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Adjunctive Use of Wide-Area Transepithelial Sampling-3D in Patients With Symptomatic Gastroesophageal Reflux Increases Detection of Barrett's Esophagus and Dysplasia

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INTRODUCTION: **Patients with gastroesophageal reflux (GERD) symptoms undergoing screening upper endoscopy for Barrett's esophagus (BE) frequently demonstrate columnar-lined epithelium, with forceps biopsies (FBs) failing to yield intestinal metaplasia (IM). Repeat endoscopy is then often necessary to confirm a BE diagnosis. The aim of this study was to assess the yield of IM leading to a diagnosis of BE by the addition of wide-area transepithelial sampling (WATS-3D) to FB in the screening of patients with GERD.**

METHODS: **We performed a prospective registry study of patients with GERD undergoing screening upper endoscopy. Patients had both WATS-3D and FB. Patients were classified by their Z line appearance: regular, irregular (<1 cm columnar-lined epithelium), possible short-segment BE (1 to <3 cm), and possible long-segment BE (≥3 cm). Demographics, IM yield, and dysplasia yield were calculated. Adjunctive yield was defined as cases identified by WATS-3D not detected by FB, divided by cases detected by FB. Clinicians were asked if WATS-3D results affected patient management.**

RESULTS: **Of 23,933 patients, 6,829 (28.5%) met endoscopic criteria for BE. Of these, 2,878 (42.1%) had IM identified by either FB or WATS-3D. Among patients fulfilling endoscopic criteria for BE, the adjunctive yield of WATS-3D was 76.5% and absolute yield was 18.1%. One thousand three hundred seventeen patients (19.3%) who fulfilled endoscopic BE criteria had IM detected solely by WATS-3D. Of 240 patients with dysplasia, 107 (44.6%) were found solely by WATS-3D. Among patients with positive WATS-3D but negative FB, the care plan changed in 90.7%.**

DISCUSSION: **The addition of WATS-3D to FB in patients with GERD being screened for BE resulted in confirmation of BE in an additional one-fifth of patients. Furthermore, dysplasia diagnoses approximately doubled.**

KEYWORDS: Barrett's esophagus; wide-area trans-epithelial sampling; dysplasia; Seattle protocol

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D258

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Barrett's esophagus (BE) is defined as esophageal columnar-lined epithelium (CLE) measuring 1 or more cm in length, with accompanying biopsies that demonstrate intestinal metaplasia (IM) (1). BE is the precursor lesion for esophageal adenocarcinoma (EAC) (2). It is recommended that patients with BE undergo routine surveillance endoscopy to detect dysplasia or early

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EAC in the hope of reducing morbidity and mortality associated with this cancer (3,4). BE develops as a complication of chronic gastroesophageal reflux disease (GERD) (5,6). Guidelines traditionally recommend that patients with chronic GERD, combined with other risk factors, warrant screening for BE. The current gold standard method for screening is peroral upper endoscopy, with the performance of forceps biopsies (FBs), in patients with suspected BE. Sampling of suspected or prevalent BE should be performed using the Seattle protocol, which consists of four-quadrant biopsies from every 1–2 cm of areas of CLE to confirm the presence of IM (7). Unfortunately, this protocol can be time-consuming, resulting in poor adherence, especially in patients with long segments of columnar mucosa (8). Since IM is invisible under white light endoscopy and is often focal in its distribution, the Seattle protocol has a high rate of sampling error and, thus, high false-negative results (9–11). False-negative results are both confusing to the patient and costly since a repeat endoscopy is often performed in the setting of endoscopic findings consistent with BE but without IM detected in the biopsies.

Given these limitations, there has been great interest in developing new technologies that may aid in the diagnosis of IM and dysplasia in patients with known or suspected BE. Wide-area transepithelial sampling with 3-dimensional computer analysis (WATS-3D; CDx Diagnostics, Suffern, NY) has been shown to significantly increase the diagnostic yield of IM and neoplasia when used as an adjunct to FB (11–14). The WATS-3D diagnostic platform uses an abrasive brush that samples the area of apparent columnar mucosa. The sample acquired by the WATS-3D brush contains disaggregated clumps of structurally intact tissue that undergo analysis using a neural network algorithm designed to detect both IM and dysplasia. Computer analysis results in the generation of 3-dimensional images that highlight potential foci of IM and dysplasia. Pathologists who are trained in WATS-3D interpretation then review these results, along with samples from a cell block stained with hematoxylin and eosin, to establish a final diagnosis.

While WATS-3D has an extensive literature demonstrating increased findings of dysplasia in patients with BE undergoing surveillance, none of the published studies evaluated the use of WATS-3D exclusively for BE screening in a community-based cohort of patients with GERD. Thus, the aim of this prospective registry study was to evaluate the efficacy of adjunctive use of WATS-3D in a large well-defined cohort of consecutive patients with GERD who were being screened for BE. Our hypothesis was that WATS-3D would show an increase in histological confirmation of a BE diagnosis in patients who fulfill endoscopic criteria for BE, by identifying IM at a higher rate than standard FB alone.

METHODS

Patient cohort

The study cohort consisted of 23,933 consecutive patients enrolled in a prospective observational registry assessing the utility of WATS-3D in the screening of symptomatic GERD patients for BE. This registry began in April 2020 and is ongoing. Patients were enrolled in 78 community practices encompassing 166 endoscopists (see Supplementary Digital Content, Appendix 1, http://links.lww.com/AJG/D258). Institutional review board approval was obtained at each site. Study patients were selected from an initial cohort of 36,355 patients who fulfilled the following inclusion criteria:

1. The indication for the endoscopic procedure was screening due to GERD.
2. Patients did not have a history of BE, IM, or dysplasia in esophageal mucosa.
3. There was no history of esophageal surgery, endoscopic ablation, or endoscopic mucosal resection (EMR) at any time before entrance into the study.
4. WATS-3D and FB were both used in the same endoscopic session.

Use of WATS-3D was at the clinical discretion of the endoscopist, and patients with any appearance of the squamocolumnar junction (Z line) could be enrolled. While all patients underwent both WATS-3D and FB at the time of endoscopy, the sequence was determined at the endoscopist's discretion. The WATS-3D database contains clinical, endoscopic, and histologic data for all samples sent to a central lab for analysis. The registry database includes patient demographics and characteristics, such as age, sex, ethnicity, race, and specifics of patient management (use of proton pump inhibitor (PPI) therapy, ablation status, EMR status, surveillance intervals). Subsequent to enrollment, any change in management as a result of the findings of WATS-3D and FB findings was also recorded.

Endoscopy and WATS-3D

All patients underwent upper endoscopy (high-definition white light +/− chromoendoscopy) with sampling of the distal esophagus/esophagogastric junction (EGJ) area, and of any areas of suspected BE, as per local practice. At the time of endoscopy, the location and characteristics of the Z line were noted and categorized into 1 of 4 groups: (i) regular, (ii) irregular (defined as $<$ 1 cm of CLE extending into the tubular esophagus), (iii) potential short-segment BE ([SSBE], defined as $\geq$1 cm but $<$3 cm of CLE extending into the tubular esophagus), or (iv) potential long-segment BE ([LSBE], defined as $\geq$3 cm of CLE extending into the tubular esophagus). The presence and size of any hiatal hernia were noted (with hernias $\leq$2 cm considered small, $>$2 to $<$4 cm considered medium, and $\geq$4 cm considered large), as well as the presence of erosive esophagitis (graded by the Los Angeles classification as A–D) (15). For this analysis, Los Angeles grades B–D were considered to be clinically significant esophagitis.

Physicians were instructed to biopsy CLE in the esophagus according to the Seattle protocol. In patients with potential BE, the maximal circumferential and longitudinal lengths of CLE were reported according to the Prague criteria (16). Endoscopists noted any focal lesions in the CLE and biopsied them separately. Regardless of endoscopic findings, all patients underwent WATS-3D brush biopsies as per the standard technique (14). One WATS-3D kit was used for each 5 cm segment of esophageal columnar mucosa. Among patients not demonstrating CLE, the area of the Z line was brushed circumferentially. In brief, the protocol of analysis of these samples was as follows: each kit contained 2 brush biopsy catheters, applied in succession to cover up to a 5 cm CLE length of mucosa. The WATS-3D sample was then evaluated at a centralized laboratory with the aid of a high-speed computer and neural network software program specifically optimized for BE tissue assessment, as per techniques described previously (17). The slide was then manually reviewed, and a final diagnosis was rendered by a pathologist trained in the analysis of WATS-3D images. For patients with CLE in the

esophagus, FB samples were evaluated as per the standard local protocol of the participating physicians in the registry. In patients undergoing WATS-3D sampling with irregular Z line or regular Z line, biopsies were taken at the EGJ. For purposes of this registry, no central re-reading of the tissue samples was performed, and the local pathologist reading was used in the analyses of FB results.

Pathology

Previously published established histologic criteria for FB and WATS-3D were used to diagnose BE (IM and dysplasia) pathology in the WATS-3D sample (18,19). IM was defined by the presence of goblet cells. Crypt dysplasia (CD) was diagnosed according to previously published criteria (20). Specimens were considered indefinite for dysplasia (IND) if there was epithelial atypia, but a definite distinction between regeneration and dysplasia could not be established. Criteria for low-grade dysplasia (LGD), high-grade dysplasia (HGD), and EAC were as per previously established methods (19). All pathologists were masked to the results of the other technique (FB or WATS-3D), as well as to the endoscopic features of the Z line and any potential BE segment length. For statistical analysis, cases were included in the "any neoplasia" category if they were assigned a reading of IND, CD, LGD, HGD, or EAC.

Statistics and ethical oversight

Adjunctive yield of WATS-3D was defined as the number of cases (either any IM or any dysplasia) identified by WATS-3D that were not detected by FB, divided by the number of cases detected by FB. Absolute yield of WATS-3D was defined as the number of cases that WATS-3D detected, divided by the total number of cases enrolled. Incremental yield of WATS-3D was defined as the number of cases that WATS-3D detected that were not detected by FB, divided by the total number of cases. Number needed to test (NNT) was defined as the number of patients with a given endoscopic finding needed to undergo WATS-3D sampling to confirm an additional case of histology-proven IM or dysplasia and was calculated as 1/absolute yield. Sensitivity of WATS-3D for dysplasia was defined as the number of cases of dysplasia diagnosed by WATS-3D divided by the total number of dysplasia cases found by either FB or WATS-3D. For all cases, both FB and WATS-3D results were stratified endoscopically by the CLE segment length into regular, irregular, potential SSBE, or potential LSBE, using the length criteria aforementioned. Only cases of IM accompanied by an endoscopic finding of CLE of $\geq$1 cm were considered to fulfill the definition of BE and define a true positive diagnosis. Statistical tests were done for trend across the Z line category. When the variables being compared were dichotomous, the Cochran-Armitage test for trend was used. If they were ordinal, the Cochran-Mantel-Haenszel test for trend was used. The overall diagnostic yield for FB and WATS-3D was compared using a Z-test for difference in proportions. All statistical tests were done with SAS V9.4 TS Level 1M7. A *P* value less than 0.05 was considered statistically significant. Central institutional review board approval of this study was given by Integrity Institutional Review Board.

RESULTS

Clinical demographics and endoscopic results

In total, 36,355 patients were screened for this prospective registry study and 23,933 were enrolled. Figure 1 demonstrates the patients enrolled in the study and reasons for exclusion.

The clinical and endoscopic characteristics of the patients are summarized in Table 1. Of the 23,933 patients (mean age, 57.4; years; 42.0% male) analyzed in the study, most were White (86.7%). Endoscopically, 23.0% of patients had a normal-appearing

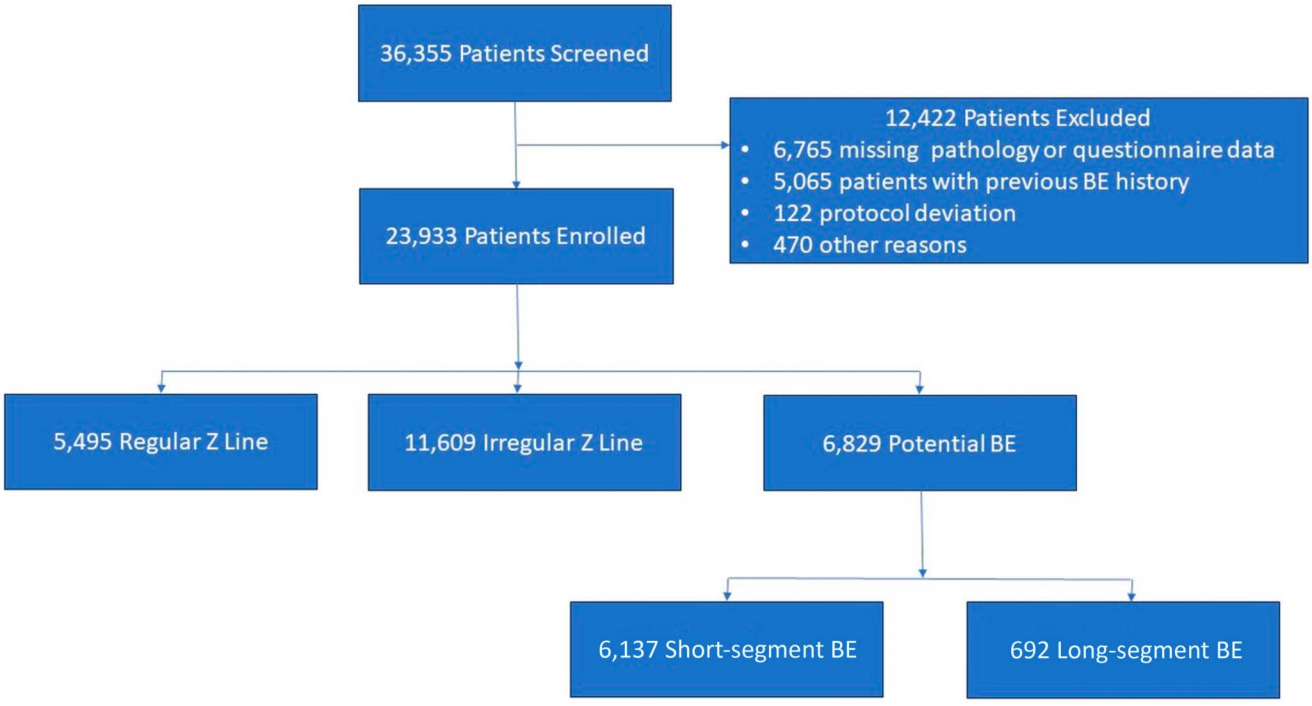

Figure 1. Flow of patients through the study, stratified by Z line appearance.

Table 1. Demographics and disease-specific characteristics, overall and by Z line appearance

	Total	Regular	Irregular, <1 cm	Possible SSBE, 1 to <3 cm	Possible LSBE, ≥3 cm	*P*
N	23,933/23,933 (100.0%)	5,495/23,933 (23.0%)	11,609/23,933 (48.5%)	6,137/23,933 (25.6%)	692/23,933 (2.9%)	
Age	57.4 (18–99)	55.4 (18–97)	56.7 (18–96)	60.0 (18–99)	62.1 (19–93)	<0.0001
Sex						
Female	13,872/23,933 (58.0%)	3,425/5,495 (62.3%)	6,700/11,609 (57.7%)	3,478/6,137 (56.7%)	269/692 (38.9%)	<0.0001
Male	10,061/23,933 (42.0%)	2,070/5,495 (37.7%)	4,909/11,609 (42.3%)	26,59/6,137 (43.3%)	423/692 (61.1%)	
Race						
Asian	790/21,640 (3.7%)	222/4,530 (4.9%)	391/10,637 (3.7%)	175/5,865 (3.0%)	2/608 (0.3%)	<0.0001
Black	1,861/21,640 (8.6%)	508/4,530 (11.2%)	1,020/10,637 (9.6%)	282/5,865 (4.8%)	51/608 (8.4%)	<0.0001
White	18,770/21,640 (86.7%)	3,722/4,530 (82.2%)	9,135/10,637 (85.9%)	5,362/5,865 (91.4%)	551/608 (90.6%)	<0.0001
Other	219/21,640 (1.0%)	78/4,530 (1.7%)	91/10,637 (0.9%)	46/5,865 (0.8%)	4/608 (0.7%)	<0.0001
Unknown	2,293/23,933 (9.6%)	965/5,495 (17.6%)	972/11,609 (8.4%)	272/6,137 (4.4%)	84/692 (12.1%)	<0.0001
Ethnicity						
Hispanic	1,761/20,082 (8.8%)	541/4,561 (11.9%)	930/9,700 (9.6%)	267/5,240 (5.1%)	23/581 (4.0%)	<0.0001
Unknown	3,851/23,933 (16.1%)	934/5,495 (17.0%)	1,909/11,609 (16.4%)	897/6,137 (14.6%)	111/692 (16.0%)	0.0013
Hiatal hernia						
Yes	9,591/23,933 (40.1%)	1,258/5,495 (22.9%)	4,555/11,608 (39.2%)	3,356/6,137 (54.7%)	422/692 (61.0%)	<0.0001
Small	6,647/9,105 (73.0%)	779/1,162 (67.0%)	3,252/4,302 (71.6%)	2,447/3,239 (75.6%)	169/402 (42.0%)	0.0016
Moderate	1,350/9,105 (14.8%)	219/1,162 (18.9%)	562/4,302 (13.1%)	454/3,239 (14.0%)	115/402 (28.6%)	
Large	1,108/9,105 (12.2%)	164/1,162 (14.1%)	488/4,302 (11.3%)	338/3,239 (10.4%)	118/402 (29.4%)	
Esophagitis (LA B–D)						
Yes	2,533/23,919 (10.6%)	525/5,494 (9.6%)	881/11,605 (7.6%)	1,020/6,134 (16.6%)	107/686 (15.5%)	<0.0001
Grade B	1,833/2,533 (72.4%)	424/525 (80.8%)	648/881 (73.6%)	723/1,020 (70.9%)	38/107 (35.5%)	
Grade C	513/2,533 (20.3%)	82/525 (15.6%)	173/881 (19.6%)	215/1,020 (21.1%)	43/107 (40.2%)	
Grade D	187/2,533 (7.4%)	19/525 (3.6%)	60/881 (6.8%)	82/1,020 (8.0%)	26/107 (24.3%)	
No	21,386/23,919 (89.4%)	4,969/5,494 (90.4%)	10,724/11,605 (92.4%)	5,114/6,134 (83.4%)	579/686 (84.4%)	
Length (Prague M, cm)				1.39 (1–2.5)	4.39 (3–17)	
Visual lesion						
Yes	416/23,924 (1.7%)	73/5,492 (1.3%)	200/11,609 (1.7%)	96/6,134 (1.6%)	47/689 (6.8%)	<0.0001

LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus.

(regular) Z line at the EGJ, 48.5% had an irregular-appearing Z line but less than 1 cm of CLE, 25.6% had potential SSBE (≥1 cm, but <3 cm of CLE), and 2.9% had potential LSBE (≥3 cm of CLE). In addition, 40.1% of patients had a hiatus hernia (73.0% small in size), 10.6% had evidence of Los Angeles grade B–D esophagitis (with 72.4% grade B, 27.6% grades C–D), and 1.7% had a focal lesion identified using high-definition white light endoscopy and/or virtual chromoendoscopy. Of the visually detected lesions, most were described as being either a nodule (38.3%) or an ulcer (32.2%).

FBs were performed first in 79% of patients, whereas the remainder had WATS-3D performed first. Table 1 demonstrates the statistically significant differences between the 4 main groups of patients (regular Z line, irregular Z line, potential SSBE, and potential LSBE) with regard to demographic and endoscopic characteristics. Significant upward trends were noted in patient age; male sex; White race; severity of esophagitis; and presence of hiatal hernia between the regular, irregular, and potential BE patient groups (Figure 2).

Pathology results (FB and WATS-3D)

Tables 2 and 3 summarize the FB and WATS-3D diagnostic yields, and the adjunctive and absolute increased yields of WATS-3D, for detection of IM (Table 2) and dysplasia/carcinoma (Table 3). Regarding IM, overall, 33.0% of patients had IM detected by either FB or WATS-3D in their index endoscopy. Of note, IM was detected in a significantly higher proportion of patients with potential SSBE or LSBE (39.1% and 68.8%, respectively) than in those with an irregular Z line (32.0%) or regular Z line (23.5%, $P < 0.0001$; Figure 3a); this finding applied to both the FB and WATS-3D when analyzed separately as well. Overall, WATS-3D diagnostic yield for IM was significantly higher than FB in the entire study cohort (25.6% vs 16.3%, $P < 0.0001$) and in each of the 4 endoscopic subgroups separately. Of

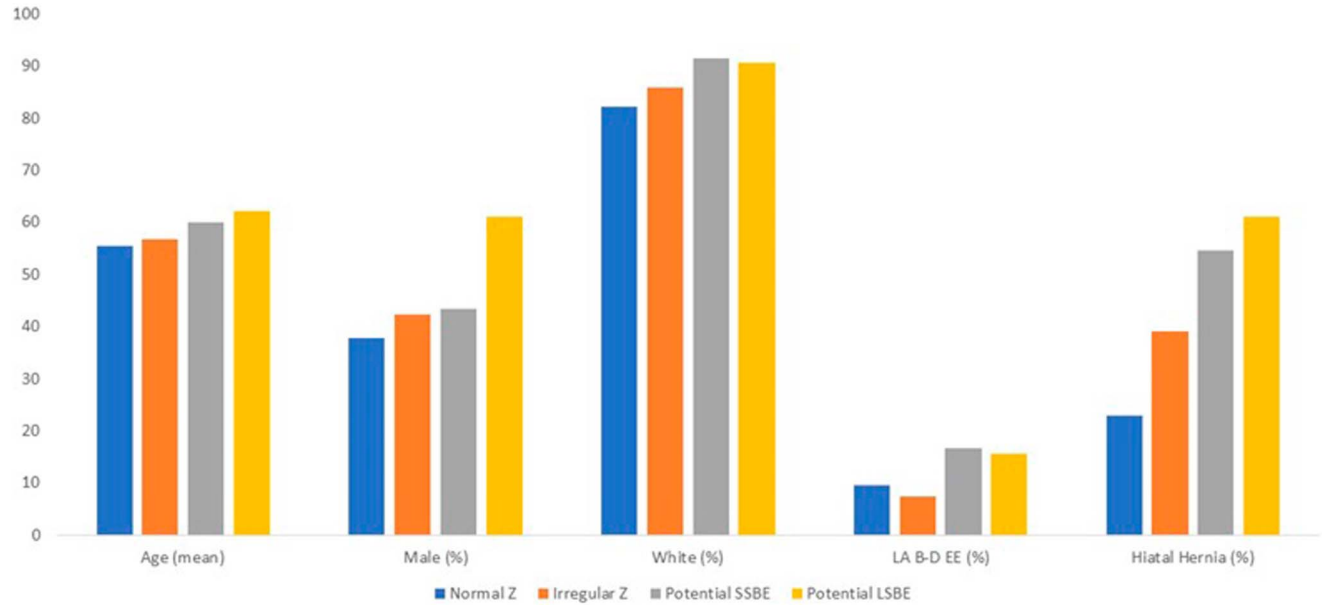

Figure 2. Clinical characteristics stratified by appearance of the Z line. Patients become older, more male, more likely to have hiatal hernia, and more likely to demonstrate erosive esophagitis with increasing amounts of CLE. CLE, columnar-lined epithelium; LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus.

particular clinical significance, of the 6,829 patients with ≥1 cm of esophageal columnar mucosa (fulfilling endoscopic criteria for BE), 2,878 (42.1%) had IM identified by either FB or WATS-3D and thus fulfilled both the endoscopic and histological criteria for BE. This included 1,317 patients (19.3% of those fulfilling endoscopic criteria for BE) detected by WATS-3D only, but not by FB (Figure 4). Table 2 also summarizes the WATS-3D adjunctive and absolute yields for IM in the whole group (103.3% and 16.8%, respectively) and in each of the respective endoscopic subgroups. Importantly, among patients who fulfilled the endoscopic criteria for BE, the adjunctive yield of WATS-3D was 76.5% and the absolute yield was 18.1%. The absolute yields of WATS-3D, also listed in Table 2, were significantly higher in the irregular Z line (18.0%) and potential BE (18.1%) endoscopic subgroups than in the regular Z line group (12.4%, $P < 0.0001$). Finally, the NNT for the total group was 6.0, and for each of the endoscopic subgroups, it was 8.1, 5.5, 5.5, and 6.8, respectively.

Regarding dysplasia (Table 3, Figure 3b), 1.0% of patients had any grade of dysplasia detected by either FB or WATS-3D (IND/CD = 0.6%, LGD = 0.1%, HGD/CA = 0.3%). Dysplasia was significantly more likely to be found in the potential BE subgroup (1.9%) than in the irregular (0.7%) and regular (0.5%) Z line groups ($P < 0.0001$). Similar significant statistical trends were observed when the FB and WATS-3D dysplasia findings were analyzed separately. No significant differences were detected between the diagnostic yields of FB compared with WATS-3D regarding detection of any grade of dysplasia, nor in any of the individual diagnostic categories of dysplasia when each of those were evaluated separately. The overall WATS-3D adjunctive and absolute yields for dysplasia detection were 80.5% and 0.5%, respectively. The WATS-3D absolute yields were significantly higher in the potential BE subgroup (1.0%) than in the regular (0.2%) and irregular (0.3%) Z line subgroups ($P < 0.0001$). The NNT value for any type of dysplasia was 224 overall. Dysplasia

Table 2. Yield of FB and WATS-3D for IM

	Total	Regular	Irregular, <1 cm	Possible short-segment BE	Possible long-segment BE	*P* value
N	23,933 (100.0%)	5,495/23,933 (23.0%)	11,609/23,933 (23.0%)	6,137/23,933 (25.6%)	692/23,933 (2.9%)	
FB yield	3,896/23,933 (16.3%)	613/5,495 (11.2%)	1,624/11,609 (14.0%)	1,285/6,137 (20.9%)	374/692 (54.1%)	<0.001
WATS-3D yield	6,114/23,933 (25.6%)	910/5,495 (16.6%)	2,904/11,609 (25.0%)	1,867/6,137 (30.4%)	433/692 (62.6%)	<0.001
FB + or WATS-3D +	7,888/23,933 (33.0%)	1,292/5,495 (23.5%)	3,718/11,609 (32.0%)	2,402/6,137 (39.1%)	476/692 (68.8%)	<0.001
WATS-3D adjunctive yield	103.3%	110.8%	128.9%	86.9%	27.3%	
WATS-3D absolute yield	3,992/23,933 (16.8%)	679/5,495 (12.4%)	2,094/11,609 (18.0%)	1,117/6,137 (18.2%)	102/692 (14.7%)	<0.001
NNT	6.0	8.1	5.5	5.5	6.8	

The table does not display 98 patients noted to have CLE ≥1 cm in length, with no discrete cm length noted.
Pairwise comparisons of WATS-3D yield to FB yield for each column are significant, $P < 0.001$.
BE, Barrett's esophagus; CLE, columnar-lined epithelium; FB, forceps biopsy; IM, intestinal metaplasia; NNT, number needed to test; WATS-3D, wide-area transepithelial sampling.

Table 3. Yield of FB and WATS-3D for dysplasia

	Total	Regular	Irregular, <1 cm	Possible SSBE	Possible LSBE	*P* value
FB yield						
Any	133/23,933 (0.6%)	17/5,495 (0.3%)	51/11,609 (0.4%)	28/6,137 (0.5%)	37/692 (5.4%)	<0.0001
IND/CD	59/23,933 (0.3%)	7/5,495 (0.1%)	28/11,609 (0.2%)	14/6,137 (0.2%)	10/692 (1.5%)	<0.0001
LGD	19/23,933 (0.08%)	2/5,495 (0.04%)	6/11,609 (0.05%)	5/6,137 (0.08%)	6/692 (0.9%)	
HGD/EAC	55/23,933 (0.2%)	8/5,495 (0.2%)	17/11,609 (0.2%)	9/6,137 (0.2%)	21/692 (3.0%)	
WATS-3D yield						
Any	167/23,933 (0.7%)	17/5,495 (0.3%)	49/11,609 (0.4%)	50/6,137 (0.8%)	51/692 (7.4%)	<0.0001
IND/CD	104/23,933 (0.4%)	7/5,495 (0.1%)	31/11,609 (0.3%)	37/6,137 (0.6%)	29/692 (4.2%)	<0.0001
LGD	19/23,933 (0.08%)	2/5,495 (0.04%)	4/11,609 (0.03%)	6/6,137 (0.1%)	7/692 (1.0%)	
HGD/EAC	44/23,933 (0.2%)	8/5,495 (0.2%)	14/11,609 (0.1%)	7/6,137 (0.1%)	15/692 (2.2%)	
FB or WATS-3D positive						
Any	240/23,933 (1.0%)	26/5,495 (0.5%)	83/11,609 (0.7%)	67/6,137 (1.1%)	64/692 (9.3%)	<0.0001
IND/CD	150/23,933 (0.6%)	14/5,495 (0.3%)	54/11,609 (0.5%)	47/6,137 (0.8%)	35/692 (5.1%)	<0.0001
LGD	27/23,933 (0.1%)	4/5,495 (0.07%)	9/11,609 (0.08%)	8/6,137 (0.1%)	6/692 (0.9%)	
HGD/EAC	63/23,933 (0.3%)	8/5,495 (0.2%)	20/11,609 (0.2%)	12/6,137 (0.2%)	23/692 (3.3%)	
WATS-3D adjunctive yield						
Any	80.5%	52.9%	62.7%	139.3%	73.0%	
IND/CD	154.2%	100.0%	92.9%	235.7%	250.0%	
LGD	52.6%	100.0%	50.0%	80.0%	16.7%	
HGD/EAC	14.5%	0.0%	17.6%	33.3%	9.5%	
WATS-3D absolute yield						
Any	107/23,933 (0.5%)	9/5,495 (0.2%)	32/11,609 (0.3%)	39/6,137 (0.6%)	27/692 (3.9%)	<0.0001
IND/CD	91/23,933 (0.4%)	7/5,495 (0.1%)	26/11,609 (0.2%)	33/6,137 (0.5%)	25/692 (3.6%)	<0.0001
LGD	10/23,933 (0.04%)	2/5,495 (0.04%)	3/11,609 (0.03%)	4/6,137 (0.07%)	1/692 (0.1%)	0.1958
HGD/EAC	8/23,933 (0.03%)	0/5,495 (0.0%)	3/11,609 (0.03%)	3/6,137 (0.05%)	2/692 (0.3%)	0.0037
NNT						
Any	224	611	363	157	26	
IND/CD	263	785	447	186	28	
LGD	2,393	2,748	3,870	1,534	692	
HGD/EAC	2,992	N.A.	3,870	2046	346	

CD, crypt dysplasia; EAC, esophageal adenocarcinoma; FB, forceps biopsy; HGD, high-grade dysplasia; IM, intestinal metaplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia; LSBE, long-segment Barrett's esophagus; NNT, number needed to test; SSBE, short-segment Barrett's esophagus; WATS-3D, wide-area transepithelial sampling.

was significantly more common in the potential LSBE group (9.3%) than in the potential SSBE group (1.1%).

Several post hoc analyses were performed. Analysis of the yield of adding WATS-3D based on which modality was used to sample the esophagus first demonstrates adjunctive and absolute yields of similar magnitudes regardless of the modality used first to sample the mucosa. Supplementary Digital Content (see Supplementary Tables 1–4, http://links.lww.com/AJG/D258) presents yield for IM with FB (Table 1) or WATS-3D (Table 2) used first and yield for dysplasia with FB (Table 3) and WATS-3D (Table 4) used first. In addition, we calculated the absolute and adjunctive yield of WATS-3D when excluding lower forms of dysplasia, IND and CD (see Supplementary Table 5, http://links.lww.com/AJG/D258). Over half of the dysplasia found in this screening population by either modality was either CD or IND. Therefore, after excluding these patients, the overall yield for dysplasia discovered by any modality dropped by about half, from 1% to 0.4%. The absolute yield of WATS-3D also decreased, from 0.5% to 0.1%. The adjunctive yield of WATS-3D also decreased, from 80.5% in the entire cohort to 21.6% excluding CD and IND. To assess the impact of the presence of erosive esophagitis on the likelihood of finding dysplasia, we analyzed the adjunctive and absolute yields of IM and dysplasia in the 10.6% of patients with erosive esophagitis. While the absolute and adjunctive yields of IM were of the same general magnitude of the overall samples (14.6% and 74.3%, respectively), the patients with erosive disease were twice

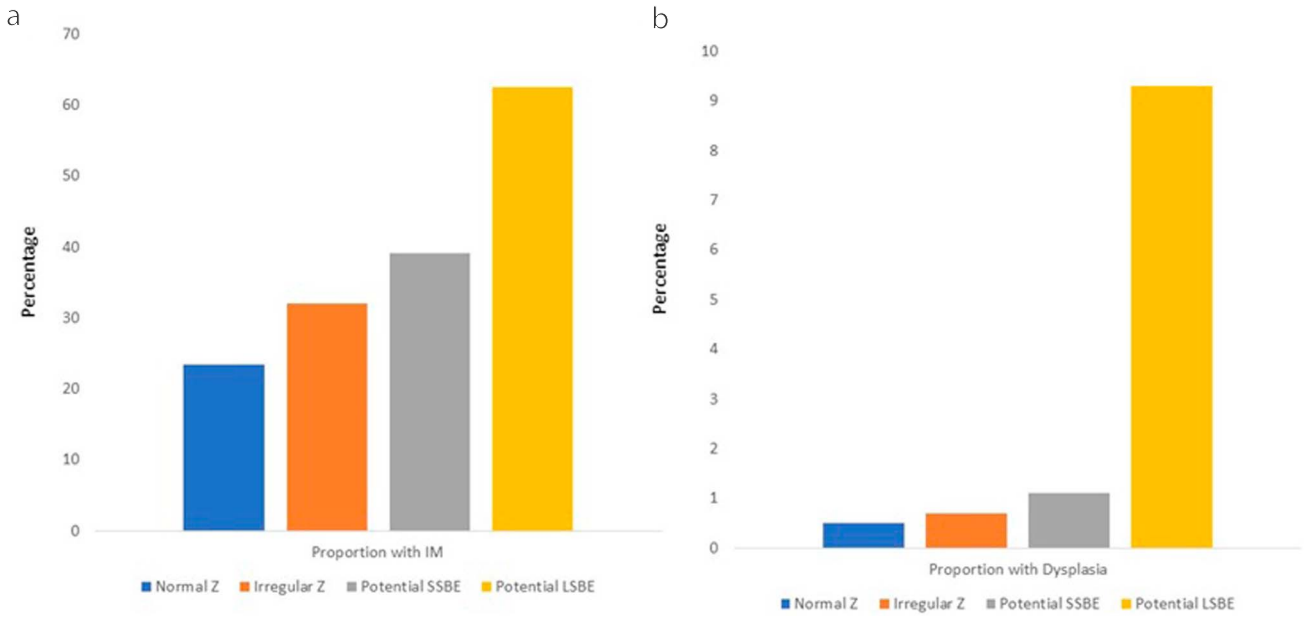

Figure 3. The likelihood of IM and dysplasia stratified by appearance of the Z line. Patients were more likely to display IM or dysplasia with increasing amounts of CLE. CLE, columnar-lined epithelium; IM, intestinal metaplasia; LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus.

as likely to show any form of dysplasia (2.0% vs 1.0%) and also twice as likely to show HGD/EAC (0.7% vs 0.3%). The absolute yield of WATS-3D for dysplasia in this subgroup improved to 0.7%, with an adjunctive yield of 51.5%.

Clinical utility results

Tables 4 and 5 summarize the clinical management actions that were instituted in the patients in this study when a diagnosis of IM (Table 4) or dysplasia (Table 5) was rendered by WATS-3D but missed by FB (designated WATS-3D+/FB−). Of these patients, there were 3,993 patients diagnosed with IM and 107 with any grade of dysplasia, representing 50.6% and 44.6% of all patients diagnosed with IM or dysplasia by either WATS-3D or FB. Regarding IM, 90.7% of these patients had a change in patient management based on the WATS-3D finding, which consisted of initiation or change in surveillance (79.0%), initiation of PPI use or increased PPI dosage (56.7%), or use of antireflux surgery or endoscopic ablation (1.2%) (cumulative numbers are >100% because multiple patients had more than 1 treatment alteration). Regarding dysplasia, 97.1% of these patients had a change in patient management (surveillance: 89.7%; PPI therapy: 69.1%; ablation, antireflux surgery, or EMR: 4.7%). A subanalysis of management changes for IM and dysplasia according to the status of the Z line revealed a greater likelihood of a change in management if IM was found as the Z line became more irregular, with larger proportions of patients starting surveillance when the Z line was more irregular. This trend was not noted if dysplasia was found, with high proportions of endoscopists altering management based on the finding of dysplasia regardless of the appearance of the Z line.

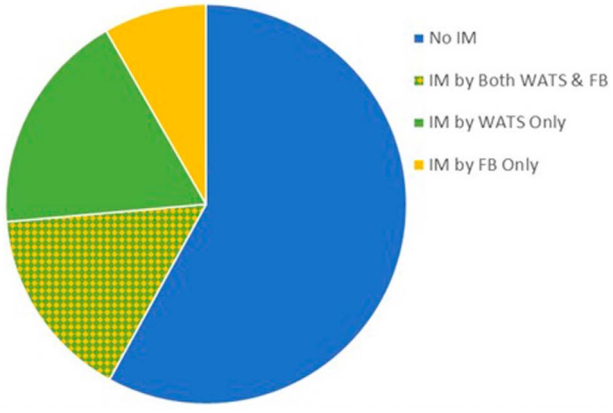

Figure 4. Histology of patients demonstrating endoscopic criteria for BE. Patients in the green area (19.3%) had their diagnosis of IM made solely by WATS-3D and would have otherwise not fulfilled criteria for BE. BE, Barrett's esophagus; FB, forceps biopsy; IM, intestinal metaplasia; WATS-3D, wide-area transepithelial sampling.

DISCUSSION

WATS-3D has been shown in previous studies to significantly increase the adjunctive and absolute yield of detection of IM and dysplasia in patients with BE undergoing surveillance for BE (9,11,13,14,21,22). However, its yield in a screening cohort has never been evaluated systematically. This question is important because an endoscopic finding consistent with BE, but without histological confirmation from associated FBs, often precipitates a second endoscopic procedure in these patients to rule out a false-negative histologic result on the initial examination. Since as many as 1 in 3 of these patients will have IM on a second examination (23,24), such a concern is warranted. If IM in a BE segment remains undiscovered, patients who are otherwise eligible for endoscopic surveillance will not be entered into such a program and thus would lose the potential benefit of early detection of neoplasia.

The purpose of this study was to prospectively evaluate, in a blinded fashion, the diagnostic utility of WATS-3D, in a large and endoscopically well-defined group of community patients with GERD symptoms. In this cohort, approximately 23%, 49%, and

Table 4. Patient management changes among patients positive for IM by WATS-3D but negative by FB (WATS-3D+/FB−)Patient management changes among those positive for intestinal metaplasia by WATS-3D, but negative by FB (WATS+/FB-)

		Total	Regular	Irregular, <1cm	Possible SSBE	Possible LSBE	*P* value
	Total (N)	3,993/3,993 (100%)	679 (17.0%)	2,094/3,993(52.4%)	1,118/3,993(28.0%)	102/3,993(2.6%)	
Surveillance	Started	2,984/3,993(74.7%)	410/679 (60.4%)	1,545/2,094(73.8%)	943/1,118 (84.4%)	86/102 (84.3%)	<0.0001
	Modified	170/3,993 (4.3%)	24/679 (3.5%)	129/2,094 (6.2%)	17/1,118 (1.5%)	0/102 (0.0%)	
	Unchanged	837/3,993 (21.0%)	245/679 (36.1%)	420/2,094 (20.1%)	156/1,118 (14.0%)	16/102 (15.7%)	
	Unknown	2/3,993 (0.05%)	0/679 (0.0%)	0/2,094 (0.0%)	2/1,118 (0.2%)	0/102 (0.0%)	
	WATS3D Impact						<0.0001
	Yes	3,154/3,991(79.0%)	434/679 (17.0%)	1,674/2,094(52.5%)	960/1,116 (86.0%)	86/102 (84.3%)	
	No	837/3,991 (21.0%)	245/679 (36.1%)	420/2,094 (20.1%)	156/1,116 (14.0%)	16/102 (15.7%)	
PPI	Started	1,822/3,393(45.6%)	316/679 (46.5%)	909/2,094 (43.4%)	547/1,118 (48.9%)	50/102 (49.0%)	0.0303
	Increased	445/3,993 (11.1%)	92/679 (13.6%)	285/2,094 (13.6%)	64/1,118 (5.7%)	4/102 (3.9%)	
	Unchanged	1,240/3,993(31.1%)	144/679 (21.2%)	613/2,094 (29.3%)	441/1,118 (39.5%)	42/102 (41.2%)	
	Unknown	486/3,993 (12.2%)	127/679 (18.7%)	287/2,094 (13.7%)	66/1,118 (5.9%)	6/102 (5.9%)	
	WATS3D Impact						
	Yes	2,267/3,507(64.6%)	408/552 (73.9%)	1,194/1,807(66.1%)	611/1,052 (58.1%)	54/96 (56.3%)	<0.001
	No	1,240/3,507(35.4%)	144/552 (26.1%)	613/1,807 (33.9%)	441/1,052 (41.9%)	42/96 (43.8%)	
Interventional Rx	Yes	49/3,993 (1.2%)	8/679 (1.2%)	21/2,094 (1.0%)	14/1,118 (1.3%)	6/102 (5.9%)	
	Antireflux Surgery	12/3,904 (0.3%)	5/652 (0.8%)	2/2,056 (0.1%)	3/1,095 (0.3%)	2/101 (2.0%)	0.9944
	Ablation	37/3,992 (0.9%)	3/679 (0.4%)	19/2,094 (0.9%)	11/1,117 (1.0%)	4/102 (3.9%)	0.0221
	EMR	0/3,992 (0.0%)	0/679 (0.0%)	0/2,094 (0.0%)	0/1,117 (0.0%)	0/102 (0.0%)	N/A
	No	3,854/3,993(96.5%)	644/679 (94.9%)	2,035/2,094(97.2%)	1,080/1,118(96.6%)	95/102 (93.1%)	
	Unknown	90/3,993 (2.3%)	27/679 (4.0%)	38/2,094 (1.8%)	24/1,118 (2.2%)	1/102 (1.0%)	
	WATS3D Impact						0.0489
	Yes	49/3,903 (1.3%)	8/652 (1.2%)	21/2,056 (1.0%)	14/1,094 (1.3%)	6/101 (5.9%)	
	No	3,854/3,903(98.7%)	644/652 (98.8%)	2,035/2,056(52.7%)	1,080/1,094(98.7%)	95/101 (94.1%)	
Overall	WATS3D Impact						0.0746
	Yes	3,416/3,767(90.7%)	531/613 (86.6%)	1,798/1,953(92.1%)	996/1,101 (90.5%)	91/100 (91.0%)	
	No	351/3,767 (9.3%)	82/613 (13.4%)	155/1,953 (7.9%)	105/1,101 (9.5%)	9/100 (9.0%)	

EMR, endoscopic mucosal resection; FB, forceps biopsy; IM, intestinal metaplasia; LSBE, long-segment Barrett's esophagus; PPI, proton pump inhibitor; SSBE, short-segment Barrett's esophagus; WATS-3D, wide-area transepithelial sampling.

29%, respectively, had an endoscopically normal Z line, irregular Z line, or ≥1 cm esophageal CLE consistent with potential BE if confirmed by histology. Overall, 33% of patients demonstrated IM and 1% had dysplasia detected by either FB or WATS-3D. For both IM and dysplasia, there was a significantly increased frequency as one moves from regular Z line to progressively more irregular Z line groups. WATS-3D detected significantly more IM, but not dysplasia, than FB. However, the adjunctive and absolute yields of WATS-3D were 103.3% and 16.8% for detection of IM and 80.5% and 0.5% for detection of any grade of dysplasia overall. Importantly, 19.3% (1,317/6,829) of patients who demonstrated endoscopic findings consistent with BE had their diagnosis confirmed solely on the basis of the WATS-3D findings. Among patients with BE who were diagnosed with IM by WATS-3D only (WATS-3D+/FB−), over 90% had a change of patient management instituted by the patient's treating physician, mostly consisting of institution of endoscopic surveillance. Finally, this gain in diagnostic yield occurred in a substantial proportion of potential BE patients. For instance, only 5–7 patients with an endoscopic finding consistent with BE need to undergo WATS-3D analysis to result in an additional case diagnosis of BE. Overall, in this cohort, if repeat endoscopy were undertaken in patients with endoscopic evidence of BE, but without histological confirmation, an additional 1,317 endoscopies would have been performed. Therefore, the use of WATS-3D as an adjunct in patients suspected of BE may save endoscopies and lead to quicker, more accurate diagnoses. Based on these results, we conclude that WATS-3D is a clinically valuable adjunct to FB for the diagnosis of BE when used as a screening tool in symptomatic GERD patients and particularly in patients with endoscopic evidence of >1 cm esophageal CLE.

The epidemiologic characteristics of our endoscopic subgroups of patients, based on the appearance of the Z line, are remarkable in a number of ways. The prevalence of risk factors of both GERD and BE increased progressively in the regular to irregular to potential BE subgroups of patients. Specifically, the patients become progressively more male, older in age, more likely to have a hiatal hernia, and more likely to demonstrate significant erosive esophagitis. The likelihood of finding both IM

Table 5. Patient management changes among patients positive for dysplasia by WATS-3D but negative by FB (WATS-3D+/FB−)

		Total	Regular	Irregular, <1 cm	Possible SSBE	Possible LSBE	*P* value
	Total (N)	107/107 (100.0%)	9/107 (8.4%)	32/107 (29.9%)	39/107 (36.5%)	27/107 (25.2%)	
Surveillance	Started	85/107 (79.4%)	7/9 (77.8%)	26/32 (31.3%)	34/39 (87.2%)	18/27 (66.7%)	0.962
	Modified	11/107 (10.3%)	0/9 (0.0%)	2/32 (6.3%)	3/39 (7.7%)	6/27 (22.2%)	
	Unchanged	10/107 (9.4%)	2/9 (22.2%)	3/32 (9.4%)	2/39 (5.1%)	3/27 (11.1%)	
	Unknown	1/107 (0.9%)	0/9 (0.0%)	1/32 (3.1%)	0/39 (0.0%)	0/27 (0.0%)	
	WATS-3D impact						0.4863
	Yes	96/106 (90.6%)	7/9 (77.8%)	28/31 (90.3%)	37/39 (94.9%)	24/27 (88.9%)	
	No	10/106 (9.4%)	2/9 (22.2%)	3/31 (9.7%)	2/39 (5.1%)	3/27 (11.1%)	
PPI	Started	50/107 (46.7%)	3/9 (33.3%)	8/32 (25.0%)	25/39 (64.1%)	14/27 (51.9%)	0.5059
	Increased	24/107 (22.4%)	4/9 (44.4%)	14/32 (43.8%)	4/39 (10.3%)	2/27 (7.4%)	
	Unchanged	23/107 (21.5%)	1/9 (11.1%)	7/32 (21.9%)	7/39 (18.0%)	8/27 (29.6%)	
	Unknown	10/107 (9.4%)	1/9 (11.1%)	3/32 (9.4%)	3/39 (7.7%)	3/27 (11.1%)	
	WATS-3D impact						0.2969
	Yes	74/97 (76.3%)	7/8 (87.5%)	22/29 (29.9%)	29/36 (80.6%)	16/24 (66.7%)	
	No	23/97 (23.7%)	1/8 (12.5%)	7/29 (24.1%)	7/36 (19.4%)	8/24 (33.3%)	
Surgical treatment	Yes	5/107 (4.7%)	1/9 (11.1%)	1/32 (3.1%)	2/39 (5.1%)	1/27 (3.7%)	
	Antireflux surgery	0/104 (0.0%)	0/9 (0.0%)	0/30 (0.0%)	0/38 (0.0%)	0/27 (0.0%)	N/A
	Ablation	4/106 (3.8%)	1/9 (11.1%)	1/31 (3.2%)	1/39 (2.6%)	1/27 (3.7%)	0.5162
	EMR	1/106 (0.9%)	0/9 (0.0%)	0/31 (0.0%)	1/39 (2.6%)	0/27 (0.0%)	0.8204
	No	99/107 (92.5%)	8/9 (88.9%)	29/32 (90.6%)	36/39 (92.3%)	26/27 (96.3%)	
	Unknown	3/107 (2.8%)	0/9 (0.0%)	2/32 (29.9%)	1/39 (36.5%)	0/27 (0.0%)	
	WATS-3D impact						0.6232
	Yes	5/104 (4.8%)	1/9 (11.1%)	1/30 (3.3%)	2/38 (5.3%)	1/27 (3.7%)	
	No	99/104 (95.2%)	8/9 (88.9%)	29/30 (96.7%)	36/38 (94.7%)	26/27 (96.3%)	
Overall	WATS-3D impact						0.3933
	Yes	100/103 (97.1%)	9/9 (100.0%)	28/30 (93.3%)	38/39 (97.4%)	25/25 (100.0%)	
	No	3/103 (2.9%)	0/9 (0.0%)	2/30 (6.7%)	1/39 (2.6%)	0/25 (0.0%)	

EMR, endoscopic mucosal resection; FB, forceps biopsy; IM, intestinal metaplasia; LSBE, long-segment Barrett's esophagus; PPI, proton pump inhibitor; SSBE, short-segment Barrett's esophagus; WATS-3D, wide-area transepithelial sampling.

and dysplasia on histology increased progressively in these groups as well. These findings suggest that these endoscopic subgroups of patients likely represent a spectrum of the same disease process, both with respect to acid exposure and, perhaps, with the risk of neoplasia development as well.

It may seem initially surprising that only a minority (42.1%) of patients who met the endoscopic criteria for BE in our study demonstrated IM on histology, but this finding is consistent with previous work. For instance, Eloubeidi et al found that, of 146 patients undergoing endoscopy at a tertiary care center who were suspected to have BE based on endoscopic findings, only 49 (34%) showed histological confirmation (25). Similar proportions have been noted by other investigators (26). While our report focuses on the yield of WATS-3D in those who satisfy endoscopic criteria for BE, an interesting aspect of our report is the relatively high number of patients with less than 1 centimeter of columnar tissue in the tubular esophagus who had IM on either WATS-3D or FB. The significance of IM of the EGJ region (in either symptomatic or nonsymptomatic patients) is incompletely understood. National guidelines require that CLE with IM extends at least 1 cm proximal to the EGJ to be considered BE and, thus, eligible for surveillance. This recommendation is based both on the poor reproducibility of a finding of BE of less than 1 cm in length (27,28), as well as the results of previous studies demonstrating a very low risk of neoplastic progression in patients with IM limited to the EGJ region (29,30). Interestingly, a recent study from a Gastroenterology Quality Improvement Consortium Registry found that societal guidelines regarding sampling the EGJ are, in fact, often disregarded by physicians (31). Thus, it is not surprising that our study contains a high proportion of symptomatic GERD patients who had samples obtained from the EGJ region although they did not fulfill the endoscopic diagnostic criteria for BE. The use of WATS-3D in this situation is of unclear utility, since a finding of IM would not confirm a diagnosis of BE. Many of the practice patterns demonstrated in the endoscopic care of these patients, as well as their follow-up, are at odds with societal

recommendations, an observation that has been recurrently demonstrated in studies of BE (8,32,33).

This study represents the single largest population of patients evaluated with WATS-3D to date, and the first to evaluate, exclusively, only symptomatic GERD patients being screened for possible BE and classified according to the appearance of their Z line. Five previous studies have evaluated WATS-3D in patients with GERD being screened for BE, but all of these studies included patients with known BE undergoing routine surveillance as well (11,13,17,22). Unfortunately, only 3 of these studies reported their screening vs surveillance patient data separately (11,13,34). The adjunctive and absolute yields of detection of IM in these 3 studies ranged from 70.5% to 213% and 12.4% to 19.7%, respectively. These data are similar to the rates of detection of IM in our study. Regarding dysplasia, 4 of these 5 studies reported WATS-3D adjunctive and absolute yields ranging from 88.5% to 274% and 0.8% to 1.2%, respectively, specifically in the screening cohorts. Our adjunctive and absolute yield values of 80.5% and 0.5% in this study are somewhat lower than these. The reasons for these differences are unknown, but possible explanations include the lower proportion of patients found to have BE ($\geq$1 cm CLE with IM) in our study compared with the screening cases in these other studies or other differences in patient risk profiles among the various studies.

There are several limitations of our study. First, given the size of our study, there was no central pathology review; thus, confirmation of the FB diagnosis could not be performed. Similarly, there was no central review of endoscopic findings, such as the appearance of the Z line. While these issues are limitations, the lack of confirmatory reads of the FBs also represents a common situation in community practices, where expert pathological assessment of tissue samples or second opinions on endoscopic findings are rarely readily available. In addition, in contrast to dysplasia diagnoses, which are known to be highly variable, IM diagnoses generally show much better concordance rates (35,36), which make our findings potentially more generalizable. Furthermore, only a small percentage of patients (1% overall) had dysplasia, and given the lack of confirmatory reads of these patients, miscategorization could have affected our reported adjunctive yields. Next, information regarding whether FBs were targeted was not available. WATS-3D is specifically not indicated for targeted sampling of visual lesions, and thus, sampling of visual lesions only by FB, and not WATS-3D, may have led to selection bias in favor of FB over WATS-3D for dysplasia detection in those patients. Furthermore, this study consisted of a larger proportion of women than men. However, this is not uncommon in studies of GERD (37–39). A significantly higher proportion of patients had FB performed before WATS-3D. If FB sampled and potentially removed the IM or dysplasia foci, it could have led to bias toward better results for this modality. While randomizing the order of these modalities would have obviated this concern, we did not undertake randomization in this registry study. Next, it should be noted that over half of the dysplasia diagnoses found by either modality in this cohort were IND or CD and that the adjunctive and absolute yield of WATS-3D for dysplasia decreased when such patients were excluded from the analysis. In addition, as a registry study, we did not mandate the use of electronic or dye-based chromoendoscopy, and the routine use of these modalities may have affected our results. Finally, the decision of who to enroll in this registry study was at the discretion of the endoscopist, and endoscopic evidence of BE was not required for enrollment. While this approach may have created selection bias in ways that are difficult to understand, it does provide us with a unique dataset to assess trends in IM yield, dysplasia yield, and demographics along the spectrum of irregularity of the Z line not previously available in the literature.

This study also had several noteworthy strengths. The data are prospective and represent the largest published experience with this assay, which decreases the chance of a type II statistical error. Patients were well characterized endoscopically, allowing assessment of variables according to the patients' Z line status and evaluation of potential biological associations. The study also included many medical centers from across the United States, most of which were community-based, which yields greater generalizability.

In summary, WATS-3D increased detection of IM in symptomatic GERD patients who demonstrated endoscopic findings consistent with BE, allowing histological confirmation of BE in a substantial proportion of patients who would otherwise need to undergo a repeat endoscopy. This study also demonstrates a high frequency of management changes rendered as a result of the positive pathologic finding on WATS-3D. The progressive and significant increase in IM and dysplasia detected in patients with increasing irregularity of the Z line and CLE provides support for a single spectrum disorder occurring in these patients. Further longitudinal studies should be performed with WATS-3D to help determine the clinical significance and rate of neoplastic progression in symptomatic GERD patients with varying degrees of irregularity of the Z line and, ideally, in asymptomatic control populations as well.

CONFLICTS OF INTEREST

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Specific author contributions: N.J.S.: study design, data analysis, data interpretation, manuscript drafting. R.D.O.: study design, data analysis, data interpretation, manuscript drafting. M.E.S.: study design, data analysis, data interpretation, manuscript drafting. J.W.S.: study design, data analysis, data interpretation, manuscript drafting. S.S.: study design, data analysis, data interpretation, manuscript drafting. V.K.: data analysis, data interpretation, manuscript drafting. A.J.T.: data analysis, data interpretation, manuscript drafting. A.A.: data analysis, data interpretation, manuscript drafting. R.H.: data analysis, data interpretation, manuscript drafting. M.S.S.: study design, data analysis, data interpretation, manuscript drafting. M.J.M.: study design, data analysis, data interpretation, manuscript drafting. All authors reviewed and approved the final manuscript.
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Study Highlights

WHAT IS KNOWN

- ✓ Sampling error in the surveillance of Barrett's esophagus limits the efficacy of endoscopic examinations.
- ✓ Use of WATS-3D as an adjunct to forceps biopsies results in additional diagnoses of intestinal metaplasia and dysplasia.

WHAT IS NEW HERE

- ✓ The use of WATS-3D in populations with GERD being screened for BE results in a finding of intestinal metaplasia confirming the BE diagnosis in an additional 1 in 5 patients with ≥1 cm of columnar-lined esophageal mucosa.
- ✓ The number of patients found to have dysplasia approximately doubled.
- ✓ Adjunctive use of WATS-3D in a GERD population being screened for BE results in more diagnoses of BE, decreasing the need for a second examination to confirm the diagnosis.

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