Adenocarcinoma of the Esophagus With and Without Barrett Mucosa

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Hypothesis: Previous studies have demonstrated an improved prognosis in patients with Barrett adenocarcinoma as compared with esophageal adenocarcinoma without Barrett. It has been suggested that an earlier presentation due to gastroesophageal reflux disease (GERD) may lead to detection of adenocarcinoma at an earlier stage.

Design: The records of 178 patients with esophageal adenocarcinoma presenting to Roswell Park Cancer Institute (Buffalo, NY) between 1991 and 1996 were reviewed.

Main Outcome Measures: The clinical presentation, work-up, therapy, and outcome were compared between patients with Barrett esophagus (n=66) and those without endoscopic or pathologic evidence of Barrett esophagus (n=112).

Results: There were several favorable prognostic signs in the Barrett group, including smaller tumors, lower grade, and earlier stage. More patients in the Barrett group had surgically resectable tumors, resulting in an improved overall survival. However, there were no differences in the type or duration of symptoms. Overall, very few patients presented because of GERD, and only slightly more in the Barrett group (14% vs 4%). While survival greatly improved in patients diagnosed with Barrett due to GERD, this did not account for the difference in prognosis.

Conclusions: Improved prognosis and survival for the Barrett group is not due to earlier presentation due to symptoms of GERD. It is more likely that all esophageal adenocarcinoma arises from Barrett esophagus, and that it is obscured by larger tumors. Reviews limited to resected patients greatly overestimate the number of adenocarcinoma cases diagnosed due to GERD. Increased efforts to identify high-risk patients and initiate screening are necessary to diagnose adenocarcinoma at an earlier stage.

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The incidence of cancer of the esophagus has been steadily rising, primarily due to the rapid increment of adenocarcinomas. It is estimated that in 1999 there will be 12,500 new cases and 12,200 deaths due to esophageal cancer. At our own institution, the number of new cases has been steadily rising during the last 26 years. Esophageal cancer was the seventh most common site of cancer among newly diagnosed patients in 1997. Adenocarcinoma has surpassed squamous cell carcinoma as the most common type of esophageal cancer. In 1997, 59% of the esophageal cancer cases seen at Roswell Park Cancer Institute (Buffalo, NY) were adenocarcinomas.

The clearest known risk factor for adenocarcinoma of the esophagus is Barrett esophagus (BE). Barrett esophagus develops when the normal squamous epithelium in the lower esophagus is replaced by a columnar epithelial lining. These changes develop as a result of chronic gastroesophageal reflux disease (GERD). About 18% of patients with chronic reflux disease develop BE. The most significant complication of BE is the development of invasive adenocarcinoma.

See Invited Critique at end of article

Not all cases of esophageal adenocarcinoma have evidence of BE when diagnosed. Reports regarding the treatment of adenocarcinoma associated with Barrett mucosa (also known as Barrett adenocarcinoma) have been mixed. Some long-term results following esophagectomy for Barrett adenocarcinoma vs esophageal adenocarcinoma without any evi-
PATIENTS, MATERIALS, AND METHODS

From 1991 to 1996, 320 patients were seen at Roswell Park Cancer Institute with the diagnosis of esophageal carcinoma. Of these patients, there were 178 patients with adenocarcinoma of the distal esophagus. Tumors with their center in the gastric cardia were excluded from this study. Each of these tumors was diagnosed by upper endoscopy with biopsy. The presence of BE was determined either by endoscopic diagnosis or pathologic identification on resected specimens or biopsies. Of the 178 patients, 66 patients (37%) had tumors that arose from clearly evident BE. One hundred twelve patients (63%) had no evidence of BE. Statistical analysis was performed using the Fisher exact test and the unpaired t test.

There were 56 men and 10 women in the BE group and 86 men and 26 women in the non-BE group. This resulted in a slightly higher male-female ratio in the BE group (a 5.6:1 ratio as compared with a 3.3:1 ratio). The age range was between 22 and 96 years. The age distribution was equal between the 2 groups with an average age of 65 years for the BE group and 62 years for the non-BE group (Figure 1).

One hundred twelve patients (63%) had no evidence of BE. Statistical analysis was performed to evaluate differences in symptoms, diagnosis, treatment, and outcome in those patients with adenocarcinoma associated with BE vs those without evidence of BE.

RESULTS

PRESENTING SYMPTOMS

The presenting symptoms of the 178 patients are presented in Table 1. The overwhelming majority of patients presented with dysphagia; 71% of patients with BE and 78% of patients without BE. The second most common symptom was weight loss, which occurred much more commonly when the adenocarcinoma arose without BE. Other symptoms such as abdominal pain or gastrointestinal bleed were rare and occurred equally among both groups.

Symptoms of GERD were more common in patients with BE (14% vs 4%), although it still represented a small fraction of the symptoms that prompted work-up. There was also no noticeable difference in the length of time that the patients had symptoms prior to seeking medical attention. This is demonstrated in Figure 2. The average duration of symptoms before diagnosis was slightly longer in the BE group (3.4 months vs 2.8 months), although this was not statistically significant.

PROGNOSTIC INDICATORS

Several indicators of prognosis for esophageal adenocarcinoma were compared between the 2 groups, including length of disease, extent of disease, stage, and tumor grade. Tumor length was determined by endoscopy and barium swallow. Patients with associated BE had significantly shorter tumors than those patients without BE ($P = .05$). This is demonstrated in Figure 3. Sixty-three percent of the tumors in the BE group were less than 6 cm as compared with 37% of the tumors without concomitant BE.

There was also a significant difference in the grade of the tumor as evaluated on the initial endoscopic biopsy or surgical specimen (Figure 4). There were very few carcinomas in situ, although these were all in the BE group. Likewise there were very few grade 1 tumors, which were equal between the 2 groups. There was a significantly higher percentage of patients without evidence of BE who presented with grade 3, poorly differentiated tumors (71%) than patients with BE (53%) ($P = .02$).

Finally, the 2 groups were compared in terms of the stage of disease at presentation (Figure 5). There were many more patients in the BE group presenting with ei-
stage 0 or I disease (18% vs 2%). This included 2 patients with carcinoma in situ in the BE group and none in the non-BE group. The distribution was approximately equal for stage II (18% vs 19%) and stage III disease (36% vs 31%). The most dramatic difference was with advanced disease, stage IV. While only one quarter of the patients in the BE group had stage IV disease, nearly half of the patients without BE were stage IV. Overall, this results in a significantly higher percentage of patients in the BE group presenting with more localized disease ($P = .04$).

**SURVIVAL**

The greater percentage of patients in the BE group with early-stage disease resulted in a significantly higher rate of surgical resection (59% vs 35%, $P < .01$) in that group. This had a predictable effect on the overall survival. With a mean follow-up of 4.1 years, the overall average survival for the BE group was 22 months. This is significantly greater than the average survival of 16.4 months for the non-BE group ($P < .02$).

When comparing the survival by stage, however, there was no significant difference between the 2 groups. The survival data is summarized in Table 2 for those patients who could be accurately staged (137/178 patients). For stage I disease, the mean survival was 33.5 months for the BE group and 28.1 months in the non-BE group. This was approximately the same for stage II dis-

| Stage at presentation. Thirty-six percent of patients with Barrett esophagus presented with earlier-stage disease (stage 0, I, or II) as compared with 21% of patients without Barrett esophagus ($P = .04$). Almost half of patients without Barrett esophagus had metastatic disease at presentation. | (REPRINTED) ARCH SURG/VOL 135, JULY 2000 WWW.ARCHSURG.COM |

<table>
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<th>Table 2. Survival by Stage*</th>
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<tr>
<td>Associated With Barrett Esophagus</td>
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<tr>
<td>Surgical resectability, %</td>
</tr>
<tr>
<td>(n = 178)</td>
</tr>
<tr>
<td>Stage I survival, mo</td>
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<tr>
<td>(n = 9)</td>
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<tr>
<td>Stage III survival, mo</td>
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<td>(n = 46)</td>
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* Median follow-up is 4.1 years.
† Ellipses indicate $P$ value is not significant.

53% of patients without Barrett esophagus (P = .05).

patients in the BE group had stage IV disease, nearly half of the patients without BE were stage IV. Overall, this results in a significantly higher percentage of patients in the BE group presenting with more localized disease ($P = .04$).
ease, with survival times of 32.8 and 33.7 months, respectively. Survival decreased greatly with advanced disease. Stage III survival was 19.7 months for the BE group and 22.2 months for the non-BE group. This dropped even further when metastatic disease was present; 8.6 and 9.6 months for the 2 groups.

While there is clearly a relationship between BE and adenocarcinoma of the esophagus, the exact nature of that relationship remains controversial. Barrett esophagus clearly represents a premalignant condition. Adenocarcinoma occurs as a result of progression of severe dysplastic changes in this abnormal mucosal lining. Numerous investigators have examined the clinical and molecular changes that occur as the Barrett mucosa evolves from minimal or mild dysplasia to severe dysplasia or carcinoma in situ and then to invasive malignancy.

Given the rising incidence of esophageal adenocarcinoma, it is becoming increasingly important to determine the exact nature of the relationship between BE and adenocarcinoma. This information will have serious implications for prevention, earlier diagnosis, and treatment. There are still many questions to be answered. While BE is the only known precursor for these tumors, it is only detectable in 21% to 34% of cases of adenocarcinoma of the esophagus. In our own study, 37% of the cases of esophageal adenocarcinoma seen between 1991 and 1996 were associated with BE.

The significance of this finding remains unknown. Some have reported that the long-term results following surgery for cancer in BE are comparable to the results obtained for other esophageal cancers. Others, however, have seen improved survival in the BE group, suggesting that the presence of BE carries with it some prognostic value. Duhlalongsod and Wolfe examined 16 patients with adenocarcinoma arising in BE, 34 patients with adenocarcinoma not related to BE, and 30 patients with BE without adenocarcinoma. The 4-year survival rate in non-BE adenocarcinoma was 35%, whereas that in BE adenocarcinoma was 60%. A prospective clinical study by Johansson et al also demonstrated a better long-term survival rate seen in those patients with Barrett epithelium than in those without. In this study, we discovered that, in concert with the findings of other authors, the BE group demonstrated several predictors of improved prognosis. Tumors that arose from Barrett metaplasia were shorter and better differentiated. More importantly, those patients tended to present with more localized disease. The BE group had a higher percentage of early-stage cancers. As would be expected, this group also had a higher percentage of patients who were able to undergo surgical resection of these tumors. This had a natural effect on survival, with a significantly improved overall survival in the BE group.

It is essential to delineate any differences between Barrett adenocarcinoma and those cancers without evidence of BE. Carcinomas without evidence of Barrett epithelium may have originated in the gastric cardia and extended into the esophagus, and thus may behave more like gastric cancer. Our study did not include any tumors suspected or known to arise within the gastric cardia. In addition, reanalysis of our data after excluding all gastroesophageal junction cancers, limiting our data to only tumors in the lower third of the esophagus, showed that there was still a significant difference in prognostic indicators and overall survival.

A second proposed theory is that adenocarcinoma that arises from BE exhibits a different biological behavior than adenocarcinoma without BE. There are molecular studies to suggest a possible difference. One such study examined the expression of Lewis antigen, Le, on adenocarcinomas of the esophagus. Those adenocarcinomas preceded by BE contained subsets of transformed cells, which progressively lost their Le epitope. Non-BE adenocarcinomas retained the expression of the Le molecule. A gradual decrease in expression from normal gastric cardia via intestinal metaplasia via dysplasia to invasive carcinoma was possible in the BE cases, but not present in the non-BE cases.

In contrast, there is also biochemical and molecular evidence to support the notion that all adenocarcinomas originate in Barrett metaplasia. Intestinal-type proteins such as sucrase isomaltase and crypt cell antigen are present on normal intestine but not present in the esophagus, stomach, or the submucosal glands of the esophagus. Specimens of BE stain positively for sucrase isomaltase and crypt cell antigen. Adenocarcinomas, either with or without BE, also stained positive. These results suggest that adenocarcinoma of the esophagus, even without evidence of BE, probably originates from preexisting BE. Cytogenic analysis of tumors associated with BE and those without evidence of BE has not shown any differences in the complex pattern of cytogenic changes. This would also suggest a common pathway of origin between both types. Our data supports this argument. Overall survival was improved in the BE group; however, this improved survival was not present when broken down by stage. If there was a difference in the biological characteristics of the 2 groups, one would expect that the survival by stage would also be improved in the BE group.

A much more popular explanation sought to explain that the better prognosis associated with BE adenocarcinoma is caused by early detection. It is asserted that patients with BE should present earlier than their non-BE counterparts because of the symptoms of GERD. Early endoscopy in these patients detects tumors at an earlier stage, thereby improving prognosis. The results of this study suggest that the clinical symptoms of GERD did not seem to lead to a detection of adenocarcinoma at an earlier stage. While there were more patients in the BE group who underwent endoscopy because of GERD symptoms, this still represented a small number in both groups (14% in the BE group and 4% in the non-BE group). The overwhelming majority of patients in both groups presented with the classic symptoms of esophageal cancer, namely dysphagia and weight loss. Even after excluding those patients who presented with GERD symptoms alone, there was no significant change in the improved prognostic indicators or improved outcome in the BE group. Therefore, it seems unlikely that the explanation for the improved prognosis seen with adenocarcinoma is caused by early detection.
cancer arising from Barrett metaplasia is that these patients are being diagnosed earlier because of GERD symptoms.

The results of this study contradict other studies of Barrett adenocarcinoma. However, those studies are small and limited exclusively to surgical patients. In studies of all patients presenting with esophageal adenocarcinoma, including those with advanced disease, only a small percentage of patients presented because of reflux symptoms. In the 66 patients who had clear endoscopic evidence of BE, 57 did not undergo endoscopy until they had symptoms of dysphagia.

Based on these data, the explanation that the improved prognosis associated with Barrett adenocarcinoma is due to earlier detection is incorrect. Furthermore, these data imply that the percentage of patients with adenocarcinoma discovered as a result of endoscopy for GERD is much smaller than that estimated by studies limited to patients undergoing resection. Only a small minority of patients with esophageal cancer are diagnosed because of symptoms of GERD, despite the clear association between the two.16

In conclusion, it is unlikely that any differences in prognosis or outcome between adenocarcinoma cases associated with BE and those not associated with BE are due to a difference in the biological characteristics of the disease. It is also unlikely that they are due to earlier diagnosis because of a difference in symptoms. If this common assumption is not true, then the most likely explanation is that the differences noted by us and other authors are due simply to an inability to diagnose Barrett mucosa in the non-BE group. The non-BE group more likely represents tumors that have originated in Barrett mucosa, but in whom the metaplasia is no longer apparent. Either the Barrett mucosa has regressed with antireflux therapy, or more aggressive, larger tumors may have overgrown all remnants of Barrett mucosa. It seems likely that all esophageal adenocarcinomas originate in BE, but by the time they are diagnosed (usually late in the course of the disease and caused by symptoms of dysphagia as opposed to reflux), the spread of the cancer has obscured any evidence of BE. This would explain the trend toward the more aggressive tumors (higher grade, increased length, advanced stage) having no evidence of Barrett mucosa at diagnosis. The results of this study also highlight the truly small fraction of adenocarcinomas diagnosed because of symptoms of GERD. These data support the notion that an early and aggressive use of endoscopy in patients with symptoms of GERD is necessary to distinguish those patients with Barrett mucosa or dysplasia who may benefit from endoscopic surveillance. Delaying endoscopy in patients with significant reflux until several attempts at medical management have failed misses the opportunity to identify patients at high risk for adenocarcinoma. This may represent our only opportunity at this time to improve the prognosis for esophageal cancer. Clearly, it will take further biochemical and molecular research to determine the exact relationship between BE and adenocarcinoma, and its implication for diagnosis and therapy.

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