AFS Position Paper- Confocal Laser Endomicroscopy For Barrett's Diagnosis and Surveillance

Key Points- Probe based Confocal Endomicroscopy (pCLE), available in the US as Cellvizio (Mauna Kea Technologies Inc.) has increased sensitivity and specificity compared to Seattle protocol biopsies in the diagnosis of Barrett's. Payor support for this technology is critical to ensure accurate diagnosis, treatment, and surveillance of patients with Barrett's esophagus.

Gastroesophageal reflux disease (GERD) affects nearly 15% of the US population and Westernized countries. The diagnosis of GERD is associated with a 10-15% risk of developing Barrett's esophagus. Compared to the general population, patients with BE have a 30-50% increased risk of developing esophageal adenocarcinoma. Despite advances in medical therapy to control acid reflux, the occurrence rates of esophageal adenocarcinoma as a result of uncontrolled GERD continues to be of great concern and has risen 600% since 1975. Barrett's esophagus is the number one risk factor for the development of esophageal adenocarcinoma. Intestinal metaplasia of the esophagus, or Barrett's esophagus (BE), comes from uncontrolled GERD. Despite these alarming numbers regarding the rise of esophageal cancer, Barrett's esophagus continues to be an underdiagnosed and undertreated condition.

Visible columnar metaplasia is characterized by replacement of normal squamous epithelium with columnar epithelium in the esophagus as a response to uncontrolled GERD. The presence of goblet cells defines BE and can be considered a risk factor for cancer.

Current ASGE guidelines recommend that tissue samples be obtained to confirm endoscopically suspected Barrett's esophagus for diagnosis and surveillance. The Seattle Protocol for Barrett's esophagus recommends four-quadrant random biopsies at 1-2-cm intervals (1-cm intervals if suspected high-grade intraepithelial neoplasia).1 This random biopsy protocol can be time consuming, expensive, and prone to sampling error, as very little of the esophageal surface area is actually sampled.

Unfortunately, the "Gold Standard" suffers from multiple problems. First, the Seattle protocol is often not followed. Second, is significant sampling error, as forcep biopsies cover only a fraction of total surface area of concern (this is exacerbated with increased length of columnar lined mucosa/Barrett's). Third, is intra-observer variability in establishing a diagnosis of Barrett's and especially dysplasia.

Of note, the ASGE just published guidelines on the screening and surveillance of Barrett's esophagus as well as addressing several questions related to the use of newer imaging and sampling techniques. Relative to pCLE the question posed to themselves was-

"In patients with BE undergoing endoscopy for surveillance of dysplasia, what is the role of CLE in increasing the rate of dysplasia detection?

Recommendation: In patients with BE undergoing surveillance, we suggest against routine use of CLE compared with WLE with Seattle protocol biopsy sampling (conditional recommendation, low quality of evidence)."

It should be noted that the question of pCLE's utility in screening for Barrett's **was not asked or answered** and this is precisely the question we are addressing with this position statement. Interestingly, the ASGE paper does go on to say, *"Although this guideline suggests against the routine use of CLE in BE patients, we acknowledge that CLE may be a helpful tool in increasing the diagnostic yield of dysplasia in centers with a high prevalence of dysplasia and significant local expertise."*

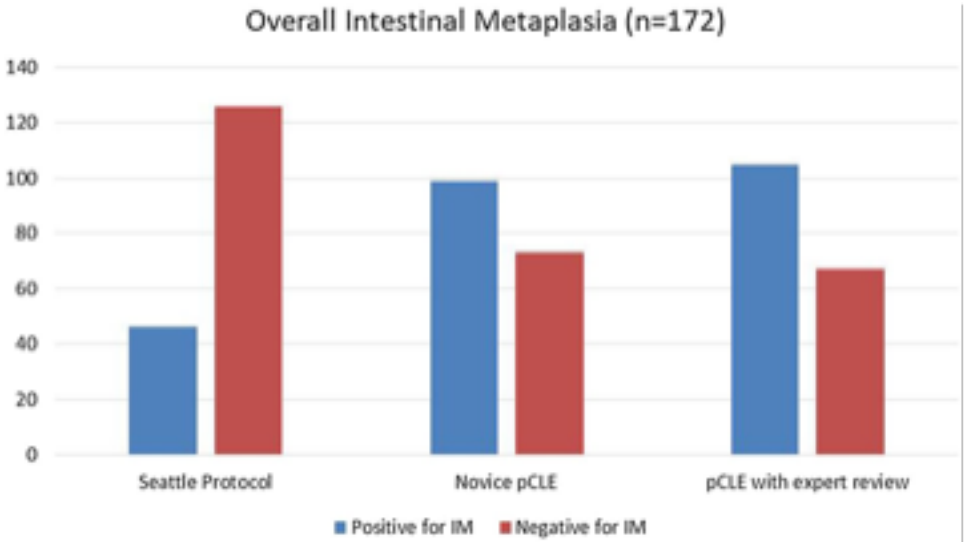
Diagnosis of BE remains difficult. The AGA White Paper addresses this issue by stating, "BE (specifically shorter disease) is often misdiagnosed during endoscopy. This misdiagnosis is often attributed to 1 of 2 reasons: (1) inability to differentiate columnar mucosa of the proximal stomach (cardia) from metaplastic epithelium in the distal esophagus or (2) lack of goblet cells in biopsies obtained from columnar lined epithelium in the esophagus." 2

Probe-based Confocal Laser Endomicroscopy (pCLE) generates digital biopsies, providing physicians with microscopic images of tissue in real time and in a minimally invasive manner. This provides endoscopists with dynamic microscopic views of gastrointestinal mucosa, allowing for real-time diagnosis of intestinal metaplasia. It also allows a greater esophageal surface area to be examined as compared to the random physical biopsy method. pCLE allows for directed biopsies when clinically appropriate of specific high risk areas. Finally, this technology is versatile and currently has FDA indications for use in the esophagus, biliary/pancreatic tree, respiratory tract, small/large intestine, and the genitourinary system.

In the DONT BIOPCE trial, a 2.7-fold increase in the diagnostic yield of BE and a 4.8-fold decrease in the number of biopsies by using pCLE and targeted biopsies have been observed. 3

The AGA White Paper published in December 2015, "…the workshop panelists agreed that in the hands of endoscopists who have met the preservation and incorporation of valuable endoscopic innovation thresholds (diagnostic accuracy) with enhanced imaging techniques (specific technologies), use of the technique in Barrett's esophagus patients is appropriate".2 This AGA White paper is also supported by the consensus statements developed by a group of 26 international experts in the United European Gastroenterology Journal. 6

Most recently Richardson, et al published, Real-time diagnosis of Barrett's esophagus: a prospective, multicenter study comparing confocal laser endomicroscopy with conventional histology for the identification of intestinal metaplasia in new users.7 In this trial they compared pCLE vs Seattle protocol biopsies and found significantly improved sensitivity and specificity, even among novice users. pCLE identified nearly 100% more Barrett's than Seattle protocol biopsies (99/172 vs. 46/172, $p < 0.0001$). There was not a statistical significance between the novice user's findings and expert review of their results.



Foregut specialists are critical to reversing the exponential rise in esophageal cancer. Properly identifying those patients at risk for Barrett's, accurately diagnosing and surveying them, is of utmost importance. To appropriately diagnose and treat patients there are multiple studies that are required to perform that comprehensive assessment. Key elements include a properly performed endoscopy, use of narrow band imaging, using to Prague Classification to characterize the columnar lined esophagus and then accurately ruling in or out Barrett's esophagus. Cellvizio® is integral to the comprehensive assessment of patients suffering from reflux disease. This technology fills a much needed diagnostic gap in patients at risk for Barrett's esophagus and/or have Barrett's. Clinicians and patients alike need and deserve access to Cellvizio® (pCLE) in order to obtain a comprehensive assessment of the extent of disease and to make real-time therapeutic treatment decisions. Employing Cellvizio® has the additional advantage of being cost effective by potentially eliminating the need for tissue biopsies, allowing for fewer biopsies. In addition to improving diagnostic yield, Cellvizio® can also be used to map an area of Barrett's prior to treatment and evaluate completeness of therapy upon follow-up.

Appendix

Extract from the Consensus

- Use of probe-based confocal laser endomicroscopy (pCLE) in gastrointestinal applications. A consensus report based on clinical evidence. Wang KK, Carr-Locke DL, Singh SK, Neumann H, Bertani H, Galmiche JP, Arsenescu RI, Caillol F, Chang KJ, Chaussade S, Coron E, Costamagna G, Dlugosz A, Ian Gan S, Giovannini M, Gress FG, Haluszka O, Ho KY, Kahaleh M, Konda VJ, Prat F, Shah RJ, Sharma P, Slivka A, Wolfsen HC, Zfass A. United European Gastroenterol J. 2015 Jun;3(3):230-54 :

- CLE should be considered in the evaluation of BE [Agreement: 95%];
- CLE should be combined with red-flag techniques (e.g. chromoendoscopy) [Agreement: 95%];

- CLE is clinically indicated in patients with BE dysplasia in lesions initially identified with red flag techniques (i.e. NBI) [Agreement: 95%];
- CLE is clinically indicated in patients with BE dysplasia in lesions initially identified endoscopically in surveillance [Agreement: 100%];
- CLE is able to distinguish cardia (non-intestinal) from intestinal metaplasia, based on the presence or absence of goblet cells [Agreement: 75%];
- CLE is superior to WLE in identifying intestinal metaplasia [Agreement: 100%];
- A negative CLE random sampling in an endoscopically benign-appearing esophagus is sufficient to reduce the need for a physical biopsy in patients with known BE [Agreement: 85%];
- CLE can improve the yield for neoplasia compared with standard WLE and random biopsies [Agreement: 95%];
- CLE and WLE-targeted biopsies are superior to WLE-targeted biopsies alone in the detection of dysplasia [Agreement: 100%];
- A positive CLE random sampling in an endoscopically neoplastic-appearing esophagus is sufficient for therapeutic intervention [Agreement: 80%];
- CLE can be used to define the location and lateral extent of neoplasia prior to therapy [Agreement: 85%].

Literature-

1. ASGE Standards of Practice Committee, Muthasamy et al. The Role of endoscopy in the management of GERD. Gastrointestinal endoscopy. 2015; 81 (6): 1305-1310.
2. Sharma, et al. White Paper AGA: Advanced Imaging in Barrett's Esophagus. Clinical Gastroenterol Hepatol. 2015 Dec; 13(13)" 2209-18.

3. Sharma, et al, Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe- based confocal laser endomicroscopy; final results of an international multi-center, prospective, randomized, controlled trial. GIE, 2011

4. Bertani, et al. Improved Detection of Incident Dysplasia by Probe-based Confocal Laser Endomicroscopy in a Barrett's Esophagus Surveillance Program. Digestive Diseases and Sciences, 2013

5. Canto et al., Confocal Endomicroscopy for Barrett's Esophagus or Confocal Endomicroscopy for Barrett's Esophagus (CEBE) Trial Group. In vivo endomicroscopy improves detection of Barrett's esophagus-related neoplasia: a multicenter international randomized controlled trial (with video). Gastrointest Endosc, 2014

6. Use of probe-based confocal laser endomicroscopy (pCLE) in gastrointestinal applications. A consensus report based on clinical evidence. Wang et al. United European Gastroenterol J. 2015 Jun;3(3):230-54

7. Real-time diagnosis of Barrett's esophagus: a prospective, multicenter study comparing confocal laser endomicroscopy with conventional histology for the identification of intestinal metaplasia in new users. Richardson, C., Colavita, P., Dunst, C. et al. Surg Endosc (2019) 33: 1585.