

Long-term Outcome of Medical and Surgical Therapies for Gastroesophageal Reflux Disease

Follow-up of a Randomized Controlled Trial

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GASTROESOPHAGEAL REFLUX disease (GERD) is one of the most common chronic disorders of the gastrointestinal tract.^{1,2} Surveys have shown that approximately 20% of US adults experience GERD symptoms such as heartburn and acid regurgitation at least once per week.^{3,4} GERD and its sequela, Barrett esophagus, are strong risk factors for esophageal adenocarcinoma,^{5,6} a malignancy that has nearly quadrupled in frequency during the past 2 decades.⁷ Medical treatment of GERD involves long-term administration of antacids and antisecretory agents,⁸ and patients in the United States may spend as much as an estimated \$5 billion annually on antireflux medicines.⁹ Anti-

Context Severe gastroesophageal reflux disease (GERD) is a lifelong problem that can be complicated by peptic esophageal stricture and adenocarcinoma of the esophagus.

Objective To determine the long-term outcome of medical and surgical therapies for GERD.

Design and Setting Follow-up study conducted from October 1997 through October 1999 of a prospective randomized trial of medical and surgical antireflux treatments in patients with complicated GERD. Mean (median) duration of follow-up was 10.6 years (7.3 years) for medical patients and 9.1 years (6.3 years) for surgical patients.

Participants Two hundred thirty-nine (97%) of the original 247 study patients were found (79 were confirmed dead). Among the 160 survivors (157 men and 3 women; mean [SD] age, 67 [12] years), 129 (91 in the medical treatment group and 38 in the surgical treatment group) participated in the follow-up.

Main Outcome Measures Use of antireflux medication, Gastroesophageal Reflux Disease Activity Index (GRACI) scores, grade of esophagitis, frequency of treatment of esophageal stricture, frequency of subsequent antireflux operations, 36-item Short Form health survey (SF-36) scores, satisfaction with antireflux therapy, survival, and incidence of esophageal adenocarcinoma, compared between the medical antireflux therapy group and the fundoplication surgery group. Information on cause of death was obtained from autopsy results, hospital records, and death certificates.

Results Eighty-three (92%) of 90 medical patients and 23 (62%) of 37 surgical patients reported that they used antireflux medications regularly ($P < .001$). During a 1-week period after discontinuation of medication, mean (SD) GRACI symptom scores were significantly lower in the surgical treatment group (82.6 [17.5] vs 96.7 [21.4] in the medical treatment group; $P = .003$). However, no significant differences between the groups were found in grade of esophagitis, frequency of treatment of esophageal stricture and subsequent antireflux operations, SF-36 standardized physical and mental component scale scores, and overall satisfaction with antireflux therapy. Survival during a period of 140 months was decreased significantly in the surgical vs the medical treatment group (relative risk of death in the medical group, 1.57; 95% confidence interval, 1.01-2.46; $P = .047$), largely because of excess deaths from heart disease. Patients with Barrett esophagus at baseline developed esophageal adenocarcinomas at an annual rate of 0.4%, whereas these cancers developed in patients without Barrett esophagus at an annual rate of only 0.07%. There was no significant difference between groups in incidence of esophageal cancer.

Conclusion This study suggests that antireflux surgery should not be advised with the expectation that patients with GERD will no longer need to take antisecretory medications or that the procedure will prevent esophageal cancer among those with GERD and Barrett esophagus.

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Table 1. Baseline Characteristics of the Treatment Groups at Randomization in the Original Study (1986-1988)*

Characteristics	Continuous Medical Treatment Group (n = 77)	Symptomatic Medical Treatment Group (n = 88)	Surgical Treatment Group (n = 82)
Age, y	58 (11)	58 (12)	58 (11)
Weight, kg	85 (16)	85 (15)	85 (14)
Pulmonary function, L			
FVC	4.0 (0.9)	4.0 (1.0)	4.2 (0.9)
FEV ₁	2.9 (0.9)	3.0 (0.8)	3.1 (0.8)
GRACI symptom score	108 (25)	107 (25)	109 (23)
Endoscopic grade of esophagitis	2.9 (1.0)	2.9 (1.0)	2.9 (1.0)
24-h esophageal pH <4, %	20 (19)	23 (22)	23 (22)
No. of patients with specialized intestinal metaplasia found at baseline endoscopy	32	42	34
Stratification groups, No. of patients†			
(1) Barrett esophagus with dysplasia	3	6	5
(2) Peptic esophageal ulcer	18	20	20
(3) Peptic esophageal stricture	11	12	11
(4) Uncomplicated Barrett esophagus	27	31	27
(5) Erosive esophagitis	18	19	19

*Data are mean (SD) unless otherwise noted. There were no significant differences among the groups for any baseline characteristic. FVC indicates forced vital capacity; FEV₁, forced expiratory volume in 1 second; and GRACI, Gastroesophageal Reflux Disease Activity Index (range, 74-172; lower scores indicate fewer symptoms).

†Patients who had 1 or more of these conditions were stratified into the lowest enumerated group. For example, patients who had both peptic esophageal ulcer and uncomplicated Barrett esophagus were stratified into the peptic esophageal ulcer group.

reflux surgery (fundoplication) has become an increasingly popular form of therapy for GERD since minimally invasive (laparoscopic) surgical approaches have been developed.^{10,11} It has been estimated that 29 000 and 34 800 laparoscopic Nissen fundoplications were performed in the United States in 1998 and 1999, respectively (Synergy, a division of Quintiles Informatics, Waltham, Mass, unpublished data, March 2000).

Modern medical and surgical anti-reflux therapies are highly effective in controlling GERD symptoms,⁸ but few published data support the efficacy of any treatment in preventing GERD complications such as adenocarcinoma.¹² Some reports have suggested that fundoplication (which creates a barrier to reflux of all gastric contents) might be more effective than medical therapy (which is directed primarily at decreasing gastric acid secretion) for preventing both peptic and neoplastic complications of GERD.¹³⁻¹⁶ Two small studies (that had methodological limitations) involving pa-

tients with Barrett esophagus who received medical and surgical therapies for GERD have provided weak support for this contention by reporting fewer cases of dysplasia and cancer among surgically treated patients.^{17,18} Some have proposed that medical treatment of GERD with antisecretory agents might predispose to cancer, perhaps by promoting reflux of deconjugated bile acids,^{19,20} and that increasing use of these drugs may be contributing to the increasing frequency of esophageal adenocarcinoma.²¹ However, the limited studies that have addressed this issue directly have found no significant association between esophageal adenocarcinoma and use of antisecretory agents per se.^{22,23}

Although severe GERD is judged to be a lifelong problem, few data are available on the long-term outcome of any anti-reflux therapy. One study of patients with severe GERD treated with omeprazole for a mean of 6.5 years found that relapses occurred frequently and that patients often required increasing dosages of omeprazole (up to 120 mg/d).²⁴ Such

observations have raised questions regarding the long-term utility and cost of medical therapy for GERD. Successful antireflux surgery might obviate the inconvenience and expense of lifelong medical treatment. Some investigators have reported success rates that exceed 90% at 10 to 20 years after open fundoplication,^{25,26} whereas others have described return of reflux esophagitis in more than 50% of cases within 6 years.²⁷ However, without additional meaningful, consistent, long-term data, it is difficult to make a rational choice between medical and surgical therapy.

In the late 1980s, the Department of Veterans Affairs (VA) Cooperative Studies Program conducted a randomized trial of medical and surgical antireflux treatments for 247 patients with complicated GERD.²⁸ For the 2-year duration of the study, surgery (open Nissen fundoplication) was found to be significantly better than medical therapy (antacids, histamine₂ receptor blockers, metoclopramide, sucralfate) for controlling the symptoms and signs of GERD. This study is one of the few randomized trials of medical and surgical antireflux therapies ever reported.^{29,30} To determine the long-term outcome of GERD therapies, we conducted a follow-up study of this well-defined cohort of patients.

METHODS

From July 1986 through October 1988, the VA conducted a cooperative study of medical and surgical therapies for GERD. Patients with complicated GERD (243 men and 4 women) were instructed to implement antireflux lifestyle modifications, stratified into 1 of 5 risk groups (TABLE 1), and then randomly assigned by concealed allocation to 1 of 3 treatment groups: (1) continuous medical therapy consisting of antacid (2 tablets 1 and 3 hours after meals) and ranitidine (150 mg twice daily) regardless of symptoms, with metoclopramide (10 mg 4 times daily) and sucralfate (1 g dissolved in 10 mL of warm water, after meals) added when necessary for persistent symptoms; (2) symptomatic medical therapy con-

sisting of the medications described for the previous group but given only when necessary to control symptoms; or (3) surgical therapy consisting of open Nissen fundoplication. Treatments were continued for the duration of the study (12 to 28 months). On completion of the study, patients returned to their primary care physicians for nonstandardized GERD management.

The present follow-up study was conducted from October 1997 through October 1999. Prior to enrolling patients, all investigators met as a group to standardize procedures and evaluation methods. We determined the whereabouts of the original study patients using the VA computer database and a professional search agency (Business Information Systems, Smyrna, Ga). For patients who had died, we obtained information regarding the cause of death from all available autopsy results, hospital records, and death certificates. Surviving patients were contacted and invited to participate in the follow-up study.

GERD Symptom Scoring

The Gastroesophageal Reflux Disease Activity Index (GRACI) score used in the original study was used to assess the severity of GERD symptoms in the follow-up study. GRACI was developed in a prospective investigation that used multiple regression analysis techniques to correlate clinical data with an experienced physician's assessment of GERD activity. These were the same methods used to develop the Crohn Disease Activity Index. Details regarding development, validation, and use of the GRACI score have been published elsewhere.^{28,31} Briefly, patients maintain a standardized diary of GERD symptoms every day for 1 week, and the GRACI score is calculated by assigning weighted numerical values to certain symptoms (eg, the percentage of each day that the patient had heartburn, general severity of heartburn for that day, episodes of odynophagia, episodes of coughing or wheezing that awakened the patient from sleep). The GRACI score can range from 74 (no symptoms) to 172 (worst symptoms); published mean scores for

patients with mild, moderate, and severe symptoms are 93, 110, and 125, respectively.³¹

Patients in this study had GRACI scores determined during 2 consecutive weeks. For the first week, patients were instructed to continue, without modification, whatever antireflux regimen they had been using on a regular basis. No new antireflux therapies were started, and patients were instructed not to alter their routine lifestyle practices. For the second week, patients were instructed to discontinue all antireflux medications. No new antireflux therapies were started, and patients were instructed not to alter their routine lifestyle practices. Antacids were allowed for relief of intolerable heartburn.

Endoscopic Examination

Patients were asked to discontinue all antireflux medications for 1 week prior to the procedure. Endoscopic severity of esophagitis was graded using the scale used in the original study (grade 1, no evidence of inflammation; grade 2, erythema, friability, or both; grade 3, esophageal erosions; and grade 4, esophageal ulcers). For patients with a columnar-lined esophagus, esophageal biopsy specimens were obtained at 1-cm intervals from the squamocolumnar junction (Z-line) to the gastroesophageal junction (the most proximal level of the gastric folds). Biopsy specimens were evaluated by the study pathologist (E.L.) for epithelial type and presence of neoplasia.

24-Hour Esophageal pH Monitoring

All antireflux medications were discontinued for 72 hours before the monitoring period. The studies were performed according to standard procedures for the monitoring systems used at each of the 8 participating centers.

Completion of Follow-up Questionnaire and SF-36

Patients were questioned regarding the frequency with which they had used

medications specifically for treatment of GERD since completion of the original study. We also obtained data regarding any subsequent antireflux operations performed, symptoms of gas-bloat syndrome, satisfaction with antireflux therapies, treatments for esophageal stricture, and development of esophageal cancer.

The 36-item Short Form general health and well-being survey (SF-36) assesses 8 health issues: limitations in physical activities due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general health perception, vitality, limitations in social activities due to physical or emotional problems, limitations in usual role activities due to emotional problems, and general mental health.

Statistical Analysis

At the time of randomization into the original study, there were no significant differences among the 3 treatment groups in demographic or functional status (Table 1). The committee that planned the original study thought that it would be unethical to include a placebo treatment for patients with complicated GERD and, instead, included a control group of patients who would be treated medically only as necessary for relief of symptoms (the symptomatic medical treatment group). Those patients quickly became symptomatic when medical therapy was stopped and, consequently, the 2 medical groups received the same medications in similar dosages for the 2-year duration of the original study. The 2 medical treatment groups did not differ significantly in any outcome measured in that study, and all patients received nonstandardized GERD management after the study ended in 1988. Since the continuous and symptomatic medical treatment groups were virtually identical in baseline characteristics, study treatments, study outcomes, and subsequent management, we have combined these 2 groups into 1 medical treatment group to simplify analyses in the present follow-up study.

Primary statistical analyses in both the original and present studies were based on the intention-to-treat principle. All tests of statistical significance are 2-sided. A log-rank statistic was used to compare survival distributions between the medical and surgical treatment groups. Kaplan-Meier analysis was used to construct life-table plots.

The study was approved by the Human Rights Committee of the VA Co-

operative Studies Program Coordinating Center (Perry Point, Md) and the institutional review boards at each of the 8 participating VA medical centers. Patients who agreed to participate provided written informed consent.

RESULTS

We determined the whereabouts of 239 (97%) of 247 patients in the original

study. Seventy-nine patients were confirmed to be dead; the 160 remaining patients (157 men and 3 women) were contacted and invited to participate in the follow-up study. The mean (SD) age of surviving patients at the time of contact was 67 (12) years. Thirty-one of the 160 patients (21 [19%] of 112 medical patients and 10 [21%] of 48 surgical patients) either refused or were unable to participate in the follow-up study; 129 patients (91 medical patients and 38 surgical patients) participated in at least some of the follow-up procedures. Thus, specific follow-up data were obtained for 208 (84%; 129 survivors and 79 deaths) of the original 247 patients. Mean and median durations of follow-up (from termination of the original study to death or last contact) were 10.6 and 7.3 years, respectively, for medical patients and 9.1 and 6.3 years, respectively, for surgical patients.

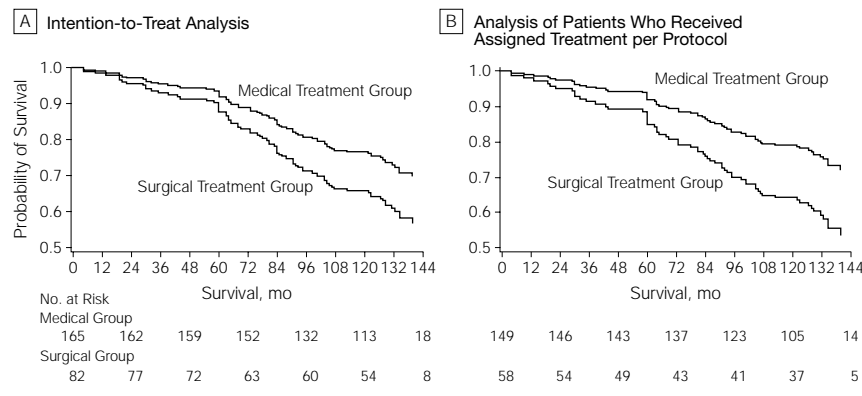
Survival

There were no surgery-related deaths in the original study. The 79 deaths that occurred during follow-up involved 33 (40%) of the 82 patients randomized to the surgical group and 46 (28%) of the 165 patients randomized to receive medical treatment. In an intention-to-treat analysis, the Cox proportional hazards model showed that survival during a period of 140 months was decreased significantly in the surgical group compared with the medical group (relative risk of death in the medical group [RR], 1.57; 95% confidence interval [CI], 1.01-2.46; *P* = .047) (FIGURE). In the original study, 24 of the 82 patients randomized to surgery and 16 of the 165 patients randomized to medical therapy refused to accept the treatments to which they were assigned. When the survival analysis was limited to the 207 patients who actually received their assigned treatments, the observed difference between the groups was greater (RR, 1.89; 95% CI, 1.14-3.13; *P* = .01) (Figure).

Causes of Death

Causes of death in the treatment groups are shown in TABLE 2. Heart disease was

Figure. Kaplan-Meier Survival Curve for Medical and Surgical Patients by Intention to Treat and for Those Who Received Treatment per Protocol



In the intention-to-treat analysis and among patients who received treatment per protocol, survival was significantly decreased in the surgical group (relative risk, 1.57; 95% confidence interval, 1.01-2.46; *P* = .047 and relative risk, 1.89; 95% confidence interval, 1.14-3.13; *P* = .01, respectively).

Table 2. Causes of Death in the Medical and Surgical Treatment Groups

Causes of Death	No. (%) of Total	
	Medical Treatment Group (n = 46)	Surgical Treatment Group (n = 33)
Heart disease	9 (20)	16 (48)*
Congestive heart failure	1 (2)	3 (9)
Myocardial infarction	2 (4)	4 (12)
Cardiopulmonary arrest	4 (9)	6 (18)
Other cardiovascular	2 (4)	3 (9)
Cerebrovascular accident	4 (9)	0
Lung failure	4 (9)	1 (3)
Cancer	10 (22)	5 (15)
Lung	2 (4)	2 (6)
Colon	1 (2)	1 (3)
Esophagus	2 (4)	0
Head and neck	1 (2)	0
Other	4 (9)	2 (6)
Pneumonia	5 (11)	1 (3)
Sepsis	4 (9)	0
Trauma	2 (4)	0
Other	1 (2)	6 (18)
Unknown	7 (15)	4 (12)

**P* = .004.

the cause of 20% and 48% of deaths in the medical and surgical groups, respectively ($P = .004$). Although deaths due to all types of heart disease were significantly more common in the surgical group, the groups did not differ significantly in frequency of any individual cardiac cause of death. Also, there were no significant differences between groups in the frequency of deaths due to any other major category of disease, including cancer of all types and esophageal cancer. There were only 2 deaths from esophageal cancer in the entire study group.

Cigarette smoking is a major factor that could influence mortality from heart disease. The observed excess mortality from heart disease was not anticipated and, consequently, data on cigarette smoking were not collected in the follow-up study. During the original study, however, there were no significant differences between the groups in the frequency of cigarette smoking (34% of the medical patients and 39% of the surgical patients were smokers; $P = .45$).

Esophageal Cancer

Five patients (all white men; 4 medical patients and 1 surgical patient) developed esophageal adenocarcinoma after a mean follow-up of 7.1 years (range, 4-12 years). There was no significant difference in the rate of esophageal cancer development between the medical and surgical groups ($P = 1.0$ by Fisher exact test). However, we calculated that a study designed to demonstrate a 50% relative reduction in risk of esophageal cancer during this period would have required a sample size of 460 patients in each treatment group (assuming a baseline cancer incidence of 0.5% per year; power = 80%; $P = .05$). Therefore, our study did not have sufficient statistical power to detect potentially important differences between groups in the rate of cancer development.

Four patients were known to have developed esophageal adenocarcinomas before the follow-up study was initiated, and 1 asymptomatic patient had cancer discovered when he underwent endoscopic evaluation as part of

Table 3. Long-term Outcomes of GERD in the Medical and Surgical Treatment Groups*

Outcomes	Medical Treatment Group	Surgical Treatment Group	P Value
GRACI score while taking medication, mean (SD)	83.1 (13.7) [n = 74]	78.7 (9.5) [n = 29]	.07
GRACI score while not taking medication, mean (SD)	96.7 (21.4) [n = 68]	82.6 (17.5) [n = 27]	.003
Endoscopic grade of esophagus, mean (SD)	1.89 (1.15) [n = 63]	1.80 (0.95) [n = 20]	.76
24-h esophageal pH <4, mean (SD) %	31.0 (61.6) [n = 38]	17.1 (41.1) [n = 10]	.50
Using antireflux medications regularly, %			
Any antireflux medication	92 [n = 90]	62 [n = 37]	<.001
Proton pump inhibitors	64 [n = 89]	32 [n = 37]	.002
Histamine ₂ receptor blockers	65 [n = 88]	41 [n = 37]	.02
Prokinetics	15 [n = 86]	8 [n = 36]	.39
≥1 Antireflux operation since end of original study, %	10 [n = 90]	16 [n = 38]	.38
Treatment for esophageal stricture since end of original study, %	8 [n = 90]	14 [n = 37]	.46

*GERD indicates gastroesophageal reflux disease; GRACI, Gastroesophageal Reflux Disease Activity Index. Numbers in brackets are the sample sizes for each outcome.

the follow-up study. Four of the 5 patients who developed cancer had Barrett esophagus with specialized intestinal metaplasia at baseline. One patient who died of metastatic esophageal adenocarcinoma had no evidence of Barrett esophagus either at baseline endoscopy or during 2 subsequent endoscopies performed at weeks 6 and 52 of the original study. Thirteen months before death, this patient's tumor was resected. We obtained the pathologic specimens from the resection and reviewed the gross photographs and histologic slides. The tumor was 8 cm in length and crossed the gastroesophageal junction, but the bulk of the adenocarcinoma (>75%) was located in the distal esophagus. Review of multiple sections revealed no specialized intestinal metaplasia in the esophagus, but the large neoplasm conceivably may have obliterated any such metaplasia. Our assessment was that the adenocarcinoma most likely originated in the distal esophagus, but the possibility that the neoplasm arose from the proximal stomach could not be excluded, as is the case for virtually any adenocarcinoma that crosses the gastroesophageal junction.³²

In the original study, 108 patients had Barrett esophagus with specialized intestinal metaplasia at entry. These 108 patients were followed up for a total of 1037 patient-years, and 4 developed ad-

enocarcinoma of the esophagus, for an incidence rate of 1 esophageal cancer per 259 patient-years of follow-up (0.4% per year). The 139 patients who had severe GERD without apparent Barrett esophagus were followed up for a total of 1357 patient-years, and 1 developed adenocarcinoma, for an incidence rate of 1 esophageal cancer per 1357 patient-years of follow-up (0.07% per year).

Long-term Outcomes of GERD

TABLE 3 summarizes the results of some long-term outcome measures of GERD. GRACI symptom scores were significantly lower in the surgical treatment group during the week when antireflux medications were discontinued. For comparison, mean (SD) GRACI scores were 89 (2) for the medical treatment group and 78 (2) for the surgical treatment group at the time of completion of the original study (after 104 weeks of therapy). After 1 week without antireflux medications, there was no significant difference in the endoscopic grade of esophagitis between the medical and surgical treatment groups.

The mean (SD) duration of acid reflux was greater in the medical treatment group (while not receiving therapy) than in the surgical treatment group (31.0% [61.6%] vs 17.1% [41.1%] of the 24-hour monitoring period), but the difference was not statistically significant. These results are

based on a relatively small sample size (because most patients refused 24-hour esophageal pH monitoring), and the SDs are large. Consequently, our data on 24-hour esophageal pH monitoring are inconclusive.

Overall, 92% of patients in the medical treatment group and 62% of those in the surgical treatment group reported that they had used antireflux medications regularly since completion of the original study ($P < .001$). Nine medical patients (10%) and 6 surgical patients (16%) had had 1 or more antireflux operations since the end of the original study ($P = .38$). Esophageal strictures requiring treatment were reported by 8% and 14% of patients in the medical and surgical treatment groups, respectively ($P = .46$).

The majority of patients in both groups were either very satisfied (67% of medical and 58% of surgical patients; $P = .42$) or satisfied (29% of medical and 31% of surgical patients; $P = .83$) with the antireflux treatments they had received since completion of the original study. When patients in the surgical group were asked to rate their satisfaction specifically with the results of the original operation, 72% said they were very satisfied, 14% were satisfied, 10% were dissatisfied, and 3% were very dissatisfied. When these same patients were asked if they would still have the operation if they could do it over again, 89% answered yes.

Patients in both treatment groups were questioned regarding symptoms that have been attributed to postfundoplication gas-bloat syndrome. There were no significant differences between groups in the frequency of any of these symptoms, including increased abdominal girth (36% of medical and 34% of surgical patients), abdominal fullness (41% of medical and 42% of surgical patients), inability to belch (20% of medical and 29% of surgical patients), and inability to vomit (20% of medical and 32% of surgical patients).

SF-36 General Health and Well-being

There were no significant differences between groups for any profile on the

SF-36 except bodily pain, which was significantly better in surgical patients (mean [SD] score, 51.7 [25.2] for medical patients vs 64.0 [28.9] for surgical patients [$P = .02$]; a higher score in this profile represents less bodily pain). No significant differences between groups were noted for the overall physical and mental component scores.

COMMENT

This study is unique in providing data on the long-term outcome of a well-defined cohort of patients who participated in a randomized trial of medical and surgical treatments for GERD. Compared with the medical treatment group, surgical patients exhibited a significant decrease in survival during the 10- to 13-year follow-up. Surgery was not the direct cause of death, and the excess late mortality resulted largely from a significant increase in deaths due to heart disease. The shortened life expectancy in surgical patients was an unexpected finding, and the study was not designed to investigate mechanisms underlying a difference in mortality rates. Consequently, the explanation for the observed excess mortality due to heart disease after fundoplication is not clear. While this issue requires further investigation, it seems prudent to advise patients who are to undergo or who have had antireflux surgery to make extra efforts to control their risk factors for cardiovascular disease.

GERD and Barrett esophagus are both risk factors for esophageal adenocarcinoma.⁵⁶ In this study, patients with Barrett esophagus developed adenocarcinoma at the rate of 1 esophageal cancer per 259 patient-years (0.4% per year). The reported annual incidence of cancer with Barrett esophagus has ranged from 0.2% to 1.9%,³³⁻³⁶ and, by pooling data from these studies, 1 widely quoted report has estimated the cancer risk in patients with this condition at 1% per year.³³ However, a recent report has suggested that the cancer risk associated with Barrett esophagus has been overestimated because of publication bias.³⁷ The au-

thors of that report have estimated the annual risk of cancer in patients with Barrett esophagus at approximately 0.5%, a rate close to the 0.4% annual incidence observed in our study and in 2 recent, prospective US studies of Barrett esophagus.^{33,38} Acceptance of this low rate of cancer incidence could have a profound influence on recommendations regarding endoscopic surveillance for patients with Barrett esophagus. Current recommendations, based on an assumed annual cancer incidence of approximately 1%, call for endoscopic surveillance at intervals of every 2 to 3 years.³⁹ A recent study using a computer model to explore the value of different surveillance strategies found that if the risk of cancer in patients with Barrett esophagus is 0.4% annually, endoscopy every 5 years would be the only reasonable surveillance strategy.⁴⁰

The Practice Parameters Committee of the American College of Gastroenterology has recommended endoscopic screening for Barrett esophagus of older patients who have chronic GERD symptoms.⁴¹ The purpose of such screening is to reduce mortality from esophageal cancer. However, 1 of the 5 patients in our study who developed esophageal adenocarcinoma had no evidence of Barrett esophagus on 3 earlier endoscopic examinations performed by study endoscopists who were specifically seeking evidence of the disorder. It is not clear whether short-segment Barrett esophagus was missed on those examinations or whether the patient indeed developed esophageal adenocarcinoma without Barrett esophagus. Nevertheless, if a substantial proportion of patients who develop esophageal adenocarcinoma do so without having endoscopically apparent Barrett esophagus, endoscopic screening programs designed to look for Barrett esophagus will have limited impact in decreasing mortality from esophageal cancer.

In our study, the cancer incidence among patients who had severe GERD without Barrett esophagus was only 0.07% per year. Furthermore, except for 2 deaths from esophageal cancer, none of the deaths in the entire study popu-

lation appeared to be a direct consequence of GERD. Thus, we found GERD to be an uncommon cause of mortality, even in our elderly population of patients with severe reflux esophagitis. We found no significant differences between treatment groups in incidence of esophageal adenocarcinoma but, with such a low incidence of this neoplasm, our study did not have sufficient statistical power to detect such differences. Even if antireflux surgery could prevent esophageal adenocarcinoma for patients with GERD, however, its use solely for this purpose cannot be sanctioned because the surgical mortality rate (at least 0.2%)¹⁰ exceeds the annual incidence of cancer (0.07%).

We found that GERD symptoms were significantly less severe in the surgical treatment group when drug therapy was discontinued but not when patients were permitted to take antireflux medications in their usual fashion. There was no significant difference in the mean endoscopic grade of esophagitis between groups, and the mean grade was in the mild category for both medical and surgical patients. However, patients had discontinued medications for only 1 week before endoscopy, and this may have been an insufficient amount of time for visible esophagitis to occur. The majority (92%) of patients in the medical treatment group continued to take antireflux medications regularly during the follow-up period, and regular use of these medications was significantly less common in the surgical treatment group. Nevertheless, 62% of surgical patients were taking antireflux medications on a regular basis. This suggests that antireflux surgery should not be advised with the expectation that patients will no longer take antisecretory medications.

During the follow-up period, a substantial number of patients in both groups had 1 or more antireflux operations (10% of medical patients and 16% of surgical patients; $P = .38$) and had treatment for esophageal stricture (8% of medical patients and 14% of surgi-

cal patients; $P = .46$). No significant differences between the groups were noted for overall physical and mental well-being as assessed by SF-36 scores. Most patients in both groups were satisfied or very satisfied with their antireflux therapy (96% of medical patients and 89% of surgical patients; $P = .24$).

The original VA Cooperative Study predated the widespread availability of proton pump inhibitors (released for general use in the United States in 1989) and laparoscopic fundoplication (introduced in 1991). Nevertheless, the results of this follow-up study are relevant for a number of reasons. First, proton pump inhibitors were available to all patients and used by most during the follow-up period, albeit in a nonstandardized fashion. Next, open fundoplication remains the surgical standard by which laparoscopic fundoplication is judged. Although the operative approaches differ, the technique of laparoscopic Nissen fundoplication is virtually identical to that of the open procedure.⁴² The laparoscopic approach has become popular not because it produces a better functional result than the open procedure but because of proposed advantages in the degree of postoperative discomfort, duration of hospital stay, and cosmetic outcome.⁴³ Two recent randomized trials of laparoscopic and open Nissen fundoplication found no significant differences in the functional results of the 2 procedures (ie, relief of GERD symptoms, reduction in esophageal acid exposure).^{44,45} However, 1 of those studies was terminated prematurely because an interim analysis showed an excess of adverse outcomes (primarily postoperative dysphagia) in the laparoscopically treated group.⁴⁵ Furthermore, at least 1 study has shown that the primary factor involved in overall patient satisfaction with antireflux surgery is relief of GERD symptoms, not operative approach.⁴⁶ Therefore, our study on the long-term outcome of open fundoplication remains highly relevant, even in this era of laparoscopic surgery.

In summary, during a follow-up period of 10 to 13 years, we found that

patients with complicated GERD who were treated with antireflux surgery were significantly less likely to take antireflux medications regularly, and, when those medicines were discontinued, their GERD symptoms were significantly less severe than those of medically treated patients. However, 62% of surgical patients took antireflux medications on a regular basis, and there were no significant differences between the medical and surgical treatment groups in rates of neoplastic and peptic complications of GERD, overall physical and mental well-being scores, and satisfaction with antireflux therapy. Patients with Barrett esophagus developed esophageal adenocarcinoma at an annual rate of 0.4%, whereas the annual rate for patients who had severe GERD without Barrett esophagus was only 0.07%. Furthermore, esophageal cancer was an uncommon cause of death. Fundoplication unexpectedly was associated with a significant decrease in long-term survival.

We conclude that antireflux surgery should not be advised with the expectation that patients will no longer take antisecretory medications or that it is clearly a cancer-preventing procedure for patients with GERD and Barrett esophagus. The low rates of esophageal cancer development and mortality due to GERD found in this prospective study call for a reevaluation of current screening and surveillance guidelines for Barrett esophagus. These findings also suggest that the first requisite for any antireflux therapy must be safety.

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REFERENCES

- Kahrilas PJ. Gastroesophageal reflux disease. *JAMA*. 1996;276:983-988.
- Orlando RC. Reflux esophagitis: an overview. *Scand J Gastroenterol*. 1995;210:36-37.
- Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. *Dig Dis*. 1976;21:953-956.
- Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997;112:1448-1456.
- Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;340:825-831.
- Falk GW, Richter JE. Reflux disease and Barrett's esophagus. *Endoscopy*. 1998;30:61-72.
- Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer*. 1998;83:2049-2053.
- DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol*. 1999;94:1434-1442.
- Jaroff L. Fire in the belly, money in the bank. *Time*. November 6, 1995. Available at: <http://www.time.com/time/magazine/archive/1995/951106/marketing.html>. Accessed April 11, 2001.
- Hinder RA, Libbey JS, Gorecki P, Bammer T. Antireflux surgery: indications, preoperative evaluation, and outcome. *Gastroenterol Clin North Am*. 1999;28:987-1005.
- Fuchs KH, Feussner H, Bonavina L, Collard JM, Coosemans W, for the European Study Group for Antireflux Surgery (ESGARS). Current status and trends in laparoscopic antireflux surgery: results of a consensus meeting. *Endoscopy*. 1997;29:298-308.
- Howden CW, Castell DO, Cohen S, Freston JW, Orlando RC, Robinson M. The rationale for continuous maintenance treatment of reflux esophagitis. *Arch Intern Med*. 1995;155:1465-1471.
- Attwood SE, Barlow AP, Norris TL, Watson A. Barrett's oesophagus: effect of antireflux surgery on symptom control and development of complications. *Br J Surg*. 1992;79:1050-1053.
- Peters JH. The surgical management of Barrett's esophagus. *Gastroenterol Clin North Am*. 1997;26:647-668.
- Ortiz A, Martinez de Haro LF, Parrilla P, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. *Br J Surg*. 1996;83:274-278.
- DeMeester SR, DeMeester TR. Columnar mucosa and intestinal metaplasia of the esophagus: fifty years of controversy. *Ann Surg*. 2000;231:303-321.
- McCallum RW, Polepalle S, Davenport K, Frierson H, Boyd S. Role of anti-reflux surgery against dysplasia in Barrett's esophagus [abstract]. *Gastroenterology*. 1991;100:A121.
- Katz D, Rothstein R, Schned A, Dunn J, Seaver K, Antonioli D. The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. *Am J Gastroenterol*. 1998;93:536-541.
- Theisen J, Nehra D, Citron D, et al. Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. *J Gastrointest Surg*. 2000;4:50-54.
- Kauer WK, Peters JH, DeMeester TR, Ireland AP, Bremner CG, Hagen JA. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone: the need for surgical therapy re-emphasized. *Ann Surg*. 1995;222:525-533.
- Wetscher GJ, Hinder RA, Smyrk T, Perdakis G, Adrian TE, Profanter C. Gastric acid blockade with omeprazole promotes gastric carcinogenesis induced by duodenogastric reflux. *Dig Dis Sci*. 1999;44:1132-1135.
- Chow WH, Findkle WD, McLaughlin JK, Frank H, Ziel HK, Fraumeni JF Jr. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA*. 1995;274:474-477.
- Garrow DC, Vaughan TL, Sweeney C, et al. Gastroesophageal reflux disease, use of H₂ receptor antagonists, and risk of esophageal and gastric cancer. *Cancer Causes Control*. 2000;11:231-238.
- Klinkenberg-Knol EC, Nelis F, Dent J, et al, and the Long-Term Study Group. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology*. 2000;118:661-669.
- DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease: evaluation of primary repair in 100 consecutive patients. *Ann Surg*. 1986;204:9-20.
- Grande L, Toledo-Pimentel V, Manterola C, et al. Value of Nissen fundoplication in patients with gastroesophageal reflux judged by long-term symptom control. *Br J Surg*. 1994;81:548-550.
- Brand DL, Eastwood IR, Martin D, Carter WB, Pope CE II. Esophageal symptoms, manometry, and histology before and after antireflux surgery: a long-term follow-up study. *Gastroenterology*. 1979;76:1393-1401.
- Spechler SJ. Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. *N Engl J Med*. 1992;326:786-792.
- Behar J, Sheahan DG, Biancani P, Spiro HM, Storer EH. Medical and surgical management of reflux esophagitis: a 38-month report of a prospective clinical trial. *N Engl J Med*. 1975;293:263-268.
- Lundell L, Miettinen P, Myrvold HE, et al. Long-term management of gastro-oesophageal reflux disease with omeprazole or open antireflux surgery: results of a prospective, randomized clinical trial. *Eur J Gastroenterol Hepatol*. 2000;12:879-887.
- Williford WO, Krol WF, Spechler SJ. Development for and the results of the use of a gastroesophageal reflux disease activity index as an outcome variable in a clinical trial. *Control Clin Trials*. 1994;15:335-348.
- Spechler SJ, Dixon MF, Genta R, Hainaut P, Lambert R, Siewert R. Adenocarcinoma of the oesophago-gastric junction. In: Hamilton SR, Aaltonen LA, eds. *World Health Organization Classification of Tumours*. Lyon, France: IARC Press; 2000:32-36.
- Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol*. 1997;92:212-215.
- Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology*. 1989;96:1249-1256.
- Bonelli L. Barrett's esophagus: results of a multicentric survey. *Endoscopy*. 1993;25:652-654.
- Robertson CS, Mayberry JF, Nicholson DA, James PD, Atkinson M. Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus. *Br J Surg*. 1988;75:760-763.
- Shaheen NJ, Crosby MA, Bozynski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology*. 2000;119:333-338.
- O'Connor JB, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. *Am J Gastroenterol*. 1999;94:2037-2042.
- Sampliner RE and the Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol*. 1998;93:1028-1032.
- Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. *Am J Gastroenterol*. 1999;94:2043-2053.
- Sampliner RE and the Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol*. 1999;94:1434-1442.
- Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. *Ann Surg*. 1994;220:137-145.
- Collard JM, De Geldere CA, De Kock M, Otte JB, Kestens PJ. Laparoscopic antireflux surgery: what is real progress? *Ann Surg*. 1994;220:146-154.
- Laine S, Rantala A, Gullichsen R, Ovaska J. Laparoscopic vs conventional Nissen fundoplication: a prospective randomized study. *Surg Endosc*. 1997;11:441-444.
- Bais JE, Bartelsman JR, Bonjer HJ, et al. Laparoscopic or conventional Nissen fundoplication for gastroesophageal reflux disease: randomised clinical trial. *Lancet*. 2000;355:170-174.
- Rattner DW, Brooks DC. Patient satisfaction following laparoscopic and open antireflux surgery. *Arch Surg*. 1995;130:289-294.