

Barrett's Esophagus with High-Grade Dysplasia

An Indication for Prophylactic Esophagectomy

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Objective

The authors review the results and outcomes of esophagectomy (prophylactic esophagectomy) for patients with Barrett's esophagus and high-grade epithelial dysplasia (HGD).

Summary Background Data

The role of prophylactic esophagectomy for Barrett's esophagus with HGD is controversial, with some authors recommending surgery and others favoring endoscopic surveillance until a biopsy diagnosis of carcinoma is made.

Methods

Between 1982 and 1994, 30 consecutive patients with HGD underwent esophagectomy and had the pre- and postoperative pathology reviewed at our institution. The medical records were reviewed to determine patient characteristics, preoperative endoscopic data, surgical approach, operative morbidity and mortality, length of hospitalization, and treatment outcome. Patients were divided into two groups based on whether invasive adenocarcinoma was found in the resection specimen (group 1) or not (group 2).

Results

The duration of reflux symptoms was 22 ± 14 years for group 1 and 9 ± 11 years for group 2 ($p = 0.05$). There was one operative death (3.3%) and six complications (20%). In 13 patients (43%, group 1), invasive adenocarcinoma was found in the resected esophagus. The American Joint Committee on Cancer stage for these patients was stage I (8 patients), stage II (2 patients), and stage III (3 patients). One stage I patient died of adenocarcinoma (72 months) in an incompletely excised HGD segment. Other stage I and II patients are alive without adenocarcinoma with an 18- and 63-month mean follow-up, respectively. Outcome for stage III patients was one operative death, one noncancer death (6 months), and one patient with metastatic adenocarcinoma (26 months). For group 2 (57%), there were no adenocarcinoma deaths (40 months).

Conclusions

High-grade epithelial dysplasia is an indication for esophagectomy because of the prevalence of occult adenocarcinoma (43%). Esophagectomy can be performed safely, and survival in patients with completely resected Barrett's esophagus and early-stage adenocarcinoma is excellent.

The evidence that Barrett's esophagus with high-grade dysplasia (HGD) of columnar epitheliums is a premalignant process continues to accumulate and generally is accepted. However, the role of prophylactic esophagectomy for HGD in Barrett's esophagus is controversial, with some authors recommending surgery and others favoring surveillance until a biopsy diagnosis of carcinoma is made. Therefore, we reviewed our results and outcome in the surgical management of 30 consecutive patients with Barrett's esophagus and HGD to determine if an aggressive surgical approach to these patients is justified.

PATIENTS AND METHODS

Review of the surgical pathology records at The Johns Hopkins Hospital between November 1982 and October 1994 identified 30 consecutive patients with Barrett's esophagus and HGD in endoscopic biopsy specimens who subsequently underwent prophylactic esophagectomy. The diagnosis of Barrett's esophagus with HGD was made or confirmed by one of the authors (SRH) using histopathologic criteria that have been reported previously.^{1,2} No patient had invasive adenocarcinoma identified preoperatively. The medical records for these patients were reviewed retrospectively to determine patient characteristics, the number of endoscopies and biopsies of Barrett's mucosa, surgical approach, operative morbidity and mortality, hospital length of stay, and treatment outcome.

The number of esophagoscopies was determined in all patients from the number of surgical pathology accessions. The number of biopsy specimens with Barrett's mucosa was calculated in 28 patients from the number of tissue fragments reported in the gross description of the biopsy specimens or by counting of the Barrett tissue fragments in the histopathologic sections. The duration of endoscopic follow-up was determined from the dates of biopsy specimen acquisition in the 27 patients who had more than one examination. The time interval from first esophagoscopy to esophagectomy was determined in all patients (Table 1).

Patients were divided into two groups based on whether invasive adenocarcinoma was discovered in the resection specimen (group 1) or not (group 2). Invasive adenocarcinoma was staged using the TNM system of the American Joint Committee on Cancer (AJCC).³

The surgical approach used for esophageal resection and reconstruction was not standardized but varied ac-

Table 1. PREOPERATIVE ENDOSCOPIC EVALUATION

	Group 1 (13 patients)	Group 2 (17 patients)	Total (30 patients)
No. of esophagoscopies	4.3 ± 0.7	3.1 ± 0.4	3.5 ± 0.4
No. of biopsy specimens	25.3 ± 6.5	24.4 ± 3.4	24.8 ± 3.3
Duration of endoscopic follow-up (mo)	15.4 ± 5.8	10.6 ± 2.9	12.9 ± 3.1
Time from first endoscopy to surgery	21.8 ± 6.6	10.7 ± 2.6	15.5 ± 3.3

ording to the surgeon's preference. In 24 patients, the surgery was performed at our institution. Twenty of these resections (8 patients, group 1; 12 patients, group 2) were performed by one of the authors (RFH) using a gastric pull-up and cervical esophagogastric anastomotic reconstructive technique whenever possible. Six patients (3 each from groups 1 and 2) underwent surgery at outside institutions. One of these patients was transferred to our institution for management of postoperative complications.

Outcome was determined for patients with invasive adenocarcinoma (group 1) to evaluate cancer-related survival, and for group 2 patients as a comparison.

Values are expressed as the mean ± standard deviation. Comparisons between groups were made using unpaired Student's *t* test, Mann Whitney *U* test, or Fisher's exact test, where appropriate.

RESULTS

Patient Characteristics

Thirteen patients (43%) were found to have invasive adenocarcinoma in the resected esophagus (group 1), whereas 17 patients (57%) were found to have only HGD (group 2). Patient characteristics are summarized in Table 2. All of the patients in our series were white, and all but one were male. Although there was a tendency for patients from group 1 to be older than those in group 2 (64 vs. 58 years), this difference did not reach statistical significance. Gastroesophageal reflux symptoms and hiatal hernia were present in all 13 group 1 patients (100%), and 12 (71%) and 9 (53%) group 2 patients, respectively. There was a significantly longer duration of gastroesophageal reflux symptoms in group 1 (22 ± 14 years) compared with group 2 (9 ± 11 years; *p* < 0.05). No statistically significant differences in the prevalence of smoking and alcohol consumption between group 1 and 2 patients was found. There was a documented previous history of Barrett's esophagus in 11 group 1 patients (85%) and 11 group 2 patients (65%), and the duration of Bar-

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Table 2. PATIENT CHARACTERISTICS

	Group 1 (13 patients)	Group 2 (17 patients)
Age (yr)	64 ± 9	58 ± 10
Sex/race	12 WM, 1 WF	17 WM
Reflux		
Symptoms	13 (100%)	12 (71%)
Duration (yr)	22 ± 14	9 ± 11
Hiatal hernia	13 (100%)	9 (53%)
Smoke	9 (69%)	11 (65%)
Alcohol	11 (85%)	12 (71%)
BE		
Previous history	11 (85%)	11 (65%)
Duration (yr)	2.7 ± 3	2.7 ± 3

WM = white male; WF = white female; BE = Barrett's esophagus.

rett's esophagus was identical between the groups at 2.7 ± 3 years.

Surgical Results

All patients underwent partial esophagogastrectomy, and the results are summarized in Table 3. The operative approach for group 1 was transhiatal in ten patients, left thoracoabdominal in one patient, and Ivor-Lewis in two patients. The operative approach for group 2 was transhiatal in 12 patients, left thoracoabdominal in 2 patients, and Ivor-Lewis in 3 patients. One of the group 2 patients undergoing a left thoracoabdominal procedure had a second left cervical incision, gastric pull-up, and cervical esophagogastric anastomosis. There was one operative death, in a 77-year-old woman in group 1 who suffered an aspiration respiratory arrest on the eighth postoperative day, after an otherwise uncomplicated early recovery. Group 1 surgical complications included

Table 3. SURGICAL RESULTS

	Group 1 (13 patients)	Group 2 (17 patients)
Surgical approach		
THE	10	12
LTA	1	2
Ivor-Lewis	2	3
Complications		
Minor	2	1
Major	1	2
Mortality	1 (3.3%)	0
LOS (days)	15 ± 9	13 ± 8

THE = transhiatal; LTA = left thoracoabdominal; LOS = length of stay.

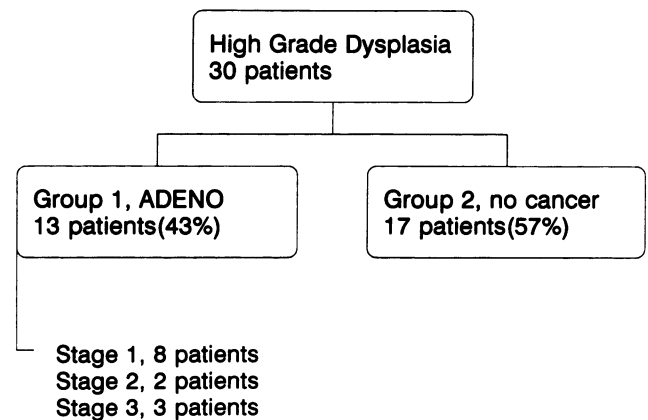


Figure 1. The frequency of occult adenocarcinoma and the American Joint Committee on Cancer stage of these tumors is shown. ADENO = adenocarcinoma.

transient hoarseness after transhiatal procedure (minor), postoperative delirium in a 73-year-old patient that delayed transfer from the intensive care unit (minor), and a superior mesenteric thrombosis in a patient with a diffusely calcified and atherosclerotic aorta, which necessitated resection of necrotic small and large bowel with resultant short-gut syndrome (major). Group 2 surgical complications included an asymptomatic transverse colon paragastric hiatal hernia (minor), an abdominal wound dehiscence requiring operative reclosure (major), and gangrene of the gastric tube used to replace the esophagus, which required subsequent resection with proximal esophageal diversion (major). The mean length of hospital stay was 15 ± 9 days for group 1, and 13 ± 8 days for group 2. This difference was not significant.

Pathologic Findings

The data from the preoperative evaluations of the patients are shown in Table 1. There was a mean of 3.5 esophagoscopies leading to 24.8 biopsy specimens over a 12.9-month period in our series of patients without the diagnosis of cancer being made. When the patients who were found to have adenocarcinoma in their esophagectomy specimens were compared with those who had dysplasia only, there were no statistically significant differences in the number of esophagoscopies, number of biopsy specimens, or length of endoscopic follow-up. There was a trend toward a longer time interval from first esophagoscopy to esophagectomy in the patients who were found to have adenocarcinoma (21.8 vs. 10.7; $p = 0.14$).

In the 13 patients in group 1 with occult invasive adenocarcinoma identified in the resected esophagus, AJCC staging was T1N0M0 (stage I) in eight patients, T2N0M0 (stage II) in two patients, T3N0M0 (stage III) in two patients, and T3N1M0 (stage III) in one patient (Fig. 1).

Outcome

The outcome for group 1 patients is shown in Table 4. Seven stage I patients are alive without cancer with a mean follow-up of 18 months (range, 1–72 months). In one patient, the Barrett's esophagus was incompletely excised at the initial resection, and high-grade dysplasia was retained as well. This patient died 72 months postoperatively from esophageal adenocarcinoma that arose in the retained segment of HGD. Both stage II patients are alive without cancer at 30 and 96 months of follow-up, respectively. Of the stage III patients, there was one operative death, one noncancer-related death at 6 months, and one patient alive with metastatic adenocarcinoma (bone metastases) 26 months postoperatively. Follow-up information was available for 15 of 17 group 2 patients. Of these patients, one died 33 months postoperatively of a colorectal carcinoma. All of the other patients were alive, without evidence of esophageal-related disease, over a 6- to 96-month follow-up (mean 40 months). The survival curves for group 1 (AJCC stage I, II, III) and group 2 (AJCC stage 0) are shown in Figure 2.

DISCUSSION

Although HGD in patients with Barrett's esophagus is a premalignant process, the length of time for the progression of HGD to invasive adenocarcinoma is unresolved. Tygat and Hameeteman,⁴ in a retrospective review, reported the development and progression of dysplasia in five patients with Barrett's esophagus who developed invasive adenocarcinoma. In their series, endoscopic biopsy specimens showed dysplastic epithe-

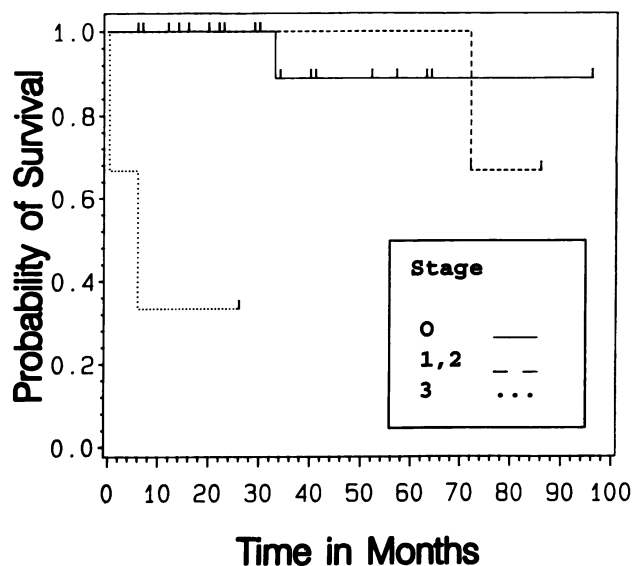


Figure 2. Actuarial survival curves for group 1 (American Joint Committee on Cancer [AJCC] stages 1–3) and group 2 (AJCC stage 0) patients.

lium before the development of invasive adenocarcinoma, and low-grade dysplasia preceded high-grade dysplasia. Although regression of low-grade dysplasia (or sampling error or histopathologic misinterpretation) was observed in two patients, once dysplasia became high grade, it progressed to invasive adenocarcinoma in all five cases within 1 year. Miros et al.⁵ prospectively followed 81 patients with biopsy-proven Barrett's esophagus and demonstrated the frequency of developing adenocarcinoma to Barrett's esophagus 0 in 58 patients without dysplasia, 1 of 20 in patients with low-grade dysplasia, and 2 in 3 in patients with HGD. The authors concluded that only patients with dysplasia develop invasive adenocarcinoma, and that persistent HGD is a reliable histopathologic marker for the subsequent development of adenocarcinoma. In our series, one patient from group 1 had an incomplete resection of high-grade dysplasia and subsequently developed invasive adenocarcinoma in this segment with bone metastases 6 years later.

Once invasive adenocarcinoma develops, it may initially be difficult to detect. Whereas some authors^{6,7} believe that reliable endoscopic differentiation between HGD alone and HGD with concomitant invasive adenocarcinoma is possible, others, including ourselves, have found early foci of adenocarcinoma difficult to detect. Some of the reasons for this difficulty are that adenocarcinoma may develop away from regions of endoscopically abnormal mucosa, that the focus of cancer often is small and subject to sampling error, and that the invasive cancer may undermine regenerated non-neoplastic squamous epithelium. In a previous, smaller se-

Table 4. SURVIVAL: GROUP 1

AJCC Stage	Duration (mo)	Outcome/Comment
1	14	NED
1	22	NED
1	23	NED
1	72	NED
1	72	Dead/recurrent adenocarcinoma in retained HGD segment
1	7	NED
1	6	NED
1	12	NED
2	30	NED
2	86	NED
3	8 days	Dead/aspiration
3	6	Dead/sudden death at home
3	26	Alive/bone metastases

NED = no evidence of disease; HGD = high-grade epithelial dysplasia.

ries from this institution, the incidence of "occult" adenocarcinoma was 50%.¹ Pera et al.⁸ (19 patients) and Altorki et al.⁹ (9 patients) have reported detecting invasive adenocarcinoma in 50% and 45% of patients undergoing "prophylactic" esophagectomy for Barrett's esophagus with HGD, respectively. In our current study, among the 30 patients who underwent prophylactic esophagectomy without a preoperative biopsy diagnosis of cancer, 13 (43%) were found to have invasive adenocarcinoma. The lack of statistically significant differences in number of preoperative esophagoscopies, number of biopsy specimens from Barrett's mucosa, and duration of endoscopic follow-up between patients with and without adenocarcinoma suggests that the diagnostic and surveillance techniques did not account for this finding (Table 1). Rather, the trend toward longer time interval between the first esophagoscopy and esophagectomy in patients with adenocarcinoma raises the possibility that these patients were later in the natural history of the Barrett's dysplasia-adenocarcinoma sequence.

Although in our series, patients with adenocarcinoma had a significantly longer duration of reflux symptoms, other characteristics including age, sex, race, smoking and drinking history, and duration of Barrett's esophagus were not significantly different between groups 1 and 2 (Table 2). Therefore, we do not believe that patient characteristics are sufficiently distinctive to identify those HGD patients with adenocarcinoma. To date, efforts to predict the presence of adenocarcinoma in patients with HGD using transesophageal ultrasound¹⁰ have failed to be reliable.

Given the premalignant nature of Barrett's esophagus with HGD, and the difficulty in detecting early invasive adenocarcinoma, we believe that aggressive surgical management is warranted in patients who are suitable surgical candidates. In some ways, patients with HGD present the greatest challenge to the esophageal surgeon because they have no dysphagia and with current antireflux medical therapy, often are totally asymptomatic. The recommended surgical approach involves esophageal resection, as for malignant disease, but esophageal reconstruction, as for benign disease. We believe that a transhiatal or multi-incisional approach with cervical esophago-gastric anastomosis, used in 23 of 30 patients in our series, optimally fulfills these guidelines. All of Barrett's esophagus, not just the dysplastic segment, must be excised to prevent the late development of HGD and adenocarcinoma,¹¹ as occurred in one of our patients. An operative approach resulting in cervical esophago-gastric anastomosis maximizes the chance that all the Barrett's esophagus is excised. In our series, there was only one postoperative death (3.3%), a 77-year-old woman who suffered an aspiration-related respiratory arrest 8 days postoperatively after a previously uncompli-

cated early recovery. The major postoperative complications included abdominal wound dehiscence (1), necrosis of the mobilized stomach (1), and thrombosis of the superior mesenteric artery (1). There were no anastomotic leaks or other major respiratory complications. The length of hospitalization for group 1 and 2 was 15 and 13 days, respectively. With a more standardized approach to these patients, the hospital stay currently is approximately 10 days (unpublished data).

A word of caution must be introduced concerning our recommendations for surgery in patients with Barrett's esophagus with HGD. Although we believe that esophageal resection and reconstruction may be performed safely, it is an operative procedure that is associated with the potential to significantly and adversely impact on survival and quality of life. Therefore, the recommendations for aggressive surgical management apply only for surgeons experienced in esophageal surgery.

Survival for those patients with invasive adenocarcinoma (group 1) is shown in Figure 2. All patients with AJCC stage I and II tumors are alive without recurrent cancer, except for one patient in whom recurrent adenocarcinoma developed, originating in an incompletely excised segment of HGD. Three of 13 patients (23%) with adenocarcinoma were found to have locally advanced staged tumors (AJCC stage III). The fact that almost a quarter of patients with adenocarcinoma may have locally advanced staged tumors is worrisome and is at variance with other reports that have shown that adenocarcinoma, when discovered in patients with HGD in Barrett's esophagus, is localized and low stage.⁶⁻⁹

High-grade epithelial dysplasia is an indication for prophylactic esophagectomy in suitable surgical candidates because of its premalignant potential and the high proportion of patients who have occult invasive adenocarcinoma. Patients with adenocarcinoma have a significantly longer/duration of reflux symptoms. Prophylactic esophagectomy can be performed safely, and survival in patients with complete resection of Barrett's esophagus and early-stage adenocarcinoma is excellent.

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