

Cytosponge: A Review on new non-endoscopic cell collection device

Shah Aayushee Nileshbhai *

Department of Pharmacy (PG), Babariya Institute of Pharmacy, Vadodara, Gujarat, India.

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Abstract

Cytosponge is a non-invasive device having a similar size to the tablets of regular taking that is used in place of endoscopy in some areas of detection because it is accurate, safe, and relatively inexpensive when compared to endoscopy. It is also called 'sponge on a string' because of pill attached with a string that is taken with water and lidocaine throat spray may be used to reduce the minor discomforts during application of the cytosponge and after 3 to 5 min withdraw by the string. It is made up of polyester sponge material compressed within a capsule 8.5 mm in diameter and 25 mm in length and the outer layer is made up of gelatin attach to 70mm long string. It is given to the patients with a sufficient amount of water and the gelatin part disappears when the cytosponge reaches the stomach. It collects about a million cells from the oral cavity and stomach, including *Fusobacterium*, *Megasphaera*, *Campylobacter*, *Capnocytophaga*, and *Dialister*. The cells are isolated and tests are performed to determine whether the cells are malignant or normal for detection and any detection is carried out by different biomarkers like TFF3, Aura-k, TFPI2, TWIST1, ZNF345, and ZNF569. The most used biomarker is TFF3. Cytosponge is used for the detection of Barrett's oesophagus, Eosinophilic Esophagitis, oesophageal microbiota, Precancerous Mucosal Changes like Gastric intestinal metaplasia (GIM) and gastric atrophy (GA), Esophageal dysplasia, other gastrointestinal pathologies, Esophageal Diseases, and *H. pylori*. It is also used as a gastrointestinal endoscopy during the COVID-19 pandemic. New research is being taken for AI and cytosponge combine technology.

Keywords: Cytosponge; Endoscopy; Biomarker TFF3; Gastrointestinal endoscopy; AI Technology

1. Introduction

Right now, there is a ratchet of non-endoscopic cell collection devices rather than endoscopy-based screening modalities because of low cost. Cytosponge is first used as OSCC (oesophageal squamous cell carcinoma) screening but it failed because of reliance on cytological assessment of atypia. The combination of Cytosponge with biomarker gives more tractability for detecting Barrett's esophagus.[1] The initial study was disappointing because of the reliance on standard cytological analysis that is plagued by difficulties in interpreting cell atypia and low cell yield. But after the rapid expansion in biomarker technologies, there is a resurgence in interest in non-endoscopic devices because this improves the sensitivity for detection and can be readily applied in a high-throughput setting. [2] After combination with biomarker, this device is proven successful. Cytosponge is developed at Cambridge University in the United Kingdom (Medical Research Council, London, UK). [3] In the world, a British hospital uses 'sponge in a string' for the first time to detect oesophageal cancer in a Covid-safe way. Cell samples from the oesophagus route are collected by health workers without the use of endoscopy, sedation, or biopsy. In a pandemic, endoscopy was suspended because it can cause the virus to be sprayed into the air. Therefore, the patient was switched to the pioneering Cytosponge. It is quick, cost-effective, and more efficient, therefore It will now be the usual standard of care. [4] It is pill like minimal invasive device. To detect oesophagus cancer it is a triage tool for endoscopy in combination with TFF3 (Trefol Factor 3) biomarker.[5] It is composed of polyester sponge material compressed into a capsule measuring 8.5 mm in diameter and 25 mm in

* Corresponding author: Shah Aayushee Nileshbhai

length and attached to a 70-cm polyester string. The capsule is made of a gelatin vegetable derivative that is disintegrated within 3 to 5 minutes in the stomach. By releasing the sponge, its 30-mm diameter is reached. [6] The cost-effectiveness analyses were conducted from the viewpoint of society. Costs for cancer treatment were obtained from the literature. As Cytosponge technology is new and not yet commercially available, there is little empirical data as to its cost in a clinical setting. A pivotal sensitivity analysis of cytosponge costs was conducted using a wide range of plausible estimates of this parameter because of the uncertainty it poses. [7] Elective screening of patients with dysplasia or intramucosal cancer followed by treatment would result in a significant drop in symptomatic esophageal adenocarcinomas for patients undergoing endoscopic screening. However, this greater benefit for Cytosponge relies on more patients accepting screening by Cytosponge compared with screening by endoscopy. [8] It was estimated that the cost of Cytosponge screening followed by the treatment of dysplastic lesions or intramucosal cancer would be higher than that of on screening. [9]

2. Procedure for use of cytosponge

In the case of a patient selected for the test, the clinical team will provide more details regarding what the patient should do if they are taking medication. Patients should also bring a list of their normal medications, along with a consent form. There is no side effect from this test that would make it impossible for the patient to use public transportation or drive to an appointment. They will be given a disposable bib to wear to their appointment. They will also be provided with disposable clothing. The patients must arrive no earlier than 30 minutes before appointment time in order to make sure the clinic or hospital can effectively manage the number of patients. The appointment will last between 30 and 60 minutes. Ask the nurse during check-in if you have any questions.[9] Clinics will be held by either a CRN (clinical research network) or local practice nurse with appropriate medical cover if participants from several practices are to participate in the study. During the study period, participants are asked not to eat or drink for 4 hours. According to the BEST3 Database, the nurse will complete a questionnaire with demographic and clinical information and the GERD Impact Scale (GIS) after the participant consents. The capsule must be swallowed with water by the patient. During insertion into the stomach, the capsule will remain attached to the string held by the patient or nurse (which, when affixed to a card, prevents the string from being swallowed inadvertently). As the capsule dissolves in the stomach for up to five minutes, the sponge expands to its full size. The research nurse then removes it with the string, collecting cells from the lining of the oesophagus as she does so. When it has been retrieved, the sphere is placed in a preservative liquid. Pathology laboratories will analyze and process linked anonymized samples from the practice for TFF3 and H&E. Patients will be asked to try again if they are unable to swallow the capsule. Whenever a Cytosponge is detached or an obvious bleed occurs, the research nurse will alert the GP since they are responsible for medical assessment. The GP will follow normal emergency procedures after the medical assessment. All participants treated with Cytosponge will receive a call from the research nurse 7 days post-procedure regarding safety and reporting adverse effects.[10]

Cytosponge is generally given to patients with adequate amounts of water and the gelatin part disappears when it reaches the stomach. It may be beneficial to use lidocaine throat spray during cytosponge application to ease any minor discomforts. The expanded sponge is then removed after about five minutes. Upon retrieval, the slightly abrasive mesh collects cells along the length of the esophagus. Swallowing the Cytosponge and extracting it are two of the most anticipated physiological problems.

2.1. Taking the sponge in

Patients get really surprised when they handle cytosponge, since they expect it to be much larger in size. When they use the cytosponge at the very beginning, they assume the capsule will be much bigger. Cytosponge actually is of the same size as the regular tablets, which means that no problems will arise when patients take the cytosponge capsule.

2.2. Taking out the sponge

It was rougher than they expected for some patients after exposure to the expanded Cytosponge. Thus, they were concerned that the Cytosponge could damage their oesophagus. Some people also believed that choking on the Cytosponge would lead to vomiting. Cytosponge can get stuck in the oesophagus or stomach if the string breaks, and this was a common concern.

2.3. Videos of reassurance

As a result of watching the videos, patients have a more positive attitude toward the cytosponge administration primarily due to how quickly the sponge is removed. A comforting aspect of the extraction was the fact that the patient did not gag.

2.4. The mechanism of action of cytosponge is as follows

A Cytosponge test is used to detect esophageal cancer by swallowing a tablet that contains the Cytosponge. After swallowing the tablet, the Cytosponge dissolves when it enters the stomach. In the stomach, the gelatin shell opens up and is attached to the string. Cells lining the esophagus are collected by the string as it travels up the esophagus. The sponge's honeycomb-like matrix can contain about a million cells. In order to determine whether the cells are malignant or not, the cells are isolated and tested. Using Cytosponge, one may determine whether a condition is malignant or premalignant in a more comfortable manner.[11]

2.4.1. Analysis of samples

Cytosponge specimens were processed in accordance with pathology laboratory procedures. To remove free cells, the container containing the sponge was vortexed. After pouring the fluid into a Falcon tube of 50 ml, the sample was centrifuged at 2500 rpm for 10 minutes, yielding a pellet that contained 3 to 4 ml. As part of the recombination process, the pellet was removed, and the supernatant and sponge were vortexed again to reveal more cells, which were added to the original pellet. Plasmalyte (40 ml) was then added to the Falcon tube with the pellet. Following centrifugation, PreservCyt was removed from the specimen, and the fluid was decanted. To create a clot, plasma and thrombin were added in a ratio of 5:1. The specimen then underwent routine processing and embedding in paraffin to create a cell block from which slides were cut for analysis.

2.4.2. Evaluation of endoscopic biopsies and cytosponge-derived cells

An experienced GI pathologist interpreted the hematoxylin and eosin-stained biopsy specimens obtained during the endoscopy using a Nikon E600 microscope equipped with a 10×25 ultra-wide eyepiece. All fragments on all slides were scanned at low power to locate the highest density of eosinophils. Analysis of esophageal biopsies was based on the area of greatest eosinophil density, regardless of the location of the esophagus. The area of the field is 0.307 mm², the field diameter is 0.625 mm, and the objective used is a *40 objective. An eosinophil peak count and HPF were recorded. Five random fields were chosen from the area with the highest eosinophil density in the low-powered review. From the five fields, the one with the highest eosinophil count was then used. Using these results, patients were divided into two categories based on a peak count: active and inactive.

The cell block was cut into two levels and hematoxylin and eosin-stained as for the cytosponge analysis. To identify eosinophil-rich tissue fragments, a low-power scan was used similarly to biopsy review. The entire sample was scanned with the *20 objective (field diameter 1.25mm) if eosinophils could not be detected at low power. When eosinophils were found, they were counted using an objective with a *40. A ratio was calculated based on the total eosinophil count based on the percentage of tissue occupied in the field and the individual tissue fragments could be small. In the case of the cytosponge sample occupying 50% of the high-power field, the count of eosinophils doubles. Endoscopic biopsies were not corrected in this way, since they uniformly filled the ×40 field. Across both the biopsy and cytosponge samples, a pathologist (T.C.S.) was blinded to the result of each modality. T.C.S. reviewed the UNC biopsies first, and the difference between their readings was only two eosinophils. We used the reading from T.C.S. to analyze the data.

2.5. Analysis of the data

2.5.1. Refer to Supplementary Methods[12]

From the data, three themes emerge: expectations regarding the physical experience, preferences regarding information content, and comparison with the current gold standard test. Overall, the test was well accepted, though some were concerned about the physical experience, which included swallowing and removing the Cytosponge. Once the device was handled and a video demonstration was shown, these worries dissipated. Cytosponge was offered to those with GERD, BE, and EAC who had poor knowledge of the relationship, and some said they preferred not to know about the link. In the study, participants felt that the Cytosponge is less expensive, more convenient, and more practical than endoscopy.[13]

A minor pharyngeal bleed occurred during cytosponge procedures, and one case consisted of a detachment that was lower than with an endoscope under sedation after the procedure. Almost all patients were successful in swallowing the Cytosponge and most were successful on the very first try. Patients who failed to swallow were more likely to have secondary problems.[14]

2.5.2. In terms of regulatory status, the situation is as follows

As of now, the Cytosponge does not have Health Canada's licensing approval, and it is not known when it will be available in Canada. CE Marking enables the Cytosponge to be marketed in Europe, and the United States Food and Drug Administration approved it as a Class II device in 2014. A UK research group at the University of Cambridge and the Medical Research Council (MRC) developed the sponge, which has now been licensed to Medtronic GI Solutions. It is expected that the Cytosponge will be available for purchase in the US and the UK soon.[15]

3. Utilizations

3.1. Barrett's oesophagus screening

In the case of Barrett's disease, patients should be offered an endoscopy by their GP. In terms of comparison with "standard care", Cytosponge is shown to be superior. Patients taking PPIs with reflux symptoms were compared in a recent study to determine whether they acquired Barrett's. In both groups, the pick-up rate differed significantly. More than 6000 patients in the Cytosponge™ group were diagnosed with Barrett's 20 times more likely than those who received standard care. In addition, the Cytosponge™ group had nine patients diagnosed with dysplasia (the first step on the path to cancer) or early cancer, whereas the standard care group had none. Conversely, most people without Cytosponge™ probably had Barrett's without knowing it .[16]

3.2. Techniques for detecting

3.2.1. With the use of Trefoil Factor-3 (TFF3)

On paraffin-embedded cytologic specimens, immunohistochemistry for Trefoil Factor-3 (TFF3), a protein that is overexpressed in BO, is performed as a biomarker to determine whether the case is positive or negative.

Cytosponge-TFF3 was shown to be applicable in primary care in the BEST-1 feasibility study and to have promising specificity and sensitivity to diagnose BO, despite not being the primary outcome.[17]

- Risk stratification of TFF3-positive patients based on model inputs

When compared to samples from patients without BE and from BE patients who never developed dysplasia over a median follow-up period of six years, analysis for TP53 mutations in Cytosponge samples can be used to diagnose high-grade dysplasia (HGD). It was modeled in a hypothetical population taking part in primary care for the diagnosis of reflux symptoms to gain a better understanding of the broader context of the Cytosponge-TFF3 test and stratified risk based on the detection of TP53 mutations. [18] Based on an automatic search of the electronic prescribing records, it was determined that these participants swallowed the Cytosponge correctly and produced a sample. An endoscopy was recommended for participants who had a positive Cytosponge-TFF3 result. Participants in the usual care group and those who declined the Cytosponge-TFF3 procedure only underwent an endoscopy if their doctor deemed it necessary. In both the intervention group and the usual care group, Barrett's oesophagus was diagnosed after an average of 12 months of follow-up. The intervention group had nine patients diagnosed with dysplastic Barrett's oesophagus or stage I gastro-oesophageal junction cancer, while the usual care group had no patients diagnosed with dysplastic Barrett's oesophagus or stage I gastro-oesophageal junction cancer. Following successful swallowing of the Cytosponge device, 13% of participants in the intervention group underwent endoscopy and 8% were diagnosed with Barrett's oesophagus or cancer. There was one patient whose Cytosponge detached from the thread, requiring the need for endoscopic removal, and 4% of participants experienced a sore throat.

It has been suggested that patients with gastro-oesophageal reflux could benefit from Cytosponge-TFF3 testing in order to detect Barrett's esophagus early. As a result of Cytosponge-TFF3 testing, symptoms of dysplasia and early cancer may also be identified. Using this strategy will result in additional endoscopies with some false positives.[19]

- A review of cytosponge's clinical data is presented below
 - Method

A pragmatic, cluster-randomized controlled trial, BEST3 takes place in primary care in England. The treatment arm, invitation to a Cytosponge-TFF3 test, or the control arm, usual care, will be randomized 1:1 to 120 practices. Men and women aged 50 or older with a prescription for acid-suppressant medication for at least six months in the past year are eligible. In the intervention arm, patients will be invited to their general practitioner to have a Cytosponge-TFF3 test. If their TFF3 test is positive, patients will be invited to a hospital-based endoscopy clinic to check for BE. In the primary

objective, it will be determined whether offering the Cytosponge-TFF3 test in primary care results in an increase in BE diagnoses within 12 months of study entry by comparing histologically confirmed BE diagnoses between intervention and control arms.

- Observation

The BEST3 trial is designed to test the Cytosponge-TFF3 test using a well-powered pragmatic approach in the same patient population expected to use it in clinical practice. NICE and other clinical bodies will be able to decide whether this test can be routinely integrated into clinical practice from the data generated from this trial.[20]

3.2.2. *As a diagnostic biomarker, the methylation panel can be used as follows*

In biopsy samples of Barrett's oesophagus, gastric cardia, and squamous oesophagus, differentially methylated genes were identified from whole methylome data. A pilot cohort and a validation cohort of Cytosponge BEST2 trial samples were then tested for selected genes.

The following results were achieved

Barrett's esophagus patients differed in methylation patterns from squamous control subjects in 18 genes. A comparison of Barrett's biopsies and biopsies of the squamous oesophagus and gastric cardia revealed hypermethylation of TFPI2, TWIST1, ZNF345, and ZNF569 in the former. Compared with patients with reflux symptoms, these four genes were hypermethylated in Cytosponge samples from patients with Barrett's oesophagus. Barrett's oesophagus was best diagnosed with TFPI2, a biomarker with high sensitivity and specificity.[21]

3.2.3. *Assembly of next-generation sequencing panels*

Because the Cytosponge™ cells yield a high number of cells, this test could be used as a secondary test for patients diagnosed as TFF3 positive. There is some evidence to suggest that TP53 could be a useful biomarker; however, the lack of sensitivity and specificity in detecting TP53 mutations in Barrett's Cytosponge samples does not suggest that this biomarker can be routinely used clinically. It is possible to achieve a higher sensitivity using a panel of biomarkers, but it would be more advantageous to use a single platform. Rather than focusing on a few genes, advances in next-generation sequencing (NGS) techniques can help identify a variety of single nucleotide variants (SNVs) present in dysplasia and OAC, making them useful for diagnosis. Studies have explored alternative methods to NGS, such as in-house hybridization (IHC) and gene expression profiling, to find differences between non-dysplastic and dysplastic Barrett's in order to aid the diagnosis. Since the Cytosponge™ sample is formalin-fixed, paraffin-embedded (FFPE), gene expression profiling cannot be done, but TFF3 immunohistochemical testing can be used to diagnose Barrett's disease. A cancer hotspot panel has been proven to be able to differentiate progressors from non-progressors when used on micro-dissect FFPE Barrett's biopsy samples. Non-progressors did not show any mutations. We considered coupling this commercial panel with the Cytosponge sampling device as a result of these observed differences. As a result of the cystosponge™ sampling a large amount of squamous epithelium coupled with glandular Barrett's epithelium, microdissection is necessary. A hot-spot panel has certain advantages that make it a potentially useful tool for diagnosing dysplastic Barrett's disease.[22]

3.2.4. *Anomaly of the P53 gene*

Using P53 immunohistochemistry has been shown to improve diagnostic confidence in the latest British Society of Gastroenterology guidelines, 19 although this practice has not yet been widely adopted. In addition to whole-gene sequencing, an Immunocore is used to determine the P53 status. Assuming that mutations can occur anywhere along the gene, we sequenced the majority of coding exons rather than relying on TP53 hotspot analysis.

3.2.5. *Staining with Aur KA*

Copy number is determined by AurKA staining, and scoring is dichotomised for as much simplicity as possible. Patients receiving surveillance do not undergo clinical evaluation for clinical features, although Barrett's oesophageal segment length has long been recognized as a risk factor.[23]

3.3. **Eosinophilic Esophagitis**

Cytosponge is a safe, well-tolerated method for obtaining esophageal tissue samples, and the histopathologic examination of these specimens seems adequate. Cytosponges can be used to assess EoE histological activity with high sensitivity and specificity. A string test for esophageal secretions also detects eosinophil-derived proteins of mucosal inflammation in EoE.[24]

3.3.1. A comparison of cytosponge and endoscopy for evaluation

Comparing the Cytosponge to endoscopy and biopsy, it offers a promising method for measuring the presence of EoE in patients. Cytosponges are not biological specimens, but rather they yield histological specimens. In addition to staining for EDN, we evaluated the utility of this approach by directly measuring eosinophils. This technique was also found to be simple and reliable to use, yield a robust cellular specimen regardless of esophageal diameter, and be safe and well-tolerated.

By using cytosponge technology, samples can be generated using routine cytology laboratory techniques that are typically comparable to those obtained using histology techniques. As a result, additional histologic findings included eosinophilic abscess, basal cell hyperplasia, and spongiosis, suggesting that EoE can be more reliably monitored with the Cytosponge than finding based solely on esophageal eosinophilia.

It was also possible to stain the Cytosponge specimen for eosinophil degranulating protein EDN. The prominence of eosinophil extrusion of degranulated proteins into the extracellular tissue can be used in conjunction with either the esophageal string test or a biopsy to further confirm the diagnosis of EoE. Patients displaying clinical and demographic features of EoE with eosinophil counts below consensus thresholds further support this conclusion.[25]

A study was conducted to determine how accurate and feasible diet-directed therapy is for EoE based on the results of esophageal cytosponge testing. Comparing cytosponge guided food reintroduction to endoscopy, this study shows that it is accurate, safe, and relatively inexpensive.[26]

3.4. Samples of the oesophageal microbiota should be obtained as follows

After vortexing and centrifuging samples of cytosponge to remove cellular debris, samples were centrifuged at high speed to isolate microbial DNA. As measured by observed operational taxonomic unit (OTU) richness, Chao estimated total richness, and Shannon diversity index, microbial diversity was decreased in oesophageal adenocarcinoma tissue compared with tissue from healthy control patients. Oesophageal adenocarcinoma is enriched with *Lactobacillus fermentum*, and lactic acid bacteria dominate the microenvironment in seven out of fifteen cases. The Cytosponge produced a significant amount of microbial DNA in comparison with endoscopic brushes or quantitative PCR-based biopsies on oesophageal samples. Biopsy and brush samples showed a high percentage of taxa from Cytosponge samples, but more genera from the oral cavity and stomach were found, including *Fusobacterium*, *Megasphaera*, *Campylobacter*, *Capnocytophaga*, and *Dialister*. As measured by the observed OTU richness, Chao estimated total richness, and Shannon diversity index, Cytosponge detected decreased microbial diversity in patients with high-grade dysplasia as compared to control patients.[27]

3.5. Detection of dysplasia of the esophagus

3.5.1. The following fluorescent in situ hybridizations are available

For the collection of esophageal cell samples, sponge cytology is a safe, effective, and tolerable technique. Despite this, our data suggest that fluorescent in situ hybridization does not improve the sensitivity for detecting cancer in these samples. [28]

3.6. Diagnosis and management of other gastrointestinal disorders

The Cytosponge and endoscopy were used to examine all patients. Cytosponge may be useful in triaging patients with troublesome reflux symptoms because it detects a variety of benign oesophageal pathologies. Research into this area is warranted.[29]

3.7. An upper gastrointestinal endoscopy may aid in the triage of the COVID-19 pandemic

COVID-19 has severely reduced access to endoscopy services throughout the country. This could affect the outcome of oesophageal cancer surgery, as low endoscopy referral rates are related to poor outcomes. With the Cytosponge, patients with reflux symptoms can detect Barrett's oesophagus without an endoscopic examination. It is possible to measure intestinal metaplasia (TFF3) and dysplasia (Atypia and p53) using the Cytosponge system by swallowing a tethered capsule that collects oesophageal cells. Three clinical trials, including the recent BEST3 trial, have assessed the safety, acceptability, and diagnostic accuracy of this method. The study evaluated whether Cytosponge was able to triage patients with oesophageal alarm symptoms referred for urgent investigation under COVID-19.

In the wake of the COVID-19 pandemic, it has been possible to make this tool more widely adopted, but its use among a different group of patients than originally intended must be carefully examined. Cytosponge is safe for patients with eosinophilic oesophagitis, even though dysphagia was an exclusion criterion in previous studies. Among patients with mild-to-moderate dysphagia and other oesophageal symptoms, less than 4% of patients are asymptomatic at endoscopy, suggesting Cytosponge may be a useful test. The presence of abnormal cells, aberrant expression of p53, and insufficient swallowing posed high cancer risks. Among the patients in their small series, all had at least one high-risk feature.[30]

3.8. Combination of cytosponge and artificial intelligence

3.8.1. Pathologists' partners in coding

This was a challenging process to design a fully-automatic system that mimics the single "positive" or "negative" diagnosis that can be made by a pathologist. Most Barrett's esophagus cases were correctly identified by pathologists. Comparatively, the AI-based approach was able to identify 99% of cases, with both the approaches identifying the negative cases correctly.

A semi-automated triage system was instead developed under the direction of experienced pathologists. In other words, based on how clear the diagnosis and quality of each sample were, the results were categorised into eight different classes. In cases where the deep-learning model was deemed to be inadequate for handling a sample, pathologists assessed it manually. It could reduce pathologists' workload related to Cytosponge by 57% .[31]

3.9. Check for precancerous changes in the stomach mucosa

A growth of the gastro-intestinal tissue called gastric intestinal metaplasia (GIM) or a decrease in the size of the gastro-intestinal tissue called gastric atrophy (GA) is associated with an increased risk of developing gastric cancer. The use of endoscopic screening for detecting gastric cancer in low-medium risk areas is not cost-effective; currently, noninvasive ways of screening are not available. An increased diagnosis of Barrett's esophagus (BE) among reflux-symptomatic patients was seen in a randomized, controlled trial (BEST3) using Cytosponge-TFF3. In addition to a Cytosponge-TFF3-positive test and no endoscopic evidence of BE, patients who perform Cytosponge-TFF3 tests should undergo careful scrutiny of their stomach for signs of GIM or GA. In order to prove the relevance of Cytosponge-TFF3 testing for stomach pathologies, prospective studies are necessary.[32]

3.10. A Non-Endoscopic Test to Diagnose Esophageal Diseases and Helicobacter

Cytosponges and related tests may diagnose benign oesophageal disorders and Helicobacter infection. To confirm the Cytosponge's utility in this setting, a larger clinical study is needed.[33]

4. Conclusion

cytosponge is simple and well tolerated method for detecting barrett's disease, cytologic specimens TTF3 and FFPE, eosinophil-derived proteins of mucosal inflammation in EoE, decreased microbial diversity, dysplasia of the esophagus, precancerous changes in the stomach mucosa, Helicobacter and patients with reflux symptoms can detect Barrett's oesophagus without an endoscopic examination. Cytosponge with AI has the potential to reduce the workload of some pathologists and identify 99% of cases.

Compliance with ethical standards

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References

- [1] W Januszewics, RC Fitzgerald. Early detection and therapeutics. Mol. Oncol. 2019 Mar;13(3):599-613

- [2] M O'Donovan, RC Fitzgerald. Screening for Barrett's Esophagus: Are New High-Volume Methods Feasible? *Dig. Dis. Sci.* 2018 Aug;63(8):2105-2114
- [3] J Offman, RC Fitzgerald. Alternatives to Traditional Per-Oral Endoscopy for Screening. *Gastrointest. Endosc. Clin. N. Am.* 2017 Jul; 27(3):379-396.
- [4] Sahun WOOLLER .NHS hospital becomes the first in the world to use a 'sponge on a string' to detect oesophageal cancer in a Covid-safe way. *Daily mail* ; March 2021. Available at <https://www.dailymail.co.uk/health/article-9373475/Hospital-world-use-sponge-string-detect-oesophageal-cancer.html>
- [5] cytosponge for detecting abnormal cells in the oesophagus. Medtech innovation briefing [MIB240]; 15 December 2020. Available at <https://www.nice.org.uk/advice/mib240/chapter/The-technology>
- [6] ASGE Technology Committee, AJ Trindade, U Navaneethan, HR Aslaninan, MS Bhutani, K Krishnan, et al. Advances in the diagnosis and surveillance of Barrett's esophagus (with videos). *Gastrointest. Endosc.* 2019 Sep; 90(3):325-334.
- [7] CR Heberle, AH Omidvari, S Kroep, CY Kong, JM Inadomi, JH Rubenstein, et al. Cost Effectiveness of Screening Patients With Gastroesophageal Reflux Disease for Barrett's Esophagus With a Minimally Invasive Cell Sampling Device. *Clin. Gastroenterol. Hepatol.* 2017 Sep; 15(9):1397-1404.
- [8] T Benaglia, LD Shorples, RC Fitzgerald, G Lyratzopoulos. Health Benefits and Cost Effectiveness of Endoscopic and Nonendoscopic Cytosponge Screening for Barrett's Esophagus. *J. Gastro.* January 2013; 144(1):62-73.
- [9] cytosponge. 9 august 2021. Available at <https://www.nhsinform.scot/tests-and-treatments/non-surgical-procedures/cytosponge>
- [10] J Offman, B Muldrew, M O'Donovan, I Debiram-Beecham, F Pesola, I Kaimi, et al. Barrett's oESophagus trial 3 (BEST3): study protocol for a randomised controlled trial comparing the Cytosponge-TFF3 test with usual care to facilitate the diagnosis of oesophageal pre-cancer in primary care patients with chronic acid reflux. *BMC Cancer.* 2018 Aug 3; 18(1):784.
- [11] Swarupananda Mukherjee, Saumyakanti Giri, Pamelika Das, Subhasis Maity In *Cancer Therapy*; MedDocs Publishers LLC, Jun 10, 2019, pp 3.
- [12] DA Katzka, TC Smyrk, JA Alexander, DM Geno, RA Beitia, AO Chang, et al. Accuracy and Safety of the Cytosponge for Assessing Histologic Activity in Eosinophilic Esophagitis: A Two-Center Study. *Am. J. Gastroenterol.* 2017 Oct; 112(10):1538-1544.
- [13] M Freeman, J Offman, FM Walter, P Sasieni, SG Smith. Acceptability of the Cytosponge procedure for detecting Barrett's oesophagus: a qualitative study. *BMJ Open.* 2017 Mar; 1,7(3): e013901.
- [14] W Januszewicz, WK Tan, K Lehovsky, I Debiram-Beecham, T Nuckcheddy, S Moist, et al. Safety and Acceptability of a Nonendoscopic Esophageal Sampling Device – Cytosponge: A Systematic Review of Multicenter Data. *Clin. Gastroenterol. Hepatol.* 2019 Mar; 17(4):647-656.
- [15] Leigh-Ann Topfer. CADTH ISSUES IN EMERGING HEALTH TECHNOLOGIES INFORMING DECISIONS ABOUT NEW HEALTH TECHNOLOGIES. *CADTH.* Oct 2015;144.
- [16] Cytosponge™ Simple Clinic Test Offers Alternative to Endoscopy when Screening for Barrett's Oesophagus. August 2021. Available at <https://refluxuk.com/symptoms-and-diagnosis/diagnostic-tests/cytosponge/>
- [17] WK Tan, M di Pietro, RC Fitzgerald. Past, present and future of Barrett's oesophagus. *Eur. J. Surg. Oncol.* 2017 Jul; 43(7):1148-1160.
- [18] CS Ross-Innes, I Debiram-Beecham, M O'Donovan, E Walker, S Varghese, P Lao-Sirieix, et al. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. *PLoS Med.* 2015 Jan 29;12(1):e1001780.
- [19] RC Fitzgerald, M di Pietro, M O'Donovan, R Maroni, B Muldrew, I Debiram-Beecham, et al. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. *Lancet.* 2020 Aug 1; 396(10247):333-344.
- [20] J Offman, B Muldrew, M O'Donovan, I Debiram-Beecham, F Pesola, I Kaimi, et al. Barrett's oESophagus trial 3 (BEST3): study protocol for a randomised controlled trial comparing the Cytosponge-TFF3 test with usual care to facilitate the diagnosis of oesophageal pre-cancer in primary care patients with chronic acid reflux. *BMC Cancer.* 2018 Aug 3; 18(1):784.

- [21] H Chettouh, O Mowforth, N Galeano-Dalmau, N Bezawada, C Ross-Innes, S MacRae, et al. Methylation panel is a diagnostic biomarker for Barrett's oesophagus in endoscopic biopsies and non-endoscopic cytology specimens. *Gut*. 2018 Nov; 67(11):1942-1949.
- [22] A Katz-Sommercom, S Anand, S Inglew, Y Huang, T Roberts, N Galeano-Dalmau, et al. Application of a multi-gene next-generation sequencing panel to a non-invasive oesophageal cell-sampling device to diagnose dysplastic Barrett's oesophagus. *J. Pathol. Clin. Res.* 2017 Aug 24;3(4):258-267.
- [23] CS Ross-Innes, H Chettouh, A Achilleos, N Galeano-Dalmau, I Debiram-Beecham, S MacRae, et al. Risk stratification of Barrett's oesophagus using a non-endoscopic sampling method coupled with a biomarker panel: a cohort study. *Lancet gastroenterol. Hepatol.* 2017 Jan;2(1):23-31.
- [24] QM Nhu, FJ Moaward. New Developments in the Diagnosis and Treatment of Eosinophilic Esophagitis. *Curr Treat Options Gastroenterol.* 2019 Mar;17(1):48-62.
- [25] DA Katzka, DM Geno, TC Smyrk, P Lao-sirieix, A Mitrnadi, I Debriam et al. Accuracy, safety, and tolerability of tissue collection by Cytosponge vs endoscopy for evaluation of eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2015 Jan;13(1):77-83.
- [26] Jeffrey A. Alexander, David A. Katzka, Karthik Ravi, R C. Fitzgerald, Debra M. Geno, Crystal Tholen, et al. EFFICACY OF CYTOSPONGE DIRECTED FOOD ELIMINATION DIET IN EOSINOPHILIC ESOPHAGITIS. A PILOT TRIAL. *Gastroenterology.* May 2018; 154(6): s-76.
- [27] DRF Elliott, AW Walker, M O'Donovan, J Parkhill, RC Fitzgerald. A non-endoscopic device to sample the oesophageal microbiota: a case-control study. *Lancet Gastroenterol Hepatol.* 2017 Jan;2(1):32-42.
- [28] Haisley KR, Dolan JP, Olson SB, Toledo-Valdovinos SA, Hart KD, Bakis G, et al. Sponge sampling with fluorescent in situ hybridization as a screening tool for the early detection of esophageal cancer. *J. Gastrointest. Surg.* 2017; 21:215–221.
- [29] Paterson AL, Lao-Sirieix P, O'donovan M, Debiram-Beecham I, di Pietro M, Miremadi A, et al. Range of pathologies diagnosed using a minimally invasive capsule sponge to evaluate patients with reflux symptoms. *Histopathology.* 2017;70:203–210
- [30] M di Pietro, I Modolell, M O'Donovan, C Prince, ND Pilonis, I Debiram-Beechan, et al. Use of Cytosponge as a triaging tool to upper gastrointestinal endoscopy during the COVID-19 pandemic. *Lancet Gastroenterol Hepatol.* 2020 Sep;5(9):805-806.
- [31] Cancer Research UK. Cytosponge-AI combo could help doctors diagnose Barrett's esophagus. 16 April 2021. Available at <https://medicalxpress.com/news/2021-04-cytosponge-ai-combo-doctors-barrett-esophagus.html>
- [32] AV Hadjinicolaou, A Azizia, M O'donovan, I Debiram, RC Fitzgerald, M Di Pietro. Cytosponge-TFF3 Testing can Detect Precancerous Mucosal Changes of the Stomach. *Cli. Gastro. And hepato.* august 2021; 20(6): 1411-1412.
- [33] Maria O'Donovan, Pierre Lao-Sirieix, Rebecca Fitzgerald. Su1088 Non-Endoscopic Diagnostic Tests for Esophageal Diseases and H. pylori Using the Cytosponge. *Gastroenterology.* May 2012; 142(5): S-421.