Best of foregut: esophagus, stomach, and duodenum

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Several major advances have occurred in endoscopic research focused on the foregut (encompassing the esophagus, stomach, and small bowel) in 2015 and 2016. In this review we attempt to briefly describe some of the research with the most impact pertaining to the foregut published in this time frame. In addition to the anatomic subdivisions, the information is subsequently categorized according to disease states.

Advances in this field include new methods for Barrett's esophagus (BE) screening, additional data on progression rates and endoscopic therapy in BE with low-grade dysplasia, and estimates of recurrence after endoscopic therapy. The role of the esophageal epithelial barrier was further defined in eosinophilic esophagitis (EoE) along with potential biomarkers for diagnosing and defining the clinical course of EoE. Several reports describing the efficacy and durability of peroral endoscopic myotomy (POEM) were published along with encouraging data on the endoscopic treatment of obesity. The utility of endoscopic submucosal dissection (ESD) in the management of early gastric cancer was further defined along with novel endoscopic methods to treat gastric varices. Additional data on the utility of video capsule endoscopy (VCE) in the management of obscure GI bleeding and small-bowel neoplastic surveillance in genetic cancer syndromes were also published.

ESOPHAGUS

Barrett's esophagus

The premise of an ideal esophageal adenocarcinoma (EAC) screening program lies in the ability to detect early cancer and improve patient outcomes.[1] Unfortunately, in a Northern Ireland study only 7.3% of EAC had a prior diagnosis of BE. However, a 23% survival benefit for patients in surveillance was reported, after accounting for lead and length time biases, likely accounted by earlier stage at diagnosis (44.2% vs 11.1%) and greater likelihood of undergoing a resection (50.0% vs 25.5%).[2]

Minimally invasive or nonendoscopic interventions are redefining current BE screening paradigms. Unsedated transnasal endoscopy, in a mobile van or hospital setting, allowed for comparable evaluation ($P = .080$, study completion) and yield for BE ($P = .37$) compared with conventional endoscopy (EGD) in a randomized community trial. Unsedated transnasal endoscopy had shorter recovery times ($P < .01$) but, although less tolerable (1.9 and 2.2 vs .4 on a visual analogue scale), had comparable participation rates.[3] Findings of an earlier study documenting the utility of a sponge capsule with a protein marker were replicated in a case-control study of 1110 individuals, reporting a sensitivity of 79.9% and a specificity of 92%.[4]

Annual progression rates in low-grade dysplasia (defined as development of EAC or high-grade dysplasia) were reported to be 2.7% per year in a natural history study from Cleveland. Prevalent cases, male gender, multifocality, and nodules were associated with the higher rates of progression.[5] Confirmation of diagnosis further enhanced progression rates. In a Dutch study, a low-grade dysplasia diagnosis was confirmed in only 27% of initial community diagnoses, and the progression risk in this group was substantially higher (9.1%) compared with .6% in those whose diagnosis was downgraded to no dysplasia.[6]

Enhanced detection of dysplasia was demonstrated to be feasible by combining autofluorescence imaging with biomarkers such as p53, aneuploidy, and cyclin A, leading to an area under the curve of .97 for detection of high-grade dysplasia/EAC.[7] Volumetric laser endomicroscopy is emerging as a broad-field imaging technology by providing high-resolution cross-sectional surface evaluation of 6-cm BE segments. It was demonstrated to be safe and feasible in a multicenter study.[8] A new scoring system for detection of dysplasia in BE improved sensitivity, specificity, and accuracy to 86%, 88%, and 87%, respectively, when evaluated on dysplasia-enriched EMR specimens, with moderately high κ values (.8).[9]

The utility of EUS in the evaluation of early cancer in BE has been debated. In a meta-analysis of 13 studies, EUS

Abbreviations: BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EoE, eosinophilic esophagitis; ESD, endoscopic submucosal dissection; POEM, peroral endoscopic myotomy; PPI, proton pump inhibitor; RFA, radiofrequency ablation; VCE, video capsule endoscopy.

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correctly identified submucosal invasion (in the absence of visible nodules) in 4% and advanced disease in 14% overall. Additionally, EUS also was highly specific (94%) with a high negative predictive value (96%) in evaluating nodal disease.[10]

ESD allows en-bloc removal of neoplastic lesions as an alternative to piecemeal EMR, and its role in BE remains unclear. In a randomized controlled trial comparing ESD (n = 20) with EMR (n = 20) in BE high-grade dysplasia or intramucosal cancer (<3 cm), ESD was able to achieve greater R0 resection, but there were no differences in complete remission of intestinal metaplasia at 3 months. Paradoxically, the only recurrence was noted in the ESD group after a mean follow-up of 23.1 months. The need for curative surgery was also not different between the 2 groups. Two severe adverse events were noted in the ESD but none in the EMR groups. This study underscores the need for additional studies to define the role of ESD in BE endotherapy.[11,12]

Despite its efficacy in reducing progression and eliminating metaplasia, radiofrequency ablation (RFA) is not a Barrett's panacea. In a U.S. RFA registry, among 4982 patients, 2% developed EAC (incidence of 7.8 per 1000 person-years) after initiation of RFA, with baseline BE length and histology predicting incidence. The most common causes of death after RFA were cardiovascular and extraesophageal cancers (both 15% individually).[13] A strong correlation between the volume of RFA performed by the endoscopist and rates of complete remission of intestinal metaplasia ($\rho = .85$, $P = .014$) was reported in a multicenter cohort study.[14] A U.K. RFA registry assessed time trends on results with RFA, and reported an improvement in clearance of all dysplasia and clearance of all intestinal metaplasia (77% and 56% to 92% and 83%, $P < .0001$) between 2008 to 2010 and 2011 to 2013. This was associated with increase in pre-RFA EMR while requiring less "rescue" EMR. This study further supports the hypothesis of improved results with increasing RFA experience.[15]

New data on the incidence of recurrence after successful endotherapy and its location were reported. A meta-analysis of 41 studies identified an annual incidence of recurrent intestinal metaplasia, dysplasia, and high-grade dysplasia/EAC of 7.1%, 1.3%, and .8%, respectively. This study confirmed increasing age and length of the BE segment as predictors of recurrence. Most recurrences (>90%) were endoscopically treatable.[16] In another study, with the exception of those associated with endoscopic findings (60%), all remaining recurrences occurred within 1 cm of the gastroesophageal junction.[17] Hence, although RFA is an effective treatment modality, post-treatment surveillance remains essential. Cost-effective practices might limit histologic acquisition to areas of highest yield.

Eosinophilic esophagitis

The prevalence of EoE is currently estimated at 50 to 100 per 100,000 persons in the Western world. The rising incidence of EoE has been variably attributed to greater disease awareness, revised histologic criteria, and a true rising incidence. A study from the Danish National Registry reported that the rising incidence of EoE outweighed the increased frequency of biopsy sampling by 20- to 25-fold.[18] Analysis of a cross-sectional pathology database confirmed seasonal and geographic variations in EoE, with the highest incidence in July (adjusted odds ratio, 1.13) and in temperate and cold climates.[19]

The overlap between EoE and GERD extends from esophageal eosinophilia to proton pump inhibitor (PPI) response. PPI-responsive eosinophilia has emerged as a distinct entity. A meta-analysis of studies on PPI-responsive eosinophilia identified clinical response and histologic remission rates of 60.8% and 50.05%, respectively. There was a trend toward increased PPI efficacy in prospective trials, pH-confirmed GERD, and twice a day administration.[20]

In an attempt to explore the role of biomarkers in predicting EoE course, histologic specimens from patients with EoE, PPI-responsive eosinophilia, and GERD with dense eosinophilia were stained for eotaxin-3 (a protein implicated in activation, recruitment, and degranulation of eosinophils). Staining scores and intensity were higher in EoE compared with GERD ($P = .002$ and $P < .001$, respectively), with a trend toward significance between EoE and PPI-responsive eosinophilia ($P = .054$). The histologic evaluation was limited by the lack of a validated scoring method for eotaxin-3 staining intensity.[21] Eotaxin-3 levels ($P = .02$) also independently predicted response to steroids in another study.[22]

Endoscopic biopsy sampling remains the criterion standard diagnostic tool for EoE. Guidelines have advocated for a threshold 15 eosinophils per high-power field. Investigators at University of North Carolina found that although a threshold of 15 eosinophils per high-power field had excellent sensitivity of 100% and specificity of 96%, marked variability in eosinophil counts existed within individual patients and between collected specimens. Inflammatory endoscopic findings (exudative plaques and furrows) also correlated with a higher yield of eosinophilia in 2 studies.[23,24] Firmness during tissue biopsy acquisition ("pull sign") performed by a single endoscopist had a specificity of 98% for EoE (area under the curve = .871), resolved with therapy, but had no correlation to predicted histology of lamina propria fibrosis ($P = .72$).[25]

Functional parameters to diagnose and monitor treatment effect have been recently described in EoE. In a prospective trial, treatment effects of swallowed fluticasone on the esophageal epithelial barrier were measured. In vivo (transepithelial electrical resistance) and ex vivo (transepithelial molecule flux) measures of mucosal integrity were analyzed. Increased impedance ($P < .01$) and reduced molecular flux ($P < .05$) suggestive of restitution of the epithelial barrier were noted on steroids.[26]

Endoscopy is used to monitor response in EoE. The capsule sponge (discussed in detail above) offers a