The Effect of Antireflux Surgery on Esophageal Carcinogenesis in Patients With Barrett Esophagus

A Systematic Review

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Objective: To determine whether patients with Barrett esophagus who undergo antireflux surgery differ from medically treated patients in incidence of esophageal adenocarcinoma and probability of disease regression/progression.

Summary Background Data: Barrett esophagus is a risk factor for the development of esophageal adenocarcinoma. A question exists as to whether antireflux surgery reduces this risk.

Methods: Query of PubMed (1966 through October 2005) using predetermined search terms revealed 2011 abstracts, of which 100 full-text articles were reviewed. Twenty-five articles met selection criteria. A review of article references and consultation with experts revealed additional articles for inclusion. Studies that enrolled adults with biopsy-proven Barrett esophagus, specified treatment-type rendered, followed up patients with endoscopic biopsies no less than12 months of instituting therapy, and provided adequate extractable data. The incidence of adenocarcinoma and the proportion of patients developing progression or regression of Barrett esophagus and/or dysplasia were extracted.

Results: In surgical and medical groups, 700 and 996 patients were followed for a total of 2939 and 3711 patient-years, respectively. The incidence rate of esophageal adenocarcinoma was 2.8 (95% confidence interval, 1.2–5.3) per 1000 patient-years among surgically treated patients and 6.3 (3.6–10.1) among medically treated patients ($P = 0.034$). Heterogeneity in incidence rates in surgically treated patients was observed between controlled studies and case series ($P = 0.014$). Among controlled studies, incidence rates were 4.8 (1.7–11.1) and 6.5 (2.6–13.8) per 1000 patient-years in surgical and medical patients, respectively ($P = 0.320$). Probability of progression was 2.9% (1.2–5.5) in surgical patients and 6.8% (2.6–12.1) in medical patients ($P = 0.054$). Probability of regression was 15.4% (6.1–31.4) in surgical patients and 1.9% (0.4–7.3) in medical patients ($P = 0.004$).

Conclusions: Antireflux surgery is associated with regression of Barrett esophagus and/or dysplasia. However, evidence suggesting that surgery reduces the incidence of adenocarcinoma is largely driven by uncontrolled studies.

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Esophageal adenocarcinoma occurs in an estimated 7000 patients each year in the United States, and its incidence has risen 350% since 1970.[1] Although still a relatively rare disease, esophageal adenocarcinoma is associated with a dismal prognosis, with a 5-year overall survival rate of less than 10%.[2–4] Furthermore, conventional curative treatment involves esophagectomy, which is associated with an in-hospital mortality rate of 7.5% to 14.5%[5] and a correspondingly high morbidity rate.[6]

Because of the relative rarity of esophageal adenocarcinoma and the associated morbidity of esophagectomy, a preventative strategy should focus on individuals at greatest risk for developing disease. Barrett esophagus, a complication of gastroesophageal reflux disease (GERD) characterized by esophageal mucosa metaplasia, is associated with a 30- to 125-fold increase in risk for the development of esophageal adenocarcinoma[7] and therefore represents a marker for patients at risk for disease progression. Barrett's metaplasia may progress from low-grade dysplasia (LGD), to high-grade dysplasia (HGD), and eventually to invasive adenocarcinoma, which may be present in up to 30% of cases of HGD and go unrecognized because of sampling error associated with endoscopic screening and surveillance.[8] The presence of HGD is therefore considered an indication for esophagectomy.[9]

In patients with GERD and Barrett esophagus without dysplasia, however, the appropriate choice of therapy (medical or surgical) is debated. A theoretical advantage of antireflux surgery is the creation of a mechanical valve which prevents all forms of gastroesophageal reflux. In contrast, proton pump inhibitors and histamine receptor antagonists reduce the acidity of gastric secretions but do not prevent nonacidic reflux,[10] which has been implicated in carcinogenesis.[11] These observations have fueled speculation that surgical antireflux procedures may prevent the development of

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esophageal adenocarcinoma more effectively than medical antisecretory therapy. At present, however, the indications for antireflux surgery in patients with Barrett esophagus are the same as those for patients without Barrett's, and, with the exception of the addition of endoscopic surveillance for disease progression,[12,13] do not extend beyond the goal of controlling symptoms and preventing reflux-related complications.[14] It remains unknown whether surgical therapy more effectively prevents progression of Barrett esophagus to cancer.

Several nonrandomized cohort studies have compared the incidence of esophageal cancer after antireflux surgery as compared with treatment with antisecretory medications in the setting of Barrett esophagus. To date, these studies have yielded inconsistent results, which may reflect insufficient study power due to the low incidence of disease progression. Indeed, the relatively low incidence of esophageal cancer makes it unlikely that an adequately powered controlled prospective trial will ever be possible. To synthesize the published data, we performed a systematic review of the literature to determine whether a significant conclusion can be drawn as to whether antireflux surgery is associated with a lower incidence of esophageal adenocarcinoma compared with antisecretory therapy alone.

METHODS

Search Strategy

The MEDLINE database was searched for articles from 1966 to October 2005 (Fig. 1), using the following search terms: Barrett esophagus AND (Nissen fundoplication OR antireflux surgery OR antireflux procedure OR proton pump inhibitor OR adenocarcinoma OR esophageal neoplasm) AND English[la]. Studies were identified that evaluated the incidence of adenocarcinoma in patients with Barrett esophagus treated specifically with medical or surgical therapy. The full text of these relevant articles was reviewed. The reference lists of these articles were also reviewed to find additional candidate studies. Experts (B.A.J., J.G.H.) were asked to list any additional articles that met inclusion criteria. Data extracted for this study were taken from the published reports; authors were not contacted to obtain additional information. Non-English language studies were not included.

Study Criteria

To be included, a study must have provided a description of the medical or surgical treatment rendered. The investigation must have presented sufficient data to determine the incidence of cancer (expressed in patient-years) separately for medical and surgical groups. Patients who underwent surgical treatment and were additionally treated with medical therapy were included in the surgical group. The goal of this systematic review was to evaluate the role of fundoplication in preventing progression to cancer; as such, studies that used predominantly nonstandard surgical procedures (eg, biliopancreatic diversion, Angelchik prostheses, and endoluminal therapies) were not included. All subjects must have had histologically proven Barrett esophagus and undergone surveillance endoscopy no less than 12 months after the institution of therapy. Barrett esophagus was defined as the presence of intestinal metaplasia in the distal esophagus. The length of intestinal metaplasia was not used as a criterion for inclusion in the analysis. Studies that were composed of mostly pediatric subjects (<18 years of age) were excluded. Studies were categorized into randomized controlled trials (RCTs), cohort studies, and case series. Cohort studies were defined as controlled observational studies comparing medical and surgical treatments for the study population. Case series are reports of outcomes in patients in one treatment arm (medical or surgical), without appropriate controls in a comparison arm. Some reports of controlled studies in-

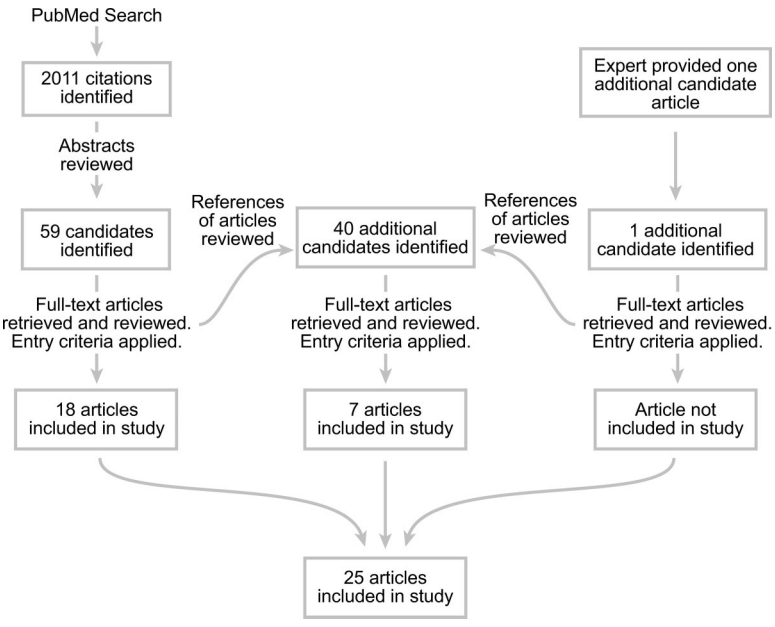

FIGURE 1. Search strategies used in systematic review and numbers of studies included at each stage.

cluded data in which adenocarcinoma incidence rate could be extracted for a subset of reported patients, even though the study was not designed to examine the question of this systematic review; these patients were included as a case series. If a cohort or case series from a group appeared to be published more than once with significant temporal overlap, only the report that included the largest number of patients was used in the analysis.

For each treatment group within a given study, we recorded the number of patients, median and range of patient-years of follow-up, and the number of subjects who developed esophageal adenocarcinoma. If available, additional data were collected on the outcomes of Barrett esophagus patients with no dysplasia, LGD and HGD, and progression or regression of disease. For this analysis, progression and regression refer to changes between the following states: HGD, LGD, nondysplastic Barrett esophagus, and squamous epithelium. Only initial and final biopsy results were considered for determination of progression and regression. Changes in the length of Barrett esophagus and the development of squamous islands were not considered in defining progression or regression.

Statistical Analysis

Data from all included studies were pooled to calculate the incidence rates of esophageal adenocarcinoma for medical and surgical treatment arms. Pooled estimates of patient age in each treatment group were calculated by taking the weighted mean ages reported in each study. For studies that reported only median ages, this value was used to approximate the mean age. Adenocarcinoma incidence rates and probability of progression or regression were compared between the 2 treatment arms. Pooled estimates and 95% credible intervals for adenocarcinoma incidence rates and progression and regression probabilities were computed under a Bayesian modeling framework.[15] Meta-regression models including a random effect for between-study variance were fitted with WinBUGS software.[16] Indicator variables for treatment arm and study design were included in the meta-regression models, which allowed for testing for differences. To assess for heterogeneity within a treatment arm, comparisons were made between controlled studies (RCTs and cohort studies) and uncontrolled studies (case series) for that treatment. Cumulative estimates and confidence intervals of adenocarcinoma incidence rates were calculated for the addition of each successive study using the Byar approximation to the Poisson.[17]

To assess the feasibility of a larger study to detect a difference in the incidence rate and probabilities of progression and regression, a simulated analysis of hypothetical studies reporting a total of 100,000 patient-years of follow up in each arm was conducted. Pooled estimates of cancer incidence and probability of progression and regression were used as inputs for this simulation. Such a larger study was considered feasible if the differences could be demonstrated to a statistically significant level in the simulation.

RESULTS

Individual Studies

A PubMed search using the specified terms yielded 2011 English-language entries (Fig. 1). Upon abstract review, 100 articles appeared to evaluate the incidence of adenocarcinoma in patients with Barrett esophagus treated surgically or medically. The full-text articles were retrieved and the inclusion criteria were reapplied. Twenty-five articles met criteria and were included. Of these studies, one was an RCT, and 4 were cohort studies. Twenty studies were either uncontrolled case series or subsets of patients from larger studies designed to investigate a different question (Table 1).

Excluded Studies

A total of 78 studies were excluded. One study was a case report of a single patient.[18] Four studies were excluded because they included patients that overlapped with another study included in this review.[19–22] Eight studies did not specify the length of follow-up.[23–30] In 3 studies, the length of follow-up was less than 12 months.[31–33] Six studies included patients with nonmetaplastic GERD and did not provide sufficient data regarding the subset of patients with Barrett esophagus.[34–39] Twenty studies did not differentiate between patients treated medically from those treated surgically.[26,27,40–57] Eight studies did not evaluate the incidence of adenocarcinoma.[58–65] Nine articles were reviews, which provided no novel clinical data.[66–74] Two articles did not document the use of endoscopic follow-up with biopsies.[23,75] Ten reports did not include enough data to express the incidence of adenocarcinoma in cases per patient-year.[76–89] One study was excluded because it did not present a mathematically consistent incidence rate of adenocarcinoma.[90] Two studies were restricted to patients with HGD or LGD.[86,91] Three studies used nonstandard surgical procedures.[29,92,93]

Pooled Data

We included 25 studies with an aggregate total of 1696 patients with Barrett esophagus. Of these patients, 700 were treated only with medical therapy (referred to as "the medically treated group") and were followed up for 3711 patient-years. The remaining 996 patients underwent antireflux surgery (referred to as "the surgically treated group") and were followed up for 2939 patient-years after therapy (Table 2). The mean age was 52.8 years in the surgical group and 59.4 years in the medical groups. Twenty-three studies reported the prevalence of LGD and HGD on initial endoscopy, although the probability of progression or regression could be extracted from only 21 of these reports.[94–116] At the baseline period for the cohorts, the prevalence of LGD was 8% in the medically treated group and 15.5% in the surgically treated group. The prevalence of HGD was 2% in the medically treated group and 0.3% in the surgically treated group. In most studies, the effectiveness of the therapy was assessed on the basis of objective testing and/or symptomatic improvement (Table 3).

TABLE 1. Studies Included in This Systematic Review and Meta-Analysis

Reference	Study Design	Treatment (patients)	No. Pts	Age (yr)	Follow-up (patient-years)	No. Cancers
Abbas et al, 2004	Case series	NF, ± partial posterior fundoplication, ± hiatal hernia repair	33	54	72.5	1
Attwood et al, 1992	Cohort	Restoration of lower esophageal sphincter and creation of flap valve per Watson	19	62	57	1
		H2RA	26	70	78	1
Bowers et al, 2002	Case series	NF, Toupet (up to 1) and Dor (up to 1); 9 also underwent KTP ablation	66	50.8	337	0
Brand et al, 1980	Case series	NF (7), Hill repair (3)	10	41.8	50	1
Chen et al, 2001	Case series	NF with Collis gastroplasty	45	53.5	180	0
Cooper et al, 1998	Case series	PPI	47	60	182	0
DeMeester et al, 1990	Case series	NF 31 (with PGV in 6), Belsey, Collis-Belsey, with esophageal resection 6 (for stricture in 4, HGD in 2)	35	59	123	0
DeMeester et al, 1998	Case series	NF (34), Toupet (1), Belsey-Mark IV 2, Collis-Belsey 8	45	53	99.5	0
Desai et al, 2003	Case series	NF, Toupet procedure	50	49	154.17	0
Drewitz et al, 1997	Case series	PPI/H2RA	170	62	807.5	4
Gurski et al, 2003	Cohort	NF (61), Collis-Belsey (14), Toupet (2)	77	54.3	322.8	0
		PPI	14	54.1	58.7	1
Hameeteman et al, 1989	Case series	PPI, H2RA, none	50	59.3	260	5
Hofstetter et al, 2001	Case series	NF, Collis-Belsey (up to 9), other (up to 3)	79	57	410	0
Low et al, 1999	Case series	Hill repair	14	51	29.283	0
Mabrut et al, 2003	Case series	Nissen-Rossetti 54%, other procedures	13	53	80.925	0
McCallum et al, 1991	Cohort	NF, Hill repair, Belsey	29	65	149.83	0
		Medical treatment, unspecified	152	62	620.67	2
O'Conner et al, 1999	Case series	PPI/H2RA	136	57.8	570	2
Oelschlager et al, 2003	Case series	Nissen ± PEHR, (6 redo Nissen), modified Toupet (up to 9)	90	50	322.5	1
Parrilla et al, 2003	RCT	Nissen (56), Collis-Nissen (2)	58	43	406	2
		PPI/H2	43	50	258	2
Sharma et al, 2000	Case series	PPI/H2/none	78	63.1	201.5	1
Srinivasaran et al, 2001	Case series	PPI ± H2RA	9	60	40.5	0
Wesdorp et al, 1981	Case series	H2RA	9	62.6	17	0
Weston et al, 1999	Case series	PPI ± cisapride, H2RA	108	61.6	362	5
Wilkinson et al, 1999	Case series	PPI	12	62	57	0
Williamson et al, 1990	Cohort	NF in 84%, 1 with esophagogastrectomy	37	52	144	3
		Medical treatment, unspecified	142	52	198	2

NF indicates Nissen fundoplication; H2RA, type II histamine receptors; PPI, proton pump inhibitor; PEHR, paraesophageal hernia repair; RCT, randomized controlled trial; PGV, proximal gastric vagotomy.

Pooled Estimates of Adenocarcinoma Incidence Rate

Because some studies reported an incidence of zero and therefore yielded an undefined confidence interval for the incidence rate of adenocarcinoma, it is not feasible to present confidence intervals of the cancer incidence rates for each study individually. Instead, graphs were constructed to show the cumulative estimates of the cancer incidence rate based on each study as it is pooled with those temporally preceding it for medically treated patients (Fig. 2a) and surgically treated patients (Fig. 2b).

When data from all included studies were pooled (Fig. 3), the median incidence of adenocarcinoma was 2.8 cases per 1000 patient-years among surgically treated patients (95% confidence interval [CI], 1.2–5.3), and 6.3 per 1000 patient-years among medically treated patients (95% CI, 3.6–10.1) ($P = 0.034$). Heterogeneity in incidence rates for surgically treated patients was observed between the controlled studies, which reported an incidence of 4.8 cases per 1000 patient-years (95% CI, 1.7–11.1), and case series, which reported an incidence rate of 1.4 cases per 1000 patient-years (95% CI, 0.3–3.9) ($P = 0.048$). When data from only the controlled studies (RCT and cohort study) were pooled, the median incidence of adenocarcinoma in the surgically treated group did not differ significantly from that of the medically treated group: 4.8 cases per 1000 patient-years (95% CI, 1.7–11.1) versus 6.5 per 1000 patient-years (95% CI, 2.6–13.8), respectively ($P = 0.32$). Among the uncontrolled studies, the median incidence of adenocarcinoma in the surgically treated group was significantly lower than that of

TABLE 2. Characteristics of Medically and Surgically Treated Groups

	Medical Treatment Group	Antireflux Surgery Group
Total no. patients	996	700
No. patients in which prevalence of dysplasia is reported	817	671
Prevalence of dysplasia		
No dysplasia	736 (90.1%)	565 (84.2%)
Low-grade dysplasia	65 (8.0%)	104 (15.5%)
High-grade dysplasia	16 (2.0%)	2 (0.3%)

the medically treated group: 1.4 cases per 1000 patient-years (95% CI, 0.3–3.9) versus 6.1 per 1000 patient-years (95% CI, 2.3–11.0), respectively ($P = 0.014$).

In 2 case series, which examined the effect of medical therapy in Barrett esophagus patients,[104,112] an unknown proportion of patients did not receive any antisecretory therapy throughout the study period. When these studies were excluded from analysis, the overall median incidence of esophageal adenocarcinoma was 2.8 per 1000 patient-years in the surgically treated group (95% CI, 1.2–5.3) and 5.8 in the medically treated group (95% CI, 3.1–9.1) ($P = 0.042$).

A widely cited cohort study by McCallum et al was included in this review,[108] which has been published only in abstract form. When the analysis was repeated excluding this study, the overall difference in cancer incidence rate between medical and surgical therapy remained statistically different (3.0 cases per 1000 patient-years among surgically treated patients versus 7.0 per 1000 patient-years among medically treated patients, $P = 0.024$).

The feasibility of a larger study to detect a difference was assessed by simulating a larger hypothetical study in which each treatment arm contained a follow-up of 100,000 patient-years. Under the conditions found in the pooled analysis of controlled studies, the predictive incidence rate difference is 1.6 more cancers per 1000 person-years in the

TABLE 3. Measures of Efficacy of Treatment and Changes With Treatment

Study	Treatment	Measure of Efficacy and Change With Treatment
Abbas et al, 2004	Surgical	Prevalence of heartburn from 92% to 4%
Attwood et al, 1992	Surgical	Median heartburn grade from 3 to 0
	Medical	Median heartburn grade from 2 to 2
Bowers et al, 2002	Surgical	Prevalence of moderate to severe symptoms from 63% to 27%
Brand et al, 1980	Surgical	pH score from 3.78 to 2.44
Chen et al, 2001	Surgical	Median no. pH episodes from 110.0 to 11.5; median percentage of time pH<4 from 10.0 to 1.0
Cooper et al, 1998	Medical	Not reported
DeMeester et al, 1990	Surgical	Symptomatic results good in 77%, fair in 20%, poor in 3%
DeMeester et al, 1998	Surgical	Symptomatic outcome was excellent or good in most patients
Desai et al, 2003	Surgical	Prevalence of heartburn from 90 to 12%
Drewitz et al, 1997	Medical	All patients treated to symptomatic control
Gurski et al, 2003	Surgical	Not reported
	Medical	Not reported
Hameeteman et al, 1989	Medical	Not reported
Hofstetter et al, 2001	Surgical	Symptomatic improvement or resolution in 90% of patients.
Low et al, 1999	Surgical	Mean DeMeester score from 158.7 to 24.5
Mabrut et al, 2003	Surgical	80% of patients asymptomatic postoperatively
McCallum et al, 1991	Surgical	Not reported
	Medical	Not reported
O'Conner et al, 1999	Medical	Not reported
Oelschlager et al, 2003	Surgical	Mean DeMeester score from 100.6 to 17.1
Parrilla et al, 2003	Surgical	Prevalence of esophagitis from 55% to 3%
	Medical	Prevalence of esophagitis from 58% to 19%
Sharma et al, 2000	Medical	Not reported
Srinivasaran et al, 2001	Medical	Mean percentage of time pH<4 treated to 0.38
Wesdorp et al, 1981	Medical	Not reported
Weston et al, 1999	Medical	Not reported
Wilkinson et al, 1999	Medical	Not reported
Williamson et al, 1990	Surgical	LES pressure normalization in 73% of patients and at least 10 mm Hg improvement in 19%.
	Medical	Not reported

Salient objective measures are presented if available. Otherwise, subjective measures are presented.

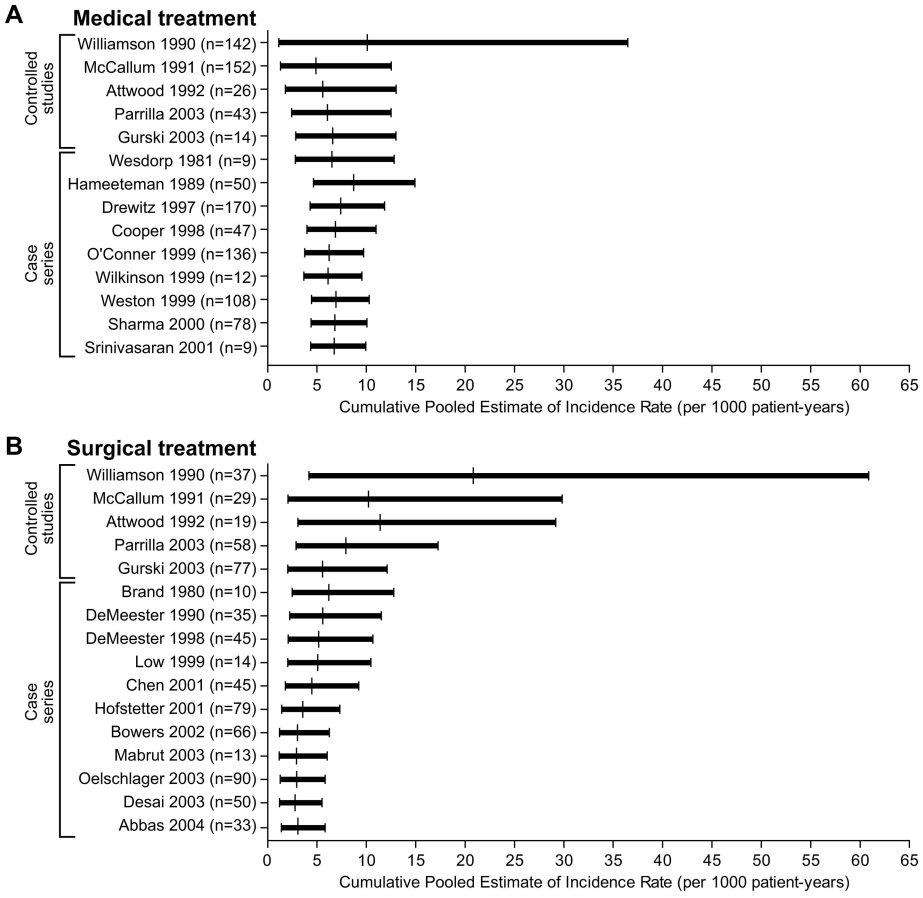

FIGURE 2. Cumulative pooled estimates of incidence of adenocarcinoma (A) for medically treated patients and (B) for surgically treated patients. Each successive row shows the cancer incidence rate and 95% confidence interval when data are pooled from that study and all studies preceding it in chronological order.

medical arm than in the surgical arm with a 95% confidence interval of −15.1 to 23.1 per 1000 person-years ($P = 0.366$).

Regression of Barrett Esophagus

Studies were pooled to estimate the proportion of patients who developed progression or regression of disease for each of the 2 groups during the follow-up period (Figs. 4 and 5). None of the included studies provided the follow-up period stratified by the initial dysplastic grade. Consequently, incidence rates of progression and regression according to initial grade of dysplasia could not be determined.

When data from all studies were pooled (Fig. 6), the probability of regression was 15.4% in surgically treated

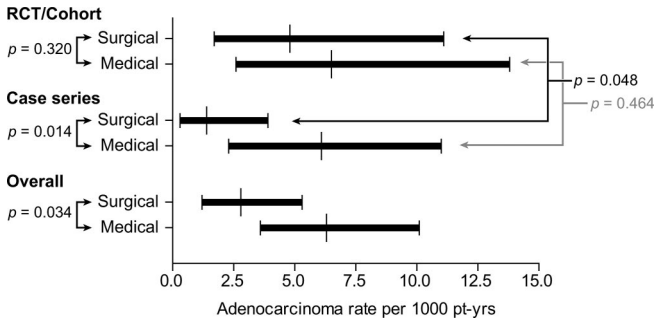

FIGURE 3. Comparison of pooled incidence rates of esophageal adenocarcinoma between surgically and medically treated patients. This comparison was repeated using only controlled studies and again using only case series. To test for heterogeneity, cancer incidence rates among each treatment group were also compared between case series and controlled studies.

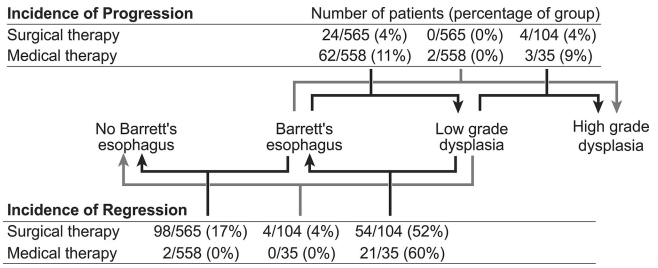

FIGURE 4. Proportions of patients with progression or regression of dysplasia and regression to squamous epithelium.

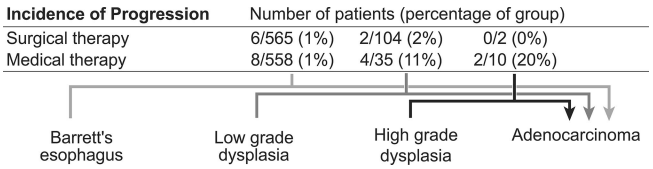

FIGURE 5. Proportions of patients progressing from each grade of dysplasia to esophageal adenocarcinoma.

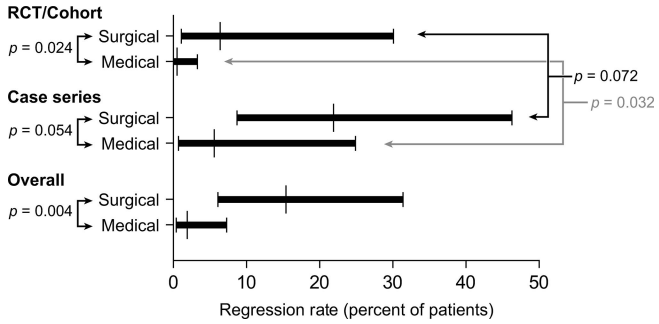

FIGURE 6. Comparison of probability of regression to lower grades of dysplasia, nondysplastic, or nonmetaplastic tissue, between surgically and medically treated patients. This comparison was repeated using only controlled studies and again using only case series. To test for heterogeneity, probability of regression was also compared between case series and controlled studies within each treatment group.

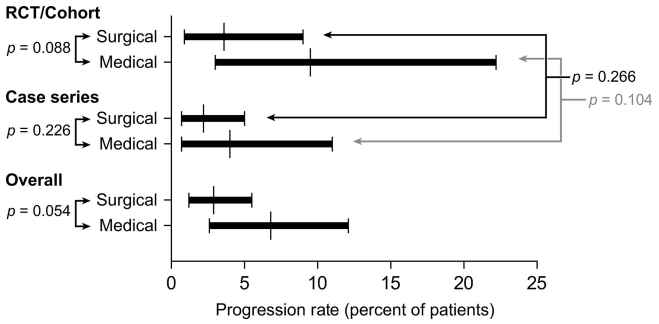

FIGURE 7. Comparison of probability of progression to more advanced grades of dysplasia, between surgically and medically treated patients. This comparison was repeated using only controlled studies and again using only case series. To test for heterogeneity, probability of progression was also compared between case series and controlled studies, within each treatment group.

patients (95% CI, 6.1%–31.4%) and 1.9% in medically treated patients (95% CI, 0.4%–7.4%) ($P = 0.004$). Among the controlled studies, 6.4% of surgically treated patients (95% CI, 1.1%–30.1%) and 0.5% of medically treated patients (95% CI, 0.0%–3.3%) demonstrated regression ($P = 0.024$). Among the uncontrolled studies, 21.9% of patients in the surgical group (95% CI, 8.7–46.3) and 5.6% of those in the medical group (95% CI, 0.7%–24.9%) demonstrated regression ($P = 0.054$). Heterogeneity was detected between the medically treated patients in controlled studies and those in case series ($P = 0.032$).

One case series by DeMeester et al[101] met the inclusion criteria for this review but did not report progression or regression for all patients in the study. Also, this study enrolled a small number of patients with HGD, who underwent fundoplication after resection of the dysplastic portion of esophagus. Therefore, any regression was likely the result of resection rather than the antireflux procedure. With the exclusion of this study, the pooled rate of regression in the case series was 25.3% (95% CI, 11.9%–44.1%) in the surgical group and 6.6% (95% CI, 1.5%–11.7%) in the medical group ($P = 0.018$). Similarly, the overall pooled regression rate was 18.6% (95% CI, 7.4%–34.7%) in the surgical group and 2.2% (95% CI, 1.5%–18.7%) for the medically treated patients ($P = 0.004$).

In 2 case series, an unknown number of patients were not treated with antisecretory medication.[104,112] When only these reports were excluded, the overall probability of regression was 15.6% (95% CI, 6.7%–30.4%) in surgically treated patients and 2.7% (95% CI, 0.5%–7.9%) in medically treated patients ($P = 0.006$).

Progression of Barrett Esophagus

When data from all studies were pooled, the probability of progression to LGD or HGD was 2.9% in surgically treated patients (95% CI, 1.2–5.5) and 6.8% in those treated medically (95% CI, 2.6–12.1) ($P = 0.054$) (Fig. 7). Among the RCT and cohort studies, probability of progression was 3.6% in the surgically treated group (95% CI, 0.9–9.0) and 9.5% in patients in the medically treated group (95% CI, 3.0–22.2) ($P = 0.088$). Among the case series, probability of progression was 2.2% in the surgically treated group (95% CI, 0.7–5.0) and 4.0% in the medically treated group (95% CI, 0.7–11.0) ($P = 0.226$).

DISCUSSION

This systematic review compares the incidence rates of esophageal adenocarcinoma in patients with Barrett esophagus treated with medical therapy versus antireflux surgery. When differences in study design are ignored, the results suggest that antireflux surgery is associated with a significantly reduced incidence rate of esophageal adenocarcinoma when compared with medically treated patients. This difference in incidence rates was maintained even after exclusion of studies in which some subjects in the medically treated arm received no antisecretory therapy.

However, heterogeneity was observed between case series and controlled studies in cancer incidence rates among patients undergoing antireflux surgery. Whereas the controlled studies reported a median incidence of 4.8 cases per 1000 patient-years for surgically treated patients, the case series demonstrated a median incidence of 1.4 cases per 1000 patient-years, a statistically significant difference. This heterogeneity suggests that the pooled estimates of cancer incidence in surgically treated patients may be artificially lowered due to publication or inclusion biases for case series. No such heterogeneity was observed among medically treated patients.

Analyzing only RCTs and cohort studies, a statistically significant difference in adenocarcinoma incidence rates could not be demonstrated between surgical and medical therapy. This lack of a detectable difference may be attributed in part to the difficulty in designing an adequately powered controlled prospective study to address such a rare disease. Under the conditions found in this systematic review, over 100,000 patient-years of follow-up in each arm would still not be sufficient to demonstrate a significant difference in observed incidence rates. Therefore, an RCT is probably infeasible.

The cumulative estimates of the incidence of adenocarcinoma among surgically treated patients demonstrate a downward shift of the incidence rate among more recent case series. A similar trend was not seen among the medically treated patients. Although this observation may be attributed to publication bias, an alternative explanation is that adenocarcinoma incidence rates may have improved with recent advances in antireflux surgery, such as the introduction of minimally invasive surgery, development of fellowship training programs, and an endemic familiarity with the procedure associated with its widespread acceptance as an effective therapy for GERD.[117–119] This hypothesis would be supported by demonstrating a temporal improvement in the efficacy of surgical therapy with respect to symptom control and normalization of distal esophageal pH. However, because the studies included in this systematic review used widely varying techniques to evaluate adequacy of therapy (Table 3), this hypothesis would be difficult to test in a retrospective fashion.

The present study calculated the incidence rate of adenocarcinoma based on the number of cases per 1000 patient-years. A limitation of this method is that no distinction is made between the incidence rate of a small number of patients followed for a long period of time and a large number of patients followed for a short length of time. Thus, this method carries the assumption that cancer risk does not vary with length of time from diagnosis of Barrett's or initiation of treatment. Because of the limitations of individual case reports, however, a more rigorous method of aggregating the data (such as a time-to-event analysis) cannot be performed.

Patients in the medically treated group were both older and had a higher prevalence of HGD when compared with the surgically treated group. Because increasing age and the presence of HGD are both risk factors for the development of esophageal adenocarcinoma,[120] one would expect a higher cancer incidence in the medically treated patients compared with surgery patients. Although this was not the case, it should be noted that, in practice, patients offered surgical therapy generally have more severe symptoms and potentially more esophageal exposure to carcinogenic refluxate. The possibility that these 2 patient populations (medically treated and surgically treated) may not be directly comparable underscores the need to account for study design when analyzing the literature.

Despite the lack of difference in disease progression, surgically treated patients demonstrated a higher incidence of disease *regression,* which was observed in 15.4% of surgically treated patients compared with 1.9% of medically treated patients. Even when only controlled studies were analyzed, the probability of developing regression was greater in surgically treated patients than in medically treated patients (6.5% vs. 0.5%, $P = 0.024$). Of note, the largest difference between surgical and medical therapy was demonstrated in the probability of regression from nondysplastic Barrett esophagus to normal squamous epithelium (17% vs. 0.4%). Regression from LGD to normal epithelium occurred in 4% of surgically treated patients and 0% of medically treated patients.

The dramatic difference in regression rates is difficult to reconcile in the face of similar cancer incidences among the 2 treatment groups in this systematic review. It is possible that the confounding effects of esophageal inflammation on making a diagnosis of dysplasia played a role in the tendency to "over-call" LGD in the surgically treated patients.[121] "Regression" in these patients may have represented the resolution of inflammation associated with surgical therapy, rather than an actual reversal of the metaplasia-dysplasia-carcinoma sequence. Indeed, the pretreatment prevalence of LGD was greater in the surgically treated group than in the medically treated group, supporting the hypothesis that patients selected for surgery may have more severe reflux disease. Alternatively, fundoplication itself may create anatomic changes, which hinder adequate esophageal sampling during surveillance endoscopy, in effect, "hiding" dysplasia from post-treatment surveillance and thus artificially lowering dysplasia rates. Arguing against this hypothesis, however, are data from DeMeester et al who reported that complete esophageal endoscopic sampling to the level of the cardia was possible after fundoplication.[100]

This systematic review demonstrates that, among controlled studies, antireflux surgery in patients with Barrett esophagus does not prevent the development of esophageal adenocarcinoma appreciably more than medical therapy. The lower pooled incidence rate of esophageal cancer after antireflux surgery is predominantly driven by case series and not controlled studies, a finding that likely reflects publication bias. The estimated reduction in incidence rate of esophageal adenocarcinoma associated with antireflux surgery when compared with medical therapy is small: 1.7 cases per 1000 patient-years, making a randomized controlled trial infeasible. Even though antireflux surgery promotes regression of Barrett esophagus, it has not demonstrably reduced the incidence rate of esophageal adenocarcinoma and therefore cannot currently be recommended as an antineoplastic procedure. A registry with carefully defined endpoints to follow the outcomes of patients with Barrett esophagus would be necessary to establish the antineoplastic effect of antireflux surgery in comparison to medical therapy.

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