Wide Area Transepithelial Sampling with Computer Assisted 3D Analysis (WATS3D)

Introduction

Barrett's esophagus is a premalignant condition that results from chronic gastroesophageal reflux. It is characterized by the replacement of squamous epithelium with columnar epithelium with intestinal metaplasia.[i] Barrett's esophagus is the number one risk factor for the development of esophageal adenocarcinoma. The current standard of care for the evaluation of Barrett's esophagus is Seattle Protocol four quadrant random biopsies that are performed every one to two centimeters of the length of visible columnar lined epithelium.[ii] This can be a time consuming and expensive endeavor and is often not followed. A review of pathology reports and operative reports showed that Seattle Protocol was only followed about 51% of the time in community practices.[iii] Another problem lies in the poor agreement between pathologists regarding the diagnosis of Barrett's esophagus with and without dysplasia. Wide Area Transepithelial Sampling offers a method to biopsy areas of Barrett's esophagus that increases both the detection of Barrett's esophagus and dysplasia while increasing the inter-observer agreement among pathologists.[vii,xi]

Technique

The CDx kit contains two abrasive brushes, a glass slide, a fixative pouch and a sample bottle containing 5ml of alcohol. The brush is placed through the biopsy channel of the endoscope and the brush is extended. The brush is passed over the surface of the tissue to be biopsied. This can be performed by moving the brush in and out of the scope while holding the scope in a stationary position or by extending the brush and moving the scope in and out. The brush is moved around the esophagus until the entire surface has been biopsied. A new set of brushes is recommended for each 5 cm of esophageal length to be biopsied. The first brush is rubbed across the slide and fixative is applied then the tip is cut off and placed in the alcohol bottle. The tip of the second brush is cut off and placed in the alcohol bottle.

The brush biopsy creates a disaggregated tissue specimen, up to 150 µm in thickness, containing a three-dimensional array of microbiopsies, cells, and cell clusters. These thick specimens cannot be effectively visualized by a standard manual microscope with a 3–4 µm depth of field. Analysis of these specimens is therefore aided by a specialized computer imaging system using neural networks specifically optimized for evaluation of esophageal mucosa. The WATS^{3D} computer captures up to fifty 3 µm 'optical slices' and integrates them together to creates a synthesized three-dimensional image of the gland that is displayed to the pathologist including the uncut, in vivo appearance of the glandular surface not typically visible on histologic specimens. The computer-assisted microscope scans this synthesized three-dimensional image and identifies and locates goblet cells and dysplasia within it for display to the pathologist. In addition, the exact coordinates of all computer-selected cells on the microscopic slide are shown on the monitor so that the pathologist can locate and confirm any

abnormality on the slide. Images identified by the computer are reviewed by pathologists in conjunction with manual microscopy and are reported utilizing standard morphologic criteria for the diagnosis of both BE and ED.[iv]

Literature

In all published studies, WATS was used adjunctively and not as a substitute to forceps biopsy (FB). Thus, increased yield of disease is the metric that is most meaningful and not sensitivity or specificity. Since FB is used to sample visible lesions (targeted biopsy) and random esophageal sites (random 4-quadrant biopsy) vs. WATS which is only used to test large segments of the esophagus which would have remained untested by both targeted and random FB, not surprisingly, FB will sometimes identify patients with BE and dysplasia not detected by WATS. This is expected as FB and WATS often test different parts of the esophagus.

A community-based study at 8 sites that had 1,266 patients enrolled showed an overall increase in the detection of Barrett's esophagus by ~40%. There were a low number of patients with dysplasia in the study with 16 patients detected by forceps biopsy and an additional 14 patients detected by WATS. WATS increased the overall detection of dysplasia by ~87%.[v]

A study performed at 4 academic centers with 151 patients enrolled, all with a prior history of dysplasia undergoing surveillance, showed a 42% increase in the overall detection of dysplasia.[vi]

These 2 early studies used a smaller sampling brush, so the increased diagnostic yields are smaller than studies that were published after the size of the brush was increased. Additionally, the analysis of WATS specimens used a significantly enhanced three-dimensional computer analysis system.

In a multicenter, prospective, randomized trial at 16 academic centers, 160 patients undergoing surveillance from an enriched population of high-risk patients, patients had WATS biopsies and Seattle protocol biopsies alternated in a random fashion. All of the forceps biopsies were analyzed by a central pathologist at the Cleveland Clinic. All WATS positive/FB negative cases were confirmed by 2 Cleveland Clinic pathologists. WATS increased detection of HGD/EAC by 428% with WATS detecting an additional 23 cases of HGD/EAC. Forceps biopsy classified 11 of these as NDBE and 12 as LGD/indefinite for dysplasia. The order of the procedures did not impact the results.[vii]

In a community-based study at 25 sites, 4203 patients were enrolled, 95% were being screened for Barrett's esophagus. WATS was performed first and FB was performed second. An overall increase in the detection of Barrett's esophagus of 83% was seen. A low number of dysplasias were seen in the study with 26 cases found by FB alone and an additional 23 cases detected by WATS. This represented an increase of 88% in the overall detection of dysplasia by WATS.[viii]

A prospective multi-center community-based study at 21 sites with 12,899 patients enrolled, 81% being screened for Barrett's esophagus showed an overall increase in the detection of

Barrett's esophagus by 153%. 88 cases of dysplasia were detected by FB alone with an additional 213 cases being detected by WATS. WATS increased the detection of dysplasia by 242%.[ix]

In a study presented at the ACG 2018 Presidential Plenary Session, progression data confirmed the clinical significance of crypt dysplasia. Barrett's esophagus with crypt dysplasia is diagnosed in instances where dysplasia-like atypia involves the crypts but not the surface of epithelium. A total of 151,244 WATS cases were catalogued, with 43,145 having goblet cell metaplasia and 4,512 patients had two samples separated by >6 months. A total of 4,049 patients who had NDBE were followed and analysis showed a progression rate from BE to LGD of 0.68%, BE to HGD/EAC of 0.33%, CD to HGD/EAC of 2.11% and LGD to HGD/EAC of 7.71%. The study concluded that a finding of NDBE or LGD on WATS predicts progression to HGD/EAC at rates that are comparable to, or higher than, the reported risk of progression in forceps biopsy confirmed NDBE and LGD. Crypt dysplasia reported on WATS has a risk of progression comparable to that of forceps biopsy confirmed LGD.[x]

Standard histopathology demonstrates a kappa value of 0.30 in the diagnosis of Barrett's esophagus and dysplasia. WATS^{3D} demonstrates an overall Kappa value of 0.86 (0.95 for high grade dysplasia/esophageal adenocarcinoma, 0.74 for indefinite for dysplasia/low grade dysplasia and 0.88 for non-dysplastic Barrett's esophagus).[xi]

Society Guidelines

The ASGE recently published guidelines on the screening and surveillance of patients with Barrett's esophagus. Their recommendation was to add WATS^{3D} in addition to Seattle protocol biopsies.[xii]

Conclusion

Esophageal cancer is increasing exponentially with a very poor overall survival rate. The one predictable precursor of esophageal adenocarcinoma is Barrett's esophagus. The American Foregut Society (AFS) Board has concluded that there are sufficient data to support the routine use of WATS^{3D} technology in the diagnosis and ongoing evaluation of Barrett's esophagus.

[i] Reid B J, Weinstein W M. Barrett's esophagus and adenocarcinoma. *Annu Rev Med* 1987; 38:477–92.

[ii] Sampliner R.E.: Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus: The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1998; 93: pp. 1028-1032

[iii] Abrams J A, Kapel R C, Lindberg G M et al.. Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States. *Clin Gastroenterol Hepatol* 2009; 7: 736–42

[iv] M S Smith, E Ikonomi, R Bhuta, N Iorio, R D Kataria, V Kaul, S A Gross. Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS) markedly improves detection of esophageal dysplasia and Barrett's esophagus: analysis from a prospective multicenter community-based study. *Diseases of the Esophagus*, Volume 32, Issue 3, March 2019

[v] Johanson JF, Frakes J, Eisen D. Computer-assisted analysis of abrasive transepithelial brush biopsies increases the effectiveness of esophageal screening: a multicenter prospective clinical trial by the EndoCDx Collaborative Group. Dig Dis Sci 2011; 56:767-72.

[vi] Anandasabapathy S, Sontag S, Graham DY, et al. Computer-assisted brush-biopsy analysis for the detection of dysplasia in a high-risk Barrett's esophagus surveillance population. Dig Dis Sci 2011 ;56 :761-6.

[vii] Vennalaganti, PR, Kaul V, Wang KK, et al. Increased Detection of Barrett's Esophagus-associated Neoplasia Using Wide-Area Trans-epithelial Sampling: A Multicenter, Prospective, Randomized Trial. Gastrointest Endosc 2018; 87,(2): 348–355.

[viii] Gross SA, Smith MS ,Kaul V, and the US Collaborative WATS^{3D} Study Group. Increased detection of Barrett's esophagus and esophageal dysplasia with adjunctive use of wide-area transepithelial sample with three-dimensional computer-assisted analysis (WATS). United European Gastroenterol Nov 27, 2017

[ix] M S Smith, E Ikonomi, R Bhuta, N Iorio, R D Kataria, V Kaul, S A Gross. Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS) markedly improves detection of esophageal dysplasia and Barrett's esophagus: analysis from a prospective multicenter community-based study. *Diseases of the Esophagus*, Volume 32, Issue 3, March 2019

[x] Nicholas J. Shaheen, Michael S. Smith, John R. Goldblum, Robert D. Odze. Progression of Barrett's Esophagus (BE) and Dysplasia Detected by Wide Area Transepithelial Sampling with Computer Assisted 3D Analysis (WATS3D) Confirms the Clinical Significance of Crypt Dysplasia. Presented at ACG 2018 Presidential Plenary Session.

[xi] Vennalaganti P R, Naag Kanakadandi V, Gross S A et al. . Interobserver agreement among pathologists using wide-area transepithelial sampling with computer-assisted analysis in patients with Barrett's esophagus. *Am J Gastroenterol* 2015; 110: 1257–60.

[xii] Bashar Qumseya, MD, MPH, FASGE, Shahnaz Sultan, Paul Bain, Laith Jamil, MD, FASGE, Brian Jacobson, Sharmila Anandasabapathy, Deepak Agrawal, MD, MPH, MBA, James L. Buxbaum, MD, FASGE, Douglas S. Fishman, MD, FASGE, Suryakanth R. Gurudu, MD, FASGE, Terry L. Jue, MD, FASGE, Sapna Kripalani, MD, Jeffrey K. Lee, MD, Mouen A. Khashab, MD, Mariam Naveed, MD, Nirav C. Thosani, MD, Julie Yang, MD, John DeWitt, Sachin Wani, MD, FASGE, ASGE Standards of Practice Committee Chair. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointestinal Endoscopy 2019; 90, (3): 335-359.