

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

## The Role of Brush Biopsy in the Management of Barrett Esophagus



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### **G&H** What is the current standard technique to confirm the presence of Barrett esophagus?

**MS** The current standard of care for making a diagnosis of Barrett esophagus (BE) involves sampling the tissue with cold biopsy forceps. These biopsies are placed in formalin and sent to a surgical pathology laboratory for processing and review by a pathologist after tissue sections are placed on slides. This process is the same as with any standard gastrointestinal biopsy.

Making a diagnosis of BE is important, as this condition is a precancerous lesion. Perhaps even more crucial is the determination of whether there are advanced precancerous changes within the segment, known as dysplasia. Properly grading the degree of abnormality within the tissue optimizes patient management by allowing the physician to more accurately estimate the patient's risk of developing esophageal adenocarcinoma. These more advanced changes often are focal. Increasing visual inspection time and use of advanced endoscopic imaging techniques such as narrow-band imaging have been shown to improve detection rates for dysplasia. However, visual cues to the presence of dysplasia are absent or very subtle most of the time, and can be missed even with a thorough evaluation. Therefore, current guidelines recommend a tissue sampling pattern referred to as a modified Seattle protocol, where 4-quadrant forceps biopsies are obtained every 1 to 2 cm throughout a BE segment.

Obtaining additional biopsies increases the likelihood of finding goblet cells and/or dysplasia; however, approximately 95% of the BE segment remains unsampled. Therefore, there is a high risk of missing a focus of advanced precancerous tissue whose detection would change a patient's plan of care. In addition, taking these biopsies is time-consuming, and studies have shown that the majority of endoscopists do not meet the minimum standard of taking at least 4 tissue samples for every 2 cm of disease. Thus, the current standard of care leaves a lot to be desired in terms of both efficacy and ease of use.

### **G&H** What other techniques have been used to take tissue samples of BE?

**MS** Prior attempts to improve detection of BE and especially dysplasia have focused on increasing the amount of surface area sampled within a segment. As the amount of tissue that is removed and evaluated under the microscope increases, the likelihood of finding a spot with dysplasia or early cancer also increases. The most widely studied technique besides forceps biopsies involves the use of a cytology brush. These soft-bristled brushes are readily available in many endoscopy rooms, as they are used for other indications in the esophagus (eg, evaluation of *Candida* esophagitis) and at other sites in the gastrointestinal tract, such as the bile duct. Running these brushes over the esophageal mucosa increases the

amount of surface area exposed to the sampling instrument; however, the soft brush removes only the most superficial cells that were already likely to slough off of an ever-regenerating esophageal wall. Recognizable dysplastic changes are often only located deeper than the most superficial cells and, therefore, would be missed with this technique. Additionally, dysplasia can be confirmed by changes within the glandular architecture, and viewing only isolated cells does not provide any clues as to whether this finding exists within a particular BE segment. These limitations have led to cytology brushes falling out of favor with respect to BE assessment.

### G&H What is Wide Area Transepithelial Sampling with 3-Dimensional Analysis?

**MS** Wide Area Transepithelial Sampling with 3-Dimensional Analysis (WATS<sup>3D</sup>; WATS<sup>3D</sup> Biopsy, CDx Diagnostics) is a relatively new brush-based sampling technique that is combined with a computer-synthesized 3-dimensional image of the resultant tissue that strives to fill the gaps left by the standard cytology brush. WATS<sup>3D</sup> also uses a brush inserted through the working channel of the endoscope; however, unlike cytology brushes, the bristles are more rigid. This characteristic generates a deeper tissue sample, extending all the way to the lamina propria, in order to assess the cells that are below surface level. In addition, the stiffness of the bristles leads to accumulation of clumps of cells on the brush, known as tissue aggregates or microbiopsies. Within each of these specimens, an endoscopist can assess the glandular architecture (in particular, the en face view of the gland) and, therefore, potentially detect additional dysplasia.

This technique is performed endoscopically in a manner similar to other tissue sampling methods. The brush, which is housed within a sheath, is advanced through the working channel of the endoscope and extended beyond the sheath once it has reached the BE segment. Either by moving the endoscope or the brush instrument, an endoscopist pushes the brush against the epithelium to sample in a zig-zag-like pattern. The brush is rotated around the circumference of the esophagus in order to sample all areas of concern. Segment lengths of up to 6 cm can be sampled with each brush, capturing approximately 100,000 cells on each brush. Once the brush is filled with tissue, it is retracted into the sheath and the whole instrument is removed from the endoscope. The brush is re-exposed and rolled over a slide to transfer the microbiopsies. The brush tip is then clipped into a jar containing formalin so that the remaining cells can be captured in a cell block and examined further as well. A second brush is used to sample the same area, and its tip is placed directly into the formalin jar to provide additional

tissue for the cell block. The slide and jar are sent to a central laboratory for processing.

While the cell blocks are prepared in a manner similar to standard techniques, it is worth noting that the slides must be evaluated using a different approach. The presence of tissue aggregates means that there is not a monolayer of cells present on the slide. Thus, a conventional microscope would have difficulty in assessing the sample. Instead, a special technique called extended depth-of-field creates a single 3-dimensional image to view the multilayered sample. This allows a pathologist to see disruptions in normal glandular architecture that would be indicative of dysplasia or neoplasia. In addition, neural network-based technology identifies the approximately 200 most suspicious cells or cell clusters for the pathologist to review, increasing the likelihood that the small focus of abnormality will not be missed, which is crucial to making the proper diagnosis.

### G&H How reliable is brush biopsy for the detection of BE or dysplasia?

**MS** It is important to understand that all of the studies utilizing the WATS<sup>3D</sup> brush biopsy have used this technique in addition to 4-quadrant forceps biopsies. Therefore, the current data have assessed the adjunctive yield achieved by adding WATS<sup>3D</sup> to forceps, not replacing one tissue sampling approach with the other.

Early studies evaluating the benefit of WATS<sup>3D</sup> demonstrated an adjunctive yield for both BE metaplasia and dysplasia of 40% or better. With improvements in brush design and greater experience with the technique, the yields increased in subsequent trials. In a recent community-based trial of 12,899 patients being evaluated for possible or known BE, use of WATS<sup>3D</sup> detected an additional 2668 cases with any BE mucosa and 213 cases of dysplasia that were missed on forceps biopsies. Adjunctive yields were 150.6% for any BE metaplasia and 242% for dysplasia or neoplasia. The number needed to test with WATS<sup>3D</sup> to detect an additional case of BE missed by forceps was only 5, and for dysplasia it was 61.

A separate trial performed at multiple academic centers also demonstrated significantly improved detection of dysplasia during surveillance of known BE. Of the 160 patients enrolled, forceps biopsies identified high-grade dysplasia or cancer in 7 patients. WATS<sup>3D</sup> picked up an additional 23 cases where neoplasia was missed with standard forceps technique. In 11 of these cases, forceps found only nondysplastic disease, while the other 12 were indefinite for dysplasia or showed only low-grade dysplasia. Overall, there was a 428% adjunctive yield when WATS<sup>3D</sup> was added to the forceps surveillance protocol.

One shortcoming of forceps biopsies in BE has been the high interobserver variability among pathologists with respect to determining the grade of dysplasia. WATS<sup>3D</sup> seems to overcome this issue by virtue of its ability to present tissue in a 3-dimensional form, which facilitates assessment of glandular architecture, and also by removing subjectivity from slide inspection, as all pathologists are presented with the most concerning findings every time the slide is reviewed. A recently published trial by Dr Prashanth Vennalaganti and colleagues demonstrated a high overall kappa value among pathologists of 0.86 when differentiating between nondysplastic BE, BE with low-grade dysplasia, and BE with neoplasia (high-grade dysplasia or carcinoma). This result is much better than studies that have looked at agreement among pathologists comparing forceps biopsy samples in a similar manner.

### G&H Can brush biopsies be used in settings outside of evaluation or surveillance of nontreated BE?

**MS** In my experience, WATS<sup>3D</sup> can help detect a greater amount of residual or recurrent intestinal metaplasia even after a BE segment appears completely eradicated on visual inspection. When my colleagues and I evaluated our postablation results in conjunction with colleagues at the University of Rochester, we found that WATS<sup>3D</sup> detected an additional 61.5% more intestinal metaplasia and 57.1% more dysplasia when added to Seattle protocol forceps biopsies. The number needed to test was 8.7 to detect an additional patient with intestinal metaplasia present. (Of note, my personal technique is to use a dedicated 2-brush WATS<sup>3D</sup> kit at the neosquamocolumnar junction, as this region seems to be the hotbed for recurrent disease.)

### G&H Are there any limitations to the use of brush biopsies when evaluating BE?

**MS** The main drawback to using WATS<sup>3D</sup> is also its greatest benefit, in that it samples a wide area of tissue. If a WATS<sup>3D</sup> biopsy reveals high-grade dysplasia or carcinoma, it is impossible to localize that finding to a specific location within the esophagus using this technique in isolation. However, thorough visual inspection and use of advanced imaging (eg, narrow-band imaging or volumetric laser endomicroscopy) could provide a more precise location.

Because these biopsies are transepithelial, microbleeding via disruption of the capillaries within the mucosa is likely. Patients on anticoagulants and antiplatelet agents likely will have more bleeding than

those who are not taking these medications. In my experience, significant bleeding (or more than is seen with Seattle protocol forceps sampling) following a WATS<sup>3D</sup> biopsy is uncommon.

Currently, WATS<sup>3D</sup> can only be performed to assess BE by introducing the brush through an endoscope. Therefore, it cannot be used to screen a population for BE without first performing upper endoscopy. However, a brush is available that can fit through a transnasal or ultrathin upper endoscope, which may provide a better tissue sample than what is obtained using the pediatric-size forceps that can fit through the smaller working channel of an endoscope.

### G&H What does the future hold for brush biopsies in the management of BE?

**MS** We need to better understand how sampling with WATS<sup>3D</sup> can be combined with enhanced imaging techniques to further augment detection of BE and dysplasia. Now that we can better assess tissue architecture via the microbiopsies provided by WATS<sup>3D</sup>, we will have a chance to explore the relevance of crypt dysplasia, which does not reach the epithelial surface and therefore is not called low-grade dysplasia. This technology may help determine which patients without confirmed low- or high-grade dysplasia are most likely to progress before their next surveillance procedure.

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### Suggested Reading

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(3):761-766.

Iorio N, Sprung B, Kaul V, et al. Transepithelial brush biopsy with computer-assisted tissue analysis increases detection of residual or recurrent intestinal metaplasia and dysplasia following endoscopic ablation of Barrett's esophagus. *Gastrointest Endosc*. 2015;81(5)(suppl):AB141.

Johanson JF, Frakes J, Eisen D; EndoCDx Collaborative Group. 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(3):767-772.

Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett esophagus. *Am J Gastroenterol*. 2016;111(1):30-50; quiz 51.

Vennalaganti P, Eisen G, Falk GW, et al. Increased detection of Barrett's esophagus-associated neoplasia using wide area transepithelial sampling in conjunction with 4-quadrant forceps biopsies: final results from a multi-center, prospective, randomized trial. *Gastrointest Endosc*. 2016;83(5)(suppl):AB122-AB123.

Vennalaganti PR, Naag Kanakadandi V, Gross SA, et al. Inter-observer agreement among pathologists using wide-area transepithelial sampling with computer-assisted analysis in patients with Barrett's esophagus. *Am J Gastroenterol*. 2015;110(9):1257-1260.