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Expert pathology review and endoscopic mucosal resection alters the diagnosis of patients referred to undergo therapy for Barrett's esophagus

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Abstract

Background—Endoscopic therapy has emerged as an alternative to surgical esophagectomy for the management of Barrett's esophagus (BE)-associated neoplasia. Accurate pretreatment staging is essential to ensure an appropriate choice of therapy and optimal long-term outcomes. This study aimed to assess the frequency with which expert histopathologic review of biopsies combined with endoscopic mucosal resection (EMR) would alter the pretreatment diagnosis of BE-associated neoplasia.

Methods—Patients referred to the Vanderbilt Barrett's Esophagus Endoscopic Treatment Program (V-BEET) were retrospectively identified. Demographic, histopathologic, and endoscopic data were extracted from the medical record.

Results—For this study, 29 subjects referred for endoscopic staging of BE fulfilled the entry criteria. The referral diagnosis was low-grade dysplasia (LGD) in 3 % (1/29), high-grade dysplasia (HGD) in 62 % (18/29), intramucosal adenocarcinoma (T1a) adenocarcinoma in 17 % (5/29), and invasive adenocarcinoma in 17 % (5/29) of the subjects. Expert histopathologic review of available referral biopsy specimens altered the diagnosis in 33 % (5/15) of the cases. Further diagnostic staging with EMR showed BE without dysplasia in 10 % (3/29), LGD in 14 % (4/29), HGD in 34 % (10/29), T1a adenocarcinoma in 28 % (8/29), and invasive adenocarcinoma in 14 % (4/29) of the patients. The combination of expert histopathologic review and EMR altered the initial diagnosis for 55 % (16/29) of the subjects, with 56 % (9/16) upstaged to more advanced disease and 44 % (7/16) downstaged to less advanced disease.

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Conclusions—The practice of combined expert histopathologic review and EMR alters the pretreatment diagnosis for the majority of patients with BE-associated neoplasia. Caution is advised for those embarking on endoscopic or surgical treatment for BE-associated neoplasia in the absence of these staging methods.

Keywords

Barrett's esophagus; BE-associated neoplasia; Endoscopic mucosal resection; Histopathologic review; Pretreatment staging

Esophageal adenocarcinoma (EAC), the fourth most common gastrointestinal malignancy, is a rapidly growing cause of cancer mortality [1]. The principal recognized risk factor for EAC is Barrett's esophagus (BE), defined as intestinal metaplasia of the distal esophageal epithelium [2].

Before the development of invasive cancer, BE may progress from intestinal metaplasia to BE containing low-grade dysplasia (LGD), high-grade dysplasia (HGD), and ultimately intramucosal adenocarcinoma (T1a). If detected and treated early, BE-associated neoplasia is curable at an intramucosal stage [3]. The risk for progression to EAC among patients with HGD is estimated to be at least 6–7 % per year [4]. Therefore, the presence of HGD is an actionable diagnosis, warranting therapeutic intervention.

Surgical esophagectomy, an established therapeutic option for BE containing HGD, can offer low rates of procedural morbidity and mortality as well as excellent long-term survival when performed at high-volume, expert centers [5]. Endoscopic mucosal treatment strategies have emerged as an alternative to surgical esophagectomy for HGD. Randomized controlled trials of photodynamic therapy and radiofrequency ablation, each compared with proton pump inhibitor therapy, have demonstrated the ability to eliminate HGD in a majority of patients and to reduce the risk of progression to EAC [6, 7] during reported follow-up periods.

A recent consensus statement has recommended that endoscopic treatment should be preferred over surgical esophagectomy for the treatment of HGD [8]. Strict validated criteria for selecting patients to undergo endoscopic versus surgical therapy do not exist. However, retrospective data suggest that the choice of therapy is likely to be influenced by whether a surgeon or gastroenterologist serves as the primary consultant [8].

Identifying an optimal treatment approach for BE HGD is contingent not only on the efficacy and durability of available surgical or endoscopic options but also on the accuracy of pretreatment staging. Historic retrospective series have reported occult malignancy in 33–73 % of surgical resection specimens from patients who underwent esophagectomy with a preoperative diagnosis of HGD [5, 9–15].

Preoperative diagnostic accuracy has improved due to advances in endoscopic technologies and techniques, including high-definition white light and narrow-band imaging, systematic biopsy protocols, and endoscopic ultrasound. In a recent study from one tertiary center, the

prevalence of occult invasive malignancy in patients who underwent esophagectomy for HGD was 5 % [16].

The potential for preoperative diagnostic inaccuracy persists due to factors including variability in histopathologic interpretation of BE-associated neoplasia [17] and biopsy sampling error. In an effort to overcome these limitations, our referral center has implemented the practice of expert histopathologic review of biopsy specimens followed by the use of endoscopic mucosal resection (EMR) for staging purposes among patients referred to undergo therapy for BE-associated neoplasia.

The hypothesis of this study was that the combination of expert histopathologic review and EMR would alter the pretreatment diagnosis of a majority of patients referred to undergo therapy for BE-associated neoplasia.

Methods

Approval to conduct this retrospective study was granted by the Vanderbilt University Institutional Review Board. The study cohort consisted of patients with BE who had been referred to the Vanderbilt Barrett's Esophagus Endoscopic Treatment Program (V-BEET) and who had undergone EMR between September 2009 and November 2011.

The endoscopic evaluations were performed by a single endoscopist (P.Y.). The candidates for EMR included patients with prior biopsies documenting the presence of LGD, HGD, or adenocarcinoma. In all cases, visual inspection of the BE segment was performed using high-definition white light and narrow-band imaging (GIF-H180 J gastro-scope, CV-180 Evis Exera II video processor, and CLV-180 light source; Olympus Medical Systems, Olympus America Inc, Center Valley, PA). The length of Barrett's was defined as the distance between the top of the gastric folds distally and the visible squamocolumnar junction proximally. Areas of nodularity or superficial mucosal erosion and areas with a hypervascular mucosal appearance were targeted for EMR. All EMRs were performed with a cap-assisted mucosectomy device (Duette Multi-Band Mucosectomy; Cook Medical, Limerick, Ireland) and an ERBE VIO 200-S electrosurgical unit (ERBE USA Inc., Marietta, GA) (set to snare hot biopsy mode with a coagulation effect of 1 and maximum power of 20 W).

Resected specimens were retrieved and submitted to pathology in formalin solution. Formalin-fixed and paraffin-embedded specimens were reviewed by two expert gastrointestinal pathologists (C.S. and M.K.W.). In cases of dysplasia, the dysplasia was graded as LGD or HGD. In cases of adenocarcinoma, depth of invasion was assessed, and a local stage was assigned (pT1a or pT1b). Both deep and lateral resection margins were assessed for involvement by dysplasia/adenocarcinoma.

Study data were collected and managed using REDCap electronic data capture tools (Vanderbilt University, Nashville, TN) hosted at Vanderbilt University. The REDCap (Research Electronic Data Capture) is a secure, Web-based application designed to support data capture for research studies [18]. Descriptive statistics were obtained using the REDCap application.

Results

The study entry criteria were fulfilled by 29 subjects during the specified period. In terms of gender, 79 % (23/29) of subjects were male, and 21 % (6/29) were female. The mean age of the subjects was 66 years, and the mean length of BE was 4.4 ± 4.0 cm.

In all cases, the pretreatment diagnosis had been rendered by cold forceps biopsies. HGD was the most common diagnosis prompting referral, and it was present in 62 % of the subjects (18/29). The pretreatment diagnoses for the remainder of the cohort consisted of LGD in 3 % (1/29), T1a adenocarcinoma in 17 % (5/29), and invasive adenocarcinoma in 17 % (5/29) of the cases (Fig. 1).

In 72 % (21/29) of the cases, the initial diagnostic endoscopy with biopsies had been performed at an outside referral institution. In the remaining eight cases (hereafter referred to as internal cases), the index endoscopy had been performed at our institution with expert histopathologic review. Biopsies were able to be obtained for expert histopathologic review in 71 % (15/21) of the referral cases. Expert histopathologic review changed the diagnosis in 33 % (5/15) of these cases. Among these, 60 % (3/5) were upstaged to more advanced pathology, whereas 40 % (2/5) were downstaged to less advanced pathology.

After expert histopathologic review, HGD remained the most prevalent diagnosis and was present in 46.7 % (7/15) of the cases. The remaining diagnoses after expert histopathologic review of available referral biopsies consisted of BE without dysplasia in 7 % (1/15), LGD in 7 % (1/15), T1a adenocarcinoma in 27 % (4/15), and invasive adenocarcinoma in 13 % (2/15) of the cases.

The diagnosis by expert biopsy review, therefore— assuming no change in diagnosis of any unavailable outside specimens and including the diagnosis rendered by review of the eight internal cases—was intestinal metaplasia without dysplasia in 3 % (1/29), LGD in 3 % (1/29), HGD in 55 % (16/29), T1a adenocarcinoma in 24 % (7/29), and invasive adenocarcinoma in 14 % (4/29) of the cases (Fig. 1).

For all 29 subjects, EMR was performed. Histopathologic diagnosis of the EMR specimens demonstrated BE without dysplasia in 10 % (3/29), LGD in 14 % (4/29), HGD in 34 % (10/29), T1a adenocarcinoma in 28 % (8/29), and invasive adenocarcinoma in 14 % (4/29) of the cases (Figs. 1, 2).

The combination of expert histopathologic review and EMR changed the pretreatment diagnosis for 55 % (16/29) of the subjects. Among, these, 56 % (9/16) were upstaged to more advanced disease, whereas 44 % (7/16) were downstaged to less advanced disease. For the 15 cases that had referral biopsies available for expert histopathologic review, the initial biopsy diagnosis, the expert review diagnosis, and the EMR diagnosis were in full agreement for 40 % (6/15) of the cases. (Table 1).

Complications of EMR were limited to esophageal stricture requiring endoscopic dilation in 3 % (1/29) of the patients; to delayed bleeding requiring endoscopic therapy, hospital admission, and packed red blood cell transfusion in one patient; and to suspected delayed

bleeding requiring repeat endoscopic evaluation but no endoscopic therapy and no transfusion in one patient. No esophageal perforations were observed.

Discussion

Accurate staging is a necessary prerequisite to the selection of optimal endoscopic or surgical therapy for BE-associated neoplasia. Factors influencing accuracy of staging include variability in histopathologic interpretation of intestinal metaplasia and associated neoplasia [17] as well as endoscopic biopsy sampling error. As a mucosal sampling technique, EMR provides a greater breadth and depth of tissue acquisition than biopsies, may be performed with both diagnostic and therapeutic intent, and may overcome the diagnostic limitations of biopsy sampling. Previous data have demonstrated that EMR may alter a diagnosis rendered by forceps biopsies in up to 48 % of cases [19].

The current study demonstrated that expert histopathologic review of biopsy specimens combined with additional tissue acquisition by EMR alters the pretreatment diagnosis of BE-associated neoplasia in the majority (55 %) of cases. In other words, a treatment recommendation based solely on a single interpretation of forceps biopsies is more likely than not to be based on an incorrect diagnosis.

In the current study, EMR was not limited to nodular areas of BE but included EMR of flat or non-raised BE, supporting recommendations that EMR be used for the staging of all visible abnormalities within a BE segment [20]. EMR is the only mucosal treatment strategy for BE that provides a histopathologic specimen, compared with ablation strategies, which are performed on the basis of prior histopathologic sampling.

Subtle alterations in the staging of BE-associated neoplasia may have significant implications for patient treatment. A patient who is downstaged from HGD to LGD may no longer require endoscopic or surgical therapy for BE. Although guidelines suggest that endoscopic treatment methods including radiofrequency ablation may be an option for LGD [21], this practice is not universal, and low progression rates—less than 2 % annual progression to the combined end point of HGD/cancer, at least in a United States multicenter cohort [22]—suggest that surveillance is an acceptable option for LGD.

Arguably, alteration in staging from HGD to T1a cancer, or vice versa, may not fundamentally alter treatment recommendations. A patient may remain a candidate for endoscopic therapy despite disease upstaging from HGD to T1a disease. An effective mucosal resection/ablation strategy would be capable of eradicating intramucosal disease. The risk of lymph node metastasis for patients with T1a cancer was reported to be 1.39 % in a recent systematic review of 1,874 subjects who underwent esophagectomy for HGD/T1a disease, prompting the authors to suggest that concern over lymph node involvement in T1a cancer should not be the determining factor in favoring esophagectomy over endoscopic therapy for such patients [23].

On the other hand, alteration in staging from T1a to smucosal invasive adenocarcinoma (T1b) cancer, or vice versa, is a critical determinant of appropriate subsequent therapy. EMR may be superior to endoscopic ultrasound in distinguishing between mucosal (T1a) and

submucosal (T1b) disease involvement [24]. When T1b disease is detected, EMR will sample to the depth of the submucosa, and tumor involvement of deep resection margins can be assessed. However, in most circumstances, endoscopic mucosal treatment methods cannot guarantee a cure of T1b disease due to a substantial rate of metastatic lymph node involvement [25,26].

That being said, recent uncontrolled data from Mayo Clinic Rochester suggest that the survival rate for T1b disease does not differ significantly between patients who undergo esophagectomy and those who did not. Rather, survival is influenced predominantly by the presence or absence of lymph node involvement [26]. Treatment decisions for patients with T1b disease can therefore be complex, and considerable uncertainty remains with respect to the optimal choice of endoscopic, surgical, or systemic treatment, or a combination thereof.

The limitations of the current study include its retrospective, single-center nature and the sample size. Most of the subjects in the cohort did not undergo esophagectomy, so no postsurgical resection specimen exists for comparison as a standard with biopsy or EMR histopathologic diagnosis.

Admittedly, the histopathologic stage alone may not be the sole factor influencing a decision to proceed with endoscopic or surgical therapy. Factors including patient age, comorbid illness, patient fitness for surgery, and patient willingness either to undergo surgery or to comply with rigorous endoscopic follow-up care may all be important determinants in selecting between treatment options. Moreover, the optimal therapy may be best determined on a patient by patient basis, with multidisciplinary consultation and collaboration. Nonetheless, we believe the results of this study have important implications for the management of BE-associated neoplasia.

The study data support our institutional protocol requiring that all prior biopsies from patients referred for the management of BE-associated neoplasia be obtained for expert histopathologic review and that all patients be offered EMR as an initial diagnostic/therapeutic intervention before mucosal ablation. Widespread implementation of such a protocol would minimize diagnostic inaccuracy in the staging of BE and ensure desirable long-term outcomes. Caution should be advised for those embarking on endoscopic or surgical treatment of BE-associated neoplasia in the absence of these staging methods.

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Fig. 1.
Distribution of disease stage based on referral diagnosis, expert histopathologic review, and endoscopic mucosal resection

Fig. 2.
Distribution of disease stage comparing the initial referral diagnosis with the final diagnosis

Table 1

Disease staging per patient comparing initial referral diagnosis with final diagnosis

Patient	Initial diagnosis	Final diagnosis
1	HGD	HGD
2	HGD	T1b/invasive
3	HGD	T1a
4	HGD	LGD
5	HGD	HGD
6	Invasive	T1a
7	HGD	T1a
8	HGD	LGD
9	HGD	HGD
10	Invasive	IM
11	T1a	T1b/invasive
12	HGD	T1a
13	HGD	HGD
14	HGD	HGD
15	HGD	HGD
16	HGD	T1a
17	T1a	T1a
18	HGD	HGD
19	Invasive	LGD
20	T1a	T1a
21	HGD	IM
22	HGD	IM
23	HGD	HGD
24	LGD	LGD
25	T1a	HGD
26	HGD	T1a
27	Invasive	T1b/Invasive
28	T1a	HGD
29	Invasive	T1b/Invasive

HGD High-grade dysplasia, *T1b/invasive* invasive adenocarcinoma stage T1b or greater, *T1a* T1a (intramucosal) adenocarcinoma, *LGD* low-grade dysplasia, *IM* intestinal metaplasia without dysplasia