

Massachusetts General Hospital
Wellman 1 Conference Room
50 Blossom Street, Boston
April 12, 2005
4:00 P.M. to 6:00 P.M.

Lester Wolfe Workshop in Laser Biomedicine

Optical Imaging of Pre-Cancer in the Esophagus

3:30 P.M. Refreshments

4:00 P.M. Screening and Surveillance of Barrett's Esophagus: The Challenge, Current Status and Opportunities

Norman Nishioka, MD, Gastroenterology Associates, Massachusetts General Hospital; Associate Professor in Medicine, Harvard Medical School, nnishioka@partners.org

The incidence of esophageal adenocarcinoma is increasing faster than any other solid tumor in Western countries. Barrett's esophagus (BE) is the major risk factor for the development of esophageal adenocarcinoma. Longstanding gastroesophageal reflux disease (GERD) is a significant risk factor for the development of BE and this has led many to recommend endoscopic screening for Barrett's esophagus in patients who have chronic GERD symptoms. Once BE is diagnosed, periodic endoscopic surveillance to detect dysplasia and early stage cancer is recommended. However, the accuracy of surveillance endoscopy is limited by sampling error and the optimal surveillance strategy for BE is not known. Low cost surveillance strategies are being examined and include novel endoscopic imaging modalities. The overall goal of these technologies is to improve the effectiveness and efficiency of screening for BE and its surveillance.

4:30 P.M. Upper Gastrointestinal Optical Coherence Tomography

Brett Bouma, PhD, Associate Professor, Department of Dermatology, Harvard Medical School; Wellman Center for Photomedicine, Massachusetts General Hospital, bouma@helix.mgh.harvard.edu

Optical coherence tomography (OCT) is a high resolution cross-sectional imaging technique capable of providing information on microscopic tissue architecture in patients. Imaging has been conducted in over 300 patients to evaluate this technology for improving management of patients with esophageal specialized intestinal metaplasia (SIM). These studies have demonstrated esophageal SIM may be distinguished from other upper gastrointestinal tissues by OCT on a morphologic basis and pathologic criteria may be applied to OCT images for grading dysplasia in patients with BE. Future studies will test OCT-based diagnosis of esophageal SIM against the standard of care, with the goal of providing a cost-effective screening tool for SIM and an improved means for conducting esophageal surveillance.

5:00 P.M. Break

(Continued)

5:05 P.M. Real Time Spectral Diagnosis of Dysplasia in Barrett's Esophagus

James Tunnell, PhD, Postdoctoral Fellow, Spectroscopy Laboratory, Massachusetts Institute of Technology, jtunnell@mit.edu

A spectral diagnosis involves the collection and analysis of optical spectra to non-invasively characterize tissue pathology. Optical spectroscopic signatures allow one to quantitatively determine both tissue structure and function. In a feasibility study (Georgakoudi *et al. Gastroenterol* 2001), the combination of three spectral techniques (diffuse reflectance, intrinsic fluorescence, and light scattering spectroscopies) provided a highly accurate diagnosis (Se and Sp = 100%) in detecting dysplasia in patients with Barrett's esophagus (BE). In a recent follow-up study involving over 80 patients, Dr. Tunnell and his team have confirmed the high accuracy of spectral diagnosis in detecting dysplasia in patients with BE, and have demonstrated the capability of a real-time diagnosis through the development of both instrumentation and algorithms. Future studies will test the accuracy of these methods prospectively for the potential to guide biopsy and avoid unnecessary biopsy.

5:30 P.M. Endoscopic Confocal Microscopy for Structure and Function

Gordon Kino, PhD, W.M. Keck Foundation Professor of Electrical Engineering, Emeritus, Stanford University, kino@stanford.edu

In order to detect dysplasia in the esophagus, one needs to observe subcellular structure and function. Structure is observed with reflection microscopy, and function with fluorescence. Dr. Gordon Kino will show images his team has taken with the Mauna Kea multiple fiber confocal fluorescence microscope in the esophagus *in vivo* with topically sprayed fluorescein for contrast enhancement. With illumination at 488 nm wavelength, the transverse resolution is 5 μ m and range resolution is 15 μ m. His group's subcellular measurements with a standard confocal microscope *ex vivo* have shown that they can mark Barrett's esophagus with peptide reagents. Dr. Kino is also developing new types of fluorescent markers for dysplasia. He will describe the MEMS scanned dual axes endoscopic confocal microscope he and his team is building. This device should have ~1 μ m transverse and ~2 μ m range resolution at 488nm wavelength. Images taken with a trial bench top dual axes microscope of vertical and horizontal tissue cross sections will also be shown.

SUMMARY 4/12/2005

The meeting was devoted to a symposium on "Optical Imaging of Pre-Cancer in the Esophagus" sponsored by the MIT Spectroscopy Laboratory, the Harvard-MIT Division of Health Sciences and Technology, the MGH Wellman Center for Photomedicine and CIMIT.

Norman Nishioka, MD, MGH introduced the topic in a talk on "Screening and Surveillance of Barrett's Esophagus: The Challenge, Current Status and Opportunities". The incidence of esophageal adenocarcinoma is increasing faster than any other solid tumor in Western countries. Barrett's esophagus (BE) is the major risk factor for the development of esophageal adenocarcinoma. Long-standing gastroesophageal reflux disease (GERD) is a significant risk factor for the development of BE and this has led many to recommend endoscopic screening for Barrett's esophagus in patients who have chronic GERD symptoms. Once BE is diagnosed, periodic endoscopic surveillance to detect dysplasia and early stage cancer is recommended. However, the accuracy of surveillance endoscopy is limited by sampling error and the optimal surveillance strategy for BE is not known. Low cost surveillance strategies are being examined and include novel endoscopic imaging modalities. The overall goal of these technologies is to improve the effectiveness and efficiency of screening for BE and its surveillance.

Sponsored by the George R. Harrison Spectroscopy Laboratory, MGH Wellman Center for Photomedicine, Harvard—MIT Division of Health Sciences and Technology, and CIMIT (Center for the Integration of Medicine and Innovative Technology).

Brett Bouma, PhD, Wellman Center for Photomedicine, MGH, then described “Upper Gastrointestinal Optical Coherence Tomography (OCT)”. The current MGH endoscopic OCT system, operating at 1300 nm, provides longitudinal scans with 10 micron depth and 25 micron lateral resolution. This system has been used to evaluate this technology for improving management of patients with esophageal specialized intestinal metaplasia (SIM). These studies, involving over 300 patients, have demonstrated esophageal SIM may be distinguished from other upper gastrointestinal tissue types by OCT on a morphologic basis and pathologic criteria may be applied to OCT images for grading dysplasia in patients with BE. The use of OCT to detect/grade dysplasia will require a depth resolution of 2 microns, a goal considered technically achievable; however the current technology is limited to identifying high-grade dysplasia in SIM. More importantly, the current endoscopic OCT system is limited to line scans which characterize a single point. Future plans include a shift to comprehensive volumetric microscopy by replacing conventional OCT with Optical Frequency-Domain Imaging (OFDI). The OFDI system is expected to operate a rate of 160 frames/sec while maintaining a 10 micron depth resolution. The anticipated data sets will be large (~ 10 GB) and will be used to provide cross-sectional images by image processing to allow rapid screening.

James Tunnell, PhD, MIT Spectroscopy Lab, described “Real Time Spectral Diagnosis of Dysplasia in Barrett's Esophagus”. The concept is to use spectral diagnosis to non-invasively characterize tissue pathology. A combination of three spectroscopic techniques (diffuse reflectance, intrinsic fluorescence, and elastic light scattering) was applied and the resulting spectroscopic signatures used to quantitatively determine both tissue structure and function. For fluorescence data excitation-emission spectra were used for the analysis. Among the diagnostic parameters used to differentiate tissue types were NADH/collagen concentration ratios, hemoglobin concentration, oxygen saturation and the slope of the tissue scattering curve. A recent study involving over 80 patients has confirmed the high accuracy (90% sensitivity and 85% specificity) of spectral diagnosis in detecting dysplasia in patients with BE. Future plans include the addition of Raman spectroscopy to the optical system. The system currently provides point information rather than images; it is hoped that it will provide a real-time guide to biopsy.

Gordon Kino, PhD, Professor Emeritus, Stanford University discussed “Endoscopic Confocal Microscopy for Structure and Function”. He described a number of novel devices, including a microendoscope, a fluorescence microscopy system which used exogenous marker tags, and a MEMS-based scanning confocal microscope. Subcellular measurements with a standard confocal microscope *ex vivo* have shown that Barrett's esophagus can be marked with peptide reagents. New types of fluorescent markers for dysplasia are under development. A fibered confocal fluorescence microscopy system designed to provide *in vivo* microvascular observations was described. It uses a probe composed of a fiber bundle and micro-optics having a diameter as small as 650 microns; the multiple 2-micron fibers act as pinholes for confocal imaging. Images taken with this fiber confocal fluorescence microscope in the esophagus *in vivo* using topically-sprayed fluorescein for contrast enhancement were shown. With illumination at 488 nm wavelength, the transverse resolution is 5 microns and the range resolution is 15microns. A MEMS scanned dual-axes endoscopic confocal microscope under construction was described. The confocal effect is provided using two low NA lenses at an angle to each other. Resolution is provided by the small volume defined by the intersection of the beam waists. This device should have ~1 micron transverse and ~2 micron range resolution at 488nm wavelength.

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