Adjunctive Yield of Wide-Area Transepithelial Sampling for Dysplasia Detection After Advanced Imaging and Random Biopsies in Barrett's Esophagus

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INTRODUCTION: **Little is known about the additive yield of wide-area transepithelial sampling with computer-assisted three-dimensional analysis (WATS-3D) after a thorough examination with advanced imaging. The aim was to evaluate the adjunctive yield of WATS-3D after advanced imaging.**

METHODS: **This is an observational cohort study from January 2017 to December 2018 for consecutive patients who underwent an examination that consists of high-definition white light endoscopy (HDWLE), narrow-band imaging (NBI), volumetric laser endomicroscopy (VLE), and Seattle protocol (SP) biopsies (collectively termed HDWLE-NBI-VLE-SP examination). Raised lesions were removed by endoscopic resection. Areas suspicious for dysplasia on NBI and VLE were biopsied. This was followed by random biopsies and WATS-3D brush biopsies.**

RESULTS: **One hundred thirty-eight cases were included in this study. Thirty-five cases (25% of the total) were identified as some degree of dysplasia on the HDWLE-NBI-VLE-SP examination. Adjunctive use of WATS-3D yielded an additional 12 new cases of dysplasia (9 with crypt dysplasia and 3 with low-grade dysplasia [LGD]), for added yield of 34.3% (=12/35, 95% confidence interval 14.6%–62.2%). When restricting the analysis to LGD and higher, 21 dysplastic cases (15% of the total cases) were identified by HDWLE-NBI-VLE-SP, while WATS-3D found 4 additional new cases (3 with LGD and 1 with high-grade dysplasia) for an added yield of 19% (=4/21, 95% confidence interval 0.6%–45.7%).**

DISCUSSION: **The addition of WATS-3D to an already thorough examination with HDWLE-NBI-VLE-SP may increase the yield of dysplasia detection.**

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INTRODUCTION

The precursor to esophageal adenocarcinoma (EAC) is Barrett's esophagus (BE). BE is specialized intestinal metaplasia of the tubular esophagus that may progress to low-grade and high-grade dysplasia (LGD and HGD) before the development of cancer (1–3). It has been estimated that the annual risk of progression to EAC in patients with BE is 0.3%; however, this risk significantly increases if dysplasia coexists (3–6). Fortunately, ablation of dysplasia with endoscopic therapies such as radiofrequency ablation and cryoablation has been shown to be effective in reducing the progression of dysplasia to cancer (7–14). Thus, it is important to perform endoscopic surveillance on patients with BE to identify dysplasia, as ablation therapy for dysplastic disease can decrease or eliminate the progression to EAC.

The currently recommended gold standard for surveillance of BE is the use of random biopsy protocols within the endoscopically visualized area of columnar epithelium. The standard method of performing random biopsies is the Seattle protocol (SP), during which random biopsies are taken in a 4-quadrant fashion for every 1–2 cm of visualized BE (2). The difficulty with this approach is that only a small proportion of the BE is sampled, and thus, it is possible to miss dysplasia and neoplasia (15,16).

Owing to this risk, over the last several years, there has been a focus on the development of adjunctive and advanced imaging modalities that better detect dysplasia in BE (16–18). Perhaps the most widely used advanced imaging modality is narrow-band imaging (NBI), which is a virtual chromoendoscopy technique that allows the surface pattern of superficial vessels and mucosal

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structures to be highlighted. Dysplasia and neoplasia have an abnormal mucosal pattern on NBI (19), and there have been several studies outlining NBI criteria for dysplasia detection (20–23). It has been shown that NBI examination is more effective in detecting metaplasia and dysplasia than standard random biopsies on white light endoscopy (18,24,25), and because NBI biopsies are targeted, fewer total biopsies are required (26). Another advanced modality is volumetric laser endomicroscopy (VLE), which is a second-generation optical coherence tomography method that uses infrared light to display high-resolution microstructure imaging of the tubular esophagus in real time. VLE can scan a 6-cm circumferential BE segment in 90 seconds. In 2016, VLE was upgraded to include the ability to perform superficial laser marking of the abnormal areas seen on VLE to help direct targeted biopsies on white light endoscopy (27). VLE has been shown to be effective in detecting esophageal dysplasia in BE (27–32), with a diagnostic sensitivity, specificity, and accuracy of 86%, 88%, and 87%, respectively, in an ex vivo study (33). Direct comparisons have suggested that there is an incremental yield in dysplasia detection using adjunctive VLE, when compared with surveillance with gold standard 4-quadrant random biopsies alone (34).

Another relatively newly developed adjunctive surveillance method for esophageal dysplasia is wide-area transepithelial sampling with computer-assisted three-dimensional analysis (WATS-3D). Compared with VLE, which requires a learning curve for the operator, WATS-3D sampling is a simple technique in which an abrasive cytology brush (Figure 1) is applied to the entire segment of BE and a transepithelial specimen is obtained. Therefore, the entire Barrett's segment is sampled. The specimen is then analyzed by a computer image processing system that identifies potentially abnormal cells based on cellular morphology. To date, several studies have shown that the addition of WATS-3D sampling to standard surveillance with random biopsies greatly increases yield of dysplasia, as high as 242% as cited in some studies (35–39).

Although NBI and VLE with laser marking increase the yield of dysplasia detection, it is possible that some dysplasia is still not detected. This may be due to areas of BE without typical visualized features of dysplasia on NBI or VLE or simply due to operator error. In these situations, a WATS-3D biopsy would be helpful because it does not require pattern recognition of dysplasia features. However, the incremental yield of WATS-3D after the application of both VLE and NBI is not described. If VLE and NBI are highly efficacious in detecting all dysplasia, then the incremental utility of WATS-3D would be negligible and its application in this setting superfluous. On the other hand, if there is substantial incremental yield after these advanced modalities are applied, clinicians should be aware of these additional benefits.

The aim of this study was to determine whether the addition of WATS-3D would increase the yield of dysplasia detection after a complete examination with high-definition white light endoscopy (HDWLE), NBI, VLE with laser marking, and SP biopsies.

Figure 1. WATS-3D biopsy brush. Image obtained and used with permission from CDx Diagnostics.

METHODS

Patient population

This is a single-center retrospective observational cohort study on a prospectively maintained database of consecutive patients undergoing surveillance for BE from January 2017 to December 2018. The center is a tertiary care academic referral center that specializes in the care of patients with BE and has routinely used VLE with laser marking for surveillance since 2016 and WATS-3D since 2017. Patients included in this study had a known diagnosis of BE, were older than 18 years, were undergoing scheduled surveillance with VLE with laser marking (Nvision VLE; Ninepoint Medical, Bedford, MA), had routine 4-quadrant biopsies based on SP, and had WATS-3D brushings performed after the aforementioned techniques were used. Patients who underwent surveillance included those with and without known dysplasia who were both preablation and postablation therapy. At our institution, it is our practice to perform surveillance endoscopy after 3 rounds of ablation to rule out progression of disease, regardless of whether complete eradication of intestinal metaplasia has been achieved. VLE examinations were not performed in patients who had endoscopically visible esophagitis or an esophageal stricture. Exclusion criteria included patients younger than 18 years or patients who did not have all 3 sampling methods performed (SP, VLE, and WATS-3D). The Zucker School of Medicine at Hofstra/Northwell granted institutional review board approval for this study.

Procedure and techniques

All procedures were performed by an experienced user (A.J.T.) in VLE imaging for Barrett's surveillance. After HDWLE and NBI examination (Olympus H190; Olympus America, Center Valley, PA) of the esophagus, VLE imaging was performed, during which abnormal targets concerning for dysplasia were identified based on the Evan's and Leggett criteria (33,40) and laser marks were applied to either side of the target. VLE was also used to confirm correct placement of the laser marks. If there was a raised lesion, this was removed with endoscopic mucosal resection, and the specimen was placed in a separate histology formalin jar. Next, VLE targeted biopsies were obtained and placed in a jar corresponding to the level of the esophagus the biopsy was taken. Afterward, HDWLE and flat NBI targets that were not resected were biopsied. Then, SP biopsies were obtained every 1 cm in a 4-quadrant fashion for the length of the BE, and these specimens were placed in histology jars based on their level in the esophagus (same jar as VLE targets). Finally, WATS-3D brushings of the entire BE segment were performed as described in the literature (38). During the WATS-3D procedure, the abrasive brush is maneuvered up and down multiple times along the entire Barrett's segment until pinpoint bleeding is observed. Two brushes are used for every 5 cm of Barrett's. One brush is used to make a slide, and the other is placed directly in formalin for cellblock. Specific details regarding the materials of the brush, technique of sampling, and analysis of the sample can be

found in a recent American Society of Gastrointestinal Endoscopy technology review (41).

Sample processing

All biopsies and resected specimens were sent to our institution's pathology department for analysis by an expert in gastrointestinal pathology. A diagnosis of dysplasia was confirmed by a second GI pathologist. The WATS-3D slides and brush tips were sent to CDx Diagnostics (Suffern, NY) for analysis, where a high-speed computer-assisted 3D analysis system is used to help detect metaplastic and dysplastic cells based on a neural-network software program. Images of the abnormal cells are displayed on a high-resolution color monitor and are then reviewed by a pathologist specially trained in WATS-3D technology, who uses the images combined with the glass slides and immunohistochemistry to establish a diagnosis. All abnormalities identified by WATS-3D are diagnosed and reported using standard pathologic criteria for BE and dysplasia.

Data analysis and statistics

Patient and endoscopic characteristics of the BE were abstracted from patient charts. Pathology reports from both the institutional laboratory and CDx Diagnostics were reviewed. Dysplasia results, including the grade of dysplasia (indefinite for dysplasia, crypt dysplasia, low-grade dysplasia, high-grade dysplasia/intramucosal adenocarcinoma, or T1b cancer) from both reports were compared. The final grade of dysplasia was the highest grade of dysplasia detected on either standard histopathology or WATS-3D analysis. The examination that consisted of HDWLE targeted biopsies, NBI targeted biopsies, VLE targeted biopsies, and SP is referred to as the HDWLE-NBI-VLE-SP examination.

Categorical variables were compared using χ^2 tests or Fisher exact tests. All statistical tests were 2-sided, and $P < 0.05$ was considered significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel (Microsoft, Redmond, WA). Added yield confidence intervals were calculated by Fieller's theorem using Wolfram Mathematica version 11.3 (Wolfram Research, Champaign, IL).

RESULTS

A total of 138 cases were included in which HDWLE targeted biopsies, NBI targeted biopsies, VLE targeted biopsies, SP biopsies, and WATS-3D brushings were obtained. The patient and endoscopic characteristics are displayed in Table 1. One hundred six patients underwent 138 procedures during the study period. Of these patients, 72.6% were men, had a mean age of 65.2 years, and had a history of on average 3 years of BE before initial surveillance endoscopy at our institution. Approximately 41.5% of the patients were previous or current smokers, and 9.4% had a positive family history of esophageal cancer. The mean Prague classification of the BE surveyed during the procedures was C2M3. An endoscopic mucosal resection of a suspicious lesion was performed in 11.6% of the procedures. Approximately two-thirds of the endoscopies were performed for surveillance on patients who had never previously undergone ablation therapy.

Table 2 demonstrates the subtypes of dysplasia that were detected by each sampling method. Thirty-five cases (25% of the total) of dysplasia were identified on the HDWLE-NBI-VLE-SP examination. HDWLE-NBI-VLE-SP detected 14 cases of indefinite for dysplasia, 11 cases of low-grade dysplasia, 8 cases of high-grade dysplasia/intramucosal cancer, and 2 cases of T1b cancer. The adjunctive yield of WATS-3D yielded 12 new cases of dysplasia (9 with crypt dysplasia and 3 with LGD), for an added yield of 34.3% (=12/35, 95% confidence interval 14.6%–62.2%). When restricting the analysis to LGD and higher, given the unclear significance of indefinite for dysplasia and crypt dysplasia, 21 dysplastic cases (15% of the total cases) were identified by HDWLE-NBI-VLE-SP, while WATS-3D found 4 additional new cases (3 with LGD and 1 with HGD) for an added yield of 19% (=4/21, 95% confidence interval 0.6%–45.7%).

Table 1. Patient and procedure characteristics

Patient characteristics		
Total no. of patients	106	
Males (no, %)	77	72.6%
Age (mean, range)	65.2	33–92
Years of Barrett's esophagus (mean, range)	3.0	0–30
Current smokers (no, %)	7	6.6%
Previous smokers (no, %)	37	34.9%
Family history esophageal cancer (no, %)	10	9.4%
Procedure characteristics		
Total no. of procedures	138	
Type of procedure		
Before ablation (no, %)	90	65.2%
After ablation (no, %)	48	34.8%
Presence of hiatal hernia (no, %)	42	30.4%
Size of hiatal hernia (mean in cm, range)	1	0–7
Prague classification—C (mean, range)	2	0–13
Prague classification—M (mean, range)	3	0–14
Lesion resected (no, %)	16	11.6%

In addition to the new cases of dysplasia found by WATS-3D, 8 cases of dysplasia found on the HDWLE-NBI-VLE-SP examination were upgraded to a higher grade of dysplasia (Table 3). Five were upgraded to crypt dysplasia from either nondysplastic BE or indefinite for dysplasia, and an additional 3 cases, which were initially read as indefinite for dysplasia or LGD, were upgraded to HGD/intramucosal cancer (IMCA) (Figure 2). This was a total absolute increase of 8.7% (12/138) for a new diagnosis of dysplasia and 14.5% (20/138) when accounting for an upgrade of dysplasia grade. Of these 20 patients who had either a new or upgraded diagnosis of dysplasia, 19 were patients undergoing surveillance who had not previously had ablation performed. Also, in 6 of the 14 cases (42.8%) diagnosed as "indefinite for dysplasia" by HDWLE/NBI/SP/VLE biopsies, the diagnosis provided from the WATS-3D brushings upgraded the overall diagnosis to a higher level of dysplasia, 5 to crypt dysplasia and 1 to high-grade dysplasia. In addition, 2 cases that were diagnosed as low-grade dysplasia by HDWLE-NBI-VLE-SP were also upgraded to high-grade dysplasia by WATS-3D (Table 3).

DISCUSSION

With the advent and advancement of new surveillance methods for BE, dysplasia detection is becoming increasingly accurate, and the ability to prevent progression to esophageal cancer is

Table 2. Yield of dysplasia by sampling method

	HDWLE-NBI-VLE-SP examination (n = 138)	WATS-3D (n = 138)	Final histology (n = 138)	*P* value (CI)[a]
Indefinite for dysplasia	14	0	8	0.187 (0.22–1.34)
Crypt dysplasia	0	17	17	<0.001 (2.37–670.49)
Low-grade dysplasia	11	4	12	0.828 (0.47–2.58)
High-grade dysplasia/IMCA	8	8	11	0.710 (0.55–3.61)
Invasive cancer	2	0	2	**1.000 (0.14–7.20)**
Total dysplasia	35	29	50	0.051 (1.00–2.80)

HDWLE, high-definition white light endoscopy; IMCA, intramucosal cancer; NBI, narrow-band imaging; SP, Seattle protocol; VLE, volumetric laser endomicroscopy; WATS-3D, wide-area transepithelial sampling with computer-assisted three-dimensional analysis.
[a]*P* value is final histology compared with HDWLE-NBI-VLE-SP examination.

improving. VLE and WATS-3D have both individually been shown to be promising surveillance methods when compared with standard random biopsy protocols that enhance dysplasia detection (34,35). This is the first study to determine whether the addition of WATS-3D would provide an added value to a complete examination with HDWLE-NBI-VLE-SP. We found that WATS-3D did provide an adjunctive diagnostic yield. In our study, WATS-3D diagnosed 12 cases of new dysplasia and upgraded 8 cases of dysplasia. Most importantly, it upgraded 3 cases to HGD from lower grades of dysplasia. Ninety-five percent of these cases were found in patients who were undergoing surveillance and had not yet received ablation. This is clinically important because those patients with dysplasia are recommended for treatment with ablation as opposed to being recommended simply for continued surveillance.

WATS-3D identified crypt dysplasia in 17 of the cases, which was not seen on standard biopsies. Crypt dysplasia is defined as dysplasia-like atypia involving the crypts, but not the surface epithelium. To date, the biological behavior of crypt dysplasia has not been well established. However, a recent study presented in abstract form by Shaheen et al. found that crypt dysplasia diagnosed by WATS-3D had a risk of progression to high-grade dysplasia/adenocarcinoma at a rate that was comparable with that of low-grade dysplasia diagnosed by random forceps biopsies (42). These preliminary data suggest that a diagnosis of crypt dysplasia is clinically significant and, as a result, may have an effect on physician's recommendations regarding ablation vs continued surveillance. In our practice, ablative therapy was recommended for patients with a WATS-3D diagnosis of crypt dysplasia only if they had additional risk factors for esophageal

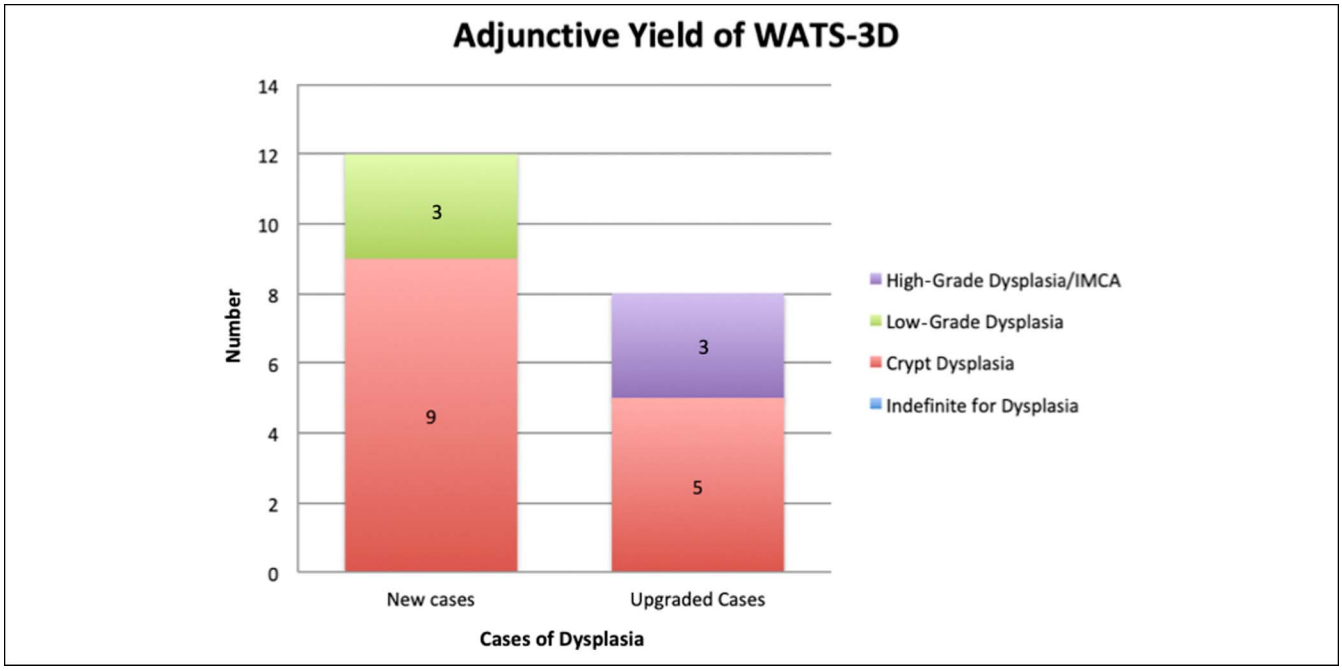

Figure 2. Adjunctive yield of wide-area transepithelial sampling after an examination that consists of high-definition white light endoscopy, narrow-band imaging, volumetric laser endomicroscopy, and random biopsies.

Table 3. Adjunctive yield of WATS

	New cases of dysplasia	Upgraded cases of dysplasia	Total	% of all cases
Indefinite for dysplasia	0	0	0	0.0
Crypt dysplasia	9	5	14	10.1
Low-grade dysplasia	3	0	3	2.2
High-grade dysplasia/ intramucosal cancer	0	3	3	2.2
Total dysplasia	12	8	20	14.5

cancer progression, including a long segment of BE and a family history of esophageal cancer. Even if crypt dysplasia is discounted as a significant finding in this study, 7 patients (4 new diagnoses and 3 upgraded diagnoses, 5% of the total cases) still were noted to have progression on WATS-3D analysis alone, 57% of which were to HGD or IMCA.

It should be noted that this study is not designed to compare WATS-3D directly to HDWLE, advanced imaging (NBI/VLE), and SP biopsies. This is because WATS-3D brushings were performed sequentially after resection of raised lesions and after biopsies of areas targeted by advanced imaging. Thus, we only report on the adjunctive yield and cannot directly compare the yield of each modality. In addition, this study is not designed to compare the yield of SP biopsies over advanced imaging because targeted biopsies were placed in the same biopsy jar corresponding to the esophageal level.

The strengths of this study include the following: (i) this is large number of patients who underwent a very standardized protocol, (ii) the same provider performed every NBI, VLE, and WATS-3D procedure and thus decreases heterogeneity among sampling standards or image interpretation, and (iii) the study is performed in a large tertiary care BE referral center, and thus, techniques and pathology readings are standardized. The limitations of the study include the following: (i) data acquisition was retrospective and thus limited by the retrospective study design, (ii) the results are most applicable to tertiary centers in which high-volume BE surveillance procedures are performed, (iii) it is possible that areas of dysplasia not detected by VLE/NBI would have been detected by another experienced VLE/NBI user, and (iv) patients noted to have dysplasia solely on WATS-3D analysis did not undergo subsequent confirmation of this dysplasia by standard histological diagnosis, and thus, there was no external gold standard to compare the positive WATS-3D result to. Although such an approach would be desirable, it would add to the cost of these patients' care. In addition, because a substantial proportion of patients found to have dysplasia had crypt dysplasia, a diagnosis not generally made by standard histology, such an approach would not be expected to confirm that subgroup. A potential limitation to the WATS-3D reading is that one pathologist is making the diagnosis of dysplasia compared with generally 2 GI pathologists for standard pinch biopsies. However, it should be noted that abnormal areas of dysplasia are already selected by the neural-network software program and the pathologist is reviewing the preselected pathology. In addition, the reported interobserver variability for WATS-3D slides is favorable for varying degrees of dysplasia in a study among 4 blinded gastrointestinal pathologists (43).

In summary, we have shown that a BE surveillance practice using WATS-3D brushings in addition to HDWLE-NBI-VLE-SP can increase dysplasia detection. WATS-3D brushings are a simple adjunctive surveillance method that can be easily incorporated into standard practice at BE surveillance centers. Further prospective studies are warranted to confirm our results and to better delineate the significance of a diagnosis of crypt dysplasia.

CONFLICTS OF INTEREST

Guarantor of the article: Arvind J. Trindade, MD.
Specific author contributions: A.J.T.: conception and design. K.L.R. and A.J.T.: analysis and interpretation of the data. K.L.R., M.S., D.V.S., M.C., M.J.W., D.H., P.C.B., C.L., L.S.M., and A.J.T.: drafting of the article. K.L.R., M.S., D.V.S., M.C., M.J.W., D.H., P.C.B., C.L., L.S.M., and A.J.T.: critical revision of the article for important intellectual content. K.L.R., M.S., D.V.S., M.C., M.J.W., D.H., P.C.B., C.L., L.S.M., and A.J.T.: final approval of the article.
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Study Highlights

WHAT IS KNOWN

- ✓ WATS-3D brush biopsies have been shown to increase the yield of dysplasia detection after random biopsies in BE surveillance.
- ✓ The dysplasia yield of WATS-3D brush biopsies after advanced imaging targeted biopsies is unknown.

WHAT IS NEW HERE

- ✓ The addition of WATS-3D brush biopsies after an advanced imaging examination, that consists of NBI and VLE, can increase dysplasia detection.

TRANSLATIONAL IMPACT

- ✓ WATS-3D brush biopsies have value not only in community settings but also in tertiary care settings where advanced imaging techniques are being used.

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