Complete Endoscopic Mucosal Resection Is Effective and Durable Treatment for Barrett's–Associated Neoplasia

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BACKGROUND & AIMS: **Barrett's esophagus (BE) with high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) is treated by complete eradication of areas of BE by endoscopic mucosal resection (EMR). By using this approach, histologic analysis also can be performed. We investigated the effectiveness, safety, and durability of this approach, as well as its use in diagnosis after a single referral.**

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METHODS: **We collected data from 107 patients who were referred to the Center for Endoscopic Research and Therapeutics at the University of Chicago for BE (mean length, 3.6 cm) with suspected HGD or IMC, from August 2003 through December 2012. All patients underwent EMR and were followed up through January 2014 (mean follow-up time, 40.6 mo). The primary outcome was treatment efficacy (complete eradication of BE and associated neoplasia); secondary outcomes included safety, durability, and accuracy of diagnosis.**

RESULTS: **BE was eradicated completely by EMR in 80.4% (86 of 107) of patients based on intention-to-treat analysis, and in 98.8% (79 of 80) of patients based on per-protocol analysis. The diagnosis was changed for 25% of patients after EMR, including 4 cases that initially were diagnosed as HGD by biopsy analysis and subsequently were found to have evidence of submucosal invasion when EMR specimens were assessed. Strictures and symptomatic dysphagia developed in 41.1% and 37.3% of patients, respectively, with an average of 2.3 dilations required. Perforations occurred in 2 patients after EMR and in 1 patient after dilation. HGD and IMC recurred in 1 patient each; both were treated successfully with EMR. Based on pathology analysis of the most recently collected specimens, 71.6% of patients (53 of 74) were in complete remission from intestinal metaplasia and 100% were in complete remission from HGD (74 of 74) or cancer (74 of 74).**

CONCLUSIONS: **For patients with BE with HGD or neoplasia, complete EMR is an effective and durable treatment and is a relatively safe technique. Specimens collected by EMR also can be analyzed histologically to aid in diagnosis. The common complication of EMR is esophageal stricture, which can be addressed with endoscopic dilation.**

Keywords: Esophageal Cancer; Endoscopy; Endotherapy; Adenocarcinoma.

Q6 Q7 The incidence of esophageal adenocarcinoma has increased approximately 7-fold over the past 30 years in the Western world. Endoscopic therapy is now the preferred option over esophagectomy in the majority of cases of patients with high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) associated with Barrett's esophagus (BE). Endoscopic management has focused on total eradication of all of the Barrett's epithelium to remove not only visible lesions but also eliminate the remaining at-risk epithelium to address synchronous and metachronous lesions.

Endoscopic mucosal resection (EMR) is a tissue-acquiring modality and not only removes the lesion but also provides a large and intact tissue specimen to stage histopathology accurately. Complete eradication of BE with EMR has been reported as one strategy to manage patients with HGD and IMC and provides complete histology of the Barrett's epithelium.[1]

Although endotherapy has emerged as a minimally invasive approach for superficial Barrett's-associated

Abbreviations used in this paper: **BE, Barrett's esophagus; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; HGD, high-grade dysplasia; HRC, high-risk characteristic; IMC, intramucosal carcinoma; RFA, radiofrequency ablation; SMC, submucosal carcinoma.**

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neoplasia, the long-term durability and disease behavior after the various endoscopic modalities are still critical to strategize options of tissue-acquiring methods vs ablative methods vs combination approaches. In 2009, we reported our single tertiary referral center's initial experience with complete EMR for the management of patients with BE and HGD/IMC based on 49 patients.[2] In this current study, we report our expanded experience in terms of treatment efficacy, impact on diagnosis, safety, and durability with complete EMR for the treatment of Barrett's-associated neoplasia.

Methods

Subjects

Patients were referred to our center for the evaluation and management of BE with suspected HGD/IMC from August 2003 until December 2012. A full discussion was conducted with each patient on the risks and benefits of available management options, including esophagectomy, surveillance, and endoscopic ablative and resection therapies, and written informed consent was obtained. All patients who initiated complete EMR treatment were entered into a prospective clinical database; the current format is REDCap and was approved by the University of Chicago Medical Center Institutional Review Board in June 2012.

Procedures and Protocol

A detailed description of selection of the treatment approach, the complete EMR protocol, evolution of treatment technique, and pathology review are provided in the Supplementary Materials and Methods.

Briefly, patients underwent procedures by a single endoscopist (I.W.). All sessions were conducted on an outpatient basis under monitored anesthesia. All referral pathology slides, EMR specimens, and biopsy specimens were reviewed independently by 2 expert gastrointestinal pathologists at our institution (J.H. and S.-Y.X.). Upper endoscopy was performed with a detailed white-light examination, with high-resolution and/or narrow-band imaging when available, and endoscopic ultrasound (EUS) was performed in cases of cancer or visible lesions (GIF-Q160, GIF-H180, GIF-HQ190, GF-UE160, GF-UC140P; Olympus America, Center Valley, PA). Macroscopically visible lesions were documented with images, descriptive terminology, and the Paris Classification when included in the report or otherwise retrospectively assigned because the study period started before the classification system was implemented.

The complete EMR protocol evolved over time. The practice evolved into a radical approach (with the intention to resect all of the BE in a single session) if complete EMR was the intended therapy and there was not a high suspicion of invasive cancer. Even after the availability of radiofrequency ablation (RFA), those patients with multifocal neoplasia or diffuse nodularity were treated with complete EMR regardless of segment length. Endoscopic multiband ligator, cap-assisted, and/or free-hand techniques were used to perform the EMR, as previously described.[2] The cap-assisted technique was the preferred technique. The resection site was inspected systematically for tears or bleeding. Patients underwent multiple mucosectomy sessions with the intention to eliminate all Barrett's epithelium every 2 to 6 months. Diminutive islands of BE, measuring 1 to 3 mm, were sometimes treated with focal RFA (HALO-90 System; BARRX Medical, Sunnyvale, CA). After mucosectomy, all patients were maintained on oral high-dose proton pump inhibitors twice daily.

Patients were monitored for dysphagia and treated as needed for symptomatic esophageal strictures. In recent years, a repeat endoscopy was scheduled 7 days after circumferential EMR to check for healing and to perform endoscopic balloon dilation prophylactically.

Follow-Up Algorithm

Follow-up data were obtained through January 2014. After the endoscopic eradication of all visible Barrett's epithelium, patients then underwent close follow-up evaluation in 3- to 6-month intervals based on factors such as presence of length of segment, concern for residual disease, or cancer, in which case they also had 2 evaluations with EUS.

Patients underwent yearly surveillance for the first 5 years and then every 2 years thereafter. Surveillance endoscopies included biopsy specimens of the squamocolumnar junction, cardia, the neosquamous epithelium, targeted areas of discoloration, and/or suspicious areas for residual disease. Patients who previously had cancer had EUS during surveillance to evaluate for malignant lymphadenopathy. Patients who were followed up elsewhere were treated at the discretion of their physician, and endoscopy reports and pathology reports were requested and recorded when provided.

Outcomes and Definitions

The primary outcome was treatment efficacy as determined by complete eradication of BE, and associated neoplasia as determined by the combination of endoscopy, histology, and, in the cases of cancer, EUS, without evidence of malignant lymphadenopathy. Secondary outcomes included accuracy of diagnosis, safety, and durability.

High-risk characteristics (HRCs) were defined as any of the following: submucosal carcinoma (SMC), IMC with poorly differentiated tumor, tumor with invasion into lymphatics or vessels, if the initial procedure included endoscopic submucosal dissection for presumed submucosal involvement, or endoscopic mucosal resection