

Low prevalence of submucosal invasive carcinoma at esophagectomy for high-grade dysplasia or intramucosal adenocarcinoma in Barrett's esophagus: a 20-year experience CME

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Background: The rate of occult adenocarcinoma at esophagectomy in patients with Barrett's esophagus (BE) and high-grade dysplasia (HGD) has been reported to be approximately 40%. Recently, it has been suggested that this risk may be overestimated.

Objective: Our purpose was to determine the rate of submucosal invasive adenocarcinoma in patients undergoing esophagectomy for BE after biopsy diagnosis of HGD or intramucosal carcinoma (IMC). A secondary aim was to identify clinical risk factors for submucosal invasive adenocarcinoma in these patients.

Design: A retrospective study.

Setting: Tertiary referral center.

Patients: All patients with preoperative BE with HGD or IMC treated with esophagectomy over a 20 year period.

Interventions: Esophagectomy.

Main Outcome Measurements: Submucosal invasive adenocarcinoma at esophagectomy.

Results: Sixty patients were included (41 with preoperative HGD, 19 with preoperative IMC). The overall rate of submucosal invasive carcinoma was 6.7% (95% CI, 1.8%-16.2%) (n = 4), with a 5% rate of submucosal invasion in patients with preoperative HGD and 11% for patients with preoperative IMC. All 4 patients with submucosal invasion at esophagectomy had either nodular or ulcerated mucosa on preoperative endoscopy. The 1-year and 5-year all-cause risks of death for the entire cohort were 1.9% and 10.9%, respectively.

Limitations: Retrospective study.

Conclusions: The rate of submucosal invasive adenocarcinoma at esophagectomy in BE patients with HGD or IMC on biopsy is much lower than 40%. After adequate sampling and staging, patients with BE with HGD and IMC, especially those without endoscopically visible lesions, can potentially be treated by nonsurgical (local) therapies. (Gastrointest Endosc 2009;69:777-83.)

Endoscopic surveillance with mucosal biopsies and histologic assessment for dysplasia remains the most clinically used method for risk assessment in Barrett's

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; HGD, high-grade dysplasia; IMC, intramucosal carcinoma; PDT, photodynamic therapy; PPI, proton pump inhibitor; RFA, radiofrequency ablation.

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esophagus (BE). The management of BE with high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) has been frequently debated among gastroenterologists and thoracic surgeons. The presence of occult submucosal invasive carcinoma in patients with biopsy diagnoses of HGD and IMC is among the top considerations for surgical versus locally ablative management.

Series of patients with BE with a biopsy diagnosis of HGD treated by esophagectomy have reported a range of 13% to 75% occult cancer in the esophagectomy specimen.¹⁻¹¹ The most frequently quoted percentage of occult cancer is 40%, which is the statistical mode of this wide range.¹² A recently published comprehensive review of

23 studies on this topic has shown that, although the overall pooled average for invasive cancer was 39.9% among 441 patients who underwent esophagectomy for HGD, only 14 studies had differentiated submucosal invasion versus lamina propria invasion in the esophagectomy specimens.¹³ Of those 14 studies, 12.7% of the 213 patients had submucosal invasion at esophagectomy, which is far less than a 40% prevalence of “cancer.” Submucosal invasion is an important end point at resection because HGD and IMC can potentially be treated by endoscopic therapy.

The current practices in HGD management vary from intensive endoscopic surveillance every 3 months, endoscopic therapies (photodynamic therapy [PDT], radiofrequency ablation [RFA], and EMR), and esophagectomy. Selection of management options is frequently individualized and depends on patient factors such as patient comorbidities, patient preference, and center experience. The mortality rate from esophagectomy varies between 3% and 10%, with a morbidity rate of 45%.^{1,2} High-volume experienced centers for esophagectomy, however, have reported mortality rates of less than 3%.^{3,4,14,15} The long-term mortality rate is influenced by progression to invasive esophageal cancer in these HGD/IMC patients or the presence of a preexisting occult cancer.

Progression of BE with HGD to invasive cancer is believed to be slow, and the reported 5-year progression rate has varied from 16% to 59%.^{15,16} A recent meta-analysis of patients with BE with HGD concluded that esophageal adenocarcinoma develops in approximately 6 patients per 100 patient-years during the first few years of follow-up.¹⁷ Given the wide range of reported rates of progression and the data that suggest a slow natural history, treatment versus observation at the time of diagnosis of HGD remains an unsettled issue, especially when more invasive treatments carry substantial risks. Encouragingly, the 5-year survival of BE patients with HGD treated with PDT with or without EMR versus esophagectomy has been shown to be similar in a recent large study.⁶

As the management of BE with HGD continues to be debated, there is renewed interest in the previously quoted ranges of prevalence of synchronous invasive carcinoma in HGD. Moreover, BE with IMC has not been extensively studied as a separate group for the presence of submucosal invasive carcinoma at surgical resection.¹⁸ This retrospective study examines the prevalence of submucosal invasive carcinoma at esophagectomy in patients with BE with a preoperative biopsy diagnosis of HGD or IMC over a 20-year period in a high-volume center for esophagectomy.

METHODS

Definitions

BE is defined as columnar metaplasia, with goblet cells, identified in biopsy specimens obtained from the esophagus

Capsule Summary

What is already known on this topic

- In patients with Barrett’s esophagus (BE) containing high-grade dysplasia (HGD) or intramucosal adenocarcinoma (IMC), the presence of occult submucosal invasive carcinoma is a key determinant of surgical versus local ablative management.

What this study adds to our knowledge

- In a retrospective study of 60 patients with preoperative BE containing HGD or IMC treated with esophagectomy over a 20-year period, the overall rate of submucosal invasive carcinoma was 6.7%, a rate that sharply contrasts with the frequently quoted 40% rate.

above the gastroesophageal junction.¹⁹ HGD in BE shows increased crypt complexity, crowding, irregularity, and branching, with more pronounced nuclear stratification, loss of nuclear polarity, pleomorphism, and mitotic activity.²⁰ IMC is defined as neoplastic epithelium that has invaded beyond the basement membrane into the surrounding lamina propria or muscularis mucosae but not into the submucosal layer.²⁰

“Single-level” HGD or IMC was defined as the presence of HGD or IMC at only one anatomic level measured by the distance in centimeters from the incisors to the location in the esophagus. “Multiple-level” HGD or IMC was defined as the presence of HGD or IMC at 2 or more different anatomic levels measured by the distance in centimeters from the incisors.

“Prevalent” HGD or IMC was defined as a diagnosis of HGD or IMC at index endoscopy or within 1 year of beginning surveillance endoscopy. “Incident” HGD or IMC was defined as a new diagnosis after having no dysplasia or cancer for at least 1 year after index endoscopy.¹⁵

Study method

The pathology database from a single high-volume center was queried for esophagectomy specimens between May 11, 1987, and February 2, 2007. The endoscopy reporting system (GI Station 5.0) was also queried for patients undergoing EGD and EUS with “high-grade dysplasia” or “HGD” from December 1, 1995, to December 31, 2006. Cases were then identified by retrospective medical chart review of pathology reports from pre-esophagectomy endoscopic biopsy specimens. All patients underwent an EGD with mucosal biopsies before esophagectomy. All biopsy specimens were reviewed by a pathologist with subspecialty expertise in GI pathology. Typically at this institution, esophageal biopsy specimens with evidence of dysplasia are reviewed by 2 GI pathologists or reviewed at a consensus conference. The study inclusion criteria included (1) patients with endoscopic- and

biopsy-confirmed BE and (2) HGD or IMC was the highest grade lesion on biopsy during endoscopic surveillance before esophagectomy. The exclusion criteria included (1) patients with submucosal invasive adenocarcinoma confirmed by mucosal biopsy before esophagectomy, (2) EUS or radiologic evidence of at least submucosal invasion (T1b or higher) before esophagectomy, or (3) endoscopic or radiologic evidence of a mass. The patient medical records were abstracted for weight, height, ethnicity, medical history, smoking and alcohol history, family history of esophageal cancer or BE, medications (proton pump inhibitors [PPI] and histamine-2 blocker use), duration of GERD, endoscopy reports (EGD, EUS), any history of endoscopic treatment (EMR or PDT), and date of last follow-up. Deaths were identified by the Social Security Death Index (<http://ssdi.rootsweb.com/>). Surviving patients were administered a standardized questionnaire that assessed weight, height, PPI use, alarm features (ie, iron deficiency anemia, GI bleeding, >10% weight loss, jaundice, or dysphagia), and frequency and severity of GERD.

Esophagectomy was performed either by transhiatal, 3-hole, Ivor-Lewis, or minimally invasive approach. Approximately 50 esophagectomies per year have been performed in the past 2 years at this institution. Pathology reports from the esophagectomy specimens were reviewed for depth of invasion, lymph node status, and degree of tumor differentiation. The primary outcome was having T1b (invasion into the submucosa) or higher stage or nodal disease in the esophagectomy specimen. The comparison group was patients who had T1a (IMC), HGD, or nondysplastic BE detected in the esophagectomy specimens.

Data were stored in Microsoft Access 2000 (Microsoft, Redmond, Wash) and analyzed by SAS version 9.1 (SAS Institute, Cary, NC). Differences between groups were presented descriptively. The proportion of invasive submucosal adenocarcinoma at esophagectomy was reported with a 95% CI. Survival was analyzed by the Kaplan-Meier method, with differences between groups tested by the log-rank test.

RESULTS

Sixty patients in total were included in the study, 41 with preoperative HGD and 19 with preoperative IMC. Table 1 summarizes the demographic features. The response rate of the administered survey was 83%. The mean age at diagnosis of HGD or IMC was 61 ± 10 years. Fifty-five (92%) patients were men, and 97% were white. Table 2 summarizes the pathologic findings in the esophagectomy specimens stratified by pre-esophagectomy diagnosis. At esophagectomy, 4 of 60 patients (6.7%; 95% CI, 1.8%-16.2%) had submucosal invasion (T1b), 1 with a poorly differentiated adenocarcinoma and concurrent lymph node metastases. This patient had HGD as the

TABLE 1. Demographic features of the study group (n = 60)

Characteristic	No. (%)
Sex	
Male	55 (92)
Female	5 (8)
Mean age (y) at diagnosis of HGD/IMC (range)	61 ± 10 (29.6-85.5)
Ethnicity	
White	58 (97)
Asian	1 (2)
Hispanic	1 (2)
Median follow-up after esophagectomy (y) (Q1, Q3)	2.5 (1.2, 5.7)
Median length of Barrett's segment (cm) (Q1, Q3)	4.0 (1.5, 7.5)

Q1, 25th percentile; Q3, 75th percentile.

TABLE 2. Pathologic results at esophagectomy comparing patients with biopsy diagnosis of HGD or IMC

Pathologic findings at esophagectomy	Pre-esophagectomy biopsy diagnosis		
	HGD (n = 41)	IMC (n = 19)	Total
Nondysplastic BE	2 (5%)	0 (0%)	2 (3%)
HGD	23 (56%)	4 (21%)	27 (45%)
T1a	14 (34%)	13 (68%)	27 (45%)
T1b	2 (5%)*	2 (11%)	4 (7%)

*One patient had poorly differentiated adenocarcinoma with positive lymph nodes.

highest pre-esophagectomy diagnosis. Notably, only 2 of 19 (11%) patients with a preoperative biopsy diagnosis of IMC were found to have submucosal invasion at esophagectomy. Of the remainder, 27 (45%) patients had IMC, 27 (45%) had HGD, and 2 (3%) had nondysplastic BE at esophagectomy. There were no significant differences between the final T stage at esophagectomy when the pre-esophagectomy diagnosis (HGD vs IMC) was compared. Because patients with T1b cancer were too few in number for adequate statistical comparison, the characteristics of the groups are listed in Table 3 for descriptive purposes. Of note, all 4 patients with submucosal invasion at esophagectomy (100%) had an abnormal appearance at endoscopy (2 nodular and 2 ulcerated) (Fig. 1). In contrast,

TABLE 3. Descriptive analysis of patients with T1b versus patients with T1a/HGD/nondysplastic BE at esophagectomy

Factor	T1b (n = 4)	T1a/HGD/nondysplastic BE (n = 56)
Age at diagnosis (y)	65 ± 11	61 ± 10
Male sex	4 (100)	51 (91)
Smoking	3 (75)	43 (77)
Alcohol use	4 (100)	44 (79)
BMI at diagnosis of HGD/IMC	31 ± 6	28 ± 4
BMI 5 y before	30 ± 7	27 ± 3
BMI at 20 y of age	25 ± 5	23 ± 3
GERD	4 (100)	51 (91)
Acid blocker use		
None	0 (0)	17 (30)
PPI	4 (100)	32 (57)
Histamine-2 blockers	0 (0)	7 (13)
Any alarm features (n = 53)*	1 (33)	31 (62)
Hiatal hernia	1 (25)	31 (55)
Levels of HGD/IMC (n = 58)		
Multiple levels	1(25)	28 (52)
Single level	3 (75)	26 (48)
Prevalent HGD/IMC	2 (50)	31 (55)
Incident HGD/IMC	2 (50)	25 (45)
Long-segment BE (> 3 cm)	1 (25)	36 (64)
Endoscopic appearance		
Flat mucosa	0 (0)	31 (60)
Abnormal mucosa†	4 (100)	21 (40)

Values are frequency (%) or mean ± SD.

*Bleeding, anemia, dysphagia, jaundice, vomiting, ≥ 10% weight loss.

†Nodular, raised, or ulcerated mucosa.

40% of the patients with a lower T stage had an abnormal appearance at endoscopy (ie, nodular, raised, or ulcerated).

The 1- and 5-year all-cause risks of death for the entire group were 1.9% and 10.9%, respectively (Fig. 2). No deaths could be directly attributed to surgery, and no deaths occurred within 30 days postoperatively. Of the 4 patients with T1b cancer, only 1 died, after 13 months of follow-up from unknown causes. This was the 1 patient with positive nodal disease. One patient (without submucosal invasion) died from metastatic prostate cancer within 1 year of follow-up. The age-adjusted Charlson comorbidity index²¹ was significantly different between the patients who died and those who survived (5.3 ± 2.2 vs. 2.4 ± 1.4 , $P < .0001$).

DISCUSSION

This study describes one of the largest series of patients undergoing esophagectomy for BE with HGD or IMC. The low rate (6.7%) of submucosal invasion at esophagectomy in patients with BE with HGD or IMC on biopsy sharply contrasts with the frequently quoted 40% risk of occult cancer. Submucosal invasion is an important end point in studies of such patients because HGD and IMC can potentially be treated by local therapies such as PDT, RFA, or EMR. Importantly, submucosal invasion confers a risk of lymph node metastasis of 8% to 33%,²²⁻²⁶ which makes local therapy inappropriate. Even IMC of the esophagus carries a small but definite risk of nodal metastases, reportedly as high as 3% to 4%.²³ The 6.7% prevalence

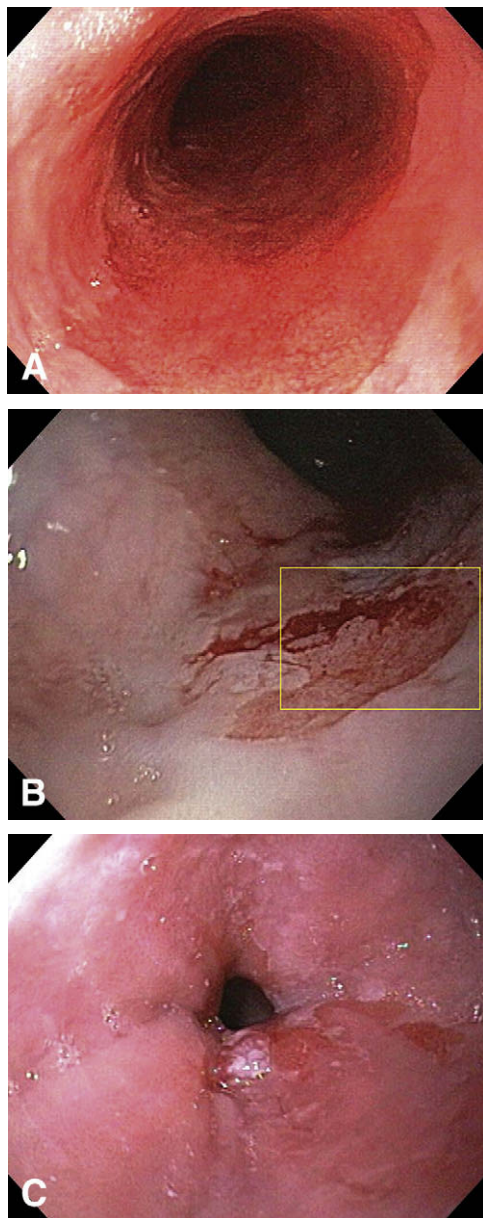


Figure 1. Endoscopic appearances of BE with HGD/IMC and findings at esophagectomy. **A**, Flat mucosa in a patient with preoperative HGD. **B**, Nodular mucosa in a patient with preoperative HGD (T1b). **C**, Nodular mucosa in a patient with preoperative IMC (T1b).

of submucosal invasive cancer at esophagectomy in patients with BE with HGD/IMC on biopsy in our study should be weighed against a 1.9% 1-year all-cause risk of death in this series. These findings should be helpful in framing treatment decisions and determining management strategies. The low mortality rate from esophagectomy in this series is notable and is lower than the majority of other reported studies.^{1-4,15}

Previous studies on this topic have varied in their description of depth of invasion of BE-associated carcinoma in esophagectomy specimens, and only a subset have distinguished submucosal invasion from IMC.¹³ In our study,

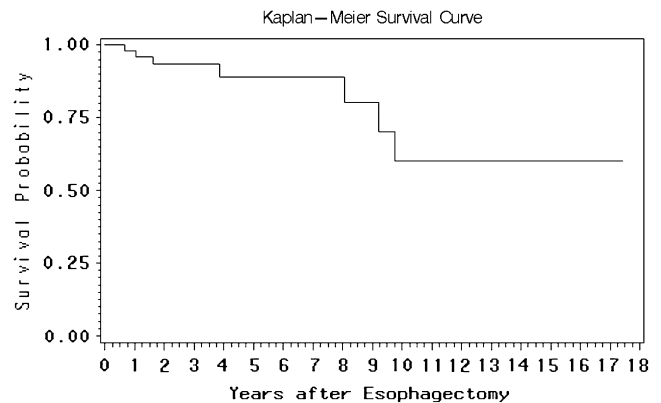


Figure 2. Overall survival of patients with BE with preoperative HGD or IMC after esophagectomy.

we excluded patients who had any preoperative evidence of submucosal invasion or an esophageal mass and defined submucosal invasion as the primary outcome measure. By making this distinction, we found even lower rates of submucosal invasion than other studies with similarly large numbers of patients.^{1,3,11} In particular, we found no T stage higher than T1b in the entire series of 60 patients, which contrasts to a recently published series of patients with preoperative HGD that reported a 22.4% rate of submucosal and deeper invasion at esophagectomy, with 16% having stage T2 or higher.³

The definition of invasive adenocarcinoma is highly variable in resection-based studies of BE with HGD. Many studies have included T1a (IMC) lesions at esophagectomy within the definition of invasive adenocarcinoma, which in part explains the high reported rates of “invasive” carcinoma. Although we have strictly defined the outcome measure in this study to be submucosal invasion and deeper, it is interesting to note that the combined rate of T1a and T1b lesions found at esophagectomy in the 41 patients with preoperative HGD is in fact 39%, which is strikingly similar to the commonly reported 40% rate of occult “cancer.” Konda et al¹³ analyzed 14 studies that had enough information to distinguish submucosal invasion and deeper at esophagectomy from IMC. They found that by using a strict definition of invasive disease as into the submucosa or deeper or with nodal metastasis, the overall rate of invasion was only 12.7% versus the overall author-defined rate of 38%. The rate of 6.7% in our study (which notably also included patients with preoperative IMC) is at the low end of submucosal invasion reported in this comprehensive review. Thus, this current series provides further evidence that the rate submucosal invasion after biopsy diagnosis of HGD is significantly lower than 40%.

Although the case numbers are too small to make meaningful conclusions, we did not find a much higher risk of submucosal invasive carcinoma in patients with preoperative IMC compared with patients with preoperative

HGD (11% vs 5%, respectively). To our knowledge, there are no previous studies that have reported esophagectomy results from preoperative IMC separately from preoperative HGD. Most prior studies have excluded preoperative IMC from their series or have not specifically reported whether submucosal invasion was found at esophagectomy for these patients. Despite the small numbers in this series, our findings suggest that distinguishing between HGD and IMC in endoscopic biopsy specimens may not be critical. Previous studies have shown that distinguishing HGD from IMC is difficult even among expert GI pathologists.^{27,28}

The endoscopic appearance of Barrett's mucosa has been shown to be important in predicting invasive carcinoma in prior studies, which is supported by our data. All patients with submucosal invasion in this series had a nodular or ulcerated appearance on endoscopy. However, a nodular appearance was also noted in 32% of the patients who did not have submucosal invasion. Analysis of pooled data from existing studies has shown that patients with BE with HGD with visible lesions at endoscopy have a higher risk of submucosal invasion than those without visible lesions, although the difference was not statistically significant (11% vs 3%, $P = .14$).¹³

A secondary aim of this study was to determine whether any clinical factors might predict submucosal invasive disease. The clinical factors examined included age, body mass index (BMI), presence of alarm features, PPI use, length of BE segment, and prevalent versus incident HGD/IMC. The low rate of stage T1b cancer at esophagectomy ($n = 4$) precluded adequate statistical analysis of the clinical factors we assessed. Ideally, a multicenter study would provide a more substantial sample size for analysis of potentially important clinical factors.

A limitation of this study was the inability to re-review the entire series of preoperative endoscopic biopsy specimens at one point in time. Because of the long time span of the study and the fact that many cases were initially reviewed in consultation, not all slides were available for re-review. Nonetheless, all the preoperative pathologic conditions were reviewed at the same institution before esophagectomy by pathologists with subspecialty expertise in GI pathology and represent the histologic basis on which an esophagectomy was recommended. As such, the diagnoses reflect routine clinical practice in this institution. In addition, analysis of the finding of submucosal invasive carcinoma at esophagectomy did not have any time period–related trend when examined over the 20-year span. A retrospective analysis can introduce selection bias, although we minimized this possibility by using multiple databases to identify cases within our institution and adhered to strict inclusion and exclusion criteria.

With regard to the preoperative biopsy sampling in these patients with BE with HGD or IMC, at least 63% of the patients ($n = 38$) had biopsy specimens obtained

from every 2 cm of the Barrett's segment, and 10% of the patients had biopsy specimens at every 1-cm interval ($n = 6$). Information regarding the number of specimens obtained at each interval or whether they were taken from all 4 quadrants is not available because of a lack of uniform reporting. Moreover, a subset of patients had preoperative EGD performed at outside institutions, and the biopsy protocol for these patients could not be assessed. Although it might be anticipated that the less thoroughly sampled subgroup of patients would be at higher risk for occult invasive carcinoma, there was no statistically significant difference between patients who had biopsy specimens documented at 1- to 2-cm intervals versus all others with regard to the primary outcome of stage T1b disease at esophagectomy (data not shown).

The low rate of submucosal invasive carcinoma in patients with preoperative HGD and IMC supports endoscopic therapy as an alternative to surgery for select patients. A recent retrospective study of 62 patients with HGD treated by endoscopic therapy and 32 patients treated by esophagectomy concluded that, although endotherapy is associated with a higher risk of tumor progression, progression to cancer is still uncommon in these patients.²⁹ Cancer progression was 6% in the endotherapy patients and 0% in the esophagectomy group; this difference was not significant. In addition, in the endotherapy versus esophagectomy groups, major and minor complications were 8% versus 13% (not significant) and 31% versus 63% ($P < .001$), respectively.

In summary, this study demonstrates that patients with BE with HGD or IMC without endoscopically visible lesions have a low risk of occult submucosal invasive carcinoma. As such, after extensive sampling and adequate staging endoscopic therapies are reasonable alternatives to esophagectomy in these patients.

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