Population Screening for Barrett Esophagus: A Prospective Randomized Pilot Study

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OBJECTIVE: To assess the feasibility of unsedated transnasal endoscopy (uTNE) and video capsule endoscopy (VCE) as alternatives to sedated endoscopy (sEGD) as screening tools for Barrett esophagus (BE) and to obtain preliminary estimates of participation rates for sEGD, uTNE, and VCE when used for community BE screening in a population cohort.

PATIENTS AND METHODS: From February 1, 2009, to May 31, 2010, patients from Olmsted County, Minnesota, who were older than 50 years and had no history of known BE were randomized (stratified by age, sex, reflux symptoms noted in a validated questionnaire) into 3 groups for esophageal evaluation with sEGD, uTNE, or VCE. Participation rates and safety profiles were estimated.

RESULTS: We contacted 127 patients to recruit 20 for each procedure arm (60 total). The probability of participation was 38% (95% confidence interval [CI], 26%-51%) for sEGD, 50% (95% CI, 35%-65%) for uTNE, and 59% (95% CI, 42%-74%) for VCE. Both uTNE and VCE were well tolerated without adverse effects. BE was identified in 3 patients and esophagitis in 8.

CONCLUSION: Unsedated techniques may be acceptable, feasible, and safe alternatives to sEGD to screen for BE in the community.

Trial Registration: clinicaltrials.gov Identifier: NCT00943280

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BE = Barrett esophagus; CI = confidence interval; EAC = esophageal adenocarcinoma; sEGD = sedated endoscopy; uTNE = unsedated transnasal endoscopy; VCE = video capsule endoscopy

Barrett esophagus (BE) is a premalignant lesion detected in most patients with esophageal adenocarcinoma (EAC)¹ and is associated with an increased risk of death from EAC.^{2,3} Survival rates for EAC remain poor, with 5-year survival of 13%.⁴

Given the poor outcomes in EAC, screening and surveillance for BE have been studied. Challenges in screening include the nonavailability of widely applicable screening techniques and the absence of a paradigm defining the most appropriate population that would benefit from screening.⁵ Symptoms of gastroesophageal reflux are not accurate predictors of the risk of developing BE or EAC; 40% of patients with EAC do not report frequent symptoms of reflux.⁵⁻⁸ Finally, limitations of endoscopic surveillance temper enthusiasm for screening.⁹ Modeling studies that document cost-effectiveness of screening are based on many assumptions, some of which may be inaccurate.

However, there is evidence to support the role of screening for BE, given that most patients with EAC do not have a previous diagnosis of BE despite its presence and that only 5% of all EACs are detected during surveillance.¹⁰⁻¹² Furthermore, detection of EAC during screening and surveillance may be associated with improved survival.^{11,13} Epidemiological data continue to indicate that most cases of BE remain undiagnosed in the community.¹⁴ More recently, screening for the presence of multiple risk factors for BE has been suggested.¹⁵ Hence, a noninvasive, acceptable, and accurate method of assessing risk of BE or EAC in high-risk populations is needed.

Unsedated transnasal endoscopy (uTNE) and esophageal video capsule endoscopy (VCE) may be alternatives to sedated endoscopy (sEGD) for BE screening. The role of uTNE is supported by referral center studies in patients with BE, which demonstrate reasonable accuracy with moderate to excellent levels of agreement for uTNE compared with sEGD.¹⁶⁻¹⁸ Similarly, VCE has been shown to have reasonable accuracy in identifying BE in enriched populations.^{19,20} However, feasibility of use in the general population is unclear. Moreover, whether these techniques are feasible alternatives to sEGD and acceptable to an at-risk general adult population remains unknown. Acceptability (and feasibility of use) of any noninvasive method is of crucial importance because an accurate but poorly tolerated test would not be useful or effective in risk stratification.

Given the absence of any data on the acceptability of these techniques in the population (particularly in com-

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FIGURE. Flow diagram illustrating recruitment process needed to fulfill accrual goals for each of the 3 procedures. EGD = upper endoscopy.

parison with sEGD), we aimed to assess their feasibility and obtain preliminary estimates of participation rates for screening with sEGD, uTNE, and VCE in a population-based cohort. Secondary aims were to assess the safety profile of these techniques when used in the general population and to make a preliminary assessment of potential predictors of participation in screening.

PATIENTS AND METHODS

HISTORICAL COHORT

A series of age- and sex-stratified random samples of Olmsted County, Minnesota, residents was previously drawn using data resources of the Rochester Epidemiology Project,¹⁴ and these persons were mailed validated gastrointestinal symptom questionnaires. These population-based

surveys have allowed identification of a cohort of persons (N=2597) with information on reflux symptoms obtained using validated questionnaires.²¹⁻²³

SAMPLING, INCLUSION, AND EXCLUSION CRITERIA

This study was conducted from February 1, 2009, to May 31, 2010. The Figure summarizes flow of patients through the study.

A medical chart review of patients (N=2957) from the established Olmsted County cohort was used to identify the subset older than 50 years who had not undergone sEGD in the past 5 years (N=2152). Then patients in this subset were stratified by age, sex, and reflux symptoms (present [symptoms more than once a week] vs absent) and randomly assigned to uTNE, VCE, and sEGD groups. Within each group, patients were sorted in a random order, and

TABLE 1. **Exclusion Criteria Used for This Study**

History of known Barrett esophagus
Upper endoscopy within past 5 y
History of dysphagia
Zenker diverticulum
Epiphrenic diverticulum
Known or suspected intestinal obstruction
Cardiac pacemaker
Any implanted electromedical device
Pregnancy
Any magnetic resonance imaging examination anticipated within 7 d
Any abdominal surgery within previous 6 mo (except cholecystectomy)
History of recurrent epistaxis
No longer an Olmsted County, Minnesota, resident
Deceased
Any serious illness that may impair ability to complete a questionnaire (eg, major stroke, metastatic malignancy)
Any contraindication to esophageal biopsy, including anticoagulation with warfarin and/or clopidogrel

an initial list of 300 potential participants (100 per group) was generated to contact for recruitment to the study. Their medical records were reviewed to assess for exclusion criteria (Table 1).

Attempts to contact these eligible patients were made in the order listed for each procedure group: sEGD, uTNE, and VCE. An extra 15 patients (next 15 in the randomized list) were subsequently provided for the sEGD group. Blocks of 20 patients were used at a time for recruitment for each screening modality until the target accrual of 20 patients per completed study group was achieved. Ultimately, only 255 of the 300 eligible randomized patients were needed to achieve the recruitment goals.

All eligible patients were mailed an introductory recruitment letter (see Supporting Online Material, a link to which is provided at the end of this article), which was followed within 2 weeks by a telephone call by one of the investigators (J.Y.C.). The investigator used 1 of 3 standardized telephone scripts (see Supporting Online Material), depending on the group to which the patient had been randomized (1 script for each group). These scripts included information on the rationale and aims of the study and details on the procedure and its adverse effects. In each group, the order for contacting patients was randomized. Patients who declined participation or could not be reached by telephone after 3 attempts were not further contacted. Patients who agreed to participate were contacted by the study coordinator to be scheduled

for the procedure and were mailed the full consent form for the technique to which they had been randomized.

Participants were seen at the General Clinical Research Center at Mayo Clinic. After completing the gastroesophageal reflux symptom questionnaire, they had anthropometric measurements taken and then underwent the method of esophageal screening based on their assigned group from randomization.

ENDOSCOPIC METHODS

Conventional Sedated Endoscopy. Patients randomized to this group underwent sEGD using a video endoscope (PENTAX Medical Company, Montvale, NJ) and titrated intravenous sedation. The squamocolumnar junction, gastroesophageal junction (top of the gastric folds with the stomach deflated), and diaphragmatic hiatus were identified and measured (as the distance from the incisors). A hiatal hernia was defined as the distance between the gastroesophageal junction and the diaphragmatic hiatus. Endoscopically suspected BE was defined as the endoscopic presence of 1 cm or more of columnar-lined distal esophagus above the gastroesophageal junction (either circumferential or in tongues).²⁴

Unsedated Transnasal Endoscopy. After application of local anesthetic into one of the nostrils and the pharynx with the patient in the left lateral position, an endoscope (EG-530N [5.9-mm outer diameter], Fujinon, Europe) was advanced through the anesthetized nostril into the proximal esophagus under direct visualization.¹⁶ The esophagus was assessed as described for sEGD. After the procedure, patients completed an endoscopy tolerability questionnaire.²⁵

Esophageal Capsule Endoscopy. The previously described simplified ingestion procedure for VCE was followed for the group in this study.²⁶ An esophageal capsule (PillCam ESO 2, Given Imaging, Fujinon, Wayne, NJ) was used for all procedures. Esophageal transit times were calculated, adequacy of visualization was graded, and images of the gastroesophageal junction were captured. Suspected BE was classified as ZAP grade 2 or 3.²⁴ Patients with findings suggestive of BE or another significant pathologic condition were offered sEGD.

SAMPLE SIZE ESTIMATION

In an inverse sampling design, the number of patients needed to undergo each type of procedure, fixed in advance (ie, 20 “index subjects” per procedure type in this study, which was selected on the basis of budget constraints), and the number of patients that needed to be contacted for each type of procedure are the random variables. The power to detect differences in participation probabilities between pairs of groups can be estimated on the basis of a conditional exact

test.²⁷ With 20 index patients required per group, this study had approximately 75% to 88% power to detect a doubling in the participation probabilities (eg, .10 vs .20, or .20 vs .30, or .30 vs .60), using a one-sided α level of 0.05 (see Table 1 in reference 27).

STATISTICAL ANALYSES

Potential selection biases associated with the ability to contact eligible patients, and separately with the willingness to follow through with the assigned procedure, were checked using logistic regression models for several a priori chosen variables (including group assignment).

The probability for following through on undergoing the randomly assigned procedure was estimated on the basis of the negative binomial distribution (ie, based on the inverse sampling method for the number needed to contact to obtain 20 patients in each group participating in their assigned procedure). Maximum likelihood estimates (ie, estimates of the probability of participation that maximize the chances of observing the number of patients that actually needed to be contacted) were calculated separately for each group and a test for group differences was assessed using PROC GENMOD in the SAS software package (version 9.2, SAS Institute, Cary, NC), assuming a negative binomial distribution and log link function.

Logistic regression was also used to assess the overall association of participation in screening with the a priori chosen variables (including group assignment).

RESULTS

Of 255 randomized patients, 185 were eligible for this study (Figure). Baseline characteristics of these eligible patients are shown in Table 2. No significant association of procedure group assignment with any of the characteristics was detected. Of the 185 eligible patients, 127 were successfully contacted. Only age was associated ($P<.001$) with success in contacting patients for participation in the study; the odds for successful contact increased with age. Baseline characteristics of the contacted patients are summarized in Table 3. Again, no significant associations with assigned group were detected ($P>.1$).

The maximum likelihood estimates for the probability of participation were 38% (95% confidence interval [CI], 26%-51%) for sEGD, 50% (95% CI, 35%-65%) for uTNE, and 59% (95% CI, 42%-74%) for VCE. The differences between groups were not statistically significant.

Endoscopic findings for each group are summarized in Table 4. All cases of BE were short-segment (C0M1-2) and had no dysplasia. Of patients with esophagitis, 5 had Los Angeles Classification (LA) grade A, 3 had LA grade B,

TABLE 2. Baseline Characteristics of Eligible Patients in 3 Study Arms (N=185)

Baseline variable	uTNE (n=52)	VCE (n=52)	sEGD (n=81)
Age (y), mean $\pm$ SEM	60 $\pm$ 1.3	60 $\pm$ 1.4	60 $\pm$ 1.2
Male sex	25 (48.1)	26 (50.0)	38 (46.9)
Education			
Less than high school	0	1 (1.9)	2 (2.5)
High school or some college	24 (46.2)	30 (57.7)	39 (48.1)
College/professional training	22 (42.3)	15 (28.8)	22 (27.2)
Reflux symptoms			
Heartburn	15 (28.8)	15 (28.8)	28 (34.6)
Acid regurgitation	9 (17.3)	6 (11.5)	10 (12.4)
Prior history of colonoscopy	16 (30.8)	15 (28.8)	19 (23.5)
Prior history of sEGD	11 (21.2)	7 (13.5)	15 (18.5)
SSC, mean $\pm$ SEM	0.7 $\pm$ 0.07	0.6 $\pm$ 0.07	0.6 $\pm$ 0.05
Charlson comorbidity score, mean $\pm$ SEM	0.6 $\pm$ 0.2	0.5 $\pm$ 0.2	1.0 $\pm$ 0.2

Data are presented as number (percentage) unless otherwise indicated. sEGD = sedated endoscopy; SSC = somatic symptom checklist; uTNE = unsedated transnasal endoscopy; VCE = video capsule endoscopy.

and 1 had LA grade C esophagitis.²⁸ Three patients who underwent VCE were offered subsequent sEGD, 2 because of suspicion of BE and 1 because of a possible erythematous nodule; all had unremarkable findings on subsequent sEGD. All procedures were well tolerated, and no complications were reported either immediately after the procedure or during the follow-up period (7 days).

Tolerability of uTNE based on responses to the endoscopy tolerability questionnaire was good, with median (range) scores as follows: pain during procedure, 1.0 (0-5); feel as if choking, 0 (0-7); experienced gagging, 0.5 (0-9); anxiety during procedure, 1.5 (0-7); and overall tolerability, 3.5 (0-9). Of patients who underwent uTNE, 89% re-

TABLE 3. Baseline Characteristics of Patients Contacted to Request Participation in 1 of 3 Study Arms (N=127)

Baseline variable	uTNE (n=40)	VCE (n=34)	sEGD (n=53)
Age (y), mean $\pm$ SEM	61 $\pm$ 1.5	64 $\pm$ 1.5	62 $\pm$ 1.4
Male sex	21 (52.5)	17 (50.0)	21 (39.6)
Education			
Less than high school	0	1 (2.9)	2 (3.8)
High school or some college	19 (47.5)	21 (61.8)	26 (49.1)
College/professional training	17 (42.5)	9 (26.5)	12 (22.6)
Reflux symptoms			
Heartburn	10 (25.0)	12 (35.3)	20 (37.7)
Acid regurgitation	6 (15.0)	6 (17.6)	9 (17.0)
Prior history of colonoscopy	14 (35.0)	11 (32.4)	13 (24.5)
Prior history of sEGD	10 (25.0)	5 (14.7)	23 (43.4)
SSC, mean $\pm$ SEM	0.7 $\pm$ 0.07	0.6 $\pm$ 0.08	0.6 $\pm$ 0.07
Charlson comorbidity score, mean $\pm$ SEM	1.8 $\pm$ 0.3	0.7 $\pm$ 0.2	1.2 $\pm$ 0.3

Data are presented as number (percentage) unless otherwise indicated. sEGD = sedated endoscopy; SSC = somatic symptom checklist; uTNE = unsedated transnasal endoscopy; VCE = video capsule endoscopy.

TABLE 4. Endoscopic Findings in Patients Undergoing Esophageal Evaluation in 3 Study Arms^a

Finding	uTNE (n=19) ^b	VCE (n=17) ^c	sEGD (n=20)
Normal GE junction	11 (58)	17 (100)	9 (45)
Erosive esophagitis ^d	4 (21)	0	5 (25)
Barrett esophagus	1 (5)	0	2 (10)
Hiatal hernia	14 (74)	...	15 (75)

^a Data are presented as number (percentage). GE = gastroesophageal; sEGD = sedated endoscopy; uTNE = unsedated transnasal endoscopy; VCE = video capsule endoscopy.

^b One uTNE could not be completed because of nasal turbinate hypertrophy.

^c Three capsule studies were incomplete because of inability to swallow the capsule (1), recorder malfunction (1), and nonvisualization of the GE junction (1). Three patients underwent follow-up sEGD for suspicion of BE; results of examination and biopsy were normal.

^d Five patients had Los Angeles Classification (LA) grade A, 3 had LA grade B, and 1 had LA grade C esophagitis.

ported that they would be willing to undergo the procedure again for screening.

A number of a priori selected variables were assessed as predictors of following through on participation. Findings are summarized in Table 5. Sex was modestly associ-

ated with participation, with men having increased odds of participation. Other variables (such as presence of reflux symptoms, prior history of undergoing endoscopy or colonoscopy, education status) were not significant predictors of participation.

DISCUSSION

In this population-based, prospective, randomized pilot study, we have demonstrated the feasibility of population screening for BE. Unsedated techniques (uTNE and VCE) appeared to have greater numerical acceptability in the population than sEGD, although this difference was not statistically significant. These alternative screening methods were well tolerated in this pilot study.

The goals of this study were to demonstrate feasibility of population-based screening for BE and to obtain preliminary estimates of participation rates for noninvasive screening techniques (uTNE, VCE) in comparison with sEGD so that sample size for a larger study could be obtained. We chose this study design as opposed to one in which all 3 techniques would be offered to every patient

TABLE 5. Multiple Variable Logistic Regression Model for Predicting Study Participation (60 Eligible Participants Undergoing the Procedure vs 67 Eligible Nonparticipants)^a

Variable	No. (%) participating	OR ^b (95% CI)	P value ^b
Age		0.99 ^c (0.94-1.04)	.68
Less than median (n=56)	26 (46)		
Greater than or equal to median (n=71)	34 (48)		
Sex			
Male (n=59)	33 (56)	2.55 (0.99-6.53)	.05
Female (n=68)	27 (40)	1.0 (ref)	
Education			
Less than high school (n=3)	1 (33)	0.71 (0.03-17.11)	.83
High school or some college (n=66)	36 (55)	1.0 (ref)	
College/professional training (n=38)	16 (42)	0.52 (0.20-1.38)	.19
Reflux symptoms			
Heartburn (n=42)	24 (57)	1.72 (0.50-5.94)	.39
No heartburn (n=85)	36 (42)	1.0 (ref)	
Acid regurgitation (n=21)	12 (57)	1.16 (0.26-5.14)	.84
No acid regurgitation (n=106)	48 (45)	1.0 (ref)	
History of colonoscopy (n=38)	22 (58)	1.80 (0.70-4.67)	.23
No history of colonoscopy (n=89)	38 (43)	1.0 (ref)	
History of sEGD (n=27)	15 (56)	1.08 (0.36-3.22)	.89
No history of sEGD (n=100)	45 (45)	1.0 (ref)	
SSC score		1.06 ^d (0.40-2.86)	.90
Less than median (n=60)	25 (42)		
Greater than or equal to median (n=61)	33 (54)		
Charlson comorbidity index		0.91 ^e (0.69-1.19)	.47
0 (n=81)	39 (48)		
≥1 (n=40)	21 (53)		

^a CI = confidence interval; OR = odds ratio; sEGD = sedated endoscopy; SSC = somatic symptom checklist.

^b Multiple variable model.

^c Per year of age.

^d Per unit score.

^e Per unit of the index.

(with the patient choosing which would be most acceptable) so that we could obtain estimates of participation for each of the 3 techniques (and compare the rates with those for sEGD), in addition to testing their tolerability, safety, and yield, which would be difficult to obtain from an alternative study design. We used a previously created population-based cohort (with data on age, sex, and reflux symptoms) to draw samples for this study because this allowed us to draw samples that were balanced in terms of demographic characteristics and reflux symptoms, in addition to enabling us to offer screening to patients with and without reflux symptoms.

Unsedated techniques could be more cost-effective as screening tools, given the direct and indirect costs of sEGD. A modeling study that assessed the costs of screening patients with uTNE found this approach to be cost-effective.²⁹ However, that study assumed a 95% acceptability rate, which may be an overestimate and underscores the need for collecting real data before valid conclusions can be drawn.

Although initial studies suggested that esophageal capsule endoscopy can identify BE in patients accurately,¹⁹ subsequent studies have shown lower accuracy³⁰ and the lack of cost-effectiveness,³¹ resulting in a consensus that it cannot be recommended for BE screening at this time. In 1 of the 17 patients completing VCE in the current study, the procedure was nondiagnostic because of nonvisualization of the gastroesophageal junction; 3 patients required follow-up endoscopy to reassess the gastroesophageal junction because of potential abnormalities seen on the capsule study. Results of all 3 endoscopic examinations were unremarkable. This further highlights the limitations of VCE in terms of accuracy at this time.

A recent study from Europe³² analyzed the ability of a capsule sponge device to provide cytologic specimens to detect biomarkers for BE. The sensitivity of this technique was 78%, leading to a false-negative rate of 22%, which could lead to a substantial number of false-negatives in a large population. Furthermore, confirmation would be required in a population with low BE prevalence and an endoscopic test would be required after a positive test, making downstream costs a concern. However, nonendoscopic techniques, if accurate, offer the potential of widespread applicability, allowing risk stratification of the population risk for EAC.³³

One of the limitations of the current study is the small sample size, potentially leading to type II error. This study was performed to demonstrate the feasibility of conducting a randomized population-based study, determine initial safety, and obtain preliminary estimates of participation rates to determine the sample size for a definitive larger-scale study. Although response bias is a possibility because the cohort consisted of responders to previous question-

naires, this is unlikely because of the lack of difference between responders and nonresponders that is now well documented in this population.³⁴

CONCLUSION

In this population-based, prospective, randomized pilot study, both uTNE and VCE appear to be feasible and acceptable screening methods for BE in the population when compared with sEGD. Larger studies are needed to confirm these findings, assess true costs, and identify high-risk populations.

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Supporting Online Material

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