Original Article

Prevalence of adenocarcinoma at esophagectomy for Barrett's esophagus with high grade dysplasia

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ABSTRACT

Background: Barrett's esophagus with high grade dysplasia (HGD) may require surgical resection because of the risk of concomitant adenocarcinoma. The prevalence of invasive, occult carcinoma (≥stage 1B) in this setting has varied. We investigated the association of adenocarcinoma at operative resection for high grade dysplasia.

Methods: Using an electronic medical record, we identified patients who underwent esophagectomy for high grade dysplasia at the University of Pittsburgh Medical Center between 1993 and 2007. Preoperative diagnosis was confirmed by reviewing endoscopic, radiologic and pathology reports. Postoperative pathology reports were compared to the preoperative diagnosis.

Results: 68 patients (12 females and 56 males) with a preoperative diagnosis of high grade dysplasia underwent operative resection. The mean age was 64 years (range 36 to 86 years). Of 68 patients, 12 (17.6%) had adenocarcinoma, 2 (2.9%) were downgraded to low grade dysplasia, and 54 (79.4%) were confirmed as HGD. Of the 12 patients with adenocarcinoma, 4 (5.9% of total cohort) had intramucosal cancer (Stage 1A) and 8 (11.7% of total cohort) had invasive cancer with submucosal invasion or more advanced disease. Of the 8 patients with invasive adenocarcinoma, 4 did not have preoperative endoscopic or radiologic testing suggestive of advanced disease.

Conclusion: The overall prevalence of adenocarcinoma in association with a preoperative diagnosis of HGD was 17.6%. Invasive adenocarcinoma was present in 11.7% of subjects and was clinically occult in 5.9%.

KEY WORDS Barrett's, high grade dysplasia, esophagectomy, adenocarcinoma of esophagus

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Introduction

In Barrett's esophagus (BE), the esophageal squamous epithelium undergoes intestinal metaplasia to columnar mucosa. This transformation has been hypothesized to occur after prolonged exposure to an acid environment and is believed to be an intermediate step in the development of adenocarcinoma. Dysplasia in Barrett's signifies progression toward adenocarcinoma and is classified as indeterminate, low grade, or high grade dysplasia (HGD). Patients with high grade dysplasia are at higher risk of developing adenocarcinoma of the esophagus, and may have concomitant cancer.

Understanding the prevalence of adenocarcinoma in patients with BE and HGD is critical due to the different potential approaches to management. Some advocate surgical treatment as the optimal approach (1-3) while some favor endoscopic therapeutic treatment (4-7), and still others prefer to monitor the disease with surveillance endoscopy to avoid the morbidity and mortality associated with esophagectomy (8,9).

Several studies have reported on the prevalence of adenocarcinoma in patients with Barrett's esophagus and HGD. In older series, the risk of concomitant adenocarcinoma in patients with BE with HGD was as high as 40% (10). A study of 49 patients who underwent esophagectomy for HGD reported a cancer incidence of 36.7% (11). More recently, a meta analysis of 23 studies of patients who underwent esophagectomy for BE and HGD reported a 12.7% incidence of invasive adenocarcinoma

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(12). Thus, there has been a wide variation in the prevalence of adenocarcinoma in patients with BE and HGD.

One factor that may have contributed to this variation is the differentiation between intramucosal carcinoma and invasive adenocarcinoma. The esophagus is unique in that intramucosal cancer does carry a small but definite 3-4% risk of nodal involvement, but the risk of nodal metastasis increases to 8 to 33 % with invasive disease, defined as disease that invades into the submucosa (13). Due to the difference in risk for nodal metastasis, differentiation of intramucosal carcinoma from invasive cancer is clinically important. In the meta-analysis the overall prevalence of intramucosal and invasive cancer, in a pooled average, from 23 studies was 39.9%. In the 14 studies that differentiated intramucosal carcinoma from invasive cancer, the prevalence of invasive cancer was only 12.7% (12).

The aim of our study was to examine the prevalence of adenocarcinoma at esophagectomy among patients with a preoperative endoscopic diagnosis of high grade dysplasia undergoing surgical resection.

Methods

Patients were identified through our institution's medical record data repository. This repository contains whole-text medical records and integrates information from central transcription, laboratory, pharmacy, finance, administrative, and other departmental databases throughout the University of Pittsburgh Medical Center hospital system. When data are imported into the medical archival record system (MARS), all terms are indexed so that they can be used for retrieval and cross correlation.

Boolean searches can be executed based on the mention of any word or combination of words in admission notes, discharge summaries, radiology reports, and other documentation.

To meet HIPAA guidelines and insure patient confidentiality, all data was de-identified using an honest broker system. This study met the criteria for exemption of informed consent by the University of Pittsburgh Institutional Review Board. We identified patients who underwent esophagectomy for high grade dysplasia in the setting of Barrett's esophagus between January 1993 and June 2007. The search terms used variations of Barrett's, high grade dysplasia, adenocarcinoma of esophagus, and esophagectomy. For inclusion, subjects had to have a pre-operative diagnosis of high grade dysplasia confirmed by the pathology department at the University of Pittsburgh Medical Center. Patients with a preoperative diagnosis of low grade dysplasia or invasive adenocarcinoma or who underwent esophagectomy for other indications were excluded. Cases were identified by retrospective review of preoperative pathology reports of biopsy specimens obtained at endoscopy. After identifying the cohort of patients undergoing resection, all available preoperative endoscopy, surgical, and radiology reports for each of the patients was reviewed.

Postoperative pathology reports were reviewed to determine whether the final pathologic diagnosis remained high grade dysplasia, was upgraded to adenocarcinoma, or was downgraded to low grade or no dysplasia.

In an attempt to provide uniformity in diagnosis of high grade dysplasia and carcinoma, all preoperative and postoperative pathology specimens were reviewed by full time academic pathologist from the Department of Pathology at the University of Pittsburgh Medical Center.

Definitions

Intramucosal carcinoma was defined as neoplasia that invaded into the lamina propria or muscularis mucosa but not into the submucosal layer. It is considered stage T1a by the American Joint Committee on Cancer. Invasive cancer was defined as neoplasia that invaded into the submucosa or beyond, and is staged as at least T1b.

Results

A total of 68 patients (12 females and 56 males) underwent esophagectomy with a preoperative diagnosis of high grade dysplasia between 1993 and 2007. The mean age was 64 years (range 36 to 86 years). The average time between diagnosis of HGD and esophagectomy was 95 days (range 5 to 872 days). Of the 68 patients, on the post operative specimen, 12 (17.6%) had adenocarcinoma, 2 (2.9%) were downgraded to low grade dysplasia, and 54 (79.4%) were confirmed as HGD. Of the 12 patients with adenocarcinoma, 4 had intramucosal cancer and 8 had invasive cancer with submucosal invasion or more advanced disease (Table 1). Therefore the rate of invasive carcinoma stage T1b or more was 11.7% (8/68).

In the 8 patients with a postoperative diagnosis of invasive cancer, the size of the tumor ranged from 0.3 cm to 5 cm, with the average 1.86 cm. The TNM staging of the tumors revealed 5 patients with T1bN0Mx, 1 with T1bN1M1, 1 with T3N1M1, and 1 with T3N1M0. The 4 patients with intramucosal cancer had tumor sizes ranging from 0.1 to 1.2 cm, with an average of 0.61 cm.

The 2 tumors with T3 staging postoperatively had tumor sizes of 4 cm and 5 cm. The patient with the 4 cm tumor had evidence of malignancy on a preoperative positron

Table 1 TNM staging of subjects with invasive adenocarcinoma

Stage	Size of tumor postoperatively(cm)
T1aN0M0	0.9
T1aN0Mx	1.2
T1aN0Mx	0.1
T1aN0Mx	0.25
T1bN0Mx	1.0
T1bN0Mx	0.3
T1bN0Mx	1.0
T1bN0Mx	0.5
T1bN0Mx	1.5
T1bN1Mx	1.6
T3N1Mx	4.0
T3N1M1b	5.0

emission tomography – computerized tomography (CT) scan. On endoscopic ultrasound, this patient had multiple enlarged thoracic lymph nodes. The patient with the 5 cm tumor had a preoperative CT scan revealing a 3.1 cm mass with multiple mediastinal lymph nodes. This same patient had a preoperative barium esophogram suggestive of an esophageal stricture. Two other patients had preoperative findings suggestive of invasive disease. The patient with a 1.6 cm tumor staged as T1b had esophageal thickening up to 7 mm noted on a preoperative computed tomography scan and on preoperative endoscopy multiple esophageal nodules were noted. The patient with T1b staging and a 1.5 cm tumor had nodular, ulcerated lesions on endoscopy and a preoperative endoscopic ultrasound was suggestive of submucosal involvement (Table 2). None of the other patients with invasive cancer or intramucosal carcinoma had radiologic or endoscopic evidence suggestive of cancer on preoperative testing.

Despite a preoperative diagnosis of HGD 2 patients staged as T3 had radiologic and endoscopic evidence to suggest invasive cancer. Two patients with subsequent T1b staging postoperatively also had preoperative suspicion for malignancy. Thus, 4 patients with preoperative HGD had occult carcinoma detected postoperatively, for an occult incidence rate of 5.9% (4/68).

We performed a time based analysis, based on date of surgical resection to see if the rate of adenocarcinoma in association with HGD decreased over time. We divided patients to 2 groups: those who underwent surgery between 1993 and 2000, and those between 2000 and 2007. Three of 20 patients (15%) were found to have adenocarcinoma in first group, while 9 of 48 (18.8%) were found to have adenocarcinoma in second group (P=0.77). Even when the groups were analyzed from 1993 to 2003 and 2004 to 2007, no significant difference was found (8/40 and 4/28

Table 2 Preoperative testing of patients with invasive adenocarcinoma

Stage	Size of tumor postoperatively(cm)	Preoperative endoscopic features	Preoperative radiologic testing
T1bN0Mx[1]	1.0	Erosion at cardia	EUS showed no mass or nodal involvement
T1bN0Mx[1]	0.3	No mass lesion	No studies preoperatively except barium swallow with no masses seen
T1bN0Mx[1]	1.0	No mass lesion	EUS shows no masses or enlarged nodes CT scan shows no enlarged nodes
T1bN0Mx[1]	0.5	No mass lesion	EUS shows no enlarged nodes -Barium esophagram negative
T1bN0Mx	1.5	Nodular ulcerated lesion	EUS suggestive of possible submucosal involvement
T1bN1Mx	1.6	Nodules	CT shows thickening of esophagus of 7 mm with no mass or nodal enlargement
T3N1Mx	4.0	No mass lesion	PET CT suggestive of malignancy and abnormal nodes CT shows 2.3 cm mass in mid esophagus with abnormal nodes
T3N1M1b	5.0	Stricture, Barium esophogram suggestive of carcinoma	CT shows 3.1x2.6 cm esophageal tumor proximal to GE junction. Multiple mediastinal nodes with possible lung and liver mets

respectively, P=0.379).

Discussion

In this large surgical series examining adenocarcinoma in Barrett's esophagus with a preoperative diagnosis of high grade dysplasia, we report an overall prevalence of adenocarcinoma of 17.6% with 11.7% invasive and 5.9% occult. This is in contrast to previous early surgical reports where a much higher rate of adenocarcinoma was observed. In the meta analysis of 23 studies involving 441 patients undergoing surgery for HGD, the pooled rate of adenocarcinoma was 39.9% (12). However, in 14 studies within the meta analysis where a distinction between intramucosal and invasive carcinoma was possible and the intramucosal cancers were excluded, the rate of invasive adenocarcinoma fell to 12.7%, consistent with our observation. In another recent surgical series, the rate of invasive adenocarcinoma at surgery for HGD was 6.7% (4/60) (14).

Several predictors of invasive carcinoma in the setting of HGD have been recognized. Nodular lesions in HGD have been shown to be at a higher risk for adenocarcinoma (15). A recent study analyzed pooled data from multiple studies, and showed that visible lesions at endoscopy are associated with a higher risk of submucosal invasion, although statistical significance was not reached (12).

Determining the true rate of occult adenocarcinoma in Barrett's with HGD is important because it impacts on the recommendations for management. If the rate of malignancy were 40% or even higher, than the associated risk of mortality to adenocarcinoma would be substantial enough that surgery would be the optimal choice. However, if the rate is more on the order of 8% -12%, than the risk of surgery must be weighed against the risk of the operation, and the potential response to less invasive treatments such as endoscopic therapy, including mucosal resection or photoablative or radioablative treatment. Esophagectomy is a procedure with a mortality risk of 3% to 8%, and with risk for significant morbidity, even at the most experienced centers. In a lower volume center, these risks are higher (10,16). A recent study from the University of Pittsburgh reported a 30 day mortality of 0% for T1 cancer patients undergoing esophagectomy, so local expertise may affect the clinical approach (17). Multiple patient factors including patient age and health status must be considered when deciding on the management of patients with HGD.

A recent review of 1074 patients from 16 studies, concluded that endoscopic therapy including photodynamic therapy, argon plasma coagulation, or radiofrequency ablation, can eradicate Barrett's disease and dysplasia, and were generally well tolerated (18). It is possible that endoscopic therapy might have been successful in the 4 patients in our cohort with T1a stage intramucosal disease.

One limitation of our study is the lack of standardized preoperative testing for the patients in our cohort. A lack of comprehensive preoperative testing may have contributed to a higher rate of occult cancer, by increasing patients in the group with no suspicion for invasive cancer. Three of the four subjects with occult invasive adenocarcinoma did not undergo radiologic assessment at our center. Because of our using deidentified data, we could not re-review the outside studies. However, these subjects had very small tumors without lymph node involvement, and the likelihood that they were truly occult is high. As with all retrospective studies, selection bias remains a concern, although we attempted to minimize bias by searching our electronic medical records using comprehensive inclusion and exclusion criteria.

The rate of invasive adenocarcinoma in association with HGD and Barrett's in this series was 11.7% with 5.9% having occult adenocarcinoma. When analyzed based on the date of surgery, we did not find any significant difference in the rate of detection of postoperative adenocarcinoma in patients with HGD over time, indicating that rate of cancer detection did not change in more recent years with the advent of more modern endoscopic techniques and imaging.

Debate continues as to the best management strategy when HGD is diagnosed in the setting of Barrett's esophagus. Prior studies may have overestimated the risk of invasive cancer, by inclusion of intramucosal carcinoma, which has a much lower risk of nodal metastasis. Our study confirms a low rate of occult cancer in patients with HGD, making endoscopic therapy an attractive alternative to surgery.

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