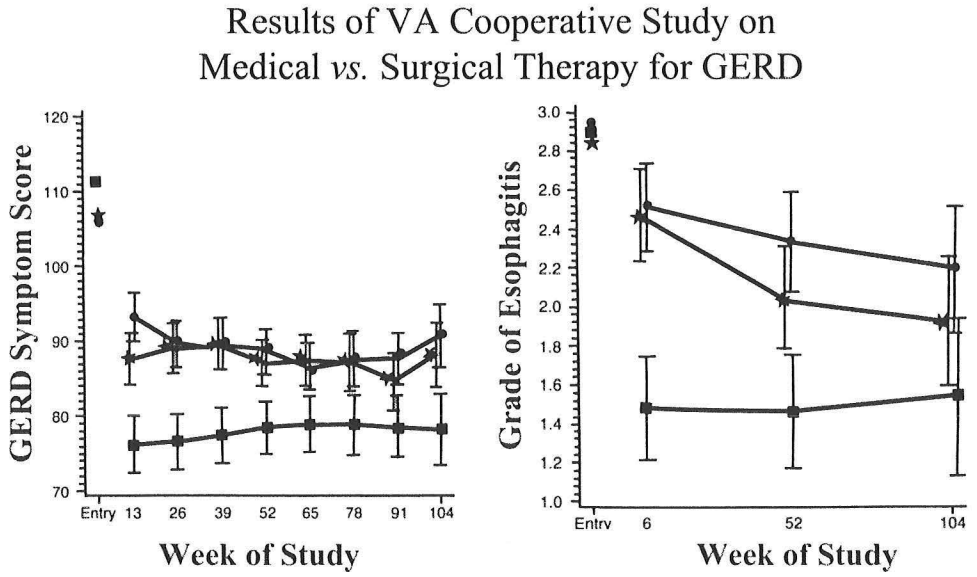
Wesdorp. Dig Dis Sci 1993;38:2287. **Figure 1**

antagonists (H_2RAs) were introduced into clinical practice in the 1970s, and these agents revolutionized the treatment of acid-peptic diseases (6). The H_2RAs rapidly emerged as the standard of care for the treatment of peptic ulcers of the stomach and duodenum, and they were used widely to treat GERD. Over the decade following their introduction, however, it became clear that the H_2-blockers were not effective treatment for patients

with severe reflux esophagitis. Acute healing rates for severe esophagitis were poor (Figure 1) (7), and the long-term utility of H_2RA treatment was limited by the frequent development of tolerance to their antisecretory effects (8).

For most of the 1980s, medical therapy for GERD involved a "step-up" treatment approach that began with the prescription of antireflux lifestyle modifications and antacids, followed by the addition of H_2RAs and other agents of limited efficacy (e.g. metoclopramide, bethanechol) for patients who did not respond to the other measures (9). Antireflux surgery generally was reserved for patients whose disease was refractory to medical therapy. Although a number of reports of retrospective surgical studies described excellent results for fundoplication (10), internists generally were reluctant to recommend the operation even for their patients with severe, refractory reflux esophagitis. There were no reports of randomized trials comparing antisecretory medications and surgery to guide therapeutic decisions in the 1980s, and disastrous anecdotal experiences with patients who had failed fundoplications caused internists to be wary of antireflux surgery.

From 1986 through 1988, the Department of Veterans Affairs (VA) conducted a multicenter, randomized trial of medical and surgical therapies for 247 patients with complicated GERD (11). Antireflux lifestyle modifications were prescribed for all patients, who then were randomized by concealed allocation to receive either medical therapy (antacids, ranitidine, metoclopramide, and sucralfate) or surgical therapy (open Nissen fundoplication). For the two-year duration of the study, surgery was found to be



Boxes=Surgical Group, Circles and Stars=Medical Groups
Spechler. N Engl J Med 1992;326:786

Figure 2

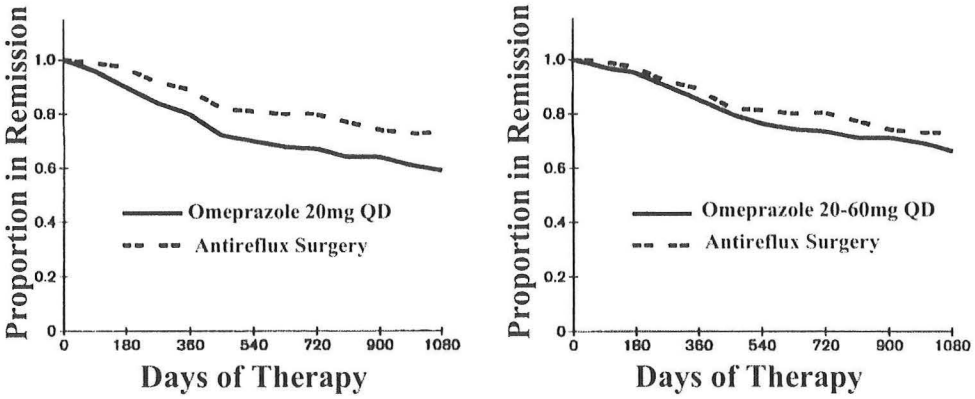
significantly more effective than medical therapy for healing the symptoms and signs of severe GERD (Figure 2). Thus, a powerful, randomized trial clearly demonstrated the superiority of surgical therapy over H_2RA-based medical therapy.

By 1990, the proton-pump inhibitor (PPI) omeprazole had been released for clinical use in the United States. With PPIs, it was finally possible to effect the profound acid suppression needed to heal severe reflux esophagitis. Studies demonstrated that, in

almost all cases, reflux esophagitis could be healed provided that PPIs were given in sufficient dosages (12). Some patients with severe reflux esophagitis required double and triple doses to effect healing but, in the large majority of patients with mild and moderate disease, esophagitis could be healed with a conventional, once daily dosing of a PPI (7). Studies also showed that treatment with PPIs improved dysphagia and decreased the need for dilatation in patients with GERD complicated by peptic esophageal stricture (13).

Laparoscopic fundoplication was introduced in 1991 (14), and this innovation further stimulated interest in antireflux surgery. Except for the minimally invasive approach to the operation, the technique of laparoscopic Nissen fundoplication is virtually identical to that of the traditional, open procedure (154). Compared to the open procedure, the proposed advantages for the laparoscopic approach include less postoperative discomfort, shorter durations of hospital stays, and better cosmetic outcomes. Most surgeons now use the minimally invasive approach, and antireflux surgery is being recommended with increasing frequency (16).

Results of Nordic Study on
Medical *vs.* Surgical Therapy for GERD



PPI dose adjustment ***not*** allowed

PPI dose adjustment allowed

Lundell. Eur J Gastroenterol Hepatol 2000;12:879. **Figure 3**

A Nordic group recently conducted a randomized trial of PPI therapy and open antireflux surgery for 310 patients with erosive esophagitis (17,18). When the medical group was treated with omeprazole in a fixed dose of 20 mg per day, then antireflux surgery was found to be superior for maintaining GERD in remission for the five-year duration of the study. In clinical practice, however, patients are not always treated with a single, fixed dose of PPI. Rather, the dose is titrated to control symptoms. When the physicians were permitted to titrate the dose of omeprazole as necessary for symptom control (up to 60 mg per day), then there was no statistically significant difference between the medical and surgical groups in remission maintenance for up to five years (Figure 3). These data suggest that PPI therapy and antireflux surgery are approximately equal in efficacy for maintaining GERD in remission for up to five years.

Although severe GERD is judged to be a lifelong problem, relatively few data are available on the long-term efficacy of any antireflux therapy. One study of patients with

severe GERD treated with omeprazole for a mean of 6.5 years found that relapses occurred frequently (at the rate of 1 per 9.4 treatment-years), and that patients often required increasing doses of omeprazole (up to 120 mg per day) to control their symptoms (19). Some retrospective surgical series have reported success rates exceeding 90% at 10 to 20 years after open fundoplication (10,20), whereas others have described breakdown of the operation and the return of reflux esophagitis in more than 50% of cases within 6 years (21).

Recently, a follow-up study was conducted on the patients who had participated in the VA GERD trial in the 1980s (22). Using a professional search agency, the investigators determined the whereabouts of 239 (97%) of the original 247 study patients. After a follow-up period of 10 to 13 years, there were no significant differences between the medical and surgical groups in overall physical and mental well-being scores, and in overall satisfaction with antireflux therapy. Surgical patients were significantly less likely to have taken antireflux medications regularly and, when antireflux medications were discontinued, their GERD symptoms were significantly less severe than those of the medical patients. However, 62% of the surgical patients reported that they were taking medications on a regular basis to treat GERD symptoms. Subsequent reports from other groups have confirmed the major findings of this study (23). These studies suggest that antireflux surgery does not effect a permanent cure for GERD in most patients with severe disease.

The history of GERD therapy is replete with irony. For decades, only surgeons had effective treatment for severe GERD, but internists were reluctant to recommend the operation. Now, when there is finally effective medical therapy for severe GERD, antireflux surgery is more popular than ever despite the recent data that raise serious doubts about the long-term efficacy of fundoplication.

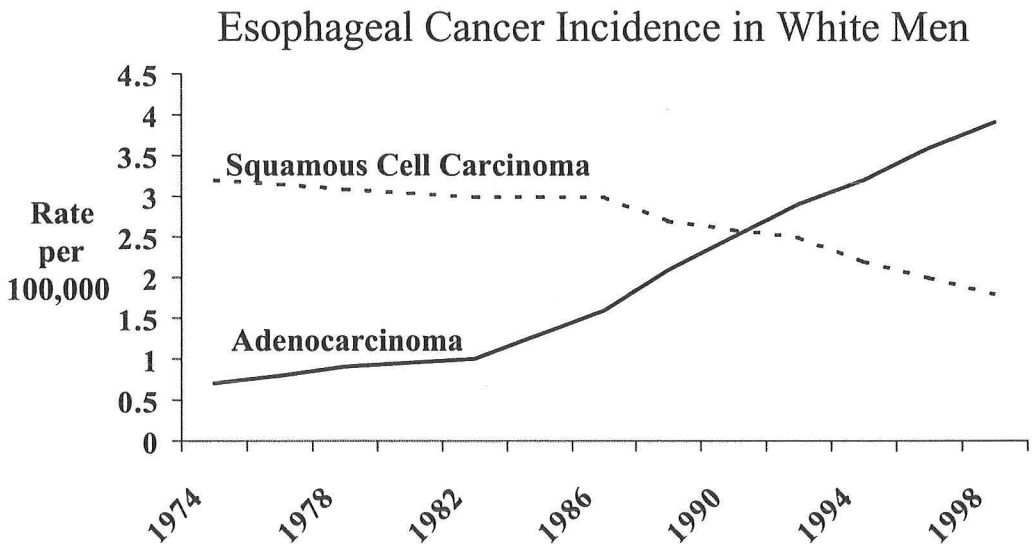
Efficacy in Preventing Complications

Severe GERD can cause peptic ulcerations in the esophageal mucosa. Deep peptic ulcerations that erode into blood vessels can cause hemorrhage, and deep ulcerations can stimulate the deposition of fibrous tissue that results in peptic esophageal strictures. One goal of GERD therapy is to prevent these peptic complications, but few data directly establish the efficacy of any GERD treatment in this regard.

Randomized trials generally provide the most meaningful data on the relative efficacy of competing therapies. In the two reported randomized trials of medical and surgical therapy for GERD (the VA and Nordic studies) (17,18,22), there were no significant differences between the medical and surgical groups in the frequency of ulcerative esophagitis or in the frequency of esophageal strictures that required dilation. During the 10-13 year follow-up period of the VA study, for example, esophageal strictures requiring treatment were reported by 8% and 14% of patients in the medical and surgical groups, respectively (NS) (22). Thus, there is no clear advantage of one therapy over the other for preventing the peptic complications of GERD.

Adenocarcinoma of the esophagus is the most dreaded GERD complication. The pathogenesis of this tumor is judged to start with GERD-induced injury to the esophageal squamous epithelium (24). For reasons that are not clear, this injury heals in some individuals through the process of metaplasia in which an intestinal-type epithelium

replaces the damaged squamous one. The resulting condition, Barrett's esophagus, is predisposed to malignancy. GERD and Barrett's esophagus are the major recognized risk factors for esophageal adenocarcinoma.



Brown and Devesa. Surg Oncol Clin N Am 2002;11:235.

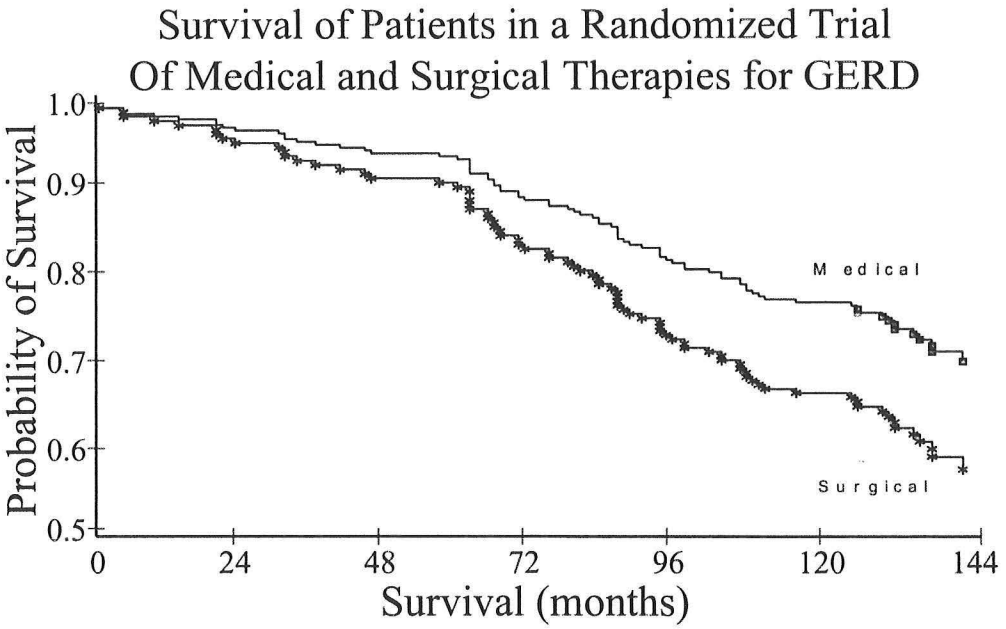
Figure 4

In 1989, my colleagues and I were the first to call attention to the rising frequency of esophageal adenocarcinoma in the United States (25). Subsequently, investigators have noted that the rate of increase in the frequency of this tumor has outpaced that of any other malignancy in this country (26-28). Among white American men, the incidence of esophageal adenocarcinoma has increased more than 500% over the past few decades (Figure 4) (28). In 1994, my group was the first to report that 18% of patients in a general endoscopy unit had short, endoscopically-inapparent segments of specialized intestinal metaplasia, the epithelium that predisposes to cancer in Barrett's esophagus, at the gastroesophageal junction (29). This finding further fueled anxiety about the burgeoning incidence of esophageal adenocarcinoma. Numerous advertisements and reports in the lay press now warn the public of the association between GERD and esophageal cancer. Concern about esophageal cancer undoubtedly underlies some of the recent interest in invasive therapies for GERD. However, there is no proof that any GERD treatment reduces the risk of esophageal cancer.

A number of arguments have been proposed to favor antireflux surgery over medical therapy for cancer prevention in GERD (30). Although medical therapy is directed almost exclusively at gastric acid control, acid is not the only potentially carcinogenic agent that refluxes into the esophagus. Indirect evidence suggests that bile, pancreatic secretions, and other noxious agents in gastric juice might promote carcinogenesis. By creating a barrier to the reflux of all gastric contents, antireflux surgery could prevent esophageal exposure to all of these potentially harmful agents. Indeed, some retrospective studies of patients with Barrett's esophagus have suggested that patients who have antireflux surgery develop dysplasia and cancer less frequently than those who receive medical therapy for GERD (31). Furthermore, acid suppression

with antisecretory agents can result in bacterial colonization in the stomach (32). These bacteria can deconjugate bile salts, and deconjugated bile salts might be particularly damaging to the esophagus when the pH of the refluxed material is in the neutral range (as it often is with potent antisecretory therapy). Also, the gastric bacteria can convert dietary nitrates to potentially carcinogenic N-nitroso compounds. Successful fundoplication would eliminate these potential problems.

The arguments favoring antireflux surgery for cancer prevention are based on indirect evidence and conjecture. Long-term data from the VA randomized trial do not support a cancer-preventive role for fundoplication (22). A primary goal of this study was to compare the mortality from esophageal cancer between the treatment groups. During the follow-up period of 10 to 13 years, 79 of the original 247 patients had died. The deaths involved 33 (40%) of the 82 surgical patients and 46 (28%) of the 165 medical patients. Survival over a period of 140 months was significantly shorter in the surgical group (P=0.047, RR 1.57, 95% CI 1.01 to 2.46) (Figure 5). For reasons that are not clear, the excess deaths in the surgical group were due to heart disease. There were only two deaths from esophageal cancer in the entire study group, both in medically-treated patients, and there was no significant difference between the groups in mortality from this tumor.



Spechler. JAMA 2001;285:2331. **Figure 5**

The incidence of esophageal cancer in the VA study was surprisingly low considering that the study group was comprised predominantly of older, white, male patients with severe GERD (i.e. individuals at highest risk for the development of esophageal adenocarcinoma) (24). The 108 study patients who had Barrett's esophagus developed this tumor at the rate of only 1 cancer per 259 patient-years (0.4% per year). The reported annual incidence of cancer in Barrett's esophagus has ranged up to 1.9%, but a recent report has suggested that the cancer risk in this condition has been overestimated because of publication bias (the selective reporting of studies that have

positive or extreme results) (33). The authors of that report estimated the annual risk of cancer in Barrett's esophagus at approximately 0.5%, a rate similar to that found in the VA study. Furthermore, the cancer incidence for the 139 study patients who had severe GERD without Barrett's esophagus was only 0.07% per year. Thus, the risk of esophageal adenocarcinoma in GERD is small. With such a low incidence of cancer development, the VA study did not have sufficient statistical power to exclude a small cancer-preventive effect for fundoplication.

Recently, a large, Swedish, population-based cohort study explored the difference in esophageal cancer development among medically- and surgically-treated patients with GERD who were followed for up to 32 years (34). The relative risk for developing esophageal adenocarcinoma (compared to the general population) among 35,274 men who received medical antireflux therapy was 6.3 (95% CI 4.5-8.7), whereas the relative risk for 6,406 men treated with fundoplication was 14.1 (95% CI 8.0-22.8). Although this retrospective study is not definitive, the data do not support the prescription of fundoplication solely as a means to prevent cancer deaths in Barrett's esophagus.

In summary, the available data show no clear advantage for surgical therapy over medical therapy for preventing the peptic and neoplastic complications of GERD.

Safety and Side Effects

The H_2RAs and proton pump inhibitors are remarkably safe medications. Mild side effects occur in fewer than 4% of patients treated with these agents, and serious side effects are rare (35). However, a number of theoretical concerns have been raised regarding the long-term safety of potent antisecretory therapy. Chronic acid suppression can elevate the serum level of gastrin (36), a hormone with trophic effects on the stomach and colon that conceivably could contribute to gastric and colonic carcinogenesis. Antisecretory treatment can result in gastric colonization with bacteria (see above) (32), and has been reported to promote gastric atrophy in patients who are infected with *H. pylori* (37). It has been proposed that suppression of bactericidal acid by PPIs might increase susceptibility to enteric infections (38), and PPI therapy has been shown to interfere with the absorption of vitamin B12 from food (39). Despite these theoretical concerns, however, there are no reports of tumors or important nutritional deficiencies clearly attributable to the use of PPIs after well over a decade of extensive clinical usage.

Fundoplication can have operative complications like esophageal perforation and bleeding, and can have long-term side effects like dysphagia, gas-bloat syndrome, and diarrhea (40). Dysphagia is the most common long-term side effect. After fundoplication, 3% to 24% of patients have dysphagia that persists beyond 3 months, or that is so severe that it requires intervention beyond dietary modifications (41). A recent study from the Mayo Clinic in Jacksonville has documented a surprisingly high frequency of bowel symptoms after fundoplication (42). Among 84 patients who responded to a telephone questionnaire after having laparoscopic fundoplication, 36% reported new bowel symptoms. In 19%, the new symptom was bloating. In 18%, the symptom was diarrhea that was associated with fecal incontinence in 4 cases.

Operative mortality is the safety issue of most concern. A review of reports on 2,453 patients who had laparoscopic Nissen fundoplications performed in expert centers described 4 deaths, a mortality rate of 0.16% (43). This suggests that approximately 1 in 600 patients dies as a result of the surgical treatment for GERD. One in 600 might be an

acceptable mortality rate for surgery to correct a life-threatening condition or to treat a severe disease for which there is no reasonable alternative therapy, but such a rate can be difficult to justify for a benign condition that responds well to safe medications.

The operative mortality rate also has important implications regarding the potential use of antireflux surgery for cancer prevention in Barrett's esophagus. One evidence-based tool that can be used to determine whether the benefits of a treatment outweigh its disadvantages is the calculation of the number needed to treat (NNT) using the formula NNT = 1/ARR (ARR is the absolute risk reduction achieved by the treatment). Assume, for the sake of argument, that antireflux surgery could reduce the risk of cancer in Barrett's esophagus by one-half, i.e. from 0.50% to 0.25% per year. This represents an absolute risk reduction of 0.25%. In this example, NNT = 1/0.25% = 400, i.e. 400 patients would need to be treated in order to prevent one cancer in one year. In this situation, the NNT approaches the surgical mortality rate. Approximately as many patients would succumb to surgical mortality as would have died from adenocarcinoma if fundoplication were recommended solely for the purpose of cancer prophylaxis in Barrett's esophagus (assuming the operation is highly effective in preventing cancer).

Convenience

It is difficult to quantify convenience, and thus it is difficult to compare GERD therapies in this regard. For most patients with GERD, the signs and symptoms of the disease can be controlled with a single PPI pill taken once a day (2). For some patients with severe GERD, as many as 6 pills per day may be needed for this purpose, presumably for lifelong (19). Some patients find this requirement for daily medication acceptable, whereas others do not. Successful fundoplication eliminates the inconvenience of taking GERD medications, but there is inconvenience involved in having the operation and recovering from it. Long-term side effects like dysphagia and diarrhea can be extremely inconvenient. Furthermore, recent data suggest that fundoplication may not be a permanent solution to the GERD problem, and that most patients will be back on antisecretory medications within 10 years (22). Some patients get permanent relief from the operation but, for many, the convenience afforded by fundoplication is short-lived. The question of the relative convenience of medical and surgical therapies is not easily answered, and therapeutic decisions based on the convenience issue should be made only after an honest and detailed discussion of reasonably expected outcomes, and careful consideration of the individual patient's personal preferences.

Costs

A number of studies have used mathematical models to compare the cost-effectiveness of medical and surgical treatments for GERD, but all of these studies have substantial limitations (44-47). Two European studies, which concluded that surgery was more cost-effective than medical therapy, did not consider the costs of surgical complications and late failures in their analyses (44,45). Another study which concluded that fundoplication was more cost-effective than medical therapy estimated the cost of fundoplication at only $3,091 Canadian dollars (47), a price that seems unrealistically low. Using a Markov model, an American group estimated the costs of medical and surgical therapies for GERD by 5 years at $6,043 and $9,426, respectively (46).

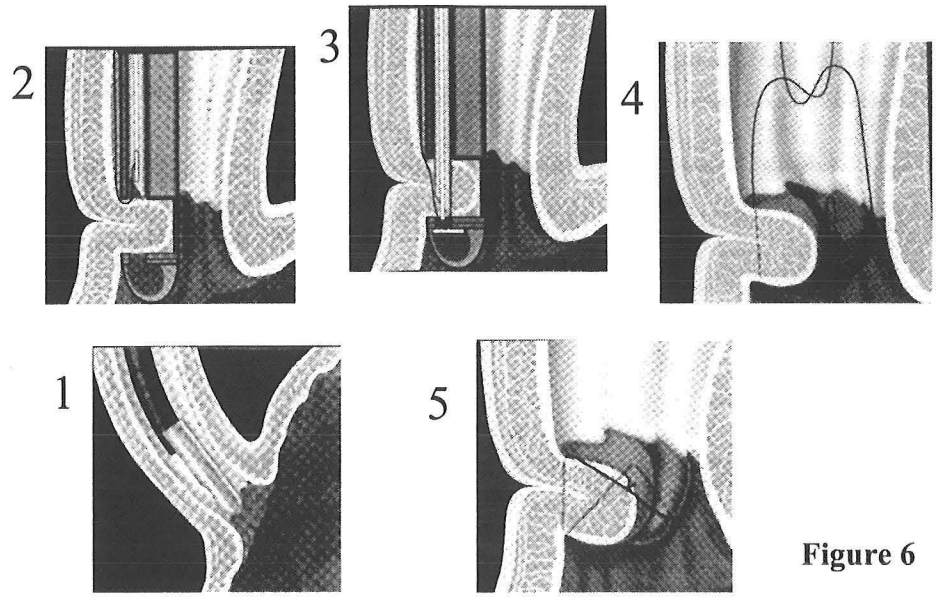


Figure 6

Although it appeared that the costs of the two therapies might equalize at 10 years, the study also assumed that patients would be permanently symptom-free after surgery.

The Nordic group that conducted the randomized trial of medical and surgical antireflux therapies discussed above recently has published a report describing treatment costs for the two groups (48). Although costs differed substantially among the various countries (Denmark, Norway, Sweden, and Finland), total costs of medical therapy were significantly lower than those of surgery for the five-year study period, especially when indirect costs such as lost productivity due to GERD-related sick leave were factored into the analyses. Thus, two of the best studies on this issue suggest that medical therapy is more cost-effective than surgical therapy at 5 years (46,48). If one considers the long-term relapse rate for antireflux surgery and the frequent use of antisecretory medications by surgical patients observed in some studies, then it seems unlikely that surgery can ever be more cost-effective than medical treatment.

Endoscopic Antireflux Procedures

Published data are available on 5 different endoscopic antireflux procedures. The Bard® endoscopic suturing system uses an endoscopic sewing machine device to plicate the gastroesophageal junction (Figure 6). The Stretta™ system delivers radiofrequency (microwave) energy that creates thermal lesions in the LES muscle (Figure 7). Enteryx® is an ethylene vinyl alcohol polymer that is injected in liquid form into the LES muscle where it hardens and incites fibrous tissue deposition (Figure 8). The Full Thickness Plicator™ uses a suturing device to create a transmural plication of tissue at the gastroesophageal junction (Figure 9). The Gatekeeper™ system delivers a polyacrylonitrile-based hydrogel prosthesis into the submucosa of the distal esophagus, where tissue water causes the prosthesis to swell and form a physical barrier to reflux (Figure 10). The Bard®, Stretta™, and Enteryx® devices have been approved for use by

the Food and Drug Administration (FDA). Approvals for the Full Thickness Plicator™ and Gatekeeper™ are pending.

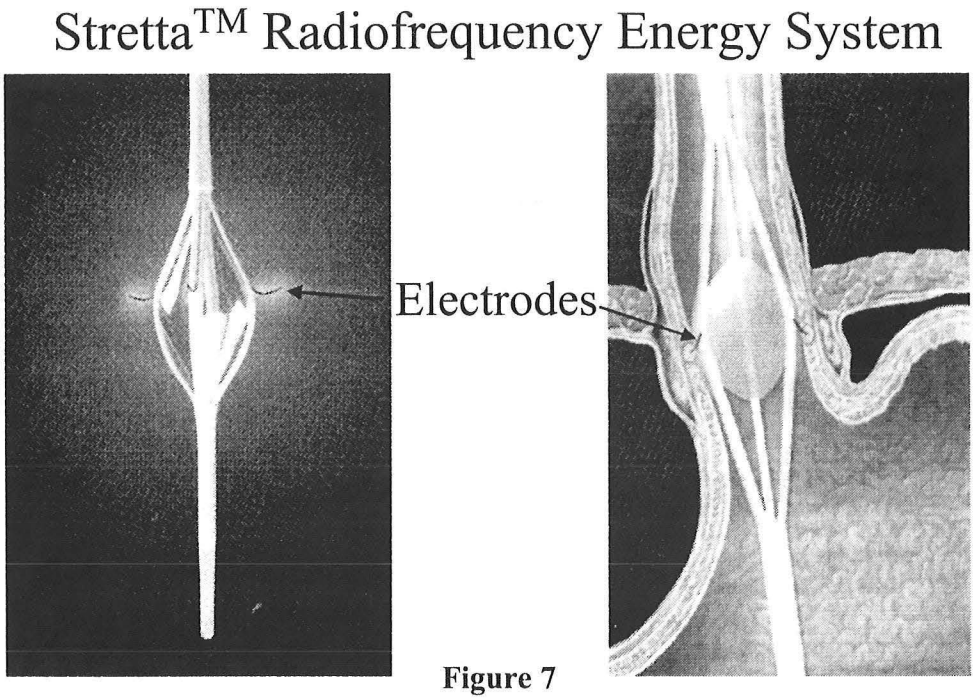


Figure 7

Most of the published information on the endoscopic antireflux procedures is available in abstract form only, and relatively few peer-reviewed reports have been published in specialty journals (49-55). To date, no peer-reviewed publication describes a controlled trial. The duration of follow-up in the published studies is short, ranging from 3 to 12 months, and patient numbers are small. In addition, the large majority of the study patients have the mildest forms of GERD with either no or only minimal esophagitis. The studies have described a number of mild and self-limited side effects, but very few serious complications (perforation, hemorrhage) and no deaths.

Presently, there are not sufficient data available to make meaningful conclusions regarding the five key features of treatments (i.e. efficacy in healing, efficacy in preventing complications, safety and side effects, convenience, and cost) for the endoscopic antireflux procedures. Non-erosive reflux disease (reflux disease without esophagitis) is an incompletely understood disorder that can have a considerable functional component and placebo response rate (56,57). With no placebo controls, therefore, the short-term efficacy of the antireflux procedures is not clear, and no long-term data are even available. Conclusions regarding the safety of the procedures also may be premature. Although the published studies describe no deaths and few serious complications, two deaths and five perforations have been reported to the FDA for one of the procedures (58). The rate with which these deaths and serious complications occurred in the community is not clear because the denominator is not provided, i.e. how many total procedures were performed. Furthermore, most published studies describe experience with fewer than 100 patients. These numbers may not be sufficient to detect a relatively low, but nonetheless substantial, procedure-related mortality such as the 1 in 600 mortality rate associated with antireflux surgery.

Enthusiasts will point out that if physicians did not have the courage to try new invasive procedures, then there would be no medical advances such as those provided by cardiac catheterization and endoscopic retrograde pancreatography. However, the history of medicine is replete with examples of procedures, like the Garren bubble for obesity, that ultimately caused far more harm than good despite the best intentions of the treating physicians (59). If a procedure is good, then it will stand through the rigors of controlled clinical trials. If the procedure is ineffective or harmful, those features may be exposed by such trials. The use of unproved procedures perhaps can be justified when treating a patient who has a life-threatening illness for which there is no effective therapy. A patient with metastatic cancer might demand a try at an unproved treatment, for example, and that might be acceptable under certain circumstances. But mild GERD is not metastatic cancer. Mild GERD is a benign disorder for which we there is effective, safe, and time-tested medical therapy. How can one condone the use of unproved and potentially hazardous invasive therapies to treat mild GERD, outside of clinical trials?

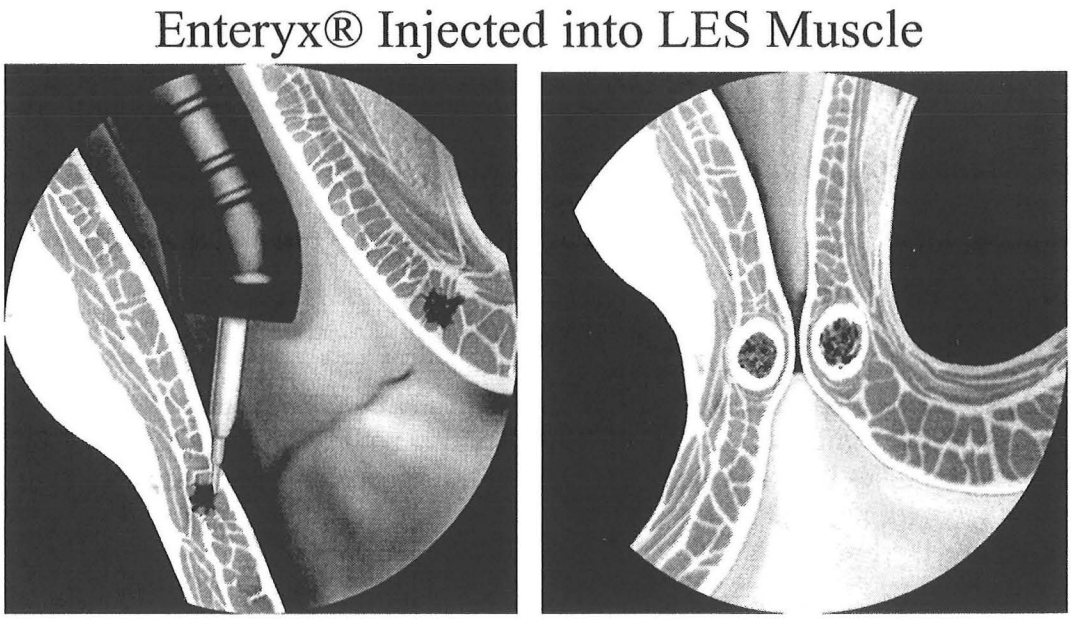


Figure 8

Conclusions

Antireflux surgery has no clear advantages over medical therapy for GERD in efficacy of healing, efficacy in preventing complications, safety and side effects, and cost. Indeed, medical therapy is safer and, probably, more cost-effective. It appears that the only benefit of surgery over medical therapy is that some patients will be less inconvenienced because they will not need to take pills on a daily basis. The patient and physician must judge whether this benefit justifies the risks of surgery for a benign condition. There is not yet sufficient data available on the endoscopic antireflux procedures to make meaningful conclusions regarding their safety and efficacy. Further studies on these procedures should be encouraged, and they should not be used outside of clinical trials.

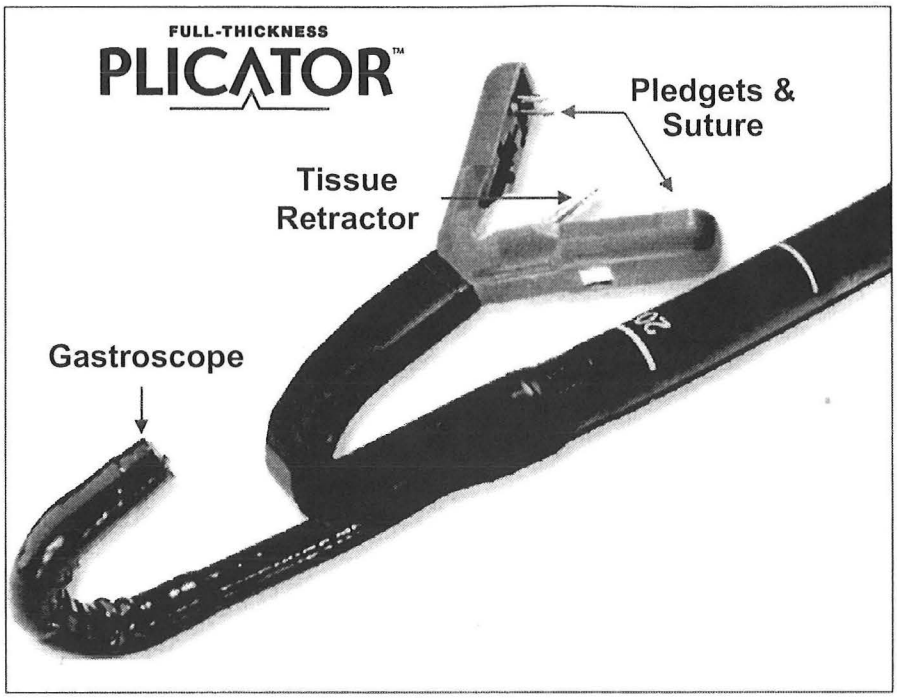
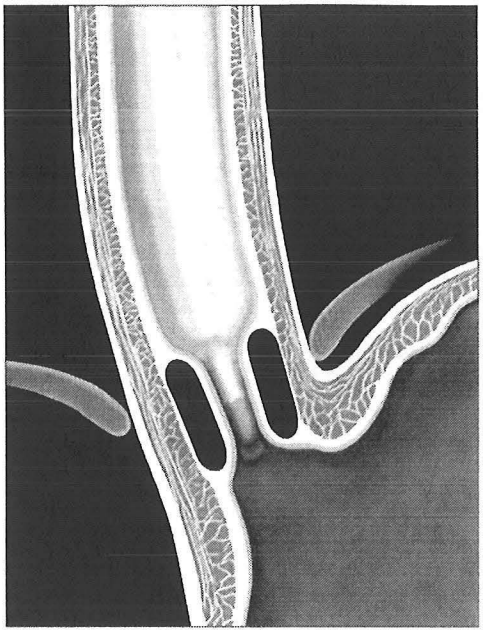
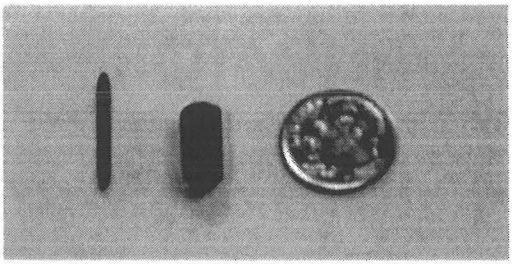


Figure 9

For patients who are interested in invasive therapy for GERD, it is important to clarify specifically what are the goals that they are trying to achieve with this treatment. For example, is the patient hoping to get relief from troublesome symptoms that are not responding to medical therapy? If that is the case, then before recommending invasive therapy the physician should ascertain that the unresponsive symptoms are in fact due to GERD, and are likely to respond to invasive treatment. For example, patients for whom regurgitation is a prominent complaint may not get adequate relief from antisecretory therapy, and may be good candidates for antireflux surgery. However, patients who have atypical symptoms that persist after adequate antisecretory therapy may have functional disorders or other problems that are unlikely to respond to procedures designed to prevent reflux. Patients who request an invasive procedure because they think it will prevent esophageal cancer should be counseled regarding their true risk for this cancer, and should be informed that a cancer-preventive role has not been established for any GERD treatment. Finally, patients who request invasive therapy because they find it inconvenient to take antisecretory medications should be informed of recent data suggesting that many patients continue to take these medications despite invasive therapy for GERD.

The Gatekeeper™ System





- Polyacrylonitrile-based hydrogel prosthesis
- Delivered into submucosa
- Expands with water
- Removable

Figure 10

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