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Session I: Barrett's esophagus

Spatial and temporal heterogeneity in Barrett's esophagus

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Within a neoplasm, there is genetic heterogeneity over both space and time. This heterogeneity is a fundamental property of the clonal evolution that drives neoplastic progression. It also poses unique challenges to the development of screening strategies and biomarkers for risk stratification and early detection of cancer. False negative results on assays may be due to a failure to sample the relevant clone in a neoplasm. Furthermore, the predictive power of accurate information gained from screening may decay with time as the neoplasm changes through the stochastic appearance and extinction of mutant clones. We have shown in premalignant Barrett's esophagus (BE) that mutant clones may cover complex, concave shapes on the surface of the esophagus. Within the Barrett's neoplasms, genetic heterogeneity in space predicts progression to cancer. We have also found that the risk of progression associated with loss of heterozygosity in p16 (CDKN2A/INK4A) decreases with time since biopsy. The ability to image the different clones in a neoplasm would allow the targeted sampling of mutations associated with risk of progression. Imaging of clones would help to illuminate how clones expand and go extinct in a neoplasm, allowing intervention in those processes to prevent or delay progression to malignancy.

Advances in Barrett's esophagus imaging: Magnification and narrow band imaging

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The past few years have seen several new developments in the field of endoscopic imaging and esophageal diseases. Advances in biomedical optics have been applied to overcome various limitations of conventional diagnostic endoscopy for the improved detection of BE and esophageal cancer. Currently, in the case of BE, the gold standard is standard endoscopy with random biopsies, which adds to the "hit and miss" nature and costs associated with the procedure. The distribution of dysplasia and early adenocarcinoma within the Barrett's segment is patchy and focal. Development of novel imaging techniques that overcome these various shortcomings is highly desirable. Much effort has been expended on developing new gastrointestinal endoscopy technologies or techniques in order to provide a precise and even a "real time" endoscopic diagnosis.

Conventional videoendoscopes are equipped with charged-coupled device (CCD) chips of 100K to 300K pixels, meaning that each image is built up from 100,000 to 300,000 individual pixels. This technical feature, also referred to as pixel density, is important because it relates to image resolution and hence the ability to discriminate two closely approximated points. The higher the pixel density, the higher the image resolution, the more likely minute lesions will be discriminated and detected. Magnification endoscopy is a relatively simple technique that enlarges the video image up to 150x, usually using a movable lens controlled by the endoscopist to vary the degree of magnification. Narrow-band imaging (NBI) is a novel endoscopic technique that changes the optical filters of the current sequential lighting video endoscopes to spectral narrow-band filters. Higher-intensity blue light with narrow-band filters enables imaging of superficial tissue structures and emphasizes imaging of features such as capillary and mucosal patterns without the use of dyes. The main chromophore in esophageal tissues in the visible wavelength range is hemoglobin, which has a maximum absorptive wavelength near 415 nm, within the wavelength range for NBI, which could thus detect vascular structures and patterns more accurately than conventional endoscopy.

BE is a well recognized premalignant condition for development of esophageal adenocarcinoma and results from chronic GERD. Once diagnosed with BE, pa-

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tients are typically enrolled in surveillance programs to monitor the lesion for progression. Current guidelines suggest obtaining systematic four-quadrant biopsies at 2 cm intervals from columnar-appearing mucosa in the distal esophagus to detect dysplasia or cancer. Stevens *et al.* used indigo carmine and Lugol's solution with magnification endoscopy (35x) to identify short segments of endoscopic Barrett's metaplasia. Identification of a raised, villiform surface pattern correlated well with the histological finding of intestinal metaplasia. In another study, Endo and colleagues used methylene blue staining with magnification endoscopy (80x) in 30 patients with columnar-distal esophagus and identified five discrete patterns of mucosal surface: small/round, straight, long oval, tubular and villous. Metaplastic tissue was predominantly detected in areas with tubular and/or villous patterns.

An increasing interest in using NBI in patients with BE and early cancer has shown encouraging preliminary results. Sharma and colleagues recently assessed the potential of NBI to predict histology during screening and surveillance endoscopy in patients with BE. Images obtained by this system were graded according to the mucosal (ridge/villous, circular, and irregular/distorted) and vascular patterns (normal and abnormal) and correlated with histology in a prospective and blinded manner. The sensitivity, specificity and positive predictive value of the ridge/villous pattern in diagnosing intestinal metaplasia without high-grade density (HGD) were 93.5%, 86.7% and 94.7% respectively. The sensitivity, specificity and positive predictive value of the irregular/distorted pattern for HGD were 100%, 98.7% and 95.3% respectively. However, NBI was unable to distinguish areas of intestinal metaplasia from those with low-grade density.

Issues related to test reproducibility, generalizability, applicability to individual patients, and favorable outcome effects will have to be established for these newer technologies. Possible indications include screening and surveillance of BE, defining the extent of esophageal cancer, and better recognition of mucosal and vascular changes. Ultimately, these innovations should improve diagnostic yields and demonstrate improved outcomes and survival; for now, detailed images seen by these advanced imaging technologies mark the beginning of an era in which new optical developments will allow a unique look at the esophagus.

Detecting precancerous cells in the human esophagus with angle-resolved low coherence interferometry

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The study of intact, living cells using non-invasive optical spectroscopic methods offers the opportunity to assess cellular structure and organization in a way that is not possible with traditional methods We have developed a novel spectroscopic technique for diagnosing disease at the cellular level based on using low-coherence interferometry (LCI) to detect the angular distribution of scattered light. Angle-resolved LCI (a/LCI) combines the ability of LCI to isolate scattering from sub-surface tissue layers with the ability of light-scattering spectroscopy to obtain structural information on sub-wavelength scales. In examining tissue structure, a/LCI enables quantitative measurements of precancerous changes in the size and texture of cell nuclei. The capabilities of a/LCI were demonstrated initially by detecting precancerous changes in epithelial cells within intact animal tissue samples without the need for exogenous fixation or staining agents. Recently, we have developed a new a/LCI system with fast acquisition times and a fiber optic probe suitable for clinical applications. Preliminary results have been obtained using this new system to examine human esophageal tissue. Data for depth-resolved nuclear morphology in the epithelium of BE show nuclear atypia with distinct changes from normal columnar tissue as well as from other diseased tissue types.

Photodynamic therapy and endoluminal therapies vs. surgery for dysplastic Barrett's esophagus

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BE is the replacement of normal squamous mucosa with specialized intestinal metaplasia in response to gastroesophageal reflux. BE can be distinguished endoscopically from normal squamous mucosa and is significant because of an associated increased risk of car-

cinoma. This increased risk is 40 times greater than the general population, affecting 1% of patients with BE. Carcinomas that arise from BE progress through grades of dysplasia before becoming invasive. BE with HGD and/or intramucosal carcinoma (IMCA) represents superficial neoplasia amenable to curative therapy. Operative esophagectomy has been the standard therapy for patients with BE and HGD/IMCA. However, it is associated with a 3–13% mortality and 30–50% significant morbidity. Alternatively, effective eradication of BE in an acid-free environment is followed by restoration of normal squamous mucosa. Successful eradication has been demonstrated with ablation and resection techniques. Ablation techniques have included contact [multipolar electrocautery and radiofrequency (RF)] and non-contact (laser and argon plasma beam coagulator) thermal therapies and photodynamic therapy (PDT). In a randomized controlled trial, PDT successfully eradicated HGD and reduced progression to carcinoma [1]. PDT is suited for eradication of circumferential long-segment BE with multi-focal HGD. The most developed esophageal endoscopic mucosal resection (EMR) techniques are the cap-aspiration/ligation/snare technique and the injection/cap-aspiration/snare technique [2,3]. EMR offers an advantage over ablation therapy because it provides a resected specimen for histopathologic interpretation, leading to a change in histopathologic staging in 44% of cases [4]. EMR may achieve effective cure in patients with short segments of BE with HGD/IMCA. Moreover, EMR is used adjunctively in combination with ablation techniques to eradicate macroscopically recognizable focal HGD/IMCA associated with longer segments of BE. This application of multimodal endoluminal therapy is a promising alternative to operative resection in selected patients with BE and HGD/IMCA.

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