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Treatment of Barrett's esophagus with high-grade dysplasia or cancer: predictors of surgical versus endoscopic therapy

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Abstract

Introduction—Patients with Barrett's esophagus (BE) and high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) are at risk of progression to invasive carcinoma. Both esophagectomy and endoscopic ablation are treatment options. The aim of this study was to identify predictors of surgical versus endoscopic therapy at a tertiary center.

Methods—An institutional database identified patients with BE between 2003 and 2007. Demographic data and ICD-9 codes for esophagectomy, endoscopic ablation, as well as selected medical comorbidities were retrieved. Individual endoscopy, operative, and pathology reports were reviewed.

Results—Among 2107 individuals with BE, 79 underwent esophagectomy and 80 underwent endoscopic ablation. Mean age was 63.1 ± 10.6 yrs in the surgical group and 69.7 ± 9.4 yrs in the ablation group (P <0.0001). Among HGD/IMC patients, 9/76 (12%) first seen by a gastroenterologist underwent esophagectomy, while 18/21 (86%) first seen by a surgeon underwent esophagectomy. In a logistic regression model, factors independently associated with esophagectomy were: patient age 60 or less (OR 4.95 [1.65, 14.9]), cancer stage T1sm or greater (OR 16.0 [5.60, 45.6]), and initial consultation performed by a surgeon (vs gastroenterologist) (OR 35.1 [9.58, 129]).

Conclusions—Patient age and cancer stage predict treatment modality for BE with neoplasia. Treatment choice is further influenced by whether initial evaluation is performed by a gastroenterologist or a surgeon.

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Introduction

Barrett's esophagus refers to specialized intestinal metaplasia of the distal esophageal mucosa, and is the principal risk factor for esophageal adenocarcinoma[1]. Among individuals with Barrett's esophagus, 1 in 200 (0.5%) per year will develop esophageal adenocarcinoma[2]. Patients with Barrett's and high grade dysplasia (HGD) are at particularly high risk, with a recent meta-analysis suggesting an annual adenocarcinoma incidence of between 6% and 7% following initial diagnosis of HGD[3].

Historically, the standard treatment for Barrett's HGD has been surgical esophagectomy. Multiple retrospective studies published between 1993 and 2005 reported occult cancer, at a rate ranging from 33% to 73%, in surgical specimens from patients undergoing esophagectomy for HGD[4–11]. In surveys of American gastroenterologists published in 1999 and 2000, 73% and 82% of respondents, respectively, favored esophagectomy for patients with HGD[12–13].

Over the past decade, however, endoscopic treatment options for Barrett's esophagus have emerged, with techniques including photodynamic therapy (PDT) and endoscopic mucosal resection (EMR). In a randomized controlled trial of PDT, five-year follow-up demonstrated ablation of HGD in 77% of subjects receiving porfimer sodium PDT plus long-term acid suppression therapy[14]. Progression to cancer occurred in 15% of PDT-treated subjects, as compared with 29% of subjects receiving acid suppression alone[14].

Retrospective data from the Mayo Clinic have demonstrated comparable 5-year survival among HGD patients who underwent esophagectomy compared with HGD patients who underwent PDT[15]. A prospective comparison of esophagectomy versus endoscopic therapy has not been performed, however, and the optimal treatment strategy is unknown. Society for Surgery of the Alimentary Tract patient care guidelines suggest that endoscopic techniques are experimental, and should be reserved for patients with prohibitive operative risk[16]. Meanwhile, recently published practice guidelines from the American College of Gastroenterology indicate that mucosal ablation or resection may represent acceptable treatment strategies, and that esophagectomy need not be the default response to Barrett's HGD[17].

The purpose of this study was to identify demographic and clinical characteristics among Barrett's esophagus patients who underwent either surgical or endoscopic therapy at a tertiary referral center, and to identify predictors of treatment modality.

Methods

The study was performed at Massachusetts General Hospital, an urban, academic teaching hospital which serves as a tertiary referral center. For an individual patient with Barrett's HGD or esophageal carcinoma, referral for gastroenterological, surgical, or oncologic consultation, respectively, is at the discretion of the referring physician.

Identification of study subjects was performed through the Research Patient Data Registry (RPDR), an institutional database consisting of comprehensive records from over 3.5 million patients dating back to 1979. The study was approved by the institutional review board.

The RPDR was queried to identify patients with an ICD-9 code diagnosis for Barrett's esophagus (530.85). Demographic data including gender, ethnicity, date of birth, and vital status were also captured. Additional search criteria included ICD-9 code diagnosis of comorbid conditions including esophageal cancer, coronary artery disease, congestive heart

failure, and chronic obstructive pulmonary disease (see Appendix 1). Dates of all diagnoses were determined on the basis of date of initial ICD-9 coding.

Following identification and characterization of the cohort, the search was further restricted to identify Barrett's esophagus patients who had undergone esophagectomy or endoscopic therapy. For Barrett's esophagus patients who had undergone either surgical therapy, endoscopic therapy, or both, individual endoscopy, operative, and pathology reports were reviewed to confirm diagnosis of Barrett's esophagus and performance of therapy targeted at Barrett's-associated neoplasia. The medical record was reviewed to confirm the presence or absence of comorbid medical conditions. Patients were not excluded from the analysis on the basis of comorbid illness or perceived fitness for surgery.

Length of Barrett's esophagus was determined by the distance between the squamocolumnar junction and upper extent of the gastric folds, as described in either upper gastrointestinal endoscopy or esophagoscopy reports. Pre-treatment neoplasia stage was determined on the basis of biopsy and endoscopic ultrasound (EUS) findings. In instances of discrepancy between biopsy and EUS staging, the higher of the two stages was selected. Neoplasia stage was classified into three groups: 1) lesions limited to the mucosa (encompassing HGD, Tis, and T1a lesions); 2) T1 cancer with submucosal invasion (T1sm or T1b lesions); and 3) stage T2 or greater. Biopsy and EUS findings were recorded either on the basis of biopsy and/or EUS performed at our institution, or as documented in the clinical record based on reports from evaluation performed at referring institutions. Central review of all outside pathology specimens was not performed.

Type of initial subspecialty consultant (gastroenterologist, surgeon, or oncologist) was defined as the treating or evaluating clinician in the earliest clinic note or endoscopy report at our institution. If the patient's initial documented medical encounter at our institution was an endoscopy or EUS with referral from a physician outside the institution, as documented in the endoscopy report, then the gastroenterologist performing endoscopy/EUS was defined as the initial subspecialty consultant. However, if the referring physician for the endoscopy was a surgeon or oncologist from our institution, then that physician was defined as the initial subspecialty consultant.

The porfimer sodium PDT protocol at our institution has previously been described in detail.[18] In general, this consists of a 2 mg/kg porfimer sodium intravenous on day 0, followed by 2 light exposures (day 2 and day 4). Light delivery is via a cylindrical diffusing fiber (without a centering balloon), at a wavelength of 630 nm and energy of 150 J/cm. EMR is performed with either a saline-assisted cap and snare technique, or a band ligator device (Duette, Cook Medical, Bloomington, IN).

Statistical analysis was performed using SAS V 9.1.3 (SAS Institute, Cary, NC, USA). Univariate analysis was performed with testing of significance by t-test or Wilcoxon rank sum testing for continuous variables (depending on assumptions of normality of distribution), and either Chi square or Fisher's exact test for categorical variables. Following univariate analysis, a multiple variable logistic regression analysis was performed. Model inputs were selected on the basis of *a priori* hypotheses, without use of a variable selection algorithm. For one model covariate, length of Barrett's esophagus, mean imputation was used to account for missing data. All reported P values are two-sided.

Results

Patient characteristics

The database query identified 2107 individual patients with Barrett's esophagus at our institution between 2003 and July 17, 2007. Mean age at diagnosis of Barrett's esophagus was 61.2 ± 14.8 years. 64% of the cohort were male, and 88% were Caucasian. Co-morbid diagnoses were present as follows: coronary artery disease in 15% (307/2107); congestive heart failure in 7% (150/2107); chronic obstructive pulmonary disease in 6% (132/2107).

Treatment groups

Esophagectomy was performed in 82 patients, and endoscopic ablation was performed in 137 patients. Three patients underwent esophagectomy for indications other than Barrett's esophagus-associated neoplasia (Boerhaave's syndrome or esophageal perforation, squamous cell carcinoma) and were excluded from further analysis. Fifty-seven patients had undergone endoscopy with ablation or destruction of tissue other than Barrett's esophagus, most commonly resection of fundic gland polyps, and were excluded from further analysis. Endoscopic ablation techniques consisted of argon plasma coagulation in one patient, and in the remaining patients, either PDT (N=37 patients, 36 with porfimer sodium photosensitizer and 1 with aminolevulinic acid photosensitizer), EMR (N=32 patients), or a combination of PDT and EMR (N=10 patients).

Treatment designation was determined on the basis of primary treatment intent. As such, the esophagectomy group includes 2 patients taken to the operating room for planned esophagectomy, but in whom esophagectomy was aborted intra-operatively; and 4 patients who had undergone EMR for diagnostic/staging purposes prior to esophagectomy. The ablation group includes 2 patients who underwent PDT, but who later underwent esophagectomy.

Patient characteristics by treatment group

The treatment cohort ultimately consisted of 79 patients in the esophagectomy group, and 80 patients in the endoscopic ablation group (Table 1). Patients undergoing esophagectomy were on average younger at the time of treatment than patients undergoing endoscopic ablation – with a mean age of 63.1 ± 10.6 years in the esophagectomy group, versus 69.7 ± 9.4 years in the ablation group ($P<0.0001$). (Table 1). Esophagectomy rates were highest in patients aged 60 years or less, whereas ablation rates were highest in patients aged 80 years or greater.

A greater proportion of patients were male in the esophagectomy group compared with the ablation group (92% versus 80%, $P=0.02$). Patients in the esophagectomy group had longer length Barrett's esophagus than patients in the ablation group (6.6 ± 3.7 cm versus 5.4 ± 3.7 cm, $P=0.03$) (Table 1).

The prevalence of documented coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease did not appear to differ between the esophagectomy and ablation groups (Table 1).

Treatment modality by cancer stage

Among patients for whom both pretreatment tissue data and pretreatment EUS (performed at our institution or a referring institution) were available, there was agreement in disease stage between tissue diagnosis and EUS diagnosis in 84% of cases (105/125). Thirteen patients with HGD/IMC had their pre-treatment stage "upgraded" on the basis of EUS findings: 9 patients with tissue diagnosis of HGD/IMC were diagnosed with T1sm disease on the basis

of EUS findings, and 4 patients with tissue diagnosis of HGD/IMC were diagnosed with T2 or greater disease on the basis of EUS findings. Alternatively, for 7 patients, biopsies and/or EMR demonstrated invasive disease not detected by EUS.

Barrett's-associated neoplasia was staged as HGD or IMC in the majority of patients (88%) undergoing endoscopic ablation (Table 1). The four patients in the ablation group with stage T2 or greater disease were each treated for palliative purposes or without curative intent. In contrast, a wider range of pre-treatment cancer stage was observed among patients undergoing esophagectomy (Table 1). The proportion of patients undergoing endoscopic ablation (versus esophagectomy) was: 71% (70/98) among patients with HGD/IMC; 43% (6/14) among patients with T1sm disease; and 9% (4/47) among patients with T2 or greater disease.

Treatment modality by initial subspecialty consultant

Among patients with Barrett's-associated neoplasia who underwent endoscopic ablation, a gastroenterologist was the initial consultant in 95% (76/80) of cases. In contrast, a wider range of initial consultant was evident in patients undergoing esophagectomy (Table 1).

Initial consultation was performed by a gastroenterologist for the majority of patients with HGD or IMC (78%, or 76/98). A surgeon was the initial consultant for 21 patients with HGD or IMC. Among patients with HGD/IMC, crude esophagectomy rates were 12% (9/76) if initial consultation was performed by a gastroenterologist, versus 86% (18/21) if initial consultation was performed by a surgeon ($P<0.0001$).

Among patients with T2 or greater disease (N=47), a gastroenterologist was the initial consultant in 23 cases and a surgeon was the initial consultant in 20 cases. Oncologists were the initial consultant for relatively few patients (3%, or 5/159), irrespective of cancer stage.

Point of referral

Data regarding the referring physician was available for 126 patients. Referring physicians consisted of gastroenterologists in 75% of cases (95/126), internists or family practitioners in 16% of cases (20/126), surgeons and oncologists each in 4% of cases (5/126), and an emergency room physician in 1 case.

Eighty-one percent (86/106) of referrals to gastroenterologists at our institution came from another gastroenterologist, 14% (15/106) came from an internist or family practitioner, and 2% (2/106) came from a surgeon. Forty-seven percent (8/17) of referrals to surgeons at our institution came from gastroenterologists, 29% (5/17) came from internists or family practitioners, and 18% (3/17) came from another surgeon.

Post-surgical pathology among patients with HGD/IMC

Thirty patients underwent esophagectomy following pre-operative evaluation indicating disease limited to the mucosa (HGD/IMC). Among these patients, disease was limited to the mucosa in surgical resection specimens for 80% (24/30). Cancer stage was "under-staged" pre-treatment in 20% of patients (6/30), including 5 patients found to have T1sm disease in the surgical specimen and 1 patient with more deeply invasive adenocarcinoma.

Logistic regression analysis

A logistic regression analysis was performed using a 4-variable model: patient age, pre-treatment cancer stage, length of Barrett's esophagus, and initial consultant seen. Unadjusted and adjusted odds ratios are presented in Table 2.

Independent predictors of esophagectomy, after adjusting for other variables in the model, were: age 60 years or less (OR 4.95 [95% CI 1.65, 14.9]), cancer stage T1sm or greater (OR 16.0 [95% CI 5.60, 45.6]), and initial consultation performed by a surgeon (OR 35.1 [95% CI 9.58, 129]).

Including patient gender in the model did not significantly alter the model results. Creation of an interaction variable as a model input did not support the influence of cancer stage as an effect modifier of the association between initial consultant (surgeon versus gastroenterologist) and esophagectomy.

Discussion

For patients with Barrett's esophagus and HGD or IMC, there are neither prospective, controlled data nor consensus algorithms to guide treatment strategy. The goal of this study was to identify predictors of surgical versus endoscopic therapy in a tertiary center offering both treatment options. Our data suggest that patient age and cancer stage independently predict whether a patient will receive surgical versus endoscopic therapy. Patient age 60 years or less, and cancer stage T1sm or greater are significant predictors of surgical versus endoscopic therapy. Our data do not support an influence of cardiac or pulmonary comorbidity on choice of therapy, although the method of capturing comorbidity data (by ICD-9 coding) may have been limited in its ability to gauge presence or severity of comorbid illness.

Our data also suggest that choice of therapeutic modality, particularly for patients with HGD/IMC, depends upon whether the patient is evaluated by a surgeon or a gastroenterologist. This likely reflects a referral or selection effect. Presumably, a particular patient with HGD/IMC is referred for esophagectomy because he/she has been deemed an appropriate surgical candidate. Other patients may be deemed more suitable for endoscopic therapy. Yet the factors which influence this treatment decision are largely unknown.

One set of factors may be related to endoscopic or biopsy features of Barrett's esophagus. Our model controlled for length of Barrett's esophagus, which did not appear to predict treatment modality. However, our model did not control for extent of HGD or IMC. A decision for surgical or endoscopic therapy could be quite different for a patient with a nodular focus of dysplasia, as compared to a patient with a long, circumferential extent of Barrett's with extensive HGD in multiple biopsy locations.

A second set of factors may be related to a patient's overall health status. Among Medicare patients undergoing esophagectomy, operative mortality varies considerably according toindividual surgeon and hospital operative volume[19–20]. As such, patients with high operative risk due to comorbid illness may be inappropriate surgical candidates. Specifically among patients undergoing esophagectomy for HGD at experienced centers, including our own institution, a 2% operative mortality has been reported as a low-end estimate[10,21].

Endoscopic therapy, while less invasive than esophagectomy, is not without procedural morbidity. Quality of life following porfimer sodium PDT, for instance, may be impacted by photosensitivity of several weeks' duration. Esophageal stricture develops in 23–27% of patients following porfimer sodium PDT for HGD or IMC, and may require multiple endoscopic dilations for palliation[18,22].

This study does not address efficacy or long-term outcomes of either esophagectomy or endoscopic ablation for treatment of Barrett's-associated neoplasia. Although esophagectomy is considered the more definitive treatment by many, caveats should accompany assurances of long-term cure for either approach. Recurrent Barrett's[23] and

adenocarcinoma[24] have been described following esophagectomy. Alternatively, in a prospective study of HGD patients receiving PDT, 15% developed cancer over 5-year follow-up[14]. The risk of recurrent HGD or cancer is a particular concern among patients with glandular epithelium buried beneath neosquamous mucosa following PDT[25–26].

Moreover, accurate disease staging is a critical prerequisite to selecting appropriate therapy for Barrett's neoplasia. Endoscopic ablation or resection can theoretically eradicate neoplasia when this is limited to the esophageal mucosa and more advanced disease has been excluded. In the current era of systematic biopsy protocols, as well as staging provided by EMR and EUS, the prevalence of occult carcinoma in patients with Barrett's HGD appears to be declining. A retrospective analysis from Johns Hopkins reported that occult cancer was found in 43% of esophagectomy specimens for HGD between 1982–1994, but in 17% of specimens between 1994 and 2001[27]. A more recent analysis has demonstrated that when a distinction is made between mucosal-limited and invasive disease among historical cohorts found to have occult carcinoma following esophagectomy for HGD, the prevalence of occult invasive carcinoma is 12.7%.[28] High rates of metastatic lymphadenopathy are present in patients with submucosal tumor invasion by EMR[29], and as such patients with T1sm disease are not ideal candidates for endoscopic therapy.

Patients in our study did not undergo uniform pre-treatment evaluation, which was instead performed at the discretion of the treating gastroenterologist or surgeon. In some instances, this evaluation may have taken place at an outside institution prior to referral. Variability in performance or interpretation of histopathologic, endoscopic, or imaging findings may impact accuracy of pre-treatment cancer stage. However, our study defined pre-treatment cancer stage on the basis of the individual data available to treating clinicians, which are the data that drive treatment decisions in clinical practice.

Additional limitations of this study include its retrospective design, although our multivariate logistic regression model attempted to control for some of the potential biases. The results have not been prospectively validated and should therefore be considered hypothesis-generating. And to the extent that availability and expertise of surgical and/or endoscopic therapy for Barrett's esophagus is likely to vary among medical centers, external validity of our findings can not be assumed. A prior survey of Barrett's practice patterns indicated that ablation therapy is more like to be performed in an academic rather than a community setting[5]. In our analysis, 86% of HGD/IMC patients evaluated by a surgeon underwent esophagectomy, as compared with 12% of HGD/IMC patients evaluated by a gastroenterologist. The latter esophagectomy rate is considerably lower than the 73–83% esophagectomy rate recommended for HGD in national surveys of gastroenterologists[12–13], though it is conceivable that national practice patterns have evolved over the past decade. Our study failed to identify subjects prior to 2003 on the basis of the specified search criteria, as an ICD-9 code specific for Barrett's esophagus was not used before this time. As such, our study can not effectively assess longer-term trends in endoscopic verus surgical management of HGD at our institution.

In addition to physician recommendations, the potential role of patient preferences in shared decision-making should be considered. Cancer risk may affect health-related quality of life for a patient with Barrett's[30]. In a survey of Barrett's patients presented with the hypothetical scenario of HGD, the majority preferred frequent endoscopic surveillance over either esophagectomy or PDT[31]. Patient choice among these strategies is likely to be influenced by perceived post-treatment quality of life, including presence or absence of dysphagia and risk of cancer[32]. The impact of patient self-referral for endoscopic or surgical therapy for Barrett's could not be assessed in this retrospective analysis, yet may be

important in an era in which the internet and other sources of patient information are readily available.

The magnitude of the difference in esophagectomy rates for HGD/IMC between surgeons and gastroenterologists in our study might be noteworthy from the patient's perspective – and further underscores the requirement that treatment decisions be based on the best available outcome, efficacy, and safety data. This burden of proof may be increasingly borne by gastroenterologists, due to the role of the gastroenterologist as endoscopist and endoscopic ultrasonographer. In this study, 75% of referrals came from gastroenterologists, and 78% (76/98) of HGD/IMC patients were first seen at our institution by a gastroenterologist. As endoscopic technologies for ablation of Barrett's mucosa continue to develop, the extent to which data emerge, and the extent to which practicing gastroenterologists become widely proficient in application of these techniques may influence the volume of both endoscopic ablations and esophagectomies performed for HGD/IMC.

In summary, at our institution between 2003 and 2007, more patients with Barrett's HGD/IMC underwent endoscopic ablation than underwent esophagectomy. Among all patients with Barrett's-associated neoplasia, age 60 years or less and cancer stage T1sm or greater predict esophagectomy over endoscopic therapy. Whether a patient is first evaluated by a gastroenterologist or a surgeon also appears to influence treatment modality; this effect persists even when controlling for age and cancer stage.

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Appendix 1

ICD 9 codes for identification of comorbid conditions, procedures in database search:

Esophageal cancer

150.0, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 150.9

Coronary artery disease

414.0, 414.1, 414.8, 414.9, 414.00

Congestive heart failure

428, 428.0, 428.1, 428.22, 428.30, 428.31, 428.32, 428.33, 428.9

Chronic obstructive pulmonary disease

491.20, 491.21, 491.8, 491.22, 491.9, 492, 492.0, 492.8

Esophagectomy

42.40, 42.41, 42.42, 42.51, 42.54, 42.58, 42.62

Endoscopic excision or destruction of lesion or tissue of the esophagus

42.33

Table 1

Patient characteristics by treatment modality

	Esophagectomy	Ablation	P value
N	79	80	
Age at treatment	63.1 ± 10.6	69.7 ± 9.4	<0.0001
Male gender	73 (92%)	64 (80%)	0.02
Vital status: deceased	10 (13%)	8 (10%)	0.60
Length BE (in cm)*	6.6 ± 3.7	5.4 ± 3.7	0.03
Co-morbid diagnoses			
CAD	19 (24%)	21 (26%)	0.75
CHF	6 (8%)	5 (6%)	0.74
COPD	5 (6%)	9 (11%)	0.27
Cancer stage			
HGD/IMC	28 (35%)	70 (88%)	<0.0001
T1sm	8 (10%)	6 (8%)	
T2 or greater	43 (54%)	4 (5%)	
Initial consultant			
Gastroenterologist	32 (41%)	76 (95%)	<0.0001
Surgeon	42 (53%)	4 (5%)	
Oncologist	5 (6%)	0	

* Pre-treatment length of Barrett's esophagus not recorded in 24 patients in esophagectomy group, and 4 patients in ablation group.

Table 2

Logistic regression model: predictors of esophagectomy

	Unadjusted OR	Adjusted OR	95% CI
Age 60 years or less	4.15	4.95	1.65, 14.9
Cancer stage T1sm or greater	12.2	16.0	5.60, 45.6
Length Barrett's	1.10	1.06	0.92, 1.23
Initial consultant (surgeon vs gastroenterologist)	24.9	35.1	9.58, 129