ORIGINAL ARTICLES

Optical Coherence Tomography to Identify Intramucosal Carcinoma and High-Grade Dysplasia in Barrett's Esophagus

JOHN A. EVANS,* JOHN M. PONEROS,† BRETT E. BOUMA,§,‖ JASON BRESSNER,§,‖ ELKAN F. HALPERN,¶ MILEN SHISHKOV,§,‖ GREGORY Y. LAUWERS,# MARI MINO–KENUDSON,# NORMAN S. NISHIOKA,*,‖ and GUILLERMO J. TEARNEY#,‖

*Gastrointestinal Unit, Departments of §Dermatology, ¶Radiology, and #Pathology, and ‖Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Boston; and †Department of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Background & Aims: **Optical coherence tomography (OCT) is an optical technique that produces high-resolution images of the esophagus during endoscopy. OCT can distinguish specialized intestinal metaplasia (SIM) from squamous mucosa, but image criteria for differentiating intramucosal carcinoma (IMC) and high-grade dysplasia (HGD) from low-grade dysplasia (LGD), indeterminate-grade dysplasia (IGD), and SIM without dysplasia have not been validated. The purpose of this study was to establish OCT image characteristics of IMC and HGD in Barrett's esophagus.** ***Methods:*** **Biopsy-correlated OCT images were acquired from patients with Barrett's esophagus undergoing endoscopic surveillance. Two pathologists rendered consensus diagnoses of the biopsy specimens. A blinded investigator reviewed the biopsy-correlated OCT images and scored each for surface maturation and gland architecture. For each image the scores were summed to determine an OCT "dysplasia index."** ***Results:*** **A total of 177 biopsy-correlated images were analyzed. The corresponding histopathology diagnosis was IMC/HGD in 49 cases, LGD in 15, IGD in 8, SIM in 100, and gastric mucosa in 5. A significant relationship was found between a histopathologic diagnosis of IMC/HGD and scores for each image feature (dysplasia index [Spearman correlation coefficient, $r = 0.50$, $P < .0001$], surface maturation [$r = 0.48$, $P < .0001$], and gland architecture [$r = 0.41$, $P < .0001$]). When a dysplasia index threshold of ≥2 was used, the sensitivity and specificity for diagnosing IMC/HGD were 83% and 75%, respectively.** ***Conclusions:*** **An OCT image scoring system based on histopathologic characteristics has the potential to identify IMC and HGD in Barrett's esophagus.**

During the past 30 years, the incidence of esophageal adenocarcinoma has increased faster than any other solid organ malignancy in Western countries.[1–3] Barrett's esophagus (BE) is the major risk factor for the development of esophageal adenocarcinoma, and gastroesophageal reflux disease is a significant risk factor for the development of BE as well as esophageal adenocarcinoma.[4] For patients with known BE, periodic endoscopic surveillance to detect intramucosal carcinoma (IMC) and high-grade dysplasia (HGD) (IMC/HGD) is usually recommended. This recommendation stems from observations noting the high incidence (25% during a period of 46 months) of adenocarcinoma in patients with IMC/HGD.[5] Current guidelines for surveillance of IMC/HGD include 4-quadrant biopsies every 2 cm along the axial length of the Barrett's segment.[6] However, the accuracy of surveillance endoscopy is limited by sampling error.[7–9] Debate continues regarding the optimal surveillance strategy for BE, but many analyses have identified surveillance frequency and the cost of endoscopy as key determinants of cost-effectiveness.[10–13] Because of the increasing prevalence of gastroesophageal reflux disease and esophageal adenocarcinoma and the medical community's increasing recognition of BE as a risk factor for esophageal cancer, the use of endoscopy as a surveillance strategy for BE will increase significantly in the near future. Such increases will incur significant costs to the health care system and to the individual patient. Surveillance strategies to lower cost are being examined and include new endoscopic technologies such as narrow band imaging, chromoendoscopy, and fluorescence endoscopy. Methods for directing biopsies to regions of the esophagus containing dysplastic tissue might improve

Abbreviations used in this paper: BE, Barrett's esophagus; HGD, high-grade dysplasia; IGD, indeterminate-grade dysplasia; IMC, intramucosal carcinoma; LGD, low-grade dysplasia; OCT, optical coherence tomography; SIM, specialized intestinal metaplasia.

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the effectiveness and efficiency of surveillance in patients with BE by increasing surveillance intervals, enabling minimally invasive surgical techniques at an earlier stage of disease progression, or preventing unnecessary interventional procedures.

Optical coherence tomography (OCT) is an optical imaging modality that uses near-infrared light to produce high-resolution (10-μm axial resolution) cross-sectional images of gastrointestinal mucosa during routine endoscopy.[14–16] Images are constructed on the basis of light reflectivity, and OCT can readily identify structures on a microscopic scale including mucosal layers, "pit and gland" morphology, and glandular structure.[14–16] Specialized intestinal metaplasia (SIM) can be reliably distinguished from squamous mucosa by OCT,[14] but image criteria to differentiate dysplastic from metaplastic tissue in the esophagus have not been studied.

Histopathologic standards for grading and characterizing HGD in BE have been established. The important features are (1) lack of epithelial surface maturation in comparison with underlying glands, (2) gland architecture disarray, and (3) cytologic atypia.[17,18] OCT characterization of SIM epithelial surface maturation and glandular architecture is possible with the 10-μm resolution currently provided by this technology. The aim of this study was to determine the relationship between epithelial surface maturation and gland architecture as assessed by OCT and a histopathologic diagnosis of IMC/HGD in subjects with BE.

Methods and Materials

The study was a blinded trial. Recruited subjects were patients with BE undergoing routine endoscopic surveillance or confirmatory biopsies for IMC or HGD. OCT images of Barrett's epithelium were obtained during endoscopy. Biopsy-correlated OCT images of the esophagus were viewed and scored by a reader blinded to the tissue diagnosis. For each image the scores for surface maturation and gland architecture were summed to establish a "dysplasia index." Two pathologists independently reviewed each biopsy specimen and rendered a consensus diagnosis.

Optical Coherence Tomography System

The OCT device used in this study has been described previously.[14,19] The light source center wavelength was 1300 nm, and the optical power incident on the tissue was 5.0 mW. The spectral bandwidth of the source was 70 nm, providing an axial resolution of 10 μm. The outside diameter of the OCT catheter was 2.5 mm. Images were acquired in a linear plane along the longitudinal axis with dimensions of 5.5 mm (1000 pixels) in length and 2.5 mm (500 pixels) in depth. During image acquisition, frames were recorded at a rate of 2 per second and numbered sequentially for reference. A visible laser beam coincident with the imaging beam allowed the endoscopist to localize the site of mucosa undergoing image acquisition, facilitating biopsy correlation of the imaged site.

Endoscopy and Subject Recruitment

The protocol was reviewed and approved by the Institutional Review Board at Massachusetts General Hospital. Informed consent was obtained before the subject's procedure. Patients with BE undergoing surveillance endoscopy and subjects with known diagnoses of HGD or IMC being evaluated for photodynamic therapy between December 1998–March 2004 were recruited. Subjects were excluded if they had previously undergone photodynamic therapy, argon plasma coagulation, endoscopic mucosal resection, or other forms of local tissue destruction to the esophagus within 3 months of the endoscopy, or if they had erosive esophagitis noted during endoscopy. Subjects received routine conscious sedation and oropharyngeal anesthesia. Standard endoscopes (either Pentax Model EG 3470K or Model EG3830TK; Pentax Medical, Tokyo, Japan) with a 3.8-mm instrument channel were used.

Optical Coherence Tomography Imaging

After adequate sedation and oropharyngeal anesthesia, upper endoscopy was performed in the standard manner. After the endoscopist identified the gastroesophageal junction and Barrett's segment, an OCT catheter probe was introduced through the instrument channel of the endoscope and positioned in gentle contact with the Barrett's mucosa. OCT images were acquired and recorded at the mucosal site as indicated by the aiming beam. OCT frames corresponding to the imaged site were documented. One jumbo biopsy (Boston Scientific, Natick, MA; 3.3-mm diameter biopsy forceps) was performed at each imaged site. The esophagus was imaged by OCT and biopsied in a retrograde fashion, typically starting at the gastroesophageal junction. To ensure adequate tissue contact between the imaging probe and the mucosa, any blood, mucus, or other foreign material was endoscopically lavaged with water before imaging. Biopsies were obtained by following the "Seattle protocol." Images were captured from 3 of the 4 quadrant biopsies at each 2-cm interval along the length of the Barrett's segment.

Histopathology

The biopsy specimens were placed in 10% formalin, embedded in paraffin, processed routinely, and stained with hematoxylin-eosin. Two pathologists (G.Y.L. and M.M.K.), blinded to the OCT data, independently reviewed the slides and rendered a diagnosis of IMC/HGD, indeterminate-grade dysplasia (IGD), LGD, SIM, or gastric mucosa. Because of the well-recognized difficulty in differentiating HGD from IMC,[20] the 2 categories were combined into a single histopathologic diagnosis. For cases in which the 2 pathologists disagreed, a consensus diagnosis was obtained. The consensus diagnosis was used as the gold standard to which the OCT results were compared.