Screening Patients for Barrett’s Esophagus with Cytosponge Coupled with Trefoil Factor 3 Expression Compared to Endoscopy

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Screening Patients for Barrett’s Esophagus with Cytosponge Coupled with Trefoil Factor 3 Expression Compared to Endoscopy

Abstract
Background: Esophageal adenocarcinoma (EAC) accounts for an estimated 15,690 deaths in the US each year. The 5-year mortality is 80% unless the disease is caught early. Barrett’s esophagus (BE) is the primary risk for developing EAC, therefore, the best method for early detection is identification of patients with BE. In addition, recent advances in the treatment of high-grade dysplasia and early esophageal carcinoma have provided safe effective alternatives to esophagectomy. Endoscopy is the current standard to screen patients with BE. This method is cost prohibitive, invasive, and requires specialty training making it unfit as a tool for screening at risk populations. The Cytosponge coupled with trefoil factor 3 (TFF3) is a novel diagnostic test used in identifying Barrett’s esophagus. Is the Cytosponge coupled with TFF3 expression an effective method to diagnose patients with Barrett’s esophagus in comparison to endoscopy with biopsy?

Methods: An exhaustive literature search using MEDLINE-Ovid, Web of Science, and Evidence Based Medical Review Multifile was conducted. The keywords used in the search included: “Barrett’s esophagus” and “Cytosponge.” Search results were subsequently scanned and eligibility criteria were applied. Studies were included if they directly compared the efficacy of Cytosponge coupled with TFF3 to endoscopy with biopsy. Other inclusion criteria required the studies to include human subjects and be in the English language. Studies were evaluated for quality using GRADE criteria.

Results: A total of 13 studies were screened. After duplicates were removed and eligibility criteria were applied, two studies remained and are contained in this systematic review. One study included 504 participants and was a prospective cohort design. The second study was a multi-center case-control design and included 1110 participants. Both studies evaluated the sensitivity and specificity of the Cytosponge-TFF3. One study demonstrated the sensitivity and specificity to be about 80% and 92% respectively.

Conclusion: In conclusion, the Cytosponge-TFF3 possesses significant potential in its ability to be used as a cost effective, patient accepted, and accurate method for screening primary care populations for Barrett’s esophagus. Further clinical studies will be needed to determine the applicability and accuracy of the Cytosponge across primary care populations. Furthermore, additional steps need to be taken to improve the sensitivity of the Cytosponge, such as improvements related to bettering the reliability of specimen collection.

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First Advisor
AJ Sommers

Keywords
Trefoil Facto 3, Barrett’s Esophagus, Esophageal Adenocarcinoma
Subject Categories

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Screening Patients for Barrett’s Esophagus with Cytosponge Coupled with Trefoil Factor 3 Expression Compared to Endoscopy

Kyle Saxe

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, 08/13/2016

Faculty Advisor: Annjanette Sommers, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

**Background:** Esophageal adenocarcinoma (EAC) accounts for an estimated 15,690 deaths in the US each year. The 5-year mortality is 80% unless the disease is caught early. Barrett’s esophagus (BE) is the primary risk for developing EAC, therefore, the best method for early detection is identification of patients with BE. In addition, recent advances in the treatment of high-grade dysplasia and early esophageal carcinoma have provided safe effective alternatives to esophagectomy. Endoscopy is the current standard to screen patients with BE. This method is cost prohibitive, invasive, and requires specialty training making it unfit as a tool for screening at risk populations. The Cytosponge coupled with trefoil factor 3 (TFF3) is a novel diagnostic test used in identifying Barrett’s esophagus. Is the Cytosponge coupled with TFF3 expression an effective method to diagnose patients with Barrett’s esophagus in comparison to endoscopy with biopsy?

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**Keywords:** Cytosponge, Barrett’s esophagus
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BE</td>
<td>Barrett’s Esophagus</td>
</tr>
<tr>
<td>EAC</td>
<td>Esophageal Adenocarcinoma</td>
</tr>
<tr>
<td>TFF3</td>
<td>Trefoil Factor 3</td>
</tr>
<tr>
<td>HGD</td>
<td>High-grade dysplasia</td>
</tr>
<tr>
<td>IMC</td>
<td>Intramucosal Carcinoma</td>
</tr>
<tr>
<td>C</td>
<td>Circumferential Segment Length</td>
</tr>
<tr>
<td>M</td>
<td>Maximal Segment Length</td>
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</table>
Screening Patients for Barrett’s Esophagus with Cytosponge Coupled with Trefoil Factor 3 Expression Compared to Endoscopy

Background

An estimated 16 910 people in the US are diagnosed with esophageal adenocarcinoma each year and 15 690 deaths occur in the same time frame.\textsuperscript{1} Esophageal adenocarcinoma (EAC) is a particularly aggressive and deadly cancer with a 5 year mortality of 80\%, which is in part due to late detection of the disease.\textsuperscript{2,3} Barrett’s esophagus is the primary risk factor for the development of EAC, making surveillance of these patients of the utmost importance. While traditional methods for treatment EAC have been invasive and wrought with complications, recent improvements in the treatment of esophageal cancer have further fueled the need for early detection of at risk populations.

Barrett’s esophagus (BE) represents a metaplastic change in the mucosal tissue located at the esophagogastric junction. Studies vary widely in their estimation of the prevalence of the BE in the general population, but one study\textsuperscript{4} estimates 6.8\% of people in the US have BE. Another study\textsuperscript{5} estimated a prevalence of 1.6\%. Even the more conservative estimate of 1.6\% would translate into 3.3 million people in the US having BE.\textsuperscript{5} Patients with frequent or severe acid reflux are at increased risk for developing BE; therefore, these patients are the targeted population for whom improved detection would most benefit.\textsuperscript{6}

Patients with Barrett’s esophagus have a 0.5\% per year risk of conversion to esophageal adenocarcinoma according to a systematic review and meta-analysis.\textsuperscript{7} Although esophageal adenocarcinoma carries a high mortality, early detection and treatment has been shown to significantly increase the rate of survival to > 80\% for superficial carcinomas.\textsuperscript{8} Esophagectomy has traditionally been the curative treatment even in early asymptomatic disease. While this treatment has been shown to be effective, it carries risks for significant morbidity and mortality.
In recent years development of less invasive esophageal sparing procedures has shown promise with improvements in safety while maintaining efficacy. Such procedures include endoscopic mucosal resection and radiofrequency ablation. These procedures have shown promise in decreasing the risk of morbidity and mortality related to the treatment of high-grade dysplasia and early esophageal carcinomas. A meta-analysis of endoscopic submucosal dissection of early esophageal carcinoma showed a 99% resection rate and low incidence of complications.\textsuperscript{9,10}

With the advent of less invasive endoscopic treatments, detection of Barrett’s esophagus across larger populations has become even more crucial. The current standard for diagnosis is through direct esophageal visualization via endoscopy coupled with biopsy, which requires expertise to perform, is commonly done under anesthesia, is expensive, and is invasive in nature.\textsuperscript{11} Therefore, endoscopy is unfit for systematic screening of Barrett’s esophagus across a large population. For these reasons, a cheap, easy to administer, safe, accurate, and acceptable screening method should be more extensively explored.

Cytosponge coupled with trefoil factor 3 (TFF3) immunocytochemistry has shown promise in its ability to detect Barrett’s esophagus in a cheap, easy to administer fashion. This device consists of a 3cm diameter spherical mesh contained within a 2cm gelatin capsule attached to a retrieval string. The patient is instructed to swallow the capsule containing the mesh, which dissolves upon reaching the stomach releasing the spherical mesh. With the mesh deployed the patient manually pulls the string, attached to the mesh, up and out through their mouth. As the mesh is pulled through the esophagus it collects esophageal cells. At which point the cells are analyzed via immunohistochemical staining for the biomarker, trefoil factor 3. TFF3 expression has been extensively studied and has been shown to be a distinguishing characteristic
in the cellular transformation related to BE. Therefore, TFF3 expression distinguishes BE cells from normal gastric and esophageal cells. Is Cytosponge coupled with trefoil factor 3 expression an effective method to diagnose patients with Barrett’s esophagus in comparison to endoscopy with biopsy?

**Methods**

An exhaustive literature search using MEDLINE-Ovid, Web of Science, and Evidence Based Medical Review Multifile was conducted. The keywords used in the search included: “Barrett’s esophagus” and “Cytosponge.” Search results were subsequently scanned and eligibility criteria were applied. Studies were included if they directly compared the efficacy of Cytosponge coupled with TFF3 to endoscopy with biopsy. Other inclusion criteria required the studies to include human subjects and be in the English language. Studies were evaluated for quality using GRADE criteria.

**Results**

An initial search resulted in 13 articles for review. Upon elimination of duplicates and application of eligibility criteria, there were a total of two articles that met the standards for this study. One study was a prospective cohort design while the other study was a multi-center case-control design. Both studies determined the sensitivity and specificity of Cytosponge coupled with TFF3 compared to endoscopy with biopsy. See Table I.

**Kadri et al**

This study was a prospective cohort study design. Researchers set out to determine whether Cytosponge would be widely accepted by the patient population as well as its ability to accurately identify the presence of Barrett’s esophagus compared to endoscopy with biopsy. The study took place in the UK across 12 general practices. Patients were asked to perform the
Cytosponge test and then were invited to undergo endoscopy. Patients were also asked to complete questionnaires regarding their sociodemographics, anxiety (as related to the tests), and visual analogue scales to determine test acceptability.\textsuperscript{14}

Eligible patients were identified by searching the prescribing databases of 12 primary care practices for patients 50-70 years old, who have had a prescription for an acid suppressant for more than a 3-month period, within the last 5 years. Exclusion criteria were a previous diagnosis of Barrett’s esophagus, endoscopy within the past year, dysphagia, known portal hypertension, drug or pathophysiologic abnormality of coagulation, important physical or psychological comorbidity precluding endoscopy, or inability to provide informed consent. General practices then sent eligible patients an invitation letter. Recruitment of patients continued until 500 people were included in the study.\textsuperscript{14}

Following enrollment, either a research nurse or research fellow administered the test. Within 30 minutes following the test patients were asked to complete an anxiety inventory, impact of event scale, and visual analogue to measure acceptability. Two independent pathologists carried out immunostaining for trefoil factor 3, and results were reported in a binary fashion as being either positive or negative. The Cohen’s kappa coefficient of the two scorers was 0.74.\textsuperscript{14}

Participants who successfully swallowed the Cytosponge were invited to undergo endoscopy within 3 weeks of the original test. All endoscopists were instructed to strictly adhere to the agreed upon Prague C&M criteria for diagnosis of BE. Barrett’s esophagus was defined as “endoscopically visible columnar lined epithelium arising at least 1cm circumferentially above the gastro-esophageal junction with intestinal metaplasia.” Endoscopists and pathologists were blinded to the results of the Cytosponge test.\textsuperscript{14}
Overall 2696 patients were identified as being eligible and were invited to participate. 504 patients were originally enrolled in the study of which 501 were able to successfully swallow the Cytosponge. Two Cytosponges did not properly deploy and 32 participants failed to undergo endoscopy. Patients who did not complete the endoscopy were considered to not have Barrett’s esophagus. No adverse events were associated with swallowing the Cytosponge. According to endoscopy 3.0% (15/501) were diagnosed with Barrett’s esophagus containing segments of circumferential length 1 cm or greater, while 2.2% (10/501) of patients were diagnosed with segments of 2 cm or greater.\(^{14}\)

The Cytosponge had a sensitivity and specificity of 73.3% (95% CI 44.9%-92.2%) and 93.8% (95% CI 91.3%-95.8%) respectively in patients containing segments of Barrett’s esophagus \(\geq1\) cm in length. The sensitivity and specificity increased to 90% (95% CI 55.5%-99.7%) and 93.5% (95% CI 90.9%-95.5%) in patients containing segments of BE that were \(\geq2\) cm in length. The positive predictive value was 26.8% and a negative predictive value of 99.1%. Response rates to questionnaires were high and showed a low level of anxiety in most patients before and after the tests.\(^{14}\)

The authors noted that this study was not designed in a manner to ascertain the accuracy of the Cytosponge test to a high degree of precision as evidenced by the wide confidence interval for the estimates of sensitivity. From this study it was concluded that the Cytosponge-TFF3 has shown to be promising as a screening tool for Barrett’s esophagus both in patient acceptability and high negative predictive value. The test has proven to be both safe and acceptable in a primary care setting. Although these results are promising, the authors concluded that more studies are needed to further evaluate the precision of the Cytosponge test.\(^{14}\)

**Ross-Innes et al**
This study was a multi-center case-control study aimed at precisely determining the sensitivity and specificity of the Cytopsponge coupled with TFF3 compared to endoscopy with biopsy. The primary outcomes were sensitivity, specificity, safety, and acceptability of the Cytopsponge-TFF3. Secondary endpoints were sensitivity of the Cytopsponge-TFF3 in patients with dysplasia and in patients who swallowed the Cytopsponge on two occasions.

Patients who were scheduled to have an endoscopy performed for a clinically indicated reason were recruited to participate in the study. Patients who had a previously determined diagnosis of Barrett’s esophagus were allocated to be in the case arm of the study. On the other hand, patients who were referred to endoscopy for dyspepsia or reflux symptoms and did not have a previous diagnosis of Barrett’s esophagus were allocated to be in the control arm of the study. Patients who were subsequently diagnosed with Barrett’s esophagus by endoscopy in accordance with the Prague C&M criteria were crossed over to the case arm of the study.

Over the course of a single visit participants completed questionnaires regarding demographics, exposures, and symptoms along with the Cytopsponge test and an endoscopy with biopsy. Patients who happen to undergo a second endoscopy during the course of the study were invited to undergo a second Cytopsponge test as well. In addition four tertiary referral centers were used to enrich the study with patients who were shown to have dysplasia.

Cytosponge samples were anonymized, processed, and scored in a binary fashion as either positive or negative. The scorers were one of two independent researchers and a gastrointestinal histo-cytopathologist. The scorers were blinded to the clinical diagnosis of each patient.

Endoscopies were performed within an hour of the Cytopsponge test. Biopsies were taken from the cardia as well as 2 cm above the squamocolumnar junction in all patients while those
with Barrett’s esophagus also had additional biopsies taken in accordance with the Seattle surveillance protocol. The biopsies were reviewed by histo-cytopathologists who were blinded to the results of the Cytosponge test.\(^{15}\)

A total of 1110 patients were enrolled in this study. There were 463 participants who were allocated as the controls and 647 patients with Barrett’s esophagus who were allocated to the cases arm of the study. Three adverse events were reported although; none were connected with the Cytosponge. One patient had onset of atrial fibrillation, one patient was admitted for bleeding from a biopsy site, and one patient was found to have unsuspected esophageal varices without evidence of bleeding. On endoscopy 16.7% of patients had oozing of blood following the Cytosponge test, but did not require intervention.\(^{15}\)

A total of 93.9% (1042/1110) of patients successfully swallowed the Cytosponge. The overall sensitivity and specificity of the Cytosponge was 79.9% (95% CI 76.4%-83.0%, \(p<0.001\)) and 92.4% (95% CI 89.5%-94.7%) respectively. Sensitivity of the Cytosponge increased to 87.2% (95% CI 83.0%-90.6%) in patients with segments of Barrett’s esophagus \(\geq 3\) cm in length. Patients who swallowed the Cytosponge twice during the course of the study had a sensitivity of 89.7% (95% CI 82.3%-94.8%). The positive and negative predictive values were determined to be 34.7% and 98.9% respectively. The median value, given by patients, on the visual analogue scale was 6 out of 10. A score of 0 representing the worst experience ever and 10 being the best experience ever.\(^{15}\)

The authors pointed out that 76% of Cytosponge tests resulting in a false negative were found to be due to the absence of columnar cells on the specimen rather than failure of the TFF3. As a result, the authors concluded that patients with a negative result and few to no columnar cells on the specimen should have a repeated test to ensure adequate sampling, if the test were
applied clinically. Other proposed alternatives to potentially improve sensitivity were to have all patients swallow the sponge twice or engineer the sponge to have improved cellular collection. Although this study was designed to precisely determine the accuracy of the Cytosponge, the data cannot be applied to a primary care population due to the case-control design.\textsuperscript{15}

The authors concluded that the Cytosponge-TFF3 can diagnose Barrett’s esophagus in an acceptable accurate manner. Furthermore, the Cytosponge has shown promise in its potential to be used as a screening tool for patients with reflux symptoms.\textsuperscript{15}

**Discussion**

After analyzing the data from these two studies\textsuperscript{14,15} the Cytosponge has proven to be both widely acceptable to patients and effective in diagnosing Barrett’s esophagus, as demonstrated with high negative predictive values and reasonable sensitivity values (see Table II). The Cytosponge offers a method for developing a more robust screening strategy regarding Barrett’s esophagus. Early detection in conjunction with treatment of esophageal adenocarcinoma has been shown to vastly improve the survival rate of patients.\textsuperscript{2,3} With Barrett’s esophagus being the greatest risk factor for developing esophageal adenocarcinoma, a need for screening at risk populations is clearly present.\textsuperscript{6} Endoscopy has proven to be cost prohibitive and requires excessive resources to be an adequate screening tool to be applied in a generalized manner across primary care populations.

One particular model estimated that screening all white males >50 years old via endoscopy would cost $10,440 per quality adjusted life year saved.\textsuperscript{11} Therefore, a cost effective, accurate, and acceptable test is needed for screening primary care populations in order to improve early detection of Barrett’s esophagus. The Cytosponge has been shown to be a much cheaper, estimated to be $152 per test, as compared with endoscopy, estimated to cost $785 per
test respectively.\textsuperscript{13} Furthermore, the Cytosponge has proven to be safe by the first study reviewed,\textsuperscript{14} finding no adverse complications and the second study reviewed,\textsuperscript{15} only finding minor esophageal abrasions none of which needed intervention. Ease of administration has proven to be yet another benefit of the Cytosponge requiring only about 10 minutes for specimen collection and being a procedure performed by research nurses.

Although the Cytosponge has shown to be imperfect with sensitivities ranging from 73.3\% to 90\% depending on the segment length of BE and the number of times the patient swallowed the sponge, there is promise in its acceptability, ease of application, and low cost (see Table II).\textsuperscript{13-15} The sensitivity and specificity of the Cytosponge are comparable with screening tests currently being used such as mammography.\textsuperscript{16} Simple improvements, such as, repeating the test in cases where few to no columnar cells were collected, have the potential to improve the sensitivity of the Cytosponge.\textsuperscript{15}

These studies\textsuperscript{14,15} were limited in their design requiring further evaluation through blind comparisons to endoscopy and biopsy which is the gold standard in order to generalize the data to a primary care population. The two articles used in this study were assessed for quality of evidence by making use of the GRADE criteria.\textsuperscript{17} Through careful consideration of these studies it was determined that there exists the potential for publication bias within both of these studies given possible conflicts of interest from companies involved with funding this research and their potential to profit from this technology.\textsuperscript{14,15} Even though the potential for publication bias exists, it is not likely, due to the objective design of these studies. Overall, no downgrades were applied to these studies through the assessment of their quality of evidence. An overall quality of evidence was rated as being “low,” which is inherent to the prospective cohort and case-control study designs.
Moving forward researchers have several areas of interest that need further evaluation. Potential for improved sensitivity through advances in engineering or altering testing procedures is of future interest. Clinical trials are also needed in order to evaluate the applicability and accuracy of this technology in any wide spread manner.

Conclusion

In conclusion, the Cytosponge-TFF3 has been shown to possess significant potential in its ability to be used as a cost-effective, patient accepted, and accurate method for screening primary care populations for Barrett’s esophagus (see Table II). The results of these two studies are compelling for the utilization of the Cytosponge-TFF3 to screen populations of patients at risk for Barrett’s esophagus within a primary care setting. Further clinical studies will be needed to definitively determine the applicability and accuracy of the Cytosponge-TFF3 in its administration across primary care populations. Furthermore, additional steps need to be taken to improve the sensitivity of the Cytosponge, specifically improvements related to bettering the reliability of specimen collection. With these proposed improvements and pending further study, the Cytosponge-TFF3 possesses the capability to accurately, cheaply, and safely screen patients potentially leading to improved early detection and treatment of esophageal adenocarcinoma.


**Table I.** Characteristics of Reviewed Studies, GRADE profile

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kadri et al</td>
<td>Prospective Cohort</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not likely</td>
</tr>
<tr>
<td>Ross-Innes et al</td>
<td>Case-control</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not likely</td>
</tr>
</tbody>
</table>


**Table II.** Sensitivity of the Cytosponge-TFF3 in different groups of patients (Ross-Innes et al 14)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total Number</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All BE patients (≥C1 or M3)</td>
<td>596</td>
<td>79.9% (76.45-83.0%)</td>
</tr>
<tr>
<td>Segment Length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥C1</td>
<td>533</td>
<td>79.5% (75.9%-82.9%)</td>
</tr>
<tr>
<td>≥C2</td>
<td>416</td>
<td>83.9% (80.0%-87.3%)</td>
</tr>
<tr>
<td>≥C3</td>
<td>320</td>
<td>87.2% (83.0-90.6%)</td>
</tr>
<tr>
<td>Indefinite for Dysplasia</td>
<td>46</td>
<td>73.9% (58.9%-85.7%)</td>
</tr>
<tr>
<td>HGD/IMC</td>
<td>101</td>
<td>84.2% (75.6%-90.7%)</td>
</tr>
<tr>
<td>Patients having two Cytosponge Tests</td>
<td>107</td>
<td>89.7% (82.3%-94.8%)</td>
</tr>
</tbody>
</table>

C: Circumferential length, M: Maximal length, IMC: Intramucosal carcinoma, BE: Barrett's esophagus