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WATS^{3D} versus forceps biopsy in screening for Barrett's esophagus: experience in community endoscopy centers

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Abstract

Background Barrett's esophagus (BE) is a premalignant condition diagnosed using systematic 4-quadrant forceps biopsies (FB) during endoscopy. This method is fraught with errors due to the randomness of sampling and variability among operators. Wide-area transepithelial sampling with 3-dimensional computer-assisted analysis (WATS^{3D}) is an emerging technique used to collect esophageal samples. The aim of this study was to evaluate WATS^{3D} as a diagnostic tool for detecting BE in addition to FB, compared to FB alone.

Methods A retrospective observational cohort study was conducted and included patients who underwent screening for BE with WATS^{3D} and FB between January 2015 and January 2019 across 3 endoscopy centers in Wichita, Kansas. The FB specimens were reviewed by community pathologists, while the WATS^{3D} samples were sent to CDX technology labs, NY.

Results A total of 108 patients were screened for BE using both modalities concurrently. FB and WATS^{3D} detected 62 (57.4%) and 83 (76%) cases of BE, respectively. The absolute difference of 21 cases (18.6%) of BE was attributed to the addition of WATS^{3D}. The number needed to test with WATS^{3D} was 5. We divided the sample into 4 groups to compare the agreement across all groups: (FB–; WATS^{3D}+), (FB–; WATS^{3D}–), (FB+; WATS^{3D}+), and (FB+ and WATS^{3D}–). Overall agreement by kappa statistic was 0.74.

Conclusion WATS^{3D} identified 21 cases of BE missed by FB. Using WATS^{3D} in addition to FB increased the yield of BE during surveillance endoscopy, with no increase in complications.

Keywords Barrett's esophagus, biopsy, cytodiagnosis, endoscopy, screening

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Introduction

Barrett's esophagus (BE) is an acquired premalignant condition that develops in patients with long-standing gastroesophageal reflux disease (GERD). In the United States, 5.6% of the population has BE, and most patients are unaware of the disease [1]. Patients can be asymptomatic or can present with dyspepsia, dysphagia, and hoarseness. The squamous epithelium normally found at the distal end of the esophagus is abnormally replaced by columnar epithelium with gastric and intestinal features, known as intestinal metaplasia [2]. The annual incidence of esophageal adenocarcinoma (EAC) in patients with BE is about 0.5% [3].

The American College of Gastroenterology's guidelines recommend screening by upper endoscopy in men with chronic symptoms of GERD (greater than 5 years) and with 2 or more of the following risk factors: white race, central obesity, age more than 50 years, current or past smoking history and a first degree

relative with BE or EAC [4]. The gold standard for screening for BE is esophagogastroduodenoscopy (EGD) with forceps biopsies (FB) [4]. According to the Seattle protocol, systematic 4-quadrant biopsies at 2 cm intervals should be taken along the entire length of the segment in patients without prior dysplasia and at 1 cm intervals in patients with prior dysplasia [4,5].

Variation in accuracy between physicians performing EGD with FB occurs because it is operator dependent, which increases the risk of sampling error and decreases the diagnostic yield. It is also time-consuming and requires a large number of biopsies. This adds to the cost of the procedure and lowers the adherence rate, further worsening the diagnostic yield [6,7]. EGD with FB is associated with complications such as bleeding and perforation, although these are rare in the hands of skilled endoscopists. Many alternatives to FB are under evaluation, such as brush cytology and needle aspiration cytology, in an attempt to overcome the limitations [8]. Among the most recent tools is wide-angle transepithelial sampling with computer-assisted 3-dimensional tissue analysis (WATS^{3D}). It utilizes a brush that samples a wide circumferential surface area and resects full thickness trans-epithelial tissue samples. Analysis of the esophageal cells is performed by a computerized microscope and neural network that create a 3-dimensional display of the tissue, locating areas of intestinal metaplasia, dysplasia and adenocarcinoma. These digital images are reviewed by a pathologist to confirm the accuracy of the diagnosis.

In our study, the charts of every adult patient who underwent screening for BE with both FB and WATS^{3D} were reviewed and the diagnostic discordance was analyzed following both modalities. The aim of this study was to evaluate WATS^{3D} as a diagnostic tool for detecting BE in addition to FB, compared to FB alone, the current gold standard.

Patients and methods

Patient population

A retrospective observational cohort study was conducted that was approved by the University of Kansas Medical Center's Institutional Review Board. Charts were reviewed of all adults (>18 years of age) who underwent screening or routine surveillance for BE with both WATS^{3D} and traditional cold FB between January 2015 and January 2019, across 3 endoscopy centers in Wichita, Kansas. Patients were excluded if they did not have both sampling methods performed (WATS^{3D} and FB).

Procedure and techniques

All procedures were performed by 3 experienced gastroenterologists using the Olympus H190 scope. After careful screening using white light and narrow-band imaging (NBI), FB were obtained every 1-2 cm in 4-quadrants along the length of the BE segment, followed by WATS^{3D} brushings of the BE segment. WATS^{3D} brushings were done after FB in all cases.

Sample processing

The biopsy specimens were processed and analyzed by 2 community pathologists, one of whom is specialized in gastrointestinal pathology. The results were reported as no dysplasia, indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), or intramucosal carcinoma. WATS^{3D} specimens were sent to CDX technology (Suffern, NY) for analysis using a computer-assisted 3-dimensional analysis system, and findings were confirmed by their pathologist. Results were reported as negative, goblet cell metaplasia, crypt dysplasia, LGD, HGD, or EAC.

Statistical analysis

Patient and endoscopy characteristics, biopsy results and CDX pathology reports were extracted from patient charts. Dysplasia as reported by biopsy and CDX pathology were compared. The highest grade of dysplasia detected on biopsy or WATS^{3D} analysis was considered as the final grade of dysplasia. For the sake of 2×2 analysis, no dysplasia was considered as a negative finding by FB (FB-) and all others were classified as positive findings by FB (FB+). WATS^{3D}- referred to those reported as negative and all others were classified as WATS^{3D}+. 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. We used Microsoft Excel (Microsoft, Redmond, WA) and SPSS v24 (IBM, NY) to conduct the analysis.

Results

A total of 108 patients were identified as having undergone both WATS^{3D} and FB at the same time for BE screening. The mean age of men was 63.5 years (standard deviation 11.7) compared to 62 years for women. Patient demographics stratified by sex and indications for EGD are reported in Table 1 and Fig. 1, respectively. FB detected 62 cases (57.4%) while WATS^{3D} detected 83 (76%) cases of BE. We divided the sample into 4 groups (Table 2): (FB–; WATS^{3D}+), (FB–; WATS^{3D}–), (FB+; WATS^{3D}+) and (FB+ and WATS^{3D}–). Overall agreement by kappa statistic was 0.74 (good). There were 62 and 23 cases identified as positive and negative, respectively, by both methods. The pathologist read both cases of FB+ that were WATS^{3D}- as intestinal metaplasia with no dysplasia.

Table 1 Patient demographics stratified by sex

Sex	Male	Female
Average age	63.5	62
Participants (%)	71	37
History of smoking	50	12
History of esophageal cancer	2.60%	0%
History of liver cirrhosis	2.60%	0%

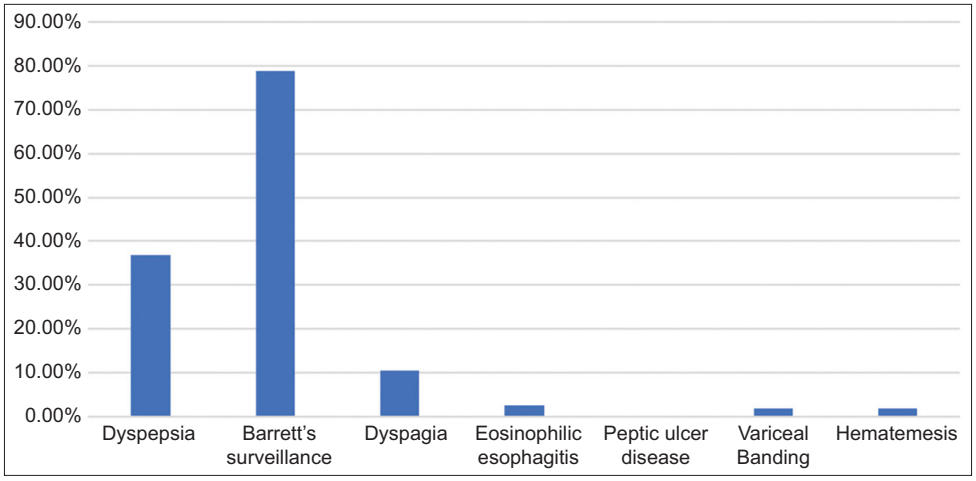

Figure 1 Indication for esophagogastroduodenoscopy

Table 2 Frequency (2×2) table comparing the patients with WATS^{3D} and FB results of BE screening

Test performed	FB+	FB-
WATS^{3D}+	62 (57.4%)	21 (19.4%)
WATS^{3D}-	2 (1.9%)	23 (21.3%)

WATS^{3D}, wide-area transepithelial sampling with 3-dimensional computer-assisted analysis; FB, 4-quadrant forceps biopsies; BE, Barrett's esophagus

There were 21 additional cases (18.6%) of incident BE detected by WATS^{3D}. The number needed to test with WATS^{3D} (to detect an additional patient with BE) was 5. Of the 21 FB- cases, WATS^{3D} identified 15 cases of goblet cell metaplasia, 4 cases of crypt dysplasia, 1 case of LGD and 1 case of EAC. There were no immediate complications reported among the patients studied.

The addition of WATS^{3D} to FB compared to FB alone demonstrated a sensitivity of 96.9% and a specificity of 52.3%. The positive likelihood ratio was 2.03 and negative likelihood ratio was 0.06.

Discussion

In this study, WATS^{3D} identified 21 cases of BE missed by FB, including 1 case of LGD and 1 case of EAC. WATS^{3D} demonstrated an 18.6% increase in detection yield compared to FB. These findings correlate with many limitations of FB. The cases missed by WATS^{3D} could have occurred because the island of BE was sampled off by FB since all patients underwent FB first followed by WATS^{3D}.

Areas of dysplasia or adenocarcinoma can be very small within the section of Barrett's esophagus and may be unevenly distributed throughout the segment of concern. In one study where the median surface area of total BE was found to be 32 cm^2, only 1.3 cm^2 contained HGD and 1.1 cm^2 contained adenocarcinoma [6]. Some areas of EAC were as small as 0.2 cm^2 and the average sample volume of standard biopsy forceps was between 4.10 and 7.33 mm^2. Harrison *et al* demonstrated that only 4-6% of the BE area is sampled when 4-quadrant biopsies are taken every 2 cm [6]. It comes as no surprise that 35% of FB are negative in patients with proven intestinal metaplasia [6]. A screening method with such impaired sensitivity hinders detection rates, and patients are found to have advanced disease at the time of diagnosis. This sampling error also has a significant impact on the subsequent recommendations for surveillance. A large percentage of EAC cases are associated with a negative screen for BE [9]. The high false negative rate of current screening techniques raises the question of how many of these cases did indeed have BE.

The rate of adherence to the Seattle protocol during surveillance for BE using FB has been shown to be low in a community setting [7]. This in turn decreases the detection yield of BE by FB. Taking 4-quadrant biopsies every 1-2 cm is time-consuming and laborious in patients with long BE segments. As the length of the BE fragment increases, the number of required biopsies increases and the rate of adherence to the screening guidelines decreases. Using WATS^{3D} could increase the detection rate, decrease the inter-operator variability and increase the efficiency of the procedure, since it does not require any biopsies. In addition, it uses a larger brush able to sample the full thickness of the epithelium and the entire circumference of the esophagus. It is designed to sample from a higher surface area, which further contributes to a higher detection rate.

Two multicenter prospective trials enrolled 1266 and 151 patients and showed a 39.5% and 42% overall increase, respectively, in the detection of BE when a computer-assisted brush biopsy was added to FB [10,11]. In a more recent prospective trial that included 160 patients, 29 cases of HGD/EAC were detected by WATS^{3D}, whereas only 7 cases were detected by FB. Among the 29 cases detected by WATS^{3D}, 23 cases were negative with FB but only 1 case detected by FB was missed by WATS^{3D} [12]. Finally, an observational cohort study that spanned 2 years and included 138 patients showed an added yield of 34.3% when WATS^{3D} was used in conjunction with FB [13].

Variation in accuracy occurs between different physicians performing the endoscopic procedures, as does variation between multiple pathologists' interpretations. False negatives can also be due to misinterpretation of the tissue's histology. Analysis of tissue samples using WATS^{3D} is performed by computer software that creates a 3-dimensional image of the specimen, filtered through thousands of images representing all known pathologic interpretations. It is capable of detecting the smallest abnormalities not noticeable to the human eye. In addition, the final diagnosis is reviewed by a pathologist for greater accuracy. One study that included 140 BE slides evaluated by 4 pathologists demonstrated a higher interobserver agreement for the diagnosis of BE using WATS^{3D} compared to FB [14].

Our study was conducted in a community setting; the results obtained reflect a real-world view influenced by intrinsic and extrinsic physician and patient characteristics. Physician-related factors include their adherence to specific protocols, their interpretation of tissues, and errors related to fatigue and burnout during EGD nearing the end of the day. Patient-related factors include difficult body anatomy and habitus complicating routine scoping, retained gastric content and difficult sedation. The outcomes of this study demonstrated that adding WATS^{3D} to FB increased the diagnostic yield and hence the quality of care to patients, even when all environmental influences were accounted for, further highlighting the effectiveness of this tool in community settings.

Risks of complications with WATS^{3D}, including bleeding and perforation, are very low, as described in the literature and from our experience [1,15]. WATS^{3D} could conceivably be more feasible in patients with a high risk of bleeding, such as those with cirrhosis or coagulopathies, although there are no studies to confirm this. Additionally, a recent study showed that sampling with WATS^{3D} in addition to FB is more cost-effective than sampling with FB alone [16].

Compared to other advanced imaging technique, WATS^{3D} seems to offer more promising results. Dye-based chromoendoscopy, which utilizes a chemical to enhance the gastrointestinal mucosal surfaces, is time-consuming and has high interobserver variability [17]. Electronic chromoendoscopy, such as NBI, which uses a narrow wavelength to improve the detection of abnormal mucosal lesions, has been shown to improve the diagnostic yield, but is also highly subject to error because it is operator-dependent [18]. Confocal laser endomicroscopy, which uses fluorescein to magnify mucosal tissues *in vivo* by 1000 times, has a high sampling error due to dye extravasation and the shallow depth of the working field; it is also expensive and time-consuming [19]. Volumetric laser endomicroscopy (VLE) uses a probe that generates high resolution cross-sectional images of the esophagus, providing a 360° circumferential view and a 3-mm deep view [19]. This technique is fast and efficient, and has been shown to have a better diagnostic yield compared to FB following the Seattle protocol [20]. However, a recent study showed that WATS^{3D} further increased the diagnostic yield when added to white light endoscopy, NBI, VLE and FB following the Seattle protocol [13].

The large number of patients and a substantially consistent protocol between physicians for obtaining and analyzing samples are some of the strengths of this study. Some of the limitations included the possible variation among the 3 gastroenterologists in sampling and the retrospective study design. Despite these limitations, this study reveals a real-world view of practice by 3 gastroenterologists, improving the generalizability of the results.

In conclusion, this study shows that WATS^{3D} in addition to traditional FB increases the yield of BE surveillance without any added complications and can be replicated across community care settings.

Summary Box

What is already known:

- Barrett's esophagus (BE) is a premalignant condition currently diagnosed using targeted 4-quadrant forceps biopsies (FB) during endoscopy
- Traditional sampling techniques using FB are prone to sampling error, have a low yield, and are time-consuming and laborious in patients with long BE segments
- Wide-area transepithelial sampling with 3-dimensional computer-assisted analysis (WATS^{3D}) utilizes a brush that samples a wide circumferential surface area and resects full-thickness transepithelial tissue samples

What the new findings are:

- Using WATS^{3D} during endoscopy decreased inter-operator variability and increased the procedure's efficiency
- Using WATS^{3D} in addition to FB increased the yield of BE during surveillance endoscopy

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