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UTILITY AND COST-EFFECTIVENESS OF A NON-ENDOSCOPIC APPROACH TO BARRETT'S ESOPHAGUS SURVEILLANCE AFTER ENDOSCOPIC THERAPY

Short Title: Cytosponge efficacy in Barrett's surveillance

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Abbreviations: AUC: area under the curve; BE: Barrett's esophagus; CE: columnar epithelium; CEIM: complete eradication of intestinal metaplasia; CED: complete eradication of dysplasia; Confidence interval: CI; EAC: esophageal adenocarcinoma; EET: endoscopic eradication therapy; EMR: endoscopic mucosal resection; HGD: high-grade dysplasia; ICER: incremental cost-effectiveness ratio; IM: intestinal metaplasia; IMC: intramucosal adenocarcinoma; LGD: low-grade dysplasia; miRNAs: micro RNAs; NDBE: non-dysplastic Barrett's esophagus; OR: odds ratio; RFA: radiofrequency ablation; Randomized controlled trial (RCT); ROC: receiver operator characteristic; QUALYs: quality adjusted life years

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ABSTRACT

Background & Aims: A non-endoscopic approach to Barrett's esophagus (BE) surveillance after radiofrequency ablation (RFA) would offer a less invasive method for monitoring. We assessed the test characteristics and cost-effectiveness of the Cytosponge® in post-RFA patients.

Methods: We performed a multicenter study of dysplastic BE patients after at least one round of RFA. A positive Cytosponge® before endoscopy was defined as intestinal metaplasia (IM) on cytological assessment and/or TFF3 immunohistochemistry. Sensitivity, specificity, and receiver operator characteristic (ROC) curves were calculated. Multivariable regression was used to estimate the odds of a positive Cytosponge® in BE. A microsimulation cost-effectiveness model was performed to assess outcomes of various surveillance strategies: endoscopy-only, Cytosponge®-only, and alternating endoscopy/Cytosponge®.

Results: Of 234 patients, Cytosponge® adequately sampled the distal esophagus in 175 (75%). Of the 142 with both endoscopic and histologic data, 19 (13%) had residual/recurrent BE. For detecting any residual Barrett's, Cytosponge® had a sensitivity of 74%, specificity of 85%, accuracy of 84%, and ROC curve showed an area under the curve of 0.74. The adjusted odds of a positive Cytosponge® in BE were 17.1 (95% CI: 5.2-55.9). Cytosponge®-only surveillance dominated all the surveillance strategies, being both less costly and more effective. Cytosponge®-only surveillance required <1/4th the endoscopies, resulting in only 0.69 additional EAC cases/1,000 patients, and no increase in EAC deaths when compared to currently-practiced endoscopy-only surveillance.

Conclusions: A positive Cytosponge® test was strongly associated with residual BE after ablation. While the assay needs further refinement in this context, it could serve as a cost-effective surveillance examination.

Key words: Barrett's esophagus; dysplasia surveillance; Cytosponge; cost-effectiveness

INTRODUCTION

Current guidelines[1, 2] recommend endoscopic eradication therapy (EET) for patients with dysplastic Barrett's esophagus (BE) or early stage esophageal adenocarcinoma (EAC), which is effective in achieving complete eradication of intestinal metaplasia (CEIM).[3-5] Following CEIM, patients undergo lifelong endoscopic surveillance exams due to the risk of recurrent disease.[3, 6] Surveillance intervals are determined by the baseline degree of dysplasia and occur at an increased frequency in the first two years following CEIM, then annually thereafter.[1] Over the course of the first 2 years alone after CEIM, a patient with high-grade dysplasia (HGD) is recommended to undergo 6 surveillance endoscopies.[1]

These endoscopic surveillance exams can induce anxiety and discomfort for patients and are associated with significant costs, resource use, and some procedure-related risks. Given the number of necessary surveillance exams following CEIM, an alternative, more cost-effective, and less invasive surveillance technique to detect residual or recurrent BE would be of great utility. One candidate method for these surveillance exams is a minimally-invasive esophageal sampling device, the Cytosponge®, which can be coupled to biomarker assays. The Cytosponge® is a sponge sampling device that is enclosed in a tablet-sized, gelatin capsule. The gelatin capsule dissolves in the stomach, allowing the sponge to expand before being withdrawn using an attached thread. As the sponge is retracted, it samples the mucosa of the GEJ and the esophagus. Previous studies have shown the Cytosponge® to be a well-tolerated and safe method for BE screening. When combined with a biomarker TFF3 to detect goblet cells, it has a sensitivity of 94%, after excluding inadequate samples in which the device did not

reach the stomach. The specificity of 92% [7, 8] for detection of intestinal metaplasia (IM) in BE patients was maintained in a screening population in a large randomised controlled trial (RCT).[9]

To date, the performance of the Cytosponge® to detect recurrent or residual BE after ablation has not been studied. Given the substantial potential difference in cost and ease of use between endoscopic and Cytosponge® sampling, a Cytosponge®-based surveillance paradigm offers the potential for cost-effective long-term post-treatment monitoring. Specific evaluation of the test performance in a post-ablation setting is required, since radiofrequency ablation (RFA) may alter esophageal motility and passage of the capsule into the stomach, and the cell collection of neo-squamous epithelium and recurrent BE may be different.[10] Therefore, the aims of this study were to determine the test characteristics and cost-effectiveness of the Cytosponge® to detect residual or recurrent BE after EET.

MATERIALS AND METHODS

Study Design, Setting, and Population

This was a prospective study conducted at four tertiary care referral centers in the United Kingdom and one tertiary care referral center in the United States. Eligible patients were adults (≥18 years) with dysplastic BE (low-grade dysplasia (LGD), HGD or intramucosal adenocarcinoma (IMC), confirmed by a second expert gastrointestinal pathologist, who had undergone at least one round of EET and were scheduled for further ablative therapy or endoscopic surveillance after CEIM. EET consisted of endoscopic mucosal resection (EMR) of any nodular areas followed by RFA. Given the high efficacy of EET at these centers, only including patients who

have completed treatment would leave only 5-8% with residual disease. While it would be most desirable to perform a study only on post-CEIM patients, the size of this study would be prohibitive to allow definition of the operating characteristics of the Cytosponge® in this setting.

Study Procedures

Cytosponge® was administered prior to endoscopy by trained research personnel. The capsule was ingested with ~50 ml of water. After a 7-minute period, to allow dissolution of the gelatin capsule and release of the Cytosponge® in the proximal stomach, the sponge was withdrawn using the attached string, sampling the esophageal lining from the stomach to the mouth. After the Cytosponge® was withdrawn, the string was cut, and the sponge was stored in BD SurePath liquid fixative at 4°C.

Cytosponge® sample processing was undertaken in Cambridge, UK as described previously.[8] Briefly, the cells were dissociated from the sponge by gentle agitation, and then the solution was centrifuged into a clot preparation, fixed in formalin, and stained with hematoxylin and eosin. Representative sections were examined by a specialist histopathologist (MO'D) who was blinded to the endoscopic findings. H&E combined with immunohistochemical assessment of TFF3 was performed to improve identification of IM from the cytological sample to help distinguish pseudo-goblet cells and respiratory epithelium.[11, 12] The presence of columnar epithelium (CE) is a quality control metric to assess if Cytosponge® reached the stomach. A sample was considered adequate if at least one gland group of columnar mucosa was present. A positive Cytosponge® was defined as the

presence of one or more goblet cells in a gastrointestinal-type columnar cell group on the H&E and/or TFF3 slide.

All patients underwent upper endoscopy approximately 2 hours after Cytosponge® administration to reduce risk of aspiration after ingesting 50 ml of water. Biopsies were obtained from BE segments in those with residual BE undergoing further endoscopic treatment, and from the cardia, GEJ and neosquamous esophagus in post-CEIM patients. A subset of patients (n=33) undergoing ablation, but had not achieved CEIM, only had endoscopic evidence of CE documented, without concurrent biopsies, due to the endoscopist's concern of biopsies interfering with ablation.

Definitions

For this study, the presence of BE was defined per guidelines[1] as CE of ≥1cm in the tubular esophagus, with concurrent IM on biopsies or EMR specimens of that area. Short segment BE was defined as <3cm of esophageal columnar mucosa and long segment BE as ≥3 cm.

Statistical Analysis

We calculated operating characteristics for the Cytosponge® as a diagnostic test for BE, including sensitivity, specificity, and positive and negative predictive value. Receiver operator characteristic (ROC) curves were created to assess the diagnostic utility of the Cytosponge®. Multivariable logistic regression adjusting for

age and sex was used to estimate the odds of a positive Cytosponge® test in those with and without residual BE.

Sensitivity Analysis

In an additional sensitivity analysis, subjects with endoscopic data without biopsies were added to those in the primary analysis. Those with ≥1cm of endoscopic CE without biopsies (because they were to undergo ablation at the same exam) were categorized as BE cases (n=19). Subjects with <1 cm CE or no CE without biopsies (n=14) were categorized as controls. All of the above statistical analyses were performed using STATA 13.

Cost-Effectiveness Analysis

We ran 1,000,000 hypothetical male patients through a microsimulation model to assess outcomes of four different BE/EAC surveillance strategies. The microsimulation surveillance model was an extension of a validated natural history model of EAC, calibrated to incidence and mortality data from the Surveillance, Epidemiology, and End Results (SEER 9) registry.[13, 14] Modelled patients were male, aged 68, and assumed to have achieved CEIM after RFA treatment for dysplastic BE. LGD patients received annual surveillance in the first two years after RFA, and every 3 years thereafter.[15] HGD patients received surveillance every 3 months in the first year after RFA, every 6 months in the second year, and every year thereafter.[1] We varied surveillance type at each interval. The following strategies were analyzed: 1) endoscopy-only surveillance; 2) alternating Cytosponge® and endoscopy at each

surveillance; 3) endoscopy every third surveillance; and 4) Cytosponge®-only surveillance. We assumed 100% adherence to endoscopy and Cytosponge® surveillance. Post-treatment surveillance continued through age 80. Patients still alive after age 80 entered natural history until death or age 100. We used a natural history comparator with no post-treatment surveillance.

Supplementary Table 1 contains all model inputs. We assumed no disutility for Cytosponge® surveillance. At each surveillance interval, the patient was tested for recurrence with either endoscopy or Cytosponge® based on the strategies above. Probabilities of misdiagnosis by endoscopy were obtained from prior literature[6] (Supplementary Table 2). Cytosponge® false positive and false negative rates were obtained from the current study. A one-way sensitivity analysis was performed addressing the uncertainty in the performance characteristics of the Cytosponge® using a sensitivity and specificity of 50% as a lower threshold or 100% as a higher threshold for both. We assumed that the same Cytosponge® false negative rate for non-dysplastic BE (NDBE), LGD, HGD, and EAC. If test results were negative, patients would receive no further treatment or surveillance until the next interval. Patients received a confirmation endoscopy two months after a positive Cytosponge®. Touch-up RFA treatment performed at the same session as a positive endoscopy result, reset the surveillance schedule. A patient could receive a maximum of three RFA touch-ups.

RESULTS

Of 234 patients, 175 (75%) had an adequate Cytosponge® sample. Of the 175 patients with adequate sponge samples, mean age was 71 ± 9 years, 83% were men, and median time from first ablation was 20 months (Table 1). On endoscopy, 65% (n=114) had no CE, 25% (n=43) had short segments, and 10% (n=18) had long segments of CE. Among those with an inadequate sponge sample, 92% (n=54) had either no BE (n=36) or short segment BE (n=18). There was some variability amongst the four centers in the proportion of patients with an inadequate sample (Supplementary Table 3). There were no differences between the groups with and without an adequate Cytosponge® sample, (Table 1).

The 175 patients with an adequate Cytosponge® sample were included in the primary analysis, among whom 142 (81%) had both endoscopic and histologic data available (Figure 1). Among the 142 subjects, 87% (n=123) were categorized as non-BE controls and 13% (n=19) as BE cases. The remaining 33 of the 175 patients had endoscopic CE but did not have biopsies performed (7 had no CE on endoscopy, 8 had long segment CE and 18 had short segment CE). These 33 subjects with unknown histology were excluded in the primary analysis.

The Cytosponge® test was positive in 74% (n=14) of BE cases vs. 15% (n=18) without BE, p<0.01 (Table 2). The Cytosponge® test was negative in 85% (n=105) of those without BE vs. 26% (n=5) with BE. The Cytosponge® assay had a sensitivity of 74% (95% confidence interval (CI): 49%,91%), specificity of 85% (95% CI: 78%,91%) for BE detection, and overall accuracy of 84% (95% CI: 77%,89%). The ROC curve showed an area under the curve (AUC) of 0.74 (Figure 2).

Of the 5 BE cases that Cytosponge® did not detect, 4 had long segment BE (mean segment length [range]: 7.8 [4-11] cm) and 1 had short segment BE. None of

these 5 cases had atypia on the sponge or dysplasia on biopsy. Of the BE cases Cytosponge® accurately detected, none had dysplasia on biopsies and 4 had atypia on the sponge. Of the 18 patients (15%) who had a positive Cytosponge and no BE, 28% (n=5) had <1cm endoscopic CE that did not meet criteria for the diagnosis of BE, and 17% (n=3) had an endoscopically normal esophagus with concurrent cardia biopsies showing IM. For the remainder 55% (n=10), the etiology of the false positive result was obscure. In multivariable logistic regression, the adjusted odds of a positive Cytosponge® in BE cases were markedly higher compared to those without BE (OR: 17.1; 95% CI: 5.2, 55.9).

When using a definition of BE which included patients with endoscopic CE of *any length* with concurrent biopsies showing IM, the sensitivity of Cytosponge® was lower at 63%, specificity was 87%, accuracy was 82%, and ROC showed an AUC of 0.75 (Supplementary Figure 1).

Sensitivity Analysis

In this sample of 175 subjects (36 BE cases and 139 controls), Cytosponge® was positive in 69% (n=36) of BE cases vs. 16% (n=22) of controls. Cytosponge® was negative in 84% (n=117) of controls vs. 31% (n=11) of BE cases, p<0.01 for both. The assay had a sensitivity of 69%, specificity of 84% and accuracy of 81% for BE detection. AUC for ROC curve was 0.75 (Supplementary Figure 2).

Cost-Effectiveness Analysis Model

Figure 3 depicts EAC incidence and mortality from each post-CEIM surveillance strategy. As expected, post-treatment surveillance substantially decreased EAC incidence and mortality. However, differences among the four post-treatment surveillance strategies were very small in terms of EAC incidence and mortality. The Cytosponge®-only strategy led to only 0.69 additional EAC cases and no increase in EAC deaths per 1000 patients compared to the endoscopy-only strategy. Importantly, the endoscopy-only strategy required more than four times as much endoscopy per surveyed person when compared to the Cytosponge®-only strategy (5,974 vs 1,442 per thousand patients surveyed).

As there were only marginal differences in EAC incidence and mortality, there were also very marginal differences in quality adjusted life years (QALYs) among the post-treatment surveillance strategies (Figure 4). The endoscopy-only surveillance strategy resulted in 11,839 QALYs/1,000 patients and the Cytosponge®-only strategy with 11,844 QALYs/1,000 patients surveyed. The QALYs of the other two mixed modality surveillance strategies fell in between. Therefore, the increased costs and disutilities associated with endoscopy drove the results (Table 3). The Cytosponge®-only strategy resulted in the lowest cost and highest QALYs among the post-treatment surveillance strategies (Figure 4), and therefore dominated all of the other surveillance strategies. The Cytosponge®-only strategy resulted in an incremental cost-effectiveness ratio (ICER) of $13,259/QALY compared to no surveillance.

In the sensitivity analysis, even at operating characteristics well below the worst reported in the literature, a Cytosponge®-only strategy remained dominant. At 50% sensitivity and specificity, the Cytosponge®- only strategy remained the most cost-effective, but resulted in an increased EAC incidence of 27.66 and increased

EAC-associated mortality of 9.73 per 1000 patients. Costs increased and QUALYs decreased to 11,842 QALYs/1,000 patients, which increased the ICER to $22,036. At 100% sensitivity and specificity, the results changed similarly in the opposite direction with a decreased EAC incidence of 24.92 and mortality of 8.88, and the ICER decreased to $9,696.

DISCUSSION

Currently, there are no clinically reliable non-endoscopic methods of disease surveillance in the post-treatment BE population, obligating such patients to the costs, inconvenience, and risks of recurrent endoscopy. In this multicenter prospective study of BE patients who have undergone at least one round of EET, the Cytosponge® assay was able to detect residual BE in the tubular esophagus with a sensitivity of 74% and specificity of 85%. The ROC curve showed an AUC of 0.74. When compared to the current practice of post-ablation endoscopic surveillance, the Cytosponge®-only surveillance strategy resulted in a negligible increase of EAC cases and no increase in EAC-associated mortality, while being more cost-effective.

The lower sensitivity of the Cytosponge® than previously reported[8] in an untreated population with >50% with long segment BE is perhaps not surprising in a post-treatment group, given the smaller area of mucosa harboring BE. This can decrease the chance that the sponge would successfully sample goblet cells, and it is also possible that cell shedding rates of residual IM differ from neo-squamous cells. Recurrent or residual BE in post-treatment patients is typically small islands or short segments, which can be easily missed even on endoscopy. Therefore, the sensitivity of the assay at 74% in this study, while lower than that in treatment naïve

patients, is promising to detect BE in post-ablation patients. The specificity is also lower than previously reported in BE screening studies using Cytosponge®,[8, 16, 17] and may reflect focal cardia IM, or minute islands of CE identified on the sponge but not on biopsies due to sampling error; although, we are unable to demonstrate this with the current study.

The cost-utility analysis showed that a Cytosponge®-only surveillance strategy was preferred over strategies incorporating endoscopy, dominating the endoscopy-only as well as the alternating endoscopy-Cytosponge® strategies. Even though Cytosponge® failed to detect about a quarter of patients with BE, the relatively benign outcome associated with these lesions, combined with the recurrent applications of surveillance exams (allowing for subsequent detection), resulted in very small increases in cancer incidence and death in the Cytosponge®-only arm, compared to large increases in cost and disutility in the strategies incorporating endoscopy. On the other hand, the endoscopy-only strategy utilized over 4 times as much endoscopy. Given the costs and inconvenience of endoscopy, as well as the trivial changes in clinical outcomes between the strategies, Cytosponge®-only was the preferred approach.

There is potential for further optimization of Cytosponge® with use of adjunct biomarkers to improve the test sensitivity in post-CEIM surveillance. Expression of microRNAs (miRNAs) when combined with TFF3 have been shown to improve the testing characteristics of Cytosponge® in differentiating between BE cases and controls with an AUC of 0.93, 93% sensitivity, and 94% specificity.[18] Therefore, identifying miRNA expression profiles in post-ablation esophageal tissue may offer an adjunctive biomarker to increase the diagnostic accuracy of Cytosponge®.

Additionally, methylation panels used in conjunction with Cytosponge® have also shown to have some promise for detection of BE.[19] One viable strategy might be to combine these markers with standard histology to improve the sensitivity of the assay in post-ablation patients, given their small burden of disease.

This study has multiple strengths. It is the first study to assess both the testing characteristics and cost-effectiveness of Cytosponge® in a post-treatment BE population. The study was prospectively conducted at multiple centers making the results more generalizable and used standardized data collection protocols. The approach it assesses, if adopted, may allow for reallocation of scarce healthcare resources without diminishing patient outcomes.

This study has limitations. First, 34% (n=59) of the subjects had an inadequate Cytosponge® sample, but given that many patients come from long distances, we did not repeat the Cytosponge® in these subjects. The higher proportion of inadequate sponges that previously reported,[17] might be especially common in this post-ablation group, who tend to have substantial hiatal hernias, diminished lower esophageal sphincter tone, and possibly some altered motility. Since a majority had no residual disease, it is likely that these “inadequate” sponges never came into contact with columnar mucosa. However, other explanations for suboptimal sampling include administration techniques, despite standardized training sessions for personnel administering Cytosponge®, as 67% of the inadequate samples were from two centers. Second, the Cytosponge® was less sensitive for detecting miniscule islands of residual IM. While the clinical significance of minute islands of IM after RFA is unclear, it is a common clinical practice to eradicate them. Finally, for the cost-effectiveness analysis we assumed 100% adherence to both

endoscopy and Cytosponge® which, while likely not reflective of real-world adherence, can be considered appropriate for this initial study. Further work using real world data on adherence to Cytosponge surveillance programs can be used when available.

In summary, Cytosponge® was able to detect residual BE, often minute in amount, in patients who have undergone EET, with promising test characteristics. Comparative modelling of endoscopy and Cytosponge® based surveillance strategies showed that a Cytosponge®-only surveillance method was cost-effective, with only a negligible increase in EAC incidence and no increase in associated mortality, when compared to endoscopy-based surveillance. While further optimization would be desirable to improve the testing characteristics before using this assay as a surveillance tool, the ability of Cytosponge® to detect BE in the post-treatment population holds promise for it as either an adjunct tool or as a stand-alone method for post-EET surveillance. In the interim, the potential utility of the assay in a paradigm including Cytosponge® alternating with endoscopy deserves further consideration.

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FIGURE LEGENDS

Figure 1: Study flow diagram

Figure 2: ROC curve for Cytosponge® Assay for Detection of Barrett's esophagus after Endoscopic Eradication Therapy

Figure 3: Incidence and Mortality of Esophageal Adenocarcinoma (EAC) among all tested surveillance strategies after Endoscopic Eradication Therapy (EET)

Figure 4: Cost/benefit curves for the four post-CEIM surveillance strategies: endoscopy-only, alternating Cytosponge® and endoscopy at each surveillance interval, endoscopy every third surveillance, and Cytosponge®-only surveillance. All numbers are reported per 1000 patients.

Table 1: Sample Characteristics

	Patients with adequate sponge sample (n=175)	Patients with inadequate sponge sample (59)	p
Age, mean±SD	70.9±8.7	68.8±8.5	0.12
Male, n(%)	146 (83)	51 (86)	0.58
BE length on endoscopy, n(%)			0.55
None	114 (65)	36 (61)	
Short (<3cm)	43 (25)	18 (31)	
Long (≥3cm)	18 (10)	5 (8)	
Intestinal metaplasia on biopsy*, n(%)	33 (23)	14 (30)	0.37
History of EMR, n(%)	114 (65)	36 (61)	0.57
Months since first ablation, median (IQR)	20 (2-113)	22 (2-166)	0.73
Months since last ablation, median (IQR)	10 (1-111)	10 (2-88)	0.74

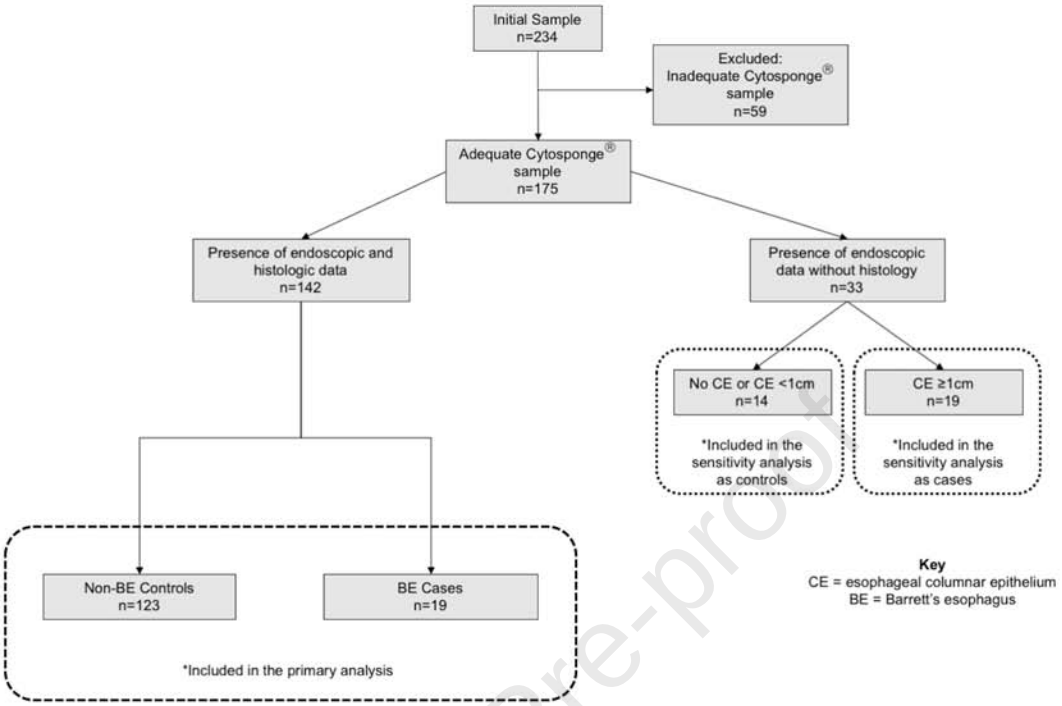
* Of the 142 with biopsies

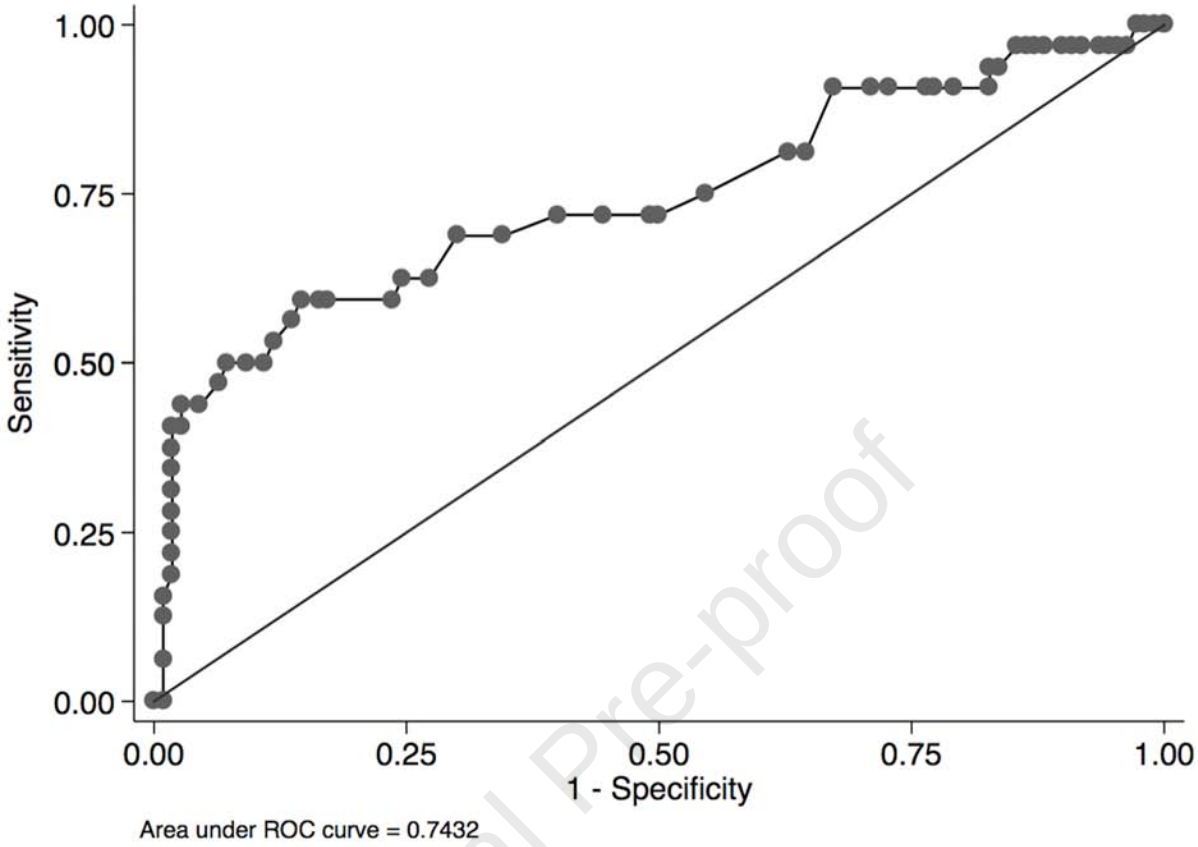
Table 2: Operating Characteristics of the Cytosponge® in detecting presence of Barrett's esophagus (BE)

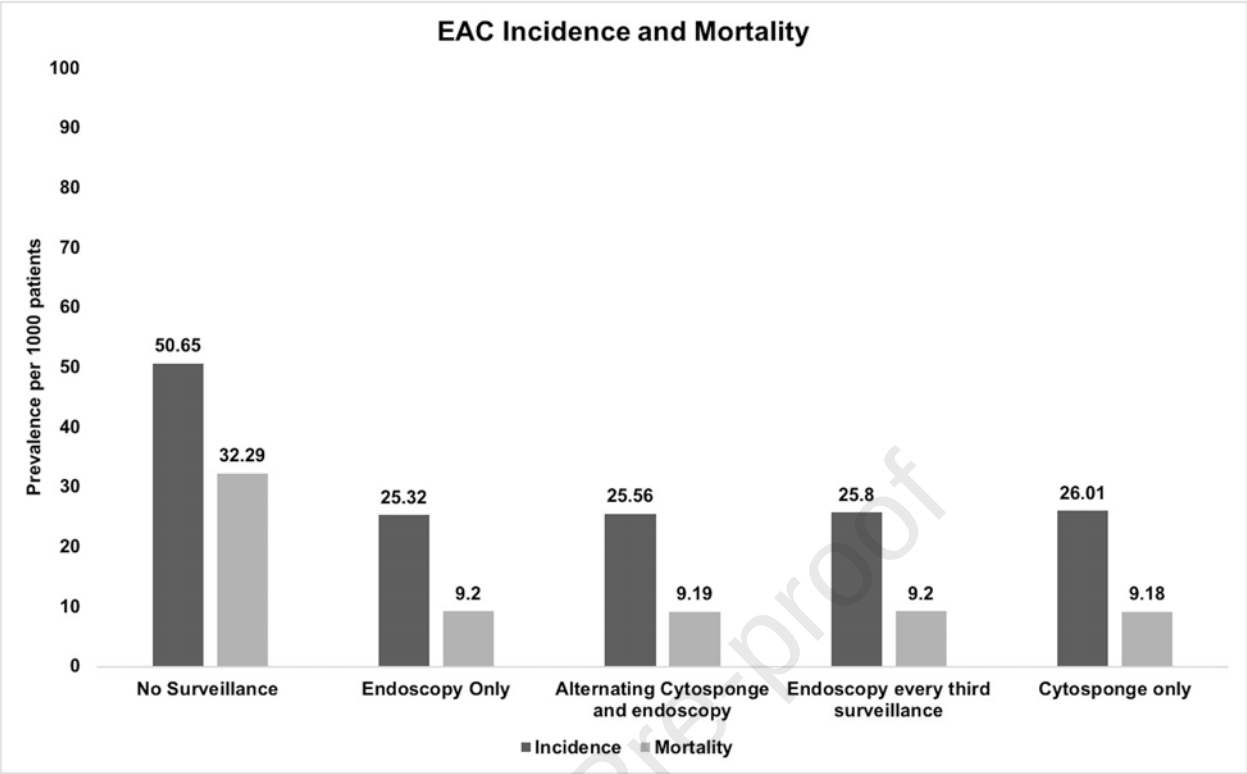
	Total (n=142)	**No BE (n=123)**	**BE[b] (n=19)**
Positive Cytosponge[a],n (%)	32 (23)	18 (15)	14 (74)
Negative Cytosponge,n (%)	110 (77)	105 (85)	5 (26)

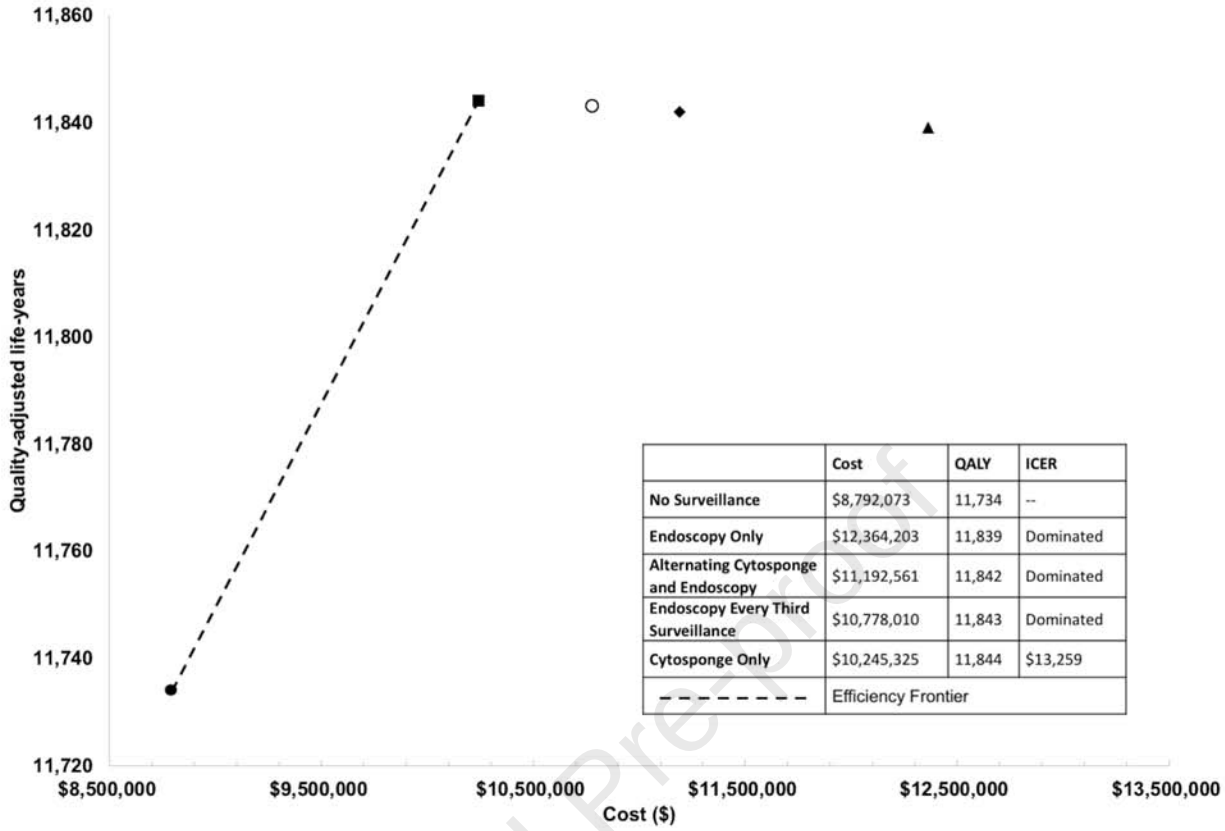
[a] Positive if presence of IM and/or TFF3

[b] Presence of endoscopic and histologic evidence of BE





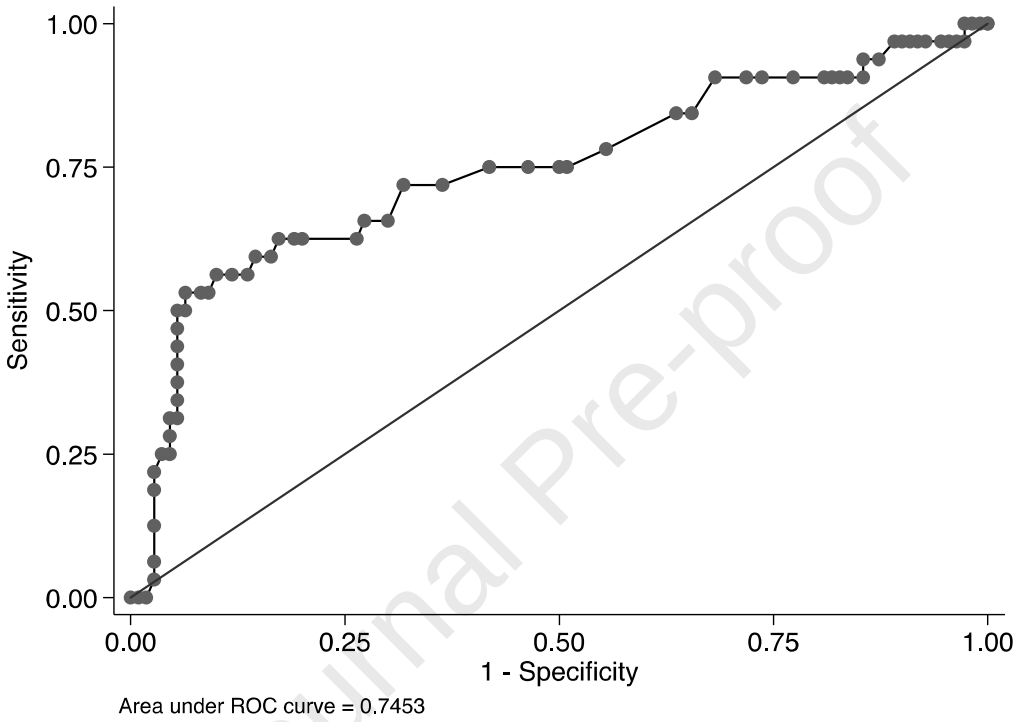




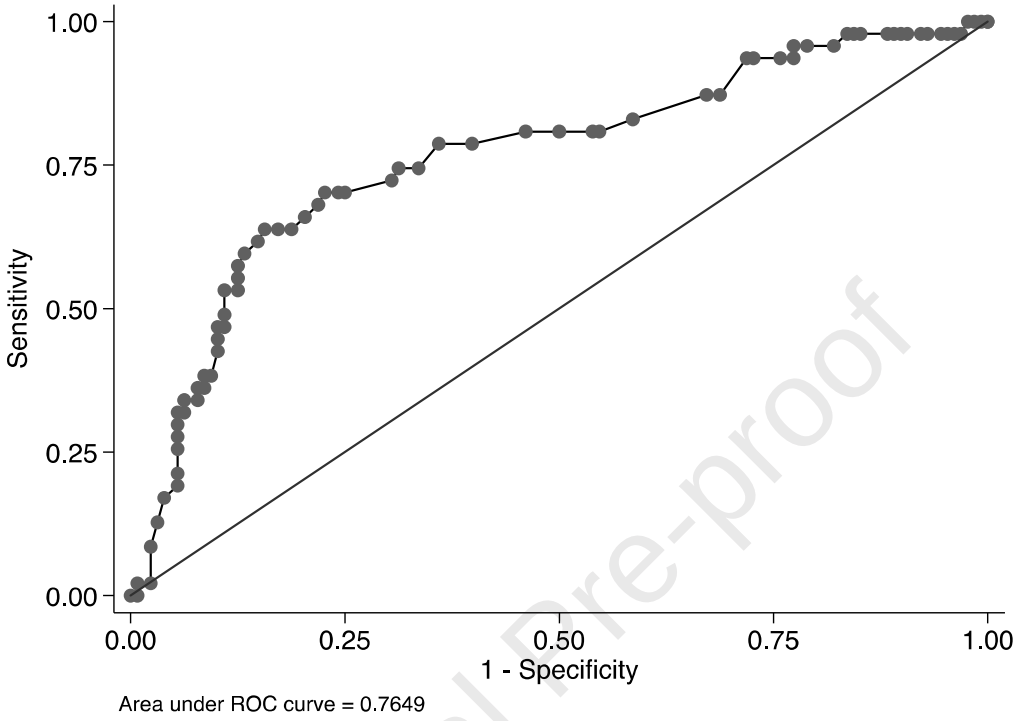
	Cost	QALY	ICER
No Surveillance	$8,792,073	11,734	--
Endoscopy Only	$12,364,203	11,839	Dominated
Alternating Cytosponge and Endoscopy	$11,192,561	11,842	Dominated
Endoscopy Every Third Surveillance	$10,778,010	11,843	Dominated
Cytosponge Only	$10,245,325	11,844	$13,259
- - - - - - - -	Efficiency Frontier		

SUPPLEMENTARY DATA

Supplementary Figure 1: ROC curve for Cytosponge® Assay for Detection of Barrett's esophagus (BE) after EET (including patients with CE of any length and IM on biopsies)



Supplementary Figure 2: ROC curve for Cytosponge® Assay for Detection of Barrett's esophagus (BE) after EET (including patients without biopsies)



Supplementary Table 1. Model inputs

Parameter/Definition	Value	Source
Maximum number of touch-ups RFA	3	[21]
Number of endoscopies during initial EET	4	[21]
Number of RFA sessions during initial EET	3.55	[21]
Complication rates		
Perforation due to surveillance endoscopy	0.00025	(22-26)
Bleeding due to surveillance endoscopy	0.00026	(22-25)
Perforation due to EET (per procedure)	0.002[#]	(27)
Bleeding due to EET (per procedure)	0.004[#]	(5, 27)
Stricture rate due to EET (per procedure)	0.019[#]	(5, 27)
Perforation rate resulting from stricture treatment	0.0009	(28)
Bleeding rate resulting from stricture treatment	0.0009	(28)
Success probabilities of touch-up EET[¥]		
In HGD patients		
CE-IM and CE-D	88.9%	(29)
Non-CE-IM, CE-D	3.7%	(29)
Non-CE-IM and non-CE-D	7.4%	(29)
In LGD patients		
CE-IM and CE-D	98.1%	(29)
Non-CE-IM, CE-D	0	(29)
Non-CE-IM and non-CE-D	1.9%	(29)
Recurrence rates by baseline histologic grade and grade of recurrence		
Annual recurrence rates after CE-IM		
Pre-treatment misdiagnosed NDBE[¥]	7%	(30, 31)
Pre-treatment IND/LGD	8.3%	(29)
Pre-treatment HGD	13.5%	(29)
Recurrent histology of misdiagnosed NDBE[¥] after CE-IM		
NDBE	92%	(30, 31)
IND/LGD	6%	(30, 31)
HGD	2%	(30, 31)
EAC	0%	(30, 31)
Recurrent histology of IND/LGD after CE-IM		
NDBE	50%	(29)
IND/LGD	25%	(29)
HGD	25%	(29)
EAC	0	(29)
Recurrent histology of HGD after CE-IM		
NDBE	50%	(29-31)
IND/LGD	15%	(29)
HGD	25%	(29)
EAC	10%	(29)
Costs		
Endoscopy	$745	(32)
Cytosponge	$182	(33)

Supplementary Table 2. Probability of endoscopic misdiagnosis of patients with Barrett's esophagus and esophageal adenocarcinoma (40).

Initial EET treatment (EMR & RFA)		$5,630	(32)
RFA Touch-Up		$1,012	(32)
	Stricture	$1,012	(32)
Complications	Bleeding	$11,815	(34)
	Perforation	$28,533	(35)
Localized EAC initial care		$58,997	(36)
Localized EAC Terminal care		$64,704	(36)
Regional EAC initial care		$75,295	(36)
Regional EAC terminal care		$77,742	(36)
Distant EAC initial care		$57,169	(36)
Distant EAC terminal care		$85,212	(36)
Unstaged[§] EAC initial care		$63,820	(36)
Unstaged[§] EAC terminal care		$75,886	(36)
EAC continuous care		$4,080	(36)
Utility			
Short term			
Endoscopy with or without EET (1 day)		0.70	(37)
After EET Treatment (1 week) *		0.70	(21)
After RFA Touch-Up (1 week)		0.70	(21)
Stricture (4 week)		0.70	(21), expert opinion
Perforation (4 weeks)		0.70	(21), expert opinion
Bleeding (1 week)		0.70	(21)
Long term (until death)			
Localized EAC initial care (yearly)		0.84	(38, 39)
Localized EAC continuous and terminal care (yearly)		0.96	(38, 39)
Regional EAC care (yearly)		0.65	(38, 39)
Distant EAC care (yearly)		0.40	(38, 39)
Unstaged[§] EAC care (yearly)		0.63	(38, 39)

BE: Barrett's esophagus, CE: complete eradication, D: dysplasia, EAC: esophageal adenocarcinoma, EET: endoscopic eradication therapy, EMR: endoscopic mucosal resection, HGD: high-grade dysplasia, IM: intestinal metaplasia, IND: indefinite dysplasia, ND: non-dysplastic, LGD: low-grade dysplasia, RFA: radiofrequency ablation.

The complication rate per patient was divided per average RFA sessions to compute the complication rate per procedure (5).

[¥] Recurrent NDBE patients or NDBE patients who are misdiagnosed as LGD/HGD receive EET as well. For NDBE, we assumed the same EET success probability rate that we assumed for LGD patients, but we assumed a different recurrence rate after CE-IM as described in the table.

[§] Unknown

* During initial EET, patients were assumed to receive an average of 3.55 RFA sessions and 0.55 EMR treatments, therefore (3.55+0.55=) 4.1 weeks with utility of 0.7 was assumed per initial 2-year EET.

		True State			
		NDBE	**LGD**	**HGD**	**EAC**
Diagnosed state	**NDBE**	83.5%	17.5%	0.0%	0.0%
	LGD	14.5%	69.2%	11.5%	5.0%
	HGD	1.0%	8.3%	77.5%	17.5%
	EAC	1.0%	5.0%	11.0%	77.5%

EAC: esophageal adenocarcinoma, HGD: high-grade dysplasia, LGD: low-grade dysplasia, NDBE: non-dysplastic Barrett's esophagus

Supplementary Table 3: Characteristics of Inadequate Cytosponge Sampling by Administration Site and Barrett's Segment Length

	University of Cambridge	University of Nottingham	University College London	University of North Carolina
Inadequate sponges, n (%)	7 (12)	12 (20)	21 (36)	19 (32)
BE Segment Length, n (%)				
No BE	3 (43)	3 (25)	11 (52)	19 (100)
Short	3 (43)	7 (58)	8 (38)	0 (0)
Long	1 (14)	2 (17)	2 (10)	0 (0)

What you need to know?

Background: Following successful treatment of Barrett's esophagus (BE) with radiofrequency ablation (RFA), patients require lifelong endoscopic surveillance to monitor for disease recurrence, which is associated with significant costs, resource utilization, patient discomfort, and some procedure-related risks. An alternate, more cost-effective, and less invasive techniques for post-ablation surveillance would be of great utility.

Findings: This is the first study to assess both the testing characteristics and cost-effectiveness of Cytosponge® to detect residual or recurrent BE after RFA. The Cytosponge® assay was able to detect residual BE in the tubular esophagus with a sensitivity of 74% and specificity of 85% in a post-ablation population, and was both less costly and more effective than endoscopy according to formal cost-effectiveness analysis.

Implications for Patient Care: While further optimization of the Cytosponge® assay to improve the testing characteristics is needed for the assay to be reliably used for surveillance in the post-ablation setting for BE patients, it holds promise to be utilized as either an adjunct or stand-alone method for post-treatment surveillance.