NICE advice

Cytosponge for detecting abnormal cells in the oesophagus

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is Cytosponge. It is a minimally invasive oesophageal sampling device. The technology is used with a biomarker test to detect abnormal cells found in conditions such as Barrett's oesophagus.
- The **innovative aspects** are the 'sponge on a string' pill for collecting oesophageal cell samples. The pill is used to collect cells from the oesophagus, which can then be tested by an antibody test to detect Trefoil Factor 3 (TFF3).
- The intended **place in the care pathway** would be as a triage tool for an endoscopy to identify people at risk of oesophageal cancer.

- The **main points from the evidence** summarised in this briefing are from 5 studies (2 systematic reviews, 1 randomised controlled trial and 2 cross-sectional studies). A review of 5 studies showed that Cytosponge was significantly more acceptable compared with the endoscopy procedure. Another review of 13 studies reported a pooled result of sensitivity of 81% and specificity of 91% using Cytosponge for detecting Barrett's oesophagus. Randomised controlled trial results showed that the estimated adjusted relative risk of detecting Barrett's oesophagus was 10.6 (95% confidence interval 6.0 to 18.8) for Cytosponge followed by an endoscopy compared with the standard care group that had endoscopy at 12-month follow up. Three included studies reported the sponge detached from the string, in a total of 4 people.
- **Key uncertainty** around the evidence is that there is limited evidence from randomised controlled trials for the technology. One large trial included over 13,000 people from 109 GP surgeries, but Cytosponge uptake was low (around 25.6%).
- The **cost** of using Cytosponge is £280 (excluding VAT), including the cost of the device and the assay test. The cost of the diagnostic endoscopy upper gastrointestinal tract procedure with biopsy is estimated to be £407.

The technology

Cytosponge (Medtronic) is a single-use device used to collect cells from the lining of the oesophagus. It is known as a 'sponge on a string' pill test. Cytosponge consists of a spherical sponge in a dissolvable capsule, which is attached to a thread. When the capsule is swallowed, it expands into a small, rough-textured sponge in a person's stomach. After around 5 to 7 minutes, the sponge is pulled back up, collecting some of the cells lining the oesophagus.

The collected sample is sent for laboratory analysis to detect any cell abnormalities. As a part of quality control, haematoxylin and eosin staining is done to evaluate the morphology and check the presence of gastric cells on the sample to make sure that the capsule reached the stomach. The lab test is an antibody test to identify Trefoil Factor 3 (TFF3), which is only found in precancerous cells. Cells that test positive for TFF3 are likely to come from people who have Barrett's oesophagus, which increases the risk of developing oesophageal cancer. The Cytosponge test is intended as a triage test for an endoscopy in people with heartburn or reflux symptoms who need acid-suppressant medicine.

This device is contraindicated for people who:

- are experiencing dysphagia or swallowing disorders
- have anatomical abnormalities of the oesophagus or stomach
- have previously had oesophagus ablation or a mucosal resection or invasive oesophageal or gastric procedure in the past 2 months
- have portal hypertension or oesophageal varices
- are pregnant
- are taking anticoagulants.

Innovations

Cytosponge is a minimally invasive device to detect abnormal cells in the oesophagus. The 'pill on a string' cell collection method is novel. This is combined with an immunohistochemical assay (TFF3).

Current care pathway

Endoscopy is the current standard practice for diagnosing Barrett's oesophagus. It allows direct visualisation of the oesophageal mucosa, specifically for assessing any changes that may indicate dysplasia or cancer in the oesophagus. During the endoscopy, samples are taken for biopsy from any abnormal areas detected. It is an invasive procedure and needs sedation. Bleeding and perforation are rare reported complications of endoscopy.

The British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus recommend that the diagnosis of Barrett's oesophagus should be confirmed histopathologically from oesophageal biopsies. The guideline notes that using an immuno-based assay shows promise for enhancing the sensitivity and specificity of a cytology collection device (Cytosponge). But, results of further trials are needed before such technologies can be recommended for use outside of research.

Population, setting and intended user

Cytosponge is intended for collecting surface oesophagus cells samples that are sent to the lab for analysis, like a biopsy sample. It is for people seeing their GP with heartburn or reflux symptoms needing acid-suppressant medicine.

The test can be done in primary care such as a GP practice. It is also a triage tool that can help doctors decide who needs to have a follow-up endoscopy.

Costs

Technology costs

The cost of Cytosponge is £280 (excluding VAT). This includes the cost of the device itself, the assay test, and haematoxylin and eosin stain.

Costs of standard care

The costs for standard care (diagnostic endoscopic upper gastrointestinal tract procedure with biopsy, FE21Z) is estimated to be £407 (NHS tariff 2020/21). This cost includes staffing costs, which are not included in the cost of Cytosponge.

Resource consequences

The company states that several NHS trusts are using the technology. Two experts noted that the device is not widely used in the NHS outside of trials.

A cost-effectiveness analysis done in the US showed that Cytosponge was cost effective as a screening tool when compared with no screening and endoscopic screening. These results were sensitive to Cytosponge cost within a plausible range of values (Heberle et al. 2017).

The comparison of 6 screening tests included sedated gastroscopy, Cytosponge with TFF3 biomarker, sponge on a string with methylated DNA markers, breath testing, hospital-based transnasal endoscopy, and mobile unit-based transnasal endoscopy. The US study showed that Cytosponge had favourable incremental cost-effectiveness ratios in both population-based and gastro-oesophageal reflux disease-specific screening for Barrett's oesophagus (Sami et al. 2019).

Regulatory information

Cytosponge is a CE-marked I medical device, covering the device as a cell collection

device and the laboratory processing and Trefoil Factor 3 (TFF3) staining.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Barrett's oesophagus is more common in men and people who are over 50. Sex and age are protected characteristics under the Equality Act. If a person has Barrett's oesophagus, they may be more likely to get oesophageal cancer. People with cancer are protected under the Equality Act from the point of diagnosis.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with NICE's interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology.

Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Five studies are summarised in this briefing that are considered the most relevant to the technology. They include 2 systematic reviews, 1 randomised controlled trial and 2 cross-sectional studies. One systematic review analysed data of 2,418 people from 5 studies to evaluate the safety and acceptability of Cytosponge (Januszewicz et al. 2019). The other review analysed the efficacy and safety of Cytosponge for diagnosing oesophageal diseases (Iqbal et al. 2018). The randomised controlled trial is a multicentre UK study (n=109 in GP surgeries) and compared the risk of detecting Barrett's oesophagus for people having Cytosponge with those having standard care.

The clinical evidence with its strengths and limitations are summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The review by Januszewicz et al. (2019) is low quality because it was limited to data largely from Barrett's Esophagus Studies (BEST). Also, there was no quality assessment of the individual studies. Iqbal et al. (2018) is a moderate quality review with pre-defined eligibility criteria and quality assessment of the included studies. But, methods for data analysis were not described in the review.

The randomised controlled trial had over 13,000 people who were randomised, but only a small proportion of people had the Cytosponge procedure (n=1,750; 25.6%). Two cross-sectional studies were abstracts. Information provided in the abstracts was limited, and the quality of these studies was not assessed.

Fitzgerald et al. (2020)

Study size, design and location

A multicentre, pragmatic, randomised controlled trial of people from 109 GP surgeries who were having medicine for gastro-oesophageal reflux in England.

Intervention and comparator

A total of 6,834 people in the intervention group had a Cytosponge Trefoil Factor 3 (TFF3) test and 6,388 people in the usual care group had standard care. In the usual care group, people had prescriptions for acid-suppressant medicine and their GP might have provided lifestyle advice or referral for an endoscopy, depending on symptom severity.

Key outcomes

The analysis showed that 140 people were diagnosed with Barrett's oesophagus in the intervention group (127 people who had the Cytosponge-TFF3 procedure, and 13 people who did not), compared with 13 people diagnosed in the usual care group. The estimated adjusted relative risk of detecting Barrett's oesophagus was 10.6 (95% confidence interval [CI] 6.0 to 18.8) comparing the intervention group with the usual care group in a 12-month follow up.

A total of 1,750 people chose to have the Cytosponge procedure. Of 1,654 people in the

intervention group who swallowed Cytosponge, 221 (13%) with a positive TFF3 result had a subsequent confirmatory endoscopy. Of these, 127 people (57%) were diagnosed with Barrett's oesophagus and 4 people (2%) were diagnosed with stage I oesophago-gastric cancer. The Cytosponge TFF3 procedure had a positive predictive value of 59% (131 of 221 confirmatory endoscopies in people with a positive Cytosponge TFF3 result) for Barrett's oesophagus, dysplasia or oesophago-gastric cancer.

Less than 1% (n=9) of people were diagnosed with dysplastic Barrett's oesophagus (n=4) or stage I oesophago-gastric cancer (n=5) in the intervention group. No one was diagnosed with dysplastic Barrett's oesophagus or stage I oesophago-gastric cancer in the usual care group (who had the endoscopy procedure).

In 1 person, the Cytosponge detached from the thread, needing endoscopic removal. The most common side effect was a sore throat in 63 (4%) of 1,654 people.

Strengths and limitations

Over 13,000 people were included in the study analysis. Randomisation happened at a GP clinic level and at an individual patient level. People in the Cytosponge group were offered a choice of Cytosponge or usual care. People who chose to have the Cytosponge procedure might have had more problematic symptoms than those who did not choose to have the procedure. More women than men had the Cytosponge procedure.

Leeds et al. (2020, an abstract)

Study size, design and location

A cross-sectional study of 113 people at risk of oesophageal adenocarcinoma. The study location was not reported in the abstract.

Intervention and comparator

The Cytosponge test was the study intervention. No comparator.

Key outcomes

A total of 76 (67.2%) people were offered the Cytosponge procedure and 46 (60.5%) chose to have the procedure. Most people (n=45; 97.8%) completed the procedure. People

who chose to have the procedure were significantly more likely to have a diagnosis of gastro-oesophageal reflux disease compared with those who chose to not have the test (69.6% compared with 36.7%; p=0.009). Also, they were more likely to have never smoked (p=0.09), have a higher body mass index (p=0.054) and have a morning appointment (p=0.12). The most common reasons for not having the test were 'not interested' (46.7%) and 'not enough time' (23.3%).

Two people (4.4%) had a positive test; 1 had a 4-cm Barrett's oesophagus segment, and the other had diffuse gastric intestinal metaplasia.

Strengths and limitations

This is a cross-sectional study. Strengths and limitations have not been assessed because limited information was reported in the abstract.

Januszewicz et al. (2019)

Study size, design and location

A systematic review assessed safety and acceptability of Cytosponge. A total of 5 prospective trials were included in the review.

Intervention and comparator

Cytosponge was used to collect oesophageal cells in the intervention group.

Key outcomes

Data were analysed from 2,418 people from 5 studies between May 2008 and August 2017. Of them, 2,284 people could complete the Cytosponge test. The overall acceptability of Cytosponge was satisfactory, with a median score of 6.0 (interquartile range 5.0 to 8.0). This was significantly higher when compared with endoscopy without sedation, with a median score of 5.0 (interquartile range 3.0 to 7.0; p<0.001). But, it was lower than endoscopy with sedation (medical score of a visual analogue scale 8.0, interquartile range 5.0 to 9.0; p<0.001).

There were 84 people (3.5%) who could not swallow the Cytosponge. The proportion of people who were unable to swallow the device was over 2 times higher in people with

Barrett's oesophagus than those with gastro-oesophageal reflux disease. Of the 2,672 Cytosponge tests done, there were 12 serious adverse events reported, and 2 could be directly associated with Cytosponge. These included 1 detachment of the sponge and 1 pharyngeal bleeding after Cytosponge withdrawal. The others were related to endoscopic therapy done immediately after the Cytosponge test.

Strengths and limitations

The review included 5 large prospective studies. Acceptability scores were not available for people enrolled in the BEST1 trial.

Shaheen et al. (2019, an abstract)

Study size, design and location

A cross-sectional study of 197 people with Barrett's oesophagus (n=129) or gastro-oesophageal reflux disease (n=62) from 6 US sites.

Intervention and comparator

Cytosponge was the study intervention. No comparator.

Key outcomes

Of 191 people in the study, 99.5% could swallow the Cytosponge. There was no significant difference in the acceptability of Cytosponge compared with the endoscopy procedures. Most people (93%) would be willing to repeat Cytosponge if the doctor indicated that it was medically necessary. There were 65% of people who preferred Cytosponge over endoscopy.

The most common adverse events included oropharyngeal pain (n=4; 2%) and throat irritation (n=2; 1%). The sponge detached in 2 people, both were retrieved during a subsequent endoscopy.

Strengths and limitations

This is a cross-sectional study. Strengths and limitations were not assessed because

limited information was reported in the abstract.

Iqbal et al. (2018)

Study size, design and location

A systematic review assessed safety and efficacy of Cytosponge in the diagnosis of oesophageal pathology. A total of 13 studies were included in the review (8 UK studies).

Intervention and comparator

Cytosponge was used to collect oesophageal cells in the intervention group. The efficacy was compared with upper gastrointestinal endoscopy with endoscopic biopsy, the gold standard test.

Key outcomes

A total of 6 studies were identified, which observed the efficacy of the Cytosponge in screening Barrett's oesophagus for people having upper endoscopy (esophagogastroduodenoscopy). A pooled sensitivity and specificity of Barrett's oesophagus detection using sponge devices were 81% and 91%, respectively.

Strengths and limitations

The review authors noted that most studies of Cytosponge were done by a single group of authors.

Sustainability benefits

Cytosponge is a single-use technology.

Recent and ongoing studies

Introducing a non-endoscopic diagnostic test into the clinical pathway to identify high-risk patients with Barrett's oesophagus. ISRCTN registry identifier: ISRCTN91655550. Status: recruiting. No interim results published. Indication: oesophageal cancer. Devices: Cytosponge. Last update on 30 June 2020.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 4 experts were familiar with or had used this technology before.

Level of innovation

Three experts agreed that this technology is an innovative way to identify people who are at increased risk of having Barrett's oesophagus. Two experts noted that in primary care, people with reflux symptoms commonly had anti-acid medicines, and they were unlikely to be referred for endoscopy, leaving their Barrett's oesophagus undiagnosed. Currently, the standard way to diagnose Barrett's oesophagus is a gastroscopy and biopsy. All experts agreed that Cytosponge can be used as a screening or triage tool to identify people who need upper gastrointestinal endoscopy. One expert is aware of a similar device called EsophaCap but it is not CE marked and not available in the NHS. Another expert also noted that, compared with classic endoscopy, transnasal endoscopy is a slightly less invasive procedure and could be done in a community setting. However, it is more invasive than Cytosponge.

Potential patient impact

Early diagnosis of oesophageal cancer or identifying people who are at risk of developing oesophageal cancer is the main benefit identified by all experts. Cytosponge enables people to access diagnostics such as endoscopy earlier, especially for those with reflux disease. This leads to improved outcomes and treatment for people with oesophageal cancer. One expert considered that Cytosponge could also be useful to monitor eosinophilic oesophagitis. During the COVID-19 pandemic, Cytosponge could be a useful triaging test in secondary care for people with oesophageal symptoms. It may also be favoured by people who are reluctant to attend an endoscopy in hospital because of the risk of COVID-19. All experts agreed that people with reflux disease and other risk factors for Barrett's oesophagus such as obesity, smoking and family history would mostly likely benefit from the technology.

Two experts considered that Cytosponge should be incorporated in the pathway for

management of gastro-oesophageal reflux disease in primary care.

Potential system impact

All experts thought Cytosponge could be cost saving to the NHS. One expert noted that the cost of the Cytosponge procedure itself is significantly lower than endoscopy. For instance, only 1 person is needed to administer Cytosponge (usually a nurse) compared with 1 doctor and 2 nurses, plus recovery nurses who are needed for endoscopy. Three experts considered that Cytosponge could improve NHS resource availability in secondary care. This is because it is given in primary care and enables targeted endoscopy with an improved pick-up rate of pathology.

One expert considered that Cytosponge is likely to lead to cost savings because early diagnosis of oesophageal cancer could have more curative treatment available. It could also reduce surgical and end of life treatment.

General comments

The experts noted that sore throat is common side effect after Cytosponge. Detachment is a possible severe adverse event but other adverse events are rare. The experts considered that Cytosponge is well tolerated and would be a lower-risk procedure compared with endoscopy. All experts agreed training is needed for primary care nurses who give treatment with Cytosponge. One expert thought the uptake would depend on the infrastructure in place to train practice nurses to give people treatment with the sponges, collect the sponges, process them and then give results in an accessible format.

Expert commentators

The following clinicians contributed to this briefing:

- Mr Bhaskar Kumar, consultant oesophago-gastric and laparoscopic surgeon oesophago-gastric cancer lead, Norfolk and Norwich University Hospitals NHS Foundation Trust. Did not declare any interests.
- Mr Christopher J Peters, consultant upper gastrointestinal and general surgeon and clinical senior lecturer, Imperial College London. Did not declare any interests.

- Dr Massimiliano di Pietro, senior clinician scientist, University of Cambridge. Investigator in BEST2, BEST3 and ongoing DELTA study.
- Dr Oliver Stovin, GP, joint cancer lead, Cambridge and Peterborough clinical commission group. On a surveillance programme for Barrett's oesophagus.

Development of this briefing

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