Treatment modality and risk of development of dysplasia and adenocarcinoma in columnar-lined esophagus

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SUMMARY. Columnar metaplasia is the precursor lesion for esophageal adenocarcinoma, resulting from prolonged gastroesophageal reflux. The influence of the efficacy of reflux control on the development of neoplastic change in columnar-lined esophagus is not established. This study compares the rate of development of dysplasia and adenocarcinoma in patients with columnar metaplasia of the esophagus between patients treated pharmacologically and those treated with antireflux surgery. This study is a retrospective review of a cohort of patients enrolled in a multicenter national registry involving 738 patients from seven UK centers. Forty-one were treated with antireflux surgery, 42 with H2 receptor antagonist, 532 with proton pump inhibitor, and 114 with a combination of these medications. Nine had none of these medications or surgery. Total follow-up was 3697 years. Mean age and follow-up for patients treated medically were 61.6 and 4.96 years and surgically were 50.5 and 6.19 years, respectively. No patient in the surgical group developed high-grade dysplasia (HGD) or adenocarcinoma. Twenty patients treated medically developed adenocarcinoma and 10 developed HGD. Hazards ratio comparing pharmacological to surgical therapy for development of all grades of dysplasia and adenocarcinoma 1.77 (P = 0.272). Log rank test comparing antireflux surgery to pharmacological therapy for development of HGD or adenocarcinoma P = 0.1287 and for adenocarcinoma P = 0.2125. Although there was a trend towards greater efficacy of antireflux surgery over pharmacological therapy in reducing the development of dysplasia and adenocarcinoma, this did not reach statistical significance.

KEY WORDS: Antireflux surgery, Barrett’s esophagus, esophageal cancer, gastroesophageal reflux disease, proton pump inhibitors.

INTRODUCTION

The symptom of gastroesophageal reflux was the major risk factor for esophageal adenocarcinoma in a landmark epidemiological study1 with the highest risk in patients with the longest and most severe symptoms of reflux. Columnar metaplasia of the esophagus is believed to be an acquired change, secondary to prolonged gastroesophageal reflux disease exposing the esophagus to gastric and duodenal contents. The function of the lower esophageal sphincter is more defective in patients with columnar metaplasia of the esophagus compared with patients with simple reflux esophagitis or normal esophageal mucosa,2 and consequently, the magnitude of both acid1 and duodenal juice4,5 reflux are greater in patients with columnar-lined esophagus than in those with simple reflux esophagitis. Furthermore, the combination of acid and duodenal juice reflux is more strongly associated with the finding of columnar-lined esophagus than either acid or duodenal juice alone.6 The duration of the symptoms of gastroesophageal reflux,7 the frequency of symptoms,7 and the duration of individual reflux episodes8 are greater in patients with columnar-lined esophagus than in patients with simple reflux esophagitis, suggesting that these patients are at the extreme end of the spectrum of gastroesophageal reflux disease.
The magnitude of gastroesophageal reflux has been shown to be higher in patients with high-grade dysplasia (HGD) in metaplastic columnar-lined esophagus than in non-dysplastic columnar-lined esophagus. The relative risk of adenocarcinoma development in patients with columnar-lined esophagus, this view is not supported in the UK for two reasons. First, UK pathological studies have shown that where intestinal metaplasia is not demonstrated at index endoscopy, this is likely to represent sampling error since if a sufficient number of biopsies are taken over a sufficiently long time frame, intestinal metaplasia is virtually always detectable. Second, a previous study from the UK National Barrett’s Oesophagus Registry (UKBOR) has not only confirmed this, but has demonstrated a similar neoplastic risk in patients with columnar metaplasia with and without demonstrable intestinal metaplasia. The relative risk of adenocarcinoma development in patients with columnar-lined esophagus has been estimated at 5–125% that of control populations, with the overall annual adenocarcinoma risk in columnar-lined esophagus at 0.69% (range 0.0–3.6%) per annum.

Controversy has surrounded the most appropriate means of reflux control in patients with columnar-lined esophagus. While pharmacological acid suppression is the least invasive and most suitable for elderly patients and those with comorbidity, the high incidence of hiatal hernia, lower esophageal sphincter failure, peristaltic impairment, and reflux of duodenal juice renders proton pump inhibitor (PPI) therapy less effective in columnar-lined esophagus than in less severe reflux disease, with up to 40% still demonstrating pathological acid exposure after receiving up to 80 mg per day of omeprazole. Several small uncontrolled series have suggested that fundoplication (by virtue of its ability to correct hiatal hernia, lower esophageal sphincter failure, and reflux of duodenal juice) confers some protection against adenocarcinoma development, and two meta-analyses have drawn opposing conclusions as to the most efficacious management of reflux control (Table 1).

This study examines the difference in adenocarcinoma development following pharmacological acid suppression and fundoplication by a retrospective review of a large cohort of patients enrolled in the multicenter UKBOR.

### MATERIALS AND METHODS

This analysis was performed on patients who had been diagnosed with columnar-lined esophagus in seven centers throughout the UK (see Appendix I), and whose management of gastroesophageal reflux and surgical history could be established. Separate analyses were performed using both UK and US definitions of columnar-lined esophagus. The patients were all registered with UKBOR and were involved in an in-depth analysis on the natural history of columnar-lined esophagus. Registry researchers visited the centers involved and extracted information from patients’ hospital records—typically including endoscopy, histology, and operation reports, and correspondence following outpatient attendances and inpatient stays. The data were entered into a Microsoft Access database. Patients were included in the analyses of dysplasia and adenocarcinoma risk, dependent on antireflux treatment if they had histology reports demonstrating columnar-lined esophagus over at least 1 year of follow-up, and medication use during this follow-up period could be established. The date of diagnosis was considered to be the first histological confirmation of columnar-lined esophagus. Examination was made for true incident cases during follow-up (i.e. those occurring at 1 year or more from index diagnosis), and all patients with less than 1 year of follow-up were excluded from the analyses.

The overall rates of progression to the 3 ‘target’ (end-point) histological changes: low-grade dysplasia (LGD), HGD, and adenocarcinoma were examined using Kaplan-Meier survival analysis. Equality of survival functions was assessed using the log rank test and comparisons between groups were made using Cox’s proportional hazards ratio analysis (with covariates of gender, age at diagnosis, diagnostic histology [grouped as non-dysplastic columnar-lined esophagi, changes indefinite for dysplasia, LGD, HGD and adenocarcinoma], and year of diagnosis). Incidence data were modeled using an exact Poisson distribution.

Table 1: Results of meta-analyses comparing medical to surgical therapy for columnar-lined esophagus

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No. Studies</th>
<th>No. Pts</th>
<th>Total follow-up</th>
<th>No. AC</th>
<th>AC Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bammer et al</td>
<td>Medical</td>
<td>21</td>
<td>669</td>
<td>2026.3</td>
<td>14</td>
<td>1/144.7</td>
</tr>
<tr>
<td></td>
<td>Surgical</td>
<td>19</td>
<td>902</td>
<td>4121.7</td>
<td>14</td>
<td>1/294.4</td>
</tr>
<tr>
<td>Corey et al</td>
<td>Medical</td>
<td>24†</td>
<td>918</td>
<td>4906.2</td>
<td>26</td>
<td>1/188.7*</td>
</tr>
<tr>
<td></td>
<td>Surgical</td>
<td>19†</td>
<td>754</td>
<td>4678.3</td>
<td>18</td>
<td>1/259.9*</td>
</tr>
</tbody>
</table>

*P = 0.29. †Nine studies had both medical and surgical arms. AC, adenocarcinoma.
The follow-up period was defined as the period from the first histology report demonstrating columnar-lined esophagus and terminated at the earliest biopsy demonstrating the ‘target’ histology (or histology demonstrating higher grades of dysplasia than this ‘target’ histology) or (if this was not attained) the final histology report.

Patients were grouped into those treated with PPIs, histamine H2-receptor antagonists (H2RAs), both of these classes of drugs simultaneously, both of these classes of drugs sequentially, patients not taking either of these classes of drugs (neither PPIs nor H2RAs), and patients who had undergone antireflux surgery.

The number of patients (and events) in the no PPI or H2RA group was too small to allow a meaningful survival analysis. The group of patients treated with both of these classes of drugs simultaneously was also small, and so this group was combined with the group of patients treated with PPIs only. Subsequently the four treatment groups analyzed in the survival analyses were: H2RAs only, H2RAs and PPIs sequentially, PPIs (with or without simultaneous H2RAs), and antireflux surgery.

If patients had undergone an intervention to the metaplastic segment (esophagectomy, endoscopic mucosal resection, or ablation), then they were censored at the date of the histological report immediately preceding the intervention.

All statistical analyses were undertaken with SPSS and $P < 0.05$ were taken to be significant.

ETHICS PERMISSION

Approval for studies of this kind conducted by UKBOR was given by the London Multi-Centre Research Ethics Committee on March 14, 2002 number MREC/02/26.

RESULTS

Influence of antireflux and acid suppression treatment on the outcome of columnar-lined esophagus

Of the entire cohort, 738 patients fulfilled the criteria for the analyses (657 of whom had proven intestinal metaplasia). The total duration of follow-up was 3697 patient-years. Of these, the total number of patients in each treatment group, mean follow-up, gender breakdown, and the number who developed LGD, HGD, and adenocarcinoma are shown in Table 2. The majority of patients diagnosed in the earliest part of the cohort were treated with no PPIs or H2RAs during the follow-up of their metaplastic columnar-lined esophagus (medical treatment was with alkaline salts, carbenoloxone, and alginites). Thereafter, H2RAs became the treatment of choice and patients treated solely by this class of medication.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Median year of CLE diagnosis</th>
<th>N (%): patients</th>
<th>Mean follow-up (years)</th>
<th>Mean age at diagnosis (years)</th>
<th>N (%): developing LGD</th>
<th>N (%): developing HGD</th>
<th>N (%): developing AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ne-H2RA/PPI</td>
<td>1992</td>
<td>48 (1.2%)</td>
<td>61.5</td>
<td>62.5</td>
<td>3.04</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H2RA only</td>
<td>1992</td>
<td>42 (5.7%)</td>
<td>63.2</td>
<td>63.2</td>
<td>5.52</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>PPI only</td>
<td>1992</td>
<td>532 (72.1%)</td>
<td>60.1</td>
<td>60.6</td>
<td>4.47</td>
<td>75</td>
<td>23</td>
</tr>
<tr>
<td>H2RA and PPI sequentially</td>
<td>1991</td>
<td>95 (12.9%)</td>
<td>60.5</td>
<td>60.5</td>
<td>7.42</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>H2RA and PPI simultaneously</td>
<td>1991</td>
<td>19 (2.6%)</td>
<td>60.3</td>
<td>60.3</td>
<td>5.17</td>
<td>107</td>
<td>20</td>
</tr>
<tr>
<td>All pharmacological therapy</td>
<td>1992</td>
<td>697 (94.4%)</td>
<td>61.6</td>
<td>61.6</td>
<td>4.96</td>
<td>107</td>
<td>20</td>
</tr>
<tr>
<td>Antireflux surgery</td>
<td>1992</td>
<td>55 (7.4%)</td>
<td>50.5</td>
<td>50.5</td>
<td>6.19</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

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were diagnosed with columnar-lined esophagus at an average of 10 years earlier than those treated solely with PPIs. Patients treated sequentially with H2RAs followed by PPIs were diagnosed on average between those treated solely with either class of drug alone. Those treated simultaneously with both PPIs and H2RAs were diagnosed (on average) at a similar time to those treated with PPIs alone. The year of diagnosis of patients treated with antireflux surgery was, on average, 1.7 years earlier than patients treated solely with PPIs, and a mean of 5.6 years later than those treated solely with H2RAs. The median year of diagnosis of each treatment group is shown in Table 2, and to allow for any potential confounding effects of year of diagnosis, this was entered as a covariate into the survival analyses.

There was no difference in the gender breakdown of the different treatment groups (Table 2; $\chi^2$ 5 degrees of freedom $P = 0.938$). There was significant variation in follow-up of the different treatment groups (analysis of variance [ANOVA] 5 degrees of freedom $P < 0.001$), but this is allowed for in the survival analyses. Additionally, the mean age at diagnosis of columnar-lined esophagus was lower in the patients who were treated with antireflux surgery by a mean of 11.4 years compared to those treated medically (independent $t$-test $P < 0.001$). Among patients treated medically, there was no significant variation in mean age at diagnosis between treatment groups (ANOVA 3 degrees of freedom $P = 0.387$) (Table 2).

From this point forward in the analyses, the patients treated simultaneously with PPI and H2RA were pooled with those treated with PPI alone. The number of patients and annual incidence (with 95% confidence interval [CI]) of LGD, HGD, and adenocarcinoma dependent on treatment group is shown in Table 3.

### Comparison of different treatment groups and dysplasia and adenocarcinoma development

#### Development of all grades of dysplasia and adenocarcinoma

The annual incidence of LGD, HGD, and adenocarcinoma was 3.6% per annum (95% CI, 2.9–4.3). The log rank test (3 degrees of freedom) comparing all treatment groups for the development of all grades of dysplasia and adenocarcinoma was not statistically significant at $P = 0.122$. The proportional hazards ratios for the development of dysplasia or adenocarcinoma examined pairwise are shown in Table 4, and the survival graph is shown in Figure 1. There were no significant differences in the hazard of LGD development between any of the pairs of treatment groups, but a tendency toward antireflux surgery (9.8% of patients developed ‘target’ histology) in being protective over all medical treatments (15.3% of patients developed ‘target’ histology). The overall hazards ratio was 1.770 (95% CI, 0.640–4.897, $P = 0.272$) comparing all medical groups with antireflux surgery.

When patients without intestinal metaplasia were excluded, the log rank test (3 degrees of freedom) comparing all treatment groups for the development of all grades of dysplasia and adenocarcinoma was not statistically significant at $P = 0.0729$, and there

### Table 3

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>All dysplasia/AC (95% CI for annual incidence)</th>
<th>HGD/AC (95% CI for annual incidence)</th>
<th>AC (95% CI for annual incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2RA only</td>
<td>3.3% (1.3–6.7)</td>
<td>1.7% (0.5–4.4)</td>
<td>1.7% (0.5–4.4)</td>
</tr>
<tr>
<td>PPI+/-simultaneous H2RA</td>
<td>4.0% (3.2–5.0)</td>
<td>0.9% (0.6–1.4)</td>
<td>0.5% (0.3–0.9)</td>
</tr>
<tr>
<td>H2RA and PPI sequentially</td>
<td>2.9% (1.7–4.7)</td>
<td>0.4% (0.1–1.2)</td>
<td>0.4% (0.1–1.2)</td>
</tr>
<tr>
<td>All pharmacological therapy</td>
<td>3.7% (2.9–4.3)</td>
<td>0.8% (0.6–1.2%)</td>
<td>0.5% (0.3–0.8)</td>
</tr>
<tr>
<td>Antireflux surgery</td>
<td>1.7% (0.5–4.3)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Overall</td>
<td>3.6% (2.9–4.3)</td>
<td>0.8% (0.6–1.2)</td>
<td>0.5% (0.3–0.8)</td>
</tr>
</tbody>
</table>

†CI for exact Poisson distribution. AC, adenocarcinoma; HGD, high-grade dysplasia; CI, confidence interval; H2RA, H2-receptor antagonists; PPI, proton pump inhibitor.

### Table 4

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>$P$-value</th>
<th>Hazards ratio</th>
<th>95% CI for hazards ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI+/-simultaneous H2RA vs. antireflux surgery</td>
<td>0.200</td>
<td>1.964</td>
<td>0.699–5.516</td>
</tr>
<tr>
<td>H2RA only vs. antireflux surgery</td>
<td>0.514</td>
<td>1.533</td>
<td>0.425–5.532</td>
</tr>
<tr>
<td>H2RA and PPI sequentially vs. antireflux surgery</td>
<td>0.671</td>
<td>1.521</td>
<td>0.219–10.532</td>
</tr>
<tr>
<td>H2RA and PPI sequentially vs. PPI+/-simultaneous H2RA</td>
<td>0.297</td>
<td>0.736</td>
<td>0.413–1.310</td>
</tr>
<tr>
<td>H2RA only vs. PPI+/-simultaneous H2RA</td>
<td>0.509</td>
<td>1.753</td>
<td>0.324–1.748</td>
</tr>
<tr>
<td>H2RA only vs. H2RA and PPI sequentially</td>
<td>0.240</td>
<td>1.767</td>
<td>0.684–4.562</td>
</tr>
<tr>
<td>All medical therapy vs. antireflux surgery</td>
<td>0.272</td>
<td>1.770</td>
<td>0.640–4.897</td>
</tr>
</tbody>
</table>

CI, confidence interval; PPI, proton pump inhibitor; H2RA, H2-receptor antagonists.

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were no significant differences in the hazard of LGD development between any of the pairs of treatment groups. There was a tendency toward antireflux surgery (11.1% of patients developed ‘target’ histology) being protective over all medical treatments (17.2% of patients developed ‘target’ histology), with an overall hazards ratio of 1.593 (95% CI, 0.571–4.445, \( P = 0.374 \)) comparing all medical groups with antireflux surgery.

**Development of HGD and adenocarcinoma**

The overall incidence of HGD and adenocarcinoma was 0.8% per annum (95% CI, 0.6–1.2). The examination for the development of HGD and adenocarcinoma (but not LGD) produced much wider CIs because of the smaller number of patients developing these target histology groups and a log rank test (3 degrees of freedom) demonstrating only weak evidence of a difference between treatment groups at \( P = 0.0799 \). As there were no events in the antireflux surgery group, Cox’s proportional hazards ratio could not be evaluated. There was a trend for a higher hazard associated with treatment with H\(_2\)RA compared with PPI (with or without simultaneous H\(_2\)RA), and a statistically significant difference in hazard for patients treated with a H\(_2\)RA compared with patients treated sequentially with H\(_2\)RA and PPIs (hazards ratio 354). Using the log rank test (1 degree of freedom) to compare the difference in risk between antireflux surgery (0% of patients developed ‘target’ histology) and all medical therapies (4.3% of patients developed ‘target’ histology) yielded \( P = 0.1287 \). These results are shown in Table 5 and Figure 2.

When patients who did not have intestinal metaplasia were excluded, the log rank test (3 degrees of freedom) demonstrated only weak evidence of a difference between treatment groups at \( P = 0.1658 \). Using the log rank test (1 degree of freedom) to compare the difference in risk between antireflux surgery (0% of patients developed HGD/adenocarcinoma) and all medical therapies (4.8% of patients developed HGD/adenocarcinoma) yielded \( P = 0.1388 \).

**Development of adenocarcinoma**

The only patients who had the detection of HGD during the course of the follow-up were in the PPIs with or without simultaneous H\(_2\)RAs group; consequently, for the most part, the results for all other pairs are similar to the analyses for the hazard of HGD and adenocarcinoma development. The annual incidence of adenocarcinoma was 0.5% per annum (95% CI 0.3–0.8). The log rank test (3 degrees of freedom) comparing all treatment groups showed a trend for a difference in risk between groups \( (P = 0.0623) \). The hazard of adenocarcinoma development was significantly higher in patients treated

![Fig. 1](image-url) Development of dysplasia and adenocarcinoma (AC) dependent on treatment group.

Table 5  Hazards ratios for high-grade dysplasia and adenocarcinoma development between treatment groups

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>( P )-value</th>
<th>Hazards ratio</th>
<th>95% CI for hazards ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)RA and PPI sequentially vs. PPI+/−simultaneous H(_2)RA</td>
<td>0.069</td>
<td>0.308</td>
<td>0.086–1.095</td>
</tr>
<tr>
<td>H(_2)RA only vs. PPI+/−simultaneous H(_2)RA</td>
<td>0.610</td>
<td>1.385</td>
<td>0.396–4.842</td>
</tr>
<tr>
<td>H(_2)RA only vs. H(_2)RA and PPI sequentially</td>
<td>0.022</td>
<td>354.015</td>
<td>2.296–54587.186</td>
</tr>
</tbody>
</table>

CI, confidence interval; H\(_2\)RA, H\(_2\)-receptor antagonists; PPI, proton pump inhibitor.

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with H2RA only over patients treated initially with this class of drug followed sequentially by PPIs (with the same results as those for the development of HGD and adenocarcinoma). Using the log rank test (1 degree of freedom), the comparison of patients who had undergone antireflux surgery (0% of patients developed ‘target’ histology) to those treated with medical therapy (2.9% of patients developed ‘target’ histology) did not demonstrate any significant difference in the risk between medical and surgical treatments, \( P = 0.2125 \) (Table 6 and Fig. 3).

When patients who did not have intestinal metaplasia detected were excluded, the log rank test (3 degrees of freedom) comparing all treatment groups did not demonstrate a significant difference in risk between groups \( (P = 0.2502) \). Using the log rank test

### Table 6 Hazards ratios for adenocarcinoma development between treatment groups

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>( P )-value</th>
<th>Hazards ratio</th>
<th>95% CI for hazards ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2RA and PPI sequentially vs. PPI+/– simultaneous H2RA</td>
<td>0.196</td>
<td>0.401</td>
<td>0.100–1.603</td>
</tr>
<tr>
<td>H2RA only vs. PPI+/– simultaneous H2RA</td>
<td>0.660</td>
<td>1.385</td>
<td>0.324–5.911</td>
</tr>
<tr>
<td>H2RA only vs. H2RA and PPI sequentially</td>
<td>0.022</td>
<td>354.015</td>
<td>2.296–5487.186</td>
</tr>
</tbody>
</table>

CI, confidence interval; H2RA, H2-receptor antagonists; PPI, proton pump inhibitor.

![Fig. 2](image) Development of high-grade dysplasia (HGD) and adenocarcinoma (AC) dependent on treatment group.

![Fig. 3](image) Development of adenocarcinoma (AC) dependent on treatment group.
(1 degree of freedom), the comparison of patients who had undergone antireflux surgery (0% of patients developed ‘target’ histology) with those treated with medical therapy (2.9% of patients developed ‘target’ histology) did not demonstrate any significant difference in risk between medical and surgical treatment, \( P = 0.2204 \).

**DISCUSSION**

**Treatment of columnar-lined esophagus**

The goal of treatment of columnar-lined esophagus is to prevent non-neoplastic complications and development of dysplasia and adenocarcinoma by control of gastroesophageal reflux while maintaining a healed mucosa.\(^9\) The escalating incidences of columnar-lined esophagus\(^{30–35}\) and adenocarcinoma\(^{36–48}\) have significant implications for the cost of surveillance,\(^{49–52}\) treatment of gastroesophageal reflux,\(^{49,50}\) and treatment of neoplastic complications.\(^{49,50,55}\) Patients with columnar-lined esophagus are among those with the most severe gastroesophageal reflux disease,\(^{2,3,7,8,53,54}\) and adequate control of reflux is difficult.\(^{20,22,23}\) Medical therapy does not prevent biliary reflux into the esophagus\(^{6,55}\) and only surgical (mechanical) correction of the defective gastroesophageal sphincter can abolish this.\(^{56,57}\) The findings of columnar-lined esophagus development in patients with gastroesophageal reflux disease taking antireflux medication,\(^{30,59}\) and subsequent development of adenocarcinoma clearly call for more aggressive measures to prevent carcinogenic reflux. While surgery is effective in the short-term at preventing reflux, the long-term failure rate\(^{60,61}\) may overcome the early benefits; a proportion of these patients may subsequently require medical therapy or even revisional antireflux surgery. This cohort showed that the treatment trends over time had altered with regard to medical therapy, with the PPIs only being used in the latter part of the cohort, and antireflux surgery being used throughout the cohort.

**Efficacy of medical treatment compared with surgical treatment**

The overall hazard ratio comparing all medical with surgical therapy for the development of all dysplasia and adenocarcinoma was 1.770 (95% CI 0.640–4.897). No hazards ratio could be evaluated for the development of HGD and adenocarcinoma between patients treated with antireflux surgery and medical therapy due to there being no patients in the surgical group who developed these changes in the cohort. There were statistically higher risks of development of HGD and adenocarcinoma or adenocarcinoma alone in the H2RA group compared with the group of patients treated with H2RAs followed by PPIs. This latter group had a very low hazard of either HGD or adenocarcinoma development. The only difference between the hazards ratios calculated between the development of HGD and adenocarcinoma and adenocarcinoma alone was because of the 10 patients in the PPI (with or without H2RA) group who developed HGD. Many of these patients treated medically who developed HGD underwent an intervention such as photodynamic therapy at this point (accounting for the difference between the outcome measures of HGD or adenocarcinoma and adenocarcinoma alone) and causing termination of follow-up as defined in the methods of this study. No cases of true incident adenocarcinoma (occurring at least 1 year after the diagnosis of columnar-lined esophagus) occurred in the antireflux surgery group. There were patients who did develop adenocarcinoma following antireflux surgery, who are interesting to examine. The first had undergone antireflux surgery 27 years prior to columnar-lined esophagus diagnosis, which required subsequent revisional surgery due to failure of the initial procedure, and it is likely that he had significant reflux due to failure of surgical control. The second had an Angelchik prosthesis inserted 5 months after the diagnosis of columnar-lined esophagus and was diagnosed with adenocarcinoma 2 months later. It is probable that the tumor had already developed by the time of the antireflux surgery in this patient, and this tumor was only detected after growth subsequent to the surgery.

While the younger ages of the patients in the antireflux surgery group will have produced a significant confounding effect, using the surrogate outcome measure of all dysplasia and adenocarcinoma (Table 3 and Fig. 1) demonstrated a trend for lower rates of all dysplasia in the surgical group. This still suggests a probable superior long-term protective effect of antireflux surgery compared with patients treated with all medical therapies that did not reach statistical significance because of the small numbers in this group, with similar results when patients without demonstrable intestinal metaplasia were excluded. There was no significant difference in segment length (which we have previously demonstrated as a marker of risk\(^{65}\)) between treatment groups (ANOVA, 3 degrees of freedom, \( P = 0.324 \)).

The groups were not controlled for the severity of reflux at commencement of treatment as measured by esophageal physiological studies, and once treatment was commenced, there was no control to ensure that patients had adequate reflux control. Furthermore, there was no examination of whether patients treated surgically were also medicating with over-the-counter antacids or prescribed antireflux medications (62% in one large series of gastroesophageal reflux disease,\(^{63}\) but a further study demonstrated that very few of this group had either proven reflux or true reflux symptoms).\(^{64}\) Approximately one-half of the patients who underwent antireflux surgery did so before the diagnosis of columnar-lined esophagus was made, and
one-half after this diagnosis. This may have been because of the failure to recognize the metaplastic segment prior to antireflux surgery or its development following surgery (many subjects had their antireflux surgery within a year of diagnosis of columnar-lined esophagus, and of those who underwent surgery over a year prior to columnar-lined esophagus, the majority had failure of the surgical procedure or reversal of the procedure). Clearly in these circumstances, this study cannot support the hypothesis that antireflux surgery reliably prevents the development of esophageal columnar metaplasia.

The results of this study are similar to both meta-analyses (Table 1). The adenocarcinoma incidence reported by Bammer et al. for patients treated medically was 0.7% per annum (95% confidence limits for exact Poisson distribution calculated at 0.2 and 1.2%), and for surgical therapy was 0.3% per annum (95% confidence limits calculated at 0.2 and 0.6%). Corey et al. reported an annual adenocarcinoma incidence in patients treated medically at 0.5% (95% confidence limits calculated at 0.3 and 0.8%), and for patients treated surgically, 0.4% per annum (95% confidence limits calculated at 0.2 and 0.6%). Parilla et al. did not demonstrate any overall benefit on antireflux surgery over medical therapy in preventing HGD or adenocarcinoma in Barrett’s esophagus, but no cases of HGD occurred in patients treated with antireflux surgery who had a competent repair. Spechler et al. did not demonstrate any difference in adenocarcinoma risk in patients with gastroesophageal reflux disease randomized to medical and surgical therapy, but there was higher mortality in the surgical group (due mainly to deaths from cardiovascular causes), and a significant proportion of patients crossed-over between groups after randomization.

Sources of error

This study was purely observational, with no influence upon individual centers or clinicians’ management as far as either treatment or surveillance practice. Consequently, there was no randomization or control of either the timing or type of treatment. Specific medication prescribed, dosing, frequency, and neither compliance of patients treated medically were examined, nor was type of antireflux surgery and the approach (transabdominal, transthoracic, thoracoabdominal, or laparoscopic) to the procedures (although this is less important than whether effective antireflux control was achieved, which was not routinely confirmed in this study).

Bias for treatment in patients with what is perceived to be the most severe disease and highest cancer risk may have caused these patients to be treated with specific therapies – which could not be controlled for in the analyses. Patients were grouped by lists of prescribed medications on any date within the follow-up period, which (with the exception of the sequential treatment group) did not ensure continuous treatment or allow for variations in dosage. The study also could not evaluate prescription information held only by the patients’ general practitioners, and it was not possible to examine compliance with the prescribed medication and whether this related to the risk of development of dysplasia and cancer. Furthermore, it is possible that patients who have fundoplication feel better, and hence seek less medical attention, and hence appear to have a longer time to dysplasia.

The hazards analyses have controlled for any confounding effects of gender, age at columnar-lined esophagus diagnosis, year at diagnosis, and diagnostic histology. However, it should be noted that the patients treated with antireflux surgery were younger than those treated medically by a mean of 11.1 years, and although their malignant risk at this age is lower than that of older patients, they are also the patients who have the longest period of gastroesophageal reflux ahead of them. The group of patients treated with neither H2RA nor PPI and the group of both H2RA and PPI simultaneously were both small, so consequently, the evaluation of proportional hazard in these groups alone was not appropriate.

Because of the low risk of HGD and adenocarcinoma, the power of this study to detect differences was limited and subject to type II statistical error. The small number of events (development of dysplasia or adenocarcinoma) produced the wide CI evaluated in the incidence analyses. Short follow-up (especially in the no H2RA or PPI group) also contributed to the small number of patients developing dysplasia or adenocarcinoma and potential for error in this analysis. The shorter follow-up of the group treated with no H2RAs or PPIs also narrowed the window, during which a medication report could be found in this group, and this may also have had a confounding effect on this group that showed a trend to have a higher hazard of development of dysplasia or adenocarcinoma. A power calculation showed that to demonstrate a significant difference between the groups treated by medical and surgical therapies would require a further 57 patients in the surgical arm.

Only patients with histological follow-up were included in the analyses. This may overestimate the risk of adenocarcinoma development as it excludes patients undergoing follow-up who were not biopsied. Clinicians may also have elected only to follow-up those patients who they perceived to be at greatest risk of dysplasia or carcinoma development (such as those with the longest metaplastic segments or dysplasia), or excluded other patients who would not be candidates for esophageal resection.

The centers practiced independently, determining their own frequency of surveillance endoscopy, biopsy protocol, and verification of histopathological reporting. This will have allowed variations in
sampling error and interobserver variability in histopathological interpretation of biopsy samples. However, the large number of patients involved and pooling of data between centers will have reduced each of these effects.

In conclusion, this large cohort study adds to the number of uncontrolled series that have demonstrated a trend toward reduced incidence of adenocarcinoma in columnar-lined esophagus patients treated with antireflux surgery compared with those treated by pharmacological reflux control. However, the failure to reach statistical significance means that fundoplication cannot be advocated on the basis of cancer prevention, and standard indications for fundoplication in gastroesophageal reflux disease must apply. Furthermore, patients with columnar-lined esophagus who have undergone antireflux surgery should still be offered endoscopic surveillance. The severity of reflux disease in columnar-lined esophagus patients, however, means that these indications will be fulfilled more frequently in columnar-lined esophagus patients compared with those with uncomplicated gastroesophageal reflux disease, and therefore, fundoplication needs to be carefully considered in younger patients with columnar-lined esophagus. Only a carefully controlled prospective randomized trial with sufficient statistical power will determine whether fundoplication has a protective effect for adenocarcinoma development in columnar-lined esophagus patients.

CONCLUSION

Although there was a trend towards greater efficacy of antireflux surgery over pharmacological therapy in reducing the development of dysplasia and adenocarcinoma, this did not reach statistical significance.

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References


APPENDIX I

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