DDW HIGHLIGHTS

Barrett’s esophagus, reflux esophagitis, and eosinophilic esophagitis

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Many new and exciting endoscopy-related studies on Barrett’s esophagus, reflux esophagitis, and eosinophilic esophagitis were presented during the 2012 Digestive Disease Week (DDW; 19-22 May, San Diego, California, USA).

Endoscopic research in Barrett’s esophagus mainly focused on surveillance, detection, and ablation therapy, while clinical studies in eosinophilic esophagitis concerned budesonide treatment and dietary measures, and those on reflux esophagitis covered various issues related to anti-reflux surgery. In this review, we discuss our top 20 DDW 2012 abstracts on these three topics.

ABLATIVE TREATMENT OF BARRETT’S ESOPHAGUS

Although various endoscopic options are available for ablation of Barrett’s esophagus, such as cryotherapy, photodynamic therapy, radiofrequency ablation (RFA), and argon plasma coagulation, RFA is currently the most frequently used technique due to its high efficacy and low complication rates. Predictive factors for complete eradication of intestinal metaplasia (CEIM) are largely unknown. Data from the multicenter U.S. RFA Registry were used to assess the relationship between Barrett’s esophagus and outcomes of RFA.1 CEIM was defined as the complete eradication of intestinal metaplasia in biopsies taken at least 12 months after enrollment. Among 5539 patients who underwent RFA for Barrett’s esophagus, 2166 (39%) had biopsies obtained 12 months or longer after enrollment. CEIM was found in 72%, after a mean number (39%) had biopsies obtained 12 months or longer after enrollment. CEIM was found in 72%, after a mean number (39%) had biopsies obtained 12 months or longer after enrollment. CEIM was found in 72%, after a mean number (39%) had biopsies obtained 12 months or longer after enrollment. CEIM was found in 72%, after a mean number of 2.6 ± 1.4 ablation sessions. The length of Barrett’s esophagus was independently associated with being difficult to ablate (odds ratio [OR]: 1.28 per additional cm; $P < 0.001$), when controlled for age, race, sex, and degree of dysplasia at baseline. On average, patients with 2-, 5-, and 8 cm of Barrett’s esophagus needed 2.4, 2.9, and 3.5 treatment sessions, respectively. The OR of failure to achieve CEIM was higher in advanced neoplasia (high grade dysplasia [HGD], intramucosal carcinoma, and invasive cancer) (OR: 2.07; 95% confidence interval [CI] 1.62-2.64) compared with early neoplasia (indefinite dysplasia, low grade dysplasia [LGD]) (OR: 1.61; 95%CI 1.26-2.06).2 These findings can be helpful in patient counseling and may be valuable for generating more tailor-made treatment regimens.

Another potential factor determining the outcome of RFA in Barrett’s esophagus may be the ablation regimen used. Currently, RFA consists of two applications of energy, cleaning of the device and the ablated zone, followed by two additional applications. A faster and simplified, yet equally safe and effective regimen may be useful. In three centers, 40 consecutive patients who were scheduled for RFA of residual islands of Barrett’s esophagus were randomized to a standard regimen (2 $\times$ 15 J/cm$^2$ – clean – 2 $\times$ 15 J/cm$^2$) or simplified regimen (3 $\times$ 15 J/cm$^2$).3 Patients underwent RFA every 2 months until complete histological response of each targeted Barrett’s area was achieved for both neoplasia and intestinal metaplasia. Complete response of intestinal metaplasia at 2 months after focal RFA was 66.7% and 73.3% for the standard and simplified regimen, respectively ($P = n.s.$). No complications occurred. The results of this trial suggest that the simplified focal ablation regimen is safe and not inferior to the standard regimen, and may be recommended for residual Barrett’s esophagus islands. The question remains however whether circular Barrett’s esophagus segments will respond in the same way to this simplified regimen.

Little is known about the effects of acid and bile reflux on mucosal healing and squamous re-epithelialization rates after treatment of Barrett’s esophagus with RFA. In theory, prior fundoplication may improve the efficacy of RFA. The same U.S. RFA Registry1 was used to compare safety and efficacy outcomes between patients with a history of fundoplication and those undergoing medical management with proton pump inhibitors (PPIs) without fundoplication.4 Among 5539 patients undergoing RFA, 318 (5.7%) had a prior fundoplication. No perforations occurred in the fundoplication group. Rates of stricture, bleeding, and hospitalization were also not significantly different between patients with and without prior fundo-

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plication. After 12 months, 2135 of 5539 patients (39%) had biopsy data available, showing similar rates of complete eradication of dysplasia (93% with vs. 87% without), CEIM (78% with vs. 72% without), and number of RFA sessions for eradication needed. So, prior fundoplication was not associated with improved efficacy nor did it reduce the number of ablation sessions needed, when compared with medical management using PPIs.

Recently, serious concerns about recurrence of intestinal metaplasia and dysplasia after RFA have arisen. Three major Barrett’s esophagus research centers therefore combined their ablation cohorts. Patients (n = 537) were treated with RFA as per the standard protocol (HALO360 for circumferential followed by HALO80 for focal lesions; 12 J/cm² for HGD and LGD). Recurrence was defined as presence of intestinal metaplasia with or without dysplasia on two consecutive endoscopies after CEIM had been established. After 12.1 months (interquartile range [IQR] 7.5-22.4 months) in 218 patients (40.5%) CEIM was achieved. Patients in this cohort were followed for a median of 1.12 years (IQR 0.67-6.46) after achieving CEIM. At 2 years, the cumulative incidence of intestinal metaplasia recurrence was 32% (95%CI 23-45). The histology of recurrences was mostly intestinal metaplasia, but also included HGD and esophageal adenocarcinoma (EAC). A total of 13 of 38 patients with a recurrence had worse histology on recurrence compared with the time of entry. No patient or endoscopic factor in this group with CEIM was associated with recurrence of intestinal metaplasia or dysplasia. Based on these results, meticulous surveillance of the original Barrett’s esophagus segment and the gastroesophageal junction after RFA is therefore advised in all patients, despite prior CEIM. It can be expected that over the next few years more follow-up data will be available, which will allow a thorough evaluation of the future role of ablation (with RFA) in Barrett’s esophagus.

A drawback of RFA is the need for a device that is apart from or attached to the outside of an endoscope. Cryoablation may therefore be an alternative; however, current cryotherapy devices, which spray CO₂ or N₂ onto the mucosa, require gastric venting and ablation depth is difficult to standardize. The aim of the pilot study by DeMeester et al. was to assess depth of injury related to time of ablation using a novel through-the-scope cryoballoon, which automatically adjusts its size to the esophageal lumen. One or two ablations of Barrett’s mucosa proximal to an EAC were performed in 13 patients scheduled for esophageal resection. No serious adverse events, pain or difficulty with swallowing were observed. After resection, the ablation areas were histologically assessed. Ablation with this novel cryoballoon device for 10-14 seconds resulted in substantial mucosal injury. Depth of necrosis was maximal at Day 4 and was typically up to the superficial muscularis propria. By Day 7 the injury was resolving. Advantages of this device include the ability to standardize the ablation along with the ease of use and speed of the procedure. Future studies are needed to assess the risk of stricture formation and efficacy of Barrett’s esophagus ablation with this device. If successful, a comparison with RFA may well be considered.

ADVANCED IMAGING IN BARRETT’S ESOPHAGUS

Multiple biopsies are often needed to detect intestinal metaplasia and neoplastic lesions within it. Confocal laser endomicroscopy (CLE) is a new imaging technique for studying cellular morphology during endoscopy (in vivo virtual histology). A large variability in sensitivity and specificity has been reported for the discrimination between intestinal metaplasia and gastric metaplasia by the endoscopist. Grisan et al. evaluated the possibility of computerized differentiation between gastric and intestinal metaplasia on CLE images, potentially increasing the accuracy of CLE. Biopsy-matched CLE images from 29 consecutive patients with Barrett’s esophagus were analyzed. Good-quality images (262 images showing intestinal metaplasia and 23 gastric metaplasia) were selected. The imaging method had a 98.85% sensitivity and a specificity of 65.22% for the detection of intestinal metaplasia. Further refinement of this computed system may potentially lead to incorporation into endoscopic processors for real-time analysis, which could then increase the sensitivity and specificity of endoscopic CLE examinations of Barrett’s esophagus.

Detection of early esophageal cancer is crucial for patient prognosis. Early stages can be treated by endoscopic resection whereas advanced neoplasia leads to far more invasive therapies. Moreover, biopsies taken from early lesions might hamper subsequent endoscopic resection. The electrical properties in inflammatory tissue and dysplasia have been shown to be sensed by electrical bio-impedance spectroscopy. A pilot study was performed in esophageal cancer to compare impedance with histology and to investigate the feasibility of this technique for the detection of early stage esophageal cancer. After endoscopic resection, the resected tissue specimens of 17 patients were investigated at different sites for electrical impedance properties. After bio-impedance measurement a punch biopsy was taken to compare histology with impedance. Bio-impedance was able to differentiate between neoplastic and non-neoplastic Barrett’s esophagus or squamous epithelium with a high accuracy (82% for non-neoplastic Barrett’s esophagus and 100% for squamous epithelium). The use of bio-impedance spectroscopy may in the future result in unnecessary biopsies being avoided during cancer surveillance and also guide endoscopic resection during endoscopy. Further studies are needed to investigate bio-impedance spectroscopy in vivo during endoscopy.

The role of endoscope-based CLE (eCLE) for prediction of Barrett’s esophagus neoplasia compared with high resolution endoscopy (HRE) is unknown. Canto et al. therefore compared the diagnostic yield, performance charac-

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teristics, and clinical impact of HRE + eCLE followed by targeted biopsy vs. HRE alone with targeted biopsy and random biopsy for the detection of Barrett’s esophagus neoplasia. Patients with Barrett’s esophagus were randomized to either HRE alone (Group A) or HRE + eCLE (Group B). Patients with known localized neoplasia, an esophageal lesion >2 cm, and prior ablation were excluded. Before and after eCLE, a diagnosis was determined for each imaging site and a plan (do nothing, biopsy, or endoscopic mucosal resection (EMR) was recorded. After eCLE, EMR and/or random biopsy were performed. Using a per biopsy analysis, the overall diagnostic yield for neoplasia (45.6% vs. 8.8%; P < 0.0001) was 5.2-fold greater using eCLE. The difference in diagnostic yield was primarily in patients with unlocalized neoplasia (59.5% vs. 12.7%; P < 0.0001). Using a per patient analysis, HRE + eCLE resulted in a 4-fold increase in diagnostic yield for Barrett’s esophagus neoplasia (79.3% vs. 20%; P < 0.0001). Compared with HRE with random biopsy, HRE + eCLE + targeted biopsy improved the detection of Barrett’s esophagus neoplasia with significantly fewer biopsies taken, and the combination of imaging modalities influenced decision-making during endoscopy.

CEI in the distal esophagus cannot be reliably determined at endoscopy. Probe-based CLE (pCLE) in this setting could aid in a more accurate determination of the presence of Barrett’s esophagus and guide continued ablation in real time. Wallace et al.10 randomized patients to follow-up of a previous ablation area with high definition white light (HDWL) endoscopy or HDWL plus pCLE. Treatment was based on whether the endoscopist suspected residual Barrett’s esophagus. In the HDWL + pCLE arm, a suspicion of Barrett’s esophagus based on HDWL had to be confirmed with pCLE for treatment to proceed. Biopsy was performed immediately after imaging and patients had a follow-up procedure 3 months later. The primary outcome was the proportion of “optimally treated” patients defined as those with residual Barrett’s esophagus who were treated and had complete ablation plus those without Barrett’s esophagus who were not treated and had no evidence of disease at follow-up. A total of 164 patients were randomized. Among the 119 patients with follow-up, there was no difference in the proportion of patients achieving optimal outcomes in the two groups (26% for HDWL, 27% with HDWL + pCLE). Other outcomes including over-treatment, under-treatment, and findings at follow-up endoscopy were also similar. This study yielded no evidence that the addition of pCLE to HDWL imaging for detecting residual Barrett’s esophagus or dysplasia can provide improved treatment results. However, the study was somewhat limited due to high rate of residual Barrett’s esophagus at follow-up examination, which implies that most patients in the study required re-treatment. The way in which pCLE could be used to guide treatment was restricted as the main potential application is to distinguish residual Barrett’s esophagus when there is endoscopic un-certainty. Therefore, further evaluation of this imaging modality is needed to understand its utility in guiding continued ablation in this setting.

**SURVEILLANCE IN BARRETT’S ESOPHAGUS**

The effectiveness of surveillance in patients with Barrett’s esophagus is still the subject of debate. Verbeek et al.11 investigated whether tumor stage and long-term outcome were better in EAC patients with Barrett’s esophagus that were included in a surveillance program compared with those who were not. All Barrett’s patients who were diagnosed with EAC between 1999 and 2009 in The Netherlands were identified by linking the Dutch cancer registry with the Dutch nationwide histopathology registry (PALGA). A prior diagnosis of Barrett’s esophagus was defined as a Barrett’s esophagus diagnosis at least 1 year before EAC diagnosis. Of 997 patients with a prior diagnosis of Barrett’s esophagus and EAC, 774 (78%) participated in a surveillance program according to the definition used. Median time between first Barrett’s esophagus diagnosis and EAC detection was 6.0 years (IQR 1.5-11.1 years) for surveillance participants and 5.0 years (IQR 2.5-8.5 years) for those not participating. Patients with Barrett’s esophagus included in a surveillance program had a higher likelihood of having a well-differentiated EAC (OR: 3.4; 95%CI 1.3-9.1), tumor stage 0 (OR: 4.3; 95%CI 1.2-15.6), stage I (OR: 2.7; 95%CI 1.5-4.9) or stage II (OR: 1.9; 95%CI 1.1-3.2), were more frequently diagnosed in a university hospital (OR: 1.7; 95%CI 1.0-2.7), and more frequently underwent surgical treatment (OR: 1.7; 95%CI 1.1-2.7) than patients not undergoing surveillance. The more favorable outcome in Barrett’s esophagus surveillance participants therefore supports its use, although a direct effect on survival could not be demonstrated.

Another positive effect of surveillance was found by Gaddam et al.12 In a large multicenter cohort (five tertiary referral centers) of Barrett’s esophagus patients undergoing surveillance, the risk of EAC and a combined endpoint of HGD/EAC in patients with persistent nondysplastic Barrett’s esophagus were evaluated. Patients developing HGD and EAC within 1 year of diagnosis of Barrett’s esophagus were considered to be prevalent cases and were excluded. Based on the number of consecutive surveillance endoscopies showing no dysplasia, five cohorts of patients (n = 1401) were constructed. The mean length of Barrett’s esophagus was 4 cm (SD 3.2). The annual risk of EAC in patients with an index endoscopy showing nondysplastic Barrett’s esophagus was 0.32%, with a decrease in risk with each subsequent nondysplastic Barrett’s esophagus endoscopy (0.25%, 0.16%, 0.15%, and 0.09%; P = 0.005). A similar significant trend (P = 0.046) was seen for combined HGD/EAC. The annual risk of EAC development decreased significantly with 50% after three and 70% after five consecutive surveillance endoscopies demonstrating no dysplasia. These findings support the notion for discontinuing surveillance or at least lengthening
surveillance intervals in patients with persistent nondysplastic Barrett’s esophagus. A potential bias in this study could be that patients that are willing to undergo repeat surveillance may be more health conscious and therefore also have a better prognosis.

Surveillance programs based only on histopathology data for identifying high risk patients with Barrett’s esophagus are likely to be inefficient. A novel biomarker assay on brush cytology using DNA fluorescence in situ hybridization (FISH) for the tumor suppressor genes p16 (9p21) and p53 (17p13.1), and for aneuploidy (for chromosomes 17 and 7) was assessed in a 5-year prospective follow-up study in a Barrett’s esophagus surveillance cohort. The assay tested a marker positive if the percentage of abnormal cells with genetic abnormalities for p16 or p53 and/or aneuploidy was higher than the cut-off value. In total, 195 patients were included. The progression-free interval was significantly shorter in the marker-positive group than in the negative group (P = 0.001). Multivariate analysis showed that a positive test correlated with a hazard ratio of 10.6 (P = 0.003) for progression when compared with other variables. This assay may serve as a useful tool to improve the risk stratification of patients with Barrett’s esophagus and to increase the efficacy of endoscopic surveillance with targeted and random biopsies.

REFLUX ESOPHAGITIS

To improve surgical outcome, many complex surgical procedures are increasingly being performed in larger and specialized hospitals (centralization). The question is whether this has also occurred with anti-reflux surgery and how outcomes have developed as a consequence of this. The Nationwide Inpatient Sample data were analyzed for all anti-reflux procedures performed in the period 1998-99 (T1) and 2008-09 (T2). Hospitals were stratified into high-, mid-, and low-volume centers (HVC, MVC, LVC, respectively). A total of 11804 anti-reflux procedures were performed in T1 and 8856 in T2. In T1, 41.0% of procedures were performed in a HVC compared with 35.4% in T2. LVC rates increased with time, from 20.53% in T1 to 26.87% in T2 (P < 0.0001). Complication rates increased in all centers with time, but were twice as common in LVCs (6.39%) compared with HVCs (3.16%; P < 0.0001) during T2. In-hospital mortality decreased in all centers with time. It was concluded that despite improved results at HVCs, LVCs were found to have increased their percentage of anti-reflux operations over time. Centralization has therefore not occurred for anti-reflux surgery; however, such a move could improve outcomes, as complication rates were found to be higher in LVCs.

Many surgeons feel comfortable performing anti-reflux surgery on the basis of symptomatic evaluation, endoscopy, and esophageal manometry, whereas pH monitoring is seldom obtained. To evaluate whether this approach is justified, the sensitivity and specificity of symptoms, barium esophagogram, endoscopy, and manometry were compared with pH monitoring in the preoperative evaluation of patients referred for anti-reflux surgery. Patients (n = 134) referred for anti-reflux surgery with a diagnosis of gastroesophageal reflux disease (GERD) based on symptoms underwent endoscopy, barium esophagogram, manometry, and 24-hour pH monitoring preoperatively. Based on the presence or absence of GERD on pH monitoring, patients were divided into two groups: GERD+ (n = 78) and GERD− (n = 56). No difference was found in the incidence of symptoms between the two groups. Within the GERD+ group, 37 patients (47%) had reflux detected on esophagogram, and 41 (53%) had no reflux. Among the GERD− patients, 17 (30%) had reflux and 39 (70%) had no reflux. The sensitivity of an esophagogram was 47% and the specificity was 70%. A hiatal hernia was found in 40% and 32% of patients, respectively. Esophagitis was found at endoscopy in 16% of GERD+ patients and in 20% of GERD− patients, accounting for a sensitivity of 16% and specificity of 80%. Esophageal manometry showed no difference in pressure of the lower esophageal sphincter or quality of peristalsis. Ambulatory 24-hour pH monitoring clearly differentiated between the two groups. This study shows that pH monitoring should be routinely performed in the preoperative work-up of patients who are suspected of having GERD in order to avoid unnecessary anti-reflux surgery.

The management of supra-esophageal reflux symptoms remains a clinical challenge. It is known that PPI therapy does not prevent the volume of the refluxate into the pharynx. The efficacy of the “UES Assist Device” (an adjustable band around the throat which provides pressure on the upper esophageal sphincter area, just below the Adam’s apple), in the management of supra-esophageal symptoms of reflux disease was tested in a clinical trial. A total of 14 patients with a variety of supra-esophageal symptoms, most notably chronic cough, excess phlegm, and throat clearing, were treated with the device. No patient complaints or complications were observed. The global symptom severity and impact score for therapeutic and sub-therapeutic pressure assist was significantly lower than that of baseline. In addition, therapeutic pressure assist resulted in a significantly lower symptom severity compared with sub-therapeutic pressure assist (P = 0.003). Therefore, the “UES Assist Device” seems safe and effective in the management of supra-esophageal complications of reflux disease.

EOSINOPHILIC ESOPHAGITIS

Little is known on the natural history of eosinophilic esophagitis. For instance, it is unclear whether the stenosing phenotype is preceded by the inflammatory phenotype, which is endoscopically characterized by whitish exudates and edema. A retrospective analysis of 44 patients (33 males; mean age at index visit 41 ± 14 years; all Caucasians) showed that the risk of finding a stenosis in the esophagus at the index endoscopy was 0% for a disease duration of 0-4
years, 37% for a disease duration of 5-10 years, and 67% for a disease duration >10 years (P = 0.0035). The frequency of esophageal stenoses was proportional to disease duration, whereas the inflammatory activity did not change over time. These findings suggest that it is essential to reduce the diagnostic delay in eosinophilic esophagitis, as this will lead to development of fibrotic stenoses, which may be prevented by early medical treatment.

It has previously been shown that up to 70% of adults with eosinophilic esophagitis respond to a treatment with a six food elimination diet (SFED). To establish predictors of response to dietary therapy, gene profiling of esophageal tissue of patients undergoing dietary therapy with SFED was performed. Patients were treated with a SFED for 6 weeks. Biopsies from 28 patients showed that the expression of several key barrier/repair genes including desmoglein1, filagrin, collagen II A2, and CRISP3 was lower in biopsies from nonresponders vs. responders. Compared with controls, adults with eosinophilic esophagitis had increased expression of key inflammatory, proliferation, and mast cell-specific genes. Epithelial barrier/repair gene expression was lower in nonresponders to a SFED compared with responders, and a specific gene expression profile of esophageal barrier/repair genes taken from a single biopsy was able to predict responsiveness to dietary therapy.

Administration of topical corticosteroids is the mainstay of therapy for eosinophilic esophagitis. It is unknown which type of topical steroid preparation has the highest efficacy. In 22 patients, an open-label randomized trial comparing two ablation regimens for focal radiofrequency ablation (RFA) results of a limited clinical trial. Administration of topical corticosteroids is the mainstay of therapy for eosinophilic esophagitis. It is unknown which type of topical steroid preparation has the highest efficacy. In 22 patients, an open-label randomized trial comparing two ablation regimens for focal radiofrequency ablation (RFA) results of a limited clinical trial. Gastroenterology 2012;142(5 Suppl):S-181.


