Outcome of adenocarcinoma arising in Barrett’s esophagus in endoscopically surveyed and nonsurveyed patients

The value of endoscopic surveillance of Barrett’s esophagus and the appropriate management of high-grade dysplasia remain unclear. Seventeen patients who were referred from endoscopic surveillance programs for management of high-grade dysplasia or adenocarcinoma developing in Barrett’s esophagus were compared with 35 patients who had a newly recognized Barrett’s adenocarcinoma, who had not been in a surveillance program. The referral diagnosis in the surveyed group was adenocarcinoma in six and high-grade dysplasia in 11. After repeat endoscopy with aggressive biopsy, two additional patients with adenocarcinoma were identified. Of the nine patients who underwent esophagectomy for high-grade dysplasia, five had invasive adenocarcinoma in the esophagectomy specimen, which had been missed before the operation, despite the fact that the median number of biopsy specimens obtained per 2 cm of Barrett’s mucosa was 7.8 (range 1.5 to 15.0). Overall, 13 patients in the surveyed group had adenocarcinoma, 12 staged early and one staged intermediate by the WNM classification. Surveyed patients were operated on at an earlier stage than the nonsurveyed patients (10 early, 14 intermediate, and 11 late stage tumors; $\chi^2 = 15.6, p < 0.01$). Despite the presence of adenocarcinoma in 13 of the 17 surveyed patients, their survival was significantly better than that of the nonsurveyed group ($\chi^2 = 5.8, p < 0.05$). Patients referred from surveillance programs for Barrett’s esophagus have a better outcome and earlier stage tumors than nonsurveyed patients. Inasmuch as multiple biopsy procedures do not exclude the presence of adenocarcinoma, continued surveillance of high-grade dysplasia is dangerous and potentially destructive to surveillance efforts. (J THORAC CARDIOVASC SURG 1994;108:813-22)

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Patients with Barrett’s esophagus have an increased risk for the development of esophageal adenocarcinoma, 30 to 125 times higher than that of the normal population.1-6 Barrett’s esophagus results from a peculiar form of healing of injured esophageal mucosa and can develop at any time in patients with reflux esophagitis.7 This phenomenon links gastroesophageal reflux disease with one of the most lethal carcinomas. For every 100,000 cases of Barrett’s esophagus, 500 will develop annually into adenoc-
carcinoma. This risk exceeds the risk of lung cancer in an individual who has smoked one pack of cigarettes per day for 20 years. Consequently, it is recommended that patients with Barrett's esophagus undergo regular endoscopic surveillance in an effort to detect malignant transformation at an early stage. Whether such programs are effective remains to be demonstrated.

The finding of high-grade dysplasia on biopsy is the best predictor of patients in whom invasive adenocarcinoma will develop or has already developed. Esophagectomy provides the best therapy for those patients with early invasive adenocarcinoma and is an effective means of eliminating the development of adenocarcinoma in those with high-grade dysplasia. The benefits of esophagectomy, however, must exceed the risk of operative mortality.

In the present study two groups of patients were compared—those who were receiving regular endoscopic surveillance and were referred for esophagectomy because of the development of high-grade dysplasia or adenocarcinoma and those who were not receiving surveillance and were referred for esophagectomy because of the discovery of a newly recognized adenocarcinoma. The purpose was to answer the following questions: (1) Does endoscopic surveillance allow the detection of tumors at an earlier stage? (2) Can further endoscopy with an extensive biopsy protocol accurately differentiate between patients with high-grade dysplasia and those with adenocarcinoma before surgical therapy is recommended? (3) Do surveyed patients have a better survival after surgical resection than those without surveillance?

Patients and methods

Between January 1985 and December 1993, 52 patients underwent esophagectomy for either high-grade dysplasia or adenocarcinoma arising in Barrett's esophagus. Barrett's metaplasia was defined by the presence of specialized intestinal metaplasia in the esophagectomy specimen. The patients were divided into two groups, those who had been referred for surgical consultation after a diagnosis of high-grade dysplasia or adenocarcinoma had been made during endoscopic surveillance and those who were not receiving surveillance and were referred for esophagectomy because of the discovery of a newly recognized adenocarcinoma. The purpose was to answer the following questions: (1) Does endoscopic surveillance allow the detection of tumors at an earlier stage? (2) Can further endoscopy with an extensive biopsy protocol accurately differentiate between patients with high-grade dysplasia and those with adenocarcinoma before surgical therapy is recommended? (3) Do surveyed patients have a better survival after surgical resection than those without surveillance?

Preoperative endoscopic evaluation was performed in all patients. The position of the crura, the anatomic gastroesophageal junction, and the most proximal limit of the squamocolumnar junction were recorded. The length of Barrett's mucosa was measured from the position of the inferred gastroesophageal junction to the squamocolumnar junction. The macroscopic appearance of the esophagus was recorded and four-quadrant biopsy specimens were obtained every 2 cm along the length of the Barrett's mucosa. Additional specimens were taken from any suspicious areas. Standard sized biopsy forceps were used (7.5 mm open span diameter). All biopsy samples were evaluated by a pathologist experienced in the assessment of high-grade dysplasia in Barrett's esophagus (T.C.S. or P.C.). Dysplasia was classified according to previously published criteria. Invasive adenocarcinoma was differentiated from high-grade dysplasia by invasion beyond the epithelial basement membrane. The classification carcinoma-in-situ was not used. The median number of biopsy specimens obtained during the preoperative endoscopic evaluation in the nine patients operated on for high-grade dysplasia was 1.5 (range 7 to 34), which was 7.8 (range 1.5 to 15.0) per 2 cm of Barrett's mucosa.

Esophageal resection was undertaken in all patients except for one patient who was referred with low-grade dysplasia and had a successful antireflux repair. Shortly after the operation the patient was found to have high-grade dysplasia on biopsy. The patient was kept under surveillance for 4½ years with high-grade dysplasia before adenocarcinoma developed. In this patient esophageal resection was deferred until carcinoma was diagnosed because of a chronic cardiac condition. Patients with a preoperative diagnosis of high-grade dysplasia underwent transhiatal esophagectomy. Patients with a preoperative diagnosis of adenocarcinoma and thought to have early tumors on preoperative computed tomography and endoscopic ultrasonography underwent en bloc esophagectomy if they were physiologically fit, that is, less than 75 years of age with an ejection fraction of more than 40% and a forced expiratory volume of less than 1.25 L.

Patients who were unfit for the en bloc procedure or who had late stage disease underwent esophagectomy by the transhiatal route. In the surveyed group 15 patients had transhiatal esophagectomy and two had en bloc esophagectomy. In the nonsurveyed group 20 had en bloc resections, 14 had transhiatal esophagectomy, and one patient whose condition was found to be inoperable received a stent.

In patients with a preoperative diagnosis of high-grade dysplasia the esophagectomy specimen was extensively sampled for evidence of an unrecognized tumor. Tumors were staged pathologically according to the TNM staging system. This staging is preferred over the TNM or International Union Against Cancer (UICC) staging systems because it takes into account the number of nodal metastases, previously reported to be an important predictor of outcome, and is superior in relating the stratification of the extent of the disease to survival. Tumors were staged early when no wall penetration (W0, W1) and fewer than five metastatic nodes (N0, N1) were present, intermediate when either transmural wall penetration (W2) or more than four lymph node metastases (N2) was present, and late when transmural wall penetration and more than four lymph node metastases (W2, N2) were present. Complete follow-up was obtained in all patients up to March 1994.
Statistics. The \( \chi^2 \) test was used for comparisons of proportions. Life tables were calculated by the Kaplan-Meier method and differences between survival curves were estimated by the log-rank test. Statistical significance was taken at the 5% level.

Results

All patients in the surveyed group reported a history of symptoms of gastroesophageal reflux disease. The median duration of symptoms was 25 years (ranging from 1 to 50 years). Sixteen of 17 had been receiving long-term \( \text{H}_2 \) blocker therapy and three had had prior antireflux procedures. In two of the patients the previous procedure had failed and in one the procedure was performed with the knowledge that the patient had Barrett’s esophagus with low-grade dysplasia. In the nonsurveyed group 22 of 35 (63%) patients reported chronic symptoms of gastroesophageal reflux disease and the remainder reported minor symptoms or denied any history. In those who were symptomatic the median duration of symptoms was 15 years (ranging from 2 to 40 years). Seventeen of the 22 symptomatic patients reported long-term use of over-the-counter antacids and 11 were receiving long-term \( \text{H}_2 \) blockers. None had a previous antireflux procedure.

Endoscopic surveillance. The duration of surveillance, frequency of endoscopic studies, number of endoscopic studies, and referral diagnosis for the patients in the surveyed group are shown in Table I. All patients underwent a repeat endoscopic examination with multiple biopsy samples at our institution. The endoscopic findings and number of biopsy specimens obtained during our preoperative evaluation are shown in Table II. Six patients were referred with a diagnosis of adenocarcinoma and two, referred with high-grade dysplasia, were discovered to have adenocarcinoma on our preoperative endoscopic examination. Seven of the eight patients with adenocarcinoma had subtle endoscopic abnormalities suggestive of malignancy on endoscopy. Nine patients were operated on with a diagnosis of high-grade dysplasia (including patient 9, in whom there was suspicion of adenocarcinoma). Seven of the nine had no mucosal abnormality to suggest adenocarcinoma, whereas one patient had a distal esophageal stricture and one patient had an esophageal ulcer.

Of interest, eight of 35 (22.8%) patients in the nonsurveyed group had undergone at least one previous endoscopic examination. The fact that a diagnosis of Barrett’s esophagus was not made in any of these patients implies that either the diagnosis was missed at the time of endoscopy or that Barrett’s metaplasia had developed during medical therapy.

Final diagnosis. All patients in this series underwent surgical resection of the esophagus. In the surveyed group, invasive adenocarcinoma was found in the resected specimen in all eight patients who had a preoperative diagnosis of adenocarcinoma. However, five of the nine patients (55.5%) who were operated on with a diagnosis of high-grade dysplasia (patients 9 to 13) had invasive adenocarcinoma in the resected specimen that had been missed on preoperative evaluation (Fig. 1). Patients 12 and 13 emphasize the inadequacy of relying on endoscopic biopsy specimens for establishing a diagnosis of adenocarcinoma. They had 7.8 and 9.7 samples taken per 2 cm of Barrett’s esophagus, respectively, yet the diagnosis of adenocarcinoma was still missed; one had intramucosal carcinoma and the other had adenocarcinoma invading the muscularis propria. Patients in the endoscopically surveyed group were operated on at a significantly earlier stage than the nonsurveyed patients with Barrett’s adenocarcinoma (Fig. 2, Table III).

Outcome of surgical resection. Survival was significantly better in patients undergoing endoscopic surveillance, 13 with adenocarcinoma and four with high-grade dysplasia, than in nonsurveyed patients (Fig. 3). One postoperative death occurred in the surveyed group (5.9% 30-day mortality). The patient had acute erosion of an ulcer in the interposed stomach into the thoracic aorta 10 days after the operation. This complication necessitated an emergency reoperation and takedown of the reconstruction. The patient subsequently died of recurrent
Table II. Outcome of preoperative endoscopic evaluation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Referral diagnosis</th>
<th>Endoscopic findings</th>
<th>Length of Barrett's segment (cm)</th>
<th>Total No. esophageal biopsies</th>
<th>Biopsies per 2 cm Barrett's</th>
<th>Histologic diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>AC*</td>
<td>Nodular area</td>
<td>7</td>
<td>12</td>
<td>3.4 AC</td>
<td>AC</td>
</tr>
<tr>
<td>2</td>
<td>AC</td>
<td>Nodular area</td>
<td>10</td>
<td>4</td>
<td>0.8 AC</td>
<td>AC</td>
</tr>
<tr>
<td>3</td>
<td>AC</td>
<td>Nodular area</td>
<td>11</td>
<td>34</td>
<td>6.2 AC</td>
<td>AC</td>
</tr>
<tr>
<td>4</td>
<td>AC</td>
<td>Mass</td>
<td>2</td>
<td>10</td>
<td>10.0 AC</td>
<td>AC</td>
</tr>
<tr>
<td>5</td>
<td>AC</td>
<td>Irregular stricture</td>
<td>9</td>
<td>7</td>
<td>1.6 AC</td>
<td>AC</td>
</tr>
<tr>
<td>6</td>
<td>AC</td>
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<td>5</td>
<td>15</td>
<td>6.0 AC</td>
<td>AC</td>
</tr>
<tr>
<td>7</td>
<td>HGD</td>
<td>Ulcer</td>
<td>10</td>
<td>17</td>
<td>3.4 AC</td>
<td>AC</td>
</tr>
<tr>
<td>8†</td>
<td>HGD</td>
<td>Normal</td>
<td>9</td>
<td>2</td>
<td>2.3 AC</td>
<td>AC</td>
</tr>
<tr>
<td>9</td>
<td>HGD</td>
<td>Normal</td>
<td>6</td>
<td>26</td>
<td>8.7 HGD/AC</td>
<td></td>
</tr>
<tr>
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<td>HGD</td>
<td>Normal</td>
<td>7</td>
<td>10</td>
<td>2.9 HGD</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>HGD</td>
<td>Normal</td>
<td>7</td>
<td>15</td>
<td>4.3 HGD</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>HGD</td>
<td>Ulcer</td>
<td>8</td>
<td>31</td>
<td>7.8 HGD</td>
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</tr>
<tr>
<td>13</td>
<td>HGD</td>
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<td>34</td>
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<tr>
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<td>2</td>
<td>7</td>
<td>7.0 HGD</td>
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</tr>
<tr>
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<td>Normal</td>
<td>6</td>
<td>28</td>
<td>9.3 HGD</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>HGD</td>
<td>Stricture</td>
<td>2</td>
<td>15</td>
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<td>17</td>
<td>HGD</td>
<td>Normal</td>
<td>13</td>
<td>10</td>
<td>1.5 HGD</td>
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</tr>
</tbody>
</table>

AC, Adenocarcinoma; HGD, high-grade dysplasia.
*Self-referred.
†Final endoscopic examination in the patient who was surveyed 4½ years with high-grade dysplasia.
‡Biopsy findings suggested adenocarcinoma on the basis of architectural characteristics but there was no invasion of the basement membrane.

Table III. Final pathologic diagnosis in surveyed patients based on examination of the esophagectomy specimen

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Final diagnosis</th>
<th>Depth of tumor</th>
<th>Lymph node metastasis</th>
<th>W stage</th>
<th>N stage</th>
<th>Final stage</th>
<th>Outcome (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AC</td>
<td>Submucosal</td>
<td>+ (2)</td>
<td>1</td>
<td>1</td>
<td>Early</td>
<td>Died postop</td>
</tr>
<tr>
<td>2</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>Died 2 mo</td>
</tr>
<tr>
<td>3</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>A/W 4</td>
</tr>
<tr>
<td>4</td>
<td>AC</td>
<td>Transmural</td>
<td>+ (1)</td>
<td>2</td>
<td>1</td>
<td>Intermediate</td>
<td>A/W 58</td>
</tr>
<tr>
<td>5</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>A/W 16</td>
</tr>
<tr>
<td>6</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>A/W 6</td>
</tr>
<tr>
<td>7</td>
<td>AC</td>
<td>Submucosal</td>
<td>-</td>
<td>1</td>
<td>0</td>
<td>Early</td>
<td>A/W 36</td>
</tr>
<tr>
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<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
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<td>0</td>
<td>Early</td>
<td>A/W 16</td>
</tr>
<tr>
<td>9</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>A/W 29</td>
</tr>
<tr>
<td>10</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>A/W 12</td>
</tr>
<tr>
<td>11</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>A/W 12</td>
</tr>
<tr>
<td>12</td>
<td>AC</td>
<td>Muscularis propria</td>
<td>-</td>
<td>1</td>
<td>0</td>
<td>Early</td>
<td>A/W 5</td>
</tr>
<tr>
<td>13</td>
<td>AC</td>
<td>Intramucosal</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Early</td>
<td>A/W 5</td>
</tr>
<tr>
<td>14</td>
<td>HGD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>HGD</td>
<td>A/W 4</td>
</tr>
<tr>
<td>15</td>
<td>HGD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>HGD</td>
<td>A/W 42</td>
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<tr>
<td>16</td>
<td>HGD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>HGD</td>
<td>A/W 9</td>
</tr>
<tr>
<td>17</td>
<td>HGD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>HGD</td>
<td>A/W 66</td>
</tr>
</tbody>
</table>

AC, Adenocarcinoma; HGD, high-grade dysplasia; A/W, alive and well with no recurrence.

aortic bleeding 21 days after the operation. The only other death in the surveyed patients was the result of a pulmonary embolus, which occurred 2 months after discharge. In both patients adenocarcinoma had been diagnosed before the operation. The remaining 15 surveyed patients have remained well and free from recurrence after resection. Removal of the four patients with high-grade dysplasia and considering only those patients with a final diagnosis of adenocarcinoma yields an improved survival for the surveyed group, although the difference was not statistically significant ($\chi^2 = 2.9$, $p = 0.09$).

In the surveyed group postoperative complications were observed in six of 15 patients. Two patients had
Fig. 1. Flow chart of the pathologic outcome of 17 patients who were referred from endoscopic surveillance programs for Barrett’s metaplasia. The diagnosis on referral, after preoperative endoscopy with rigorous biopsy, and the final diagnosis in the resected specimen are indicated. Among the 17 patients the final diagnosis was adenocarcinoma in 13 and high-grade dysplasia in only four. *One patient was referred with low-grade dysplasia and underwent a successful antireflux repair but shortly after the operation was found to have high-grade dysplasia on biopsy. The patient was kept under surveillance for 4 1/2 years before adenocarcinoma developed. Esophageal resection was deferred until carcinoma was diagnosed because of a chronic cardiac condition.

Fig. 2. Stage of adenocarcinomas from the resected specimens of endoscopically surveyed and nonsurveyed patients. There was a significant difference in the stages of disease between the two groups ($\chi^2 = 15.6, p < 0.01$).

bleeding in the early postoperative period, which necessitated a second laparotomy in one and a thoracotomy in the other. One patient had a prolonged postoperative course with multiple complications including a small bowel infarction, multiple episodes of sepsis, and recurrent episodes of respiratory failure. One patient had a thoracic duct fistula that necessitated reoperation with ligation of the thoracic duct and two had postoperative chest infections. Nine patients had uneventful recoveries.
Fig. 3. Survival after esophageal resection in endoscopically surveyed and nonsurveyed patients. There was a significant difference between the groups (log rank $\chi^2 = 5.8, p < 0.05$). Bars indicate standard errors of the mean. Surveyed group included 13 patients with adenocarcinoma and four with high-grade dysplasia. The number of patients followed up at each of the intervals indicated along the horizontal axis is shown in the rectangle beneath “months.”

Discussion

The results of this study indicate that endoscopic surveillance of patients with Barrett’s esophagus allows the detection of esophageal adenocarcinoma at an earlier stage than in patients with newly recognized adenocarcinoma who were not undergoing endoscopic surveillance. The reliance on endoscopic biopsy samples to distinguish invasive adenocarcinoma from high-grade dysplasia before proceeding with the operation is flawed because an extensive preoperative biopsy protocol failed to identify invasive adenocarcinoma in five patients. When early surgical resection was advocated for all the surveyed patients with either high-grade dysplasia or invasive adenocarcinoma, their survival was significantly better than that of nonsurveyed patients undergoing resection.

The premalignant condition of Barrett’s esophagus is a consequence of gastroesophageal reflux disease. This fact was highlighted in this study by the observation that the majority of patients had long-standing reflux symptoms, often of more than 20 years in duration. The observation raises a hypothetical question: Could the development of adenocarcinoma have been prevented by an earlier antireflux procedure? The factors that are responsible for the malignant degeneration of Barrett’s mucosa are unknown. However, adequate control of reflux esophagitis would appear to be a reasonable objective, inasmuch as it might be expected to reduce the chances of the esophagitis healing with Barrett’s metaplasia and the beginning of a progression to malignancy. Medical therapy is focused on acid suppression to heal esophagitis and chronic acid suppression to maintain a healed mucosa. A potential problem is that in addition to acid reflux the reflux of alkaline material (bile and pancreatic juice) has been demonstrated in patients with Barrett’s esophagus. Increased alkaline exposure has been shown to be associated with complications in Barrett’s esophagus, that is, stricture, ulcer, and dysplasia.

Further, reflux of duodenal content experimentally has been shown to promote the formation of esophageal adenocarcinoma in rats. Most patients with Barrett’s esophagus are initially treated with medical therapy, with the purpose to control reflux symptoms. Medical therapy, particularly omeprazole, controls reflux symptoms but fails to heal mucosal injury in 10% to 20% of patients with severe esophagitis. This observation might be explained by the continued reflux of alkalinized gastric juice containing duodenal content. The most effective way of controlling reflux disease is by an antireflux operation that stops all reflux of gastric or duodenal origin by reestablishing the natural mechanical barrier. Several reports of adenocarcinoma developing in Barrett’s esophagus after antireflux operations have been published, but in none were efforts made to exclude dysplasia before the operation and none documented the effectiveness of the repair after the operation.

Whether a properly functioning antireflux repair can indeed reduce the rate of malignant progression in Bar-
rett's esophagus waits confirmation. One prospective registry showed that dysplasia and adenocarcinoma were significantly more prevalent after medical therapy than after surgical therapy.38

It is of concern that 63% of the patients in the nonsurveyed group had chronic symptoms of reflux disease, many of whom had been receiving H2 blockers and, that in the 25% who had a previous endoscopic examination the diagnosis of Barrett's esophagus was missed. Could it be that Barrett's metaplasia developed only during medical therapy? If so, this failure should seriously discourage the sale of H2 blockers over the counter, as has been proposed. Rather, these findings underscore the need to search for Barrett's metaplasia in all patients with symptoms of chronic reflux disease before the initiation of therapy. We have recently performed endoscopy in 87 patients with chronic reflux disease. As a routine, biopsy specimens were taken from the columnar mucosa 1 cm distal to the squamocolumnar junction on the gastric side of the sphincter, by means of a retroflexed approach. With this policy, 6% of the patients were identified with unsuspected Barrett's change, one of whom had high-grade dysplasia (unpublished data).

Endoscopic surveillance of patients with Barrett's esophagus is associated with controversy over its cost, the low yield of adenocarcinomas that have been reported in prospective studies, and the benefit of such a program.1-5 The latter remains unclear because most centers see only a small number of patients in whom esophageal adenocarcinoma has developed during surveillance. Because the surveillance in our study was performed at outside institutions it is not possible to comment on the yield of adenocarcinomas or the cost efficiency, but the study does show that the outcome of surveillance programs provides a distinct survival advantage. In addition, the concepts regarding surveillance have evolved over the period of this study such that the patients in the early part of the series tended to be referred with a diagnosis of adenocarcinoma while more recently patients have been referred at the high-grade dysplasia stage.

A major controversy exists regarding the most appropriate management of patients found to have high-grade dysplasia in Barrett's esophagus. Some investigators consider that high-grade dysplasia should be managed expectantly39,40 with continued endoscopic surveillance, arguing that high-grade dysplasia does not equate with the presence of invasive adenocarcinoma. They point out that a small number of patients have been followed up for several years with high-grade dysplasia and have remained well with no evidence of cancer.4,39,40 Furthermore, they argue that esophagectomy for high-grade dysplasia has resulted in death in a few patients free from invasive adenocarcinoma and carries a risk of some significant morbidity.39,40 This approach is based on the fundamental assumption that it is possible to accurately differentiate high-grade dysplasia from early adenocarcinoma by endoscopic examination and histologic evaluation of the biopsy specimens. In contrast, we and other investigators have advocated proceeding with esophagectomy for high-grade dysplasia unless the patient is unfit for surgical intervention. Our study has shown that endoscopic biopsy in our hands does not accurately differentiate patients with high-grade dysplasia from those with invasive adenocarcinoma, a view which supports that of Altorki,1 Pera,42 Rice,43 Streitz,44 and their associates. We have shown that even when the whole length of the Barrett's segment is aggressively sampled, one cannot be confident that invasive adenocarcinoma has not already developed. If we had continued to survey our patients with high-grade dysplasia, we would have been withholding surgical treatment from five patients who already had esophageal cancer, one of whom had tumor invasion into the muscularis propria yet was still free from nodal metastases.

Esophageal adenocarcinoma tends to metastasize to the lymph nodes early in the disease process. It has been shown45 that of patients undergoing en bloc esophagectomy with extended abdominal and mediastinal lymphadenectomy for intramucosal adenocarcinoma, 33% had lymph node metastases. The prevalence of nodal metastases rose to 66% for those whose tumor had spread into the muscularis propria and to 89% in those with transmural tumors. Because esophageal adenocarcinoma has a poor prognosis, there is a reluctance to wait for the development of adenocarcinoma and possible nodal spread of the disease in patients who could be cured with a high degree of certainty if esophagectomy were performed. Even in the surveyed group two patients already had nodal metastases at the time of surgical resection, indicating the prudence of early rather than delayed surgical intervention.

The finding that patients in the surveyed group had early stage tumors is encouraging and in keeping with the findings of others.44 No late stage tumors were identified in the surveyed group. A significant survival advantage was observed after operation for the surveyed patients despite two patients dying in the early postoperative period. None of the survivors has recurrent disease to date.

In conclusion, endoscopic surveillance of patients with Barrett's esophagus allows the early detection of malignant change. Esophagectomy is indicated for high-grade dysplasia or early adenocarcinoma detected during endoscopic surveillance and affords a significant survival
advantage over that of patients with newly recognized adenocarcinomas who were not surveyed. Differentiation between high-grade dysplasia and adenocarcinoma on the basis of endoscopic and biopsy examination is unreliable, so that continued surveillance of patients with high-grade dysplasia is risky and potentially destructive to surveillance efforts.

REFERENCES


Discussion

Dr. F. Henry Ellis, Jr. (Boston, Mass.). I was particularly pleased to hear the data presented by Dr. Clark and his associates, for they confirm the findings that we presented 2 years ago to this Society of a similar comparative study. We, too, found that invasive carcinoma may not be detected by surveillance endoscopic biopsy that discloses only high-grade dysplasia. In fact, over 50% of our resected specimens showed invasive cancer when the preoperative endoscopic biopsy disclosed only high-grade dysplasia. It is important to point out, though, that most pathologists now believe that high-grade dysplasia is synonymous with carcinoma in situ, so it is invasive cancer that can be missed by surveillance endoscopic biopsy.

Let me briefly review our findings and pose a few questions. Our group of patients was similar to that just presented. There were 19 patients with Barrett's esophagus under surveillance and 58 in whom the diagnosis of adenocarcinoma in Barrett's esophagus was made when first seen by us. Three quarters of the patients under surveillance were in stages 0, 1, and IIA, whereas the situation was reversed for those not under surveillance, three quarters of them being in the higher grades, III and IV. The beneficial effect of close surveillance was evident when actuarial survival data were calculated. Although the 5-year survival was not quite as good as that just reported, 62% of those under surveillance were alive 5 years later, whereas only 20% of those not under surveillance had a similar survival.

I would like to ask you two questions. At the University of Washington an average of 30 biopsies are performed per endoscopy. Your number of biopsies per patient was about half of that. Do you think that by making your biopsy protocol more rigorous and increasing the number of biopsies, you would support their recommendations that high-grade dysplasia should not be an indication for resection? I personally don't think so, but I would be interested in your thoughts.

One other question: How do you manage patients who have low-grade dysplasia? Does low-grade dysplasia always become high-grade dysplasia? We have increased the frequency of endoscopic surveillance in such patients to every 3 to 6 months instead of yearly but without any assurance that this is appropriate.

Dr. Peters. Thank you, Dr. Ellis, for your kind comments. It was the University of Washington paper that stimulated us to evaluate our patients. As you know, the Washington group suggested that with a rigorous biopsy protocol, one could safely monitor patients with high-grade dysplasia, a tenet with which we would strongly disagree. Most believe that even an aggressive biopsy protocol, a very detailed endoscopic examination, and, as others have shown, even endoscopic ultrasonic examination cannot distinguish patients who have high-grade dysplasia from those with invasive cancer. We believe strongly that high-grade dysplasia ought to be surgically resected. It is just not clinically possible at the present state of technology to be certain invasive cancer is not present.

What to do with low-grade dysplasia remains problematic. There is not enough information regarding its natural history. The available data would suggest that high-grade dysplasia and, ultimately, cancer will develop in most of these patients. The exact time course is open to question, probably over the span of years.

We would recommend increasing the surveillance frequency to every 3 to 6 months in anyone who has dysplasia in the presence of Barrett's esophagus.

Dr. Valerie W. Rusch (New York, N.Y.). As one of the surgeons who worked very closely with the gastroenterology group at the University of Washington on their Barrett's surveillance program, I would like to make a couple of comments. I think the most recent manuscript from that group (Gastroenterology 1993;105:40-50) has been somewhat misinterpreted. It is important to understand that the way biopsies are performed in this surveillance program is unique, because of the number of biopsy specimens obtained, the way in which they are obtained...
Their recommendation is not that patients with dysplasia should be followed up. The important points made in that article are as follows: (1) The factors that dictate progression from dysplasia to overt malignancy are not understood; (2) there is tremendous variation in the pace at which the condition progresses to overt malignancy; and (3) the clinical parameters currently available to observe patients, including histology, multiparameter flow cytometry, and even some of the molecular markers, such as p53 abnormalities, are insufficient to determine exactly in which patients the disease will progress and when. The recommendation of the Seattle group is that patients who have high-grade dysplasia should be considered for operation unless they have concurrent medical problems that would make esophagectomy particularly hazardous. In that case, a rigorous endoscopic program, specifically as they have practiced it, may be an appropriate alternative. Their current efforts focus on identifying specific molecular markers that will enable us to determine accurately in which patients the disease will progress to overt malignancy and when.

Dr. Peters: Thank you for your comments. We certainly would agree that the group in Washington has a great deal of expertise, uses a rigorous biopsy protocol, and has excellent pathologists to interpret their specimens, but we would still argue that despite this, it is extremely difficult, if not impossible, to differentiate patients with high-grade dysplasia from those with invasive cancer. It is important to keep in mind the fact that operated on at this early stage, as this and as Dr. Ellis's study have demonstrated, a high percentage of patients can expect long-term survival. Thus it becomes very problematic to merely observe those patients unless they are prohibitive surgical candidates.

Dr. William H. Warren (Chicago, Ill.). The limitations of doing routine surveillance are, of course, cost and patient compliance. In an attempt to address this, some gastroenterologists are suggesting using brushings through a nasogastric tube. Have you tried that?

Dr. Peters. We have not used brushings through a nasogastric tube. We have occasionally used them in conjunction with endoscopic surveillance. We have not found that brushings enhance the ability to distinguish between high-grade dysplasia and invasive cancer. Just about any technology that is now available fails to make that distinction. I would also add that visual inspection of the mucosa is an important component. I am not sure that we should fall back on simply inserting a nasogastric tube and brushing, although that is certainly a potentially less costly alternative.