
CADTH ISSUES IN EMERGING HEALTH TECHNOLOGIES

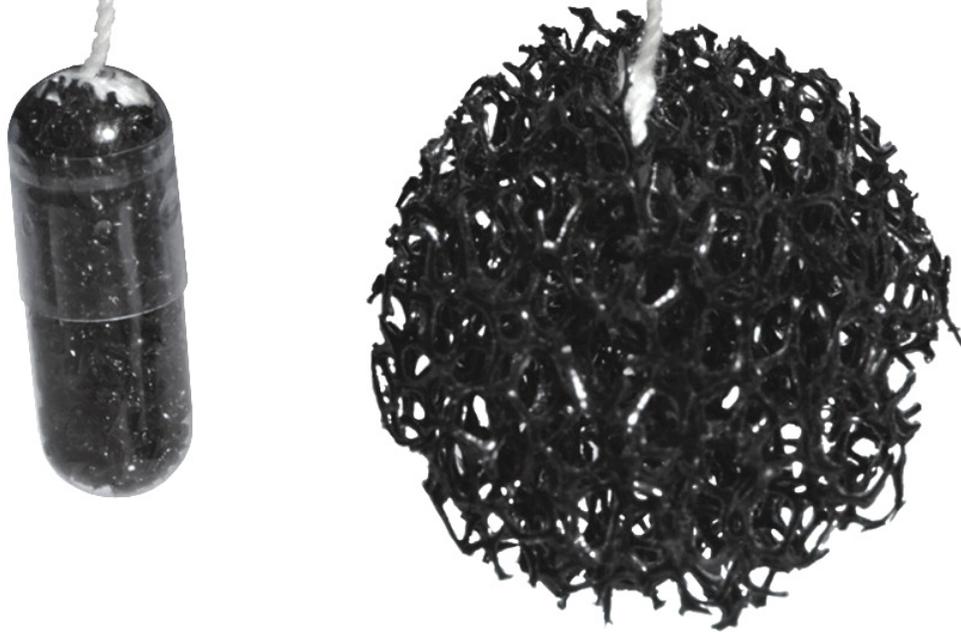
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The Cytosponge:
An Alternative to
Endoscopy in Detecting
Barrett Esophagus

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Summary

- Barrett esophagus, also called Barrett's esophagus (BE), can be a precursor to esophageal adenocarcinoma – the most common type of esophageal cancer in Canada. Identifying individuals with BE allows them to be monitored, and if necessary, treated to remove abnormal cells and reduce their risk for developing esophageal cancer.
- Endoscopy and biopsy, the standard for identifying BE, is an expensive procedure that is uncomfortable for patients, requires sedation, and carries some risks.
- The Cytosponge is a small mesh sponge within a soluble gelatin capsule that can safely be administered orally by a nurse in primary care settings to collect esophageal cells for analysis. In combination with biomarker analysis, the Cytosponge has good sensitivity and specificity for detecting individuals likely to have BE.
- Use of the Cytosponge with biomarker analysis could improve identification of individuals with BE through a test that is less onerous for patients than endoscopy, as well as less costly.

Background

Barrett's esophagus (BE) is a benign condition where abnormal cells develop in the lining of the esophagus (the digestive tube that connects the throat to the stomach). Individuals who have experienced long-term gastroesophageal reflux, commonly known as acid reflux or heartburn, are more likely to develop BE, because chronic exposure to regurgitated stomach acids inflames the esophageal lining.

In some individuals, the abnormal Barrett's cells in the esophagus may change to low-grade and then high-grade dysplasia (abnormal tissue). Dysplasias can be a precursor to esophageal adenocarcinoma, one of the two main types of esophageal cancer.^{2,3}

Although BE confers a higher risk for esophageal adenocarcinoma and is present in more than 80% of new cases of esophageal adenocarcinoma, most individuals with BE will not develop esophageal cancer.^{3,8} Moreover, BE does not always follow a linear path from abnormal tissue proliferation (metaplasia, to low- and then high-grade dysplasia) to esophageal cancer, and in some patients, BE can regress.²

Early detection and monitoring of BE – and, if necessary, treatment to remove dysplasia – may prevent the development of esophageal cancer or allow for it to be treated at an earlier stage.⁹ The five-year survival rate for early-stage esophageal adenocarcinoma, where cancer is confined to the superficial layers of the lining of the esophagus, is about 95%.⁴

Figure 1: The Cytosponge



Source: Kadri et al. 2010.¹ (Licensed under [CC BY-NC 2.0](#))

However, not all individuals with BE have symptoms of chronic gastroesophageal reflux,¹⁰ and most cases of esophageal cancer are not detected until an advanced stage.^{3,11} The five-year survival rate when advanced disease is present at diagnosis (cancer involving deeper esophageal tissue, the lymph nodes, or spread elsewhere in the body) ranges from 5% to 40%.^{4,6,12}

The Technology

The Cytosponge (Medtronic GI Solutions) is a single-use device used to collect cells from the lining of the esophagus. It consists of a small mesh sponge, about 30 mm in diameter, contained in a gelatin capsule and attached to a string.¹¹ The patient swallows the capsule with water and the gelatin coating dissolves once the Cytosponge reaches the stomach. The patient may be offered a lidocaine throat spray to reduce discomfort. After approximately five minutes, the health care provider uses the string to retrieve the expanded sponge.¹ As it is retrieved, the slightly abrasive mesh collects cells along the length of the esophagus. The collected cells are analyzed using immunohistochemical staining to detect a biomarker that has been validated as an indicator of BE: Trefoil factor 3 (TFF3).^{6,11,13,14}

Regulatory Status

The Cytosponge does not have Health Canada licencing approval and when it may become available in Canada is not yet known. The Cytosponge has a CE Marking, which allows it to be marketed in Europe,¹⁵ and received United States (US) Food

and Drug Administration 510(k) approval as a Class II device in 2014.¹⁶ The sponge was developed by a United Kingdom (UK) research group at the University of Cambridge/Medical Research Council (MRC) and is now licensed to Medtronic GI Solutions. The Cytosponge is expected to be commercially available in the US and the UK in late 2015 to 2016.¹⁵

Patient Group

BE and esophageal adenocarcinoma have the same risk factors: long-term gastroesophageal reflux disease, obesity, smoking, Caucasian ethnicity, hiatal hernia, family history, and older age.^{3,11,17-19} BE is much more common in men than in women and is usually diagnosed at around 55 to 60 years of age.²⁰ Because these are well-defined risk factors, those with multiple risks and who might benefit most from screening for BE can be fairly readily identified.^{9,11,21}

One Canadian study found that of patients in primary care who were being investigated for chronic gastrointestinal reflux disease, 2% had BE.²² The Canadian Digestive Health Foundation estimates that five million Canadians experience gastroesophageal reflux at least once per week, and approximately 800,000 Canadians have BE.¹⁷ However, most individuals with BE (one estimate is more than 80%) have not been diagnosed and are therefore not being monitored to detect and treat high-grade dysplasia or early esophageal cancer at a curable stage.^{6,9,23}

In 2015, an estimated 2,200 Canadians will be diagnosed with cancer of the esophagus (1,700 men and 500 women).²⁴

Esophageal adenocarcinoma and squamous cell carcinoma are the two main subtypes of esophageal cancer. Of these, esophageal adenocarcinoma is now the most common type in Canada, particularly in men.¹²

Over the past 30 years, Western countries have seen an increase in the incidence of esophageal adenocarcinoma, though recent data suggest this increase may have reached a plateau.^{4,11} In Canada, while the overall incidence of esophageal cancer has been similar since the 1980s, the number of cases of squamous cell esophageal cancer has decreased (due to declining rates of smoking). However, the incidence of esophageal adenocarcinoma has doubled (because of increasing rates of obesity and gastroesophageal reflux disease).^{12,25}

Current Practice

As BE does not cause symptoms, most patients are being investigated for symptoms of gastroesophageal reflux or dyspepsia (indigestion, nausea, bloating, or upper abdominal pain).²⁰ The evidence on the benefits of screening for BE is currently unclear, but both US and UK guidelines recommend screening patients with chronic gastroesophageal reflux and other risk factors.^{18,26} Endoscopy (upper gastrointestinal endoscopy or gastroscopy) with sedation, followed by tissue biopsy, is the standard test for identifying BE.¹⁸ However, endoscopy is costly; requires special expertise (including anaesthesiology); is invasive, inconvenient, and uncomfortable for patients; and is not without risk.^{27,28,29} A further disadvantage is the variation in interpretation and errors in diagnosis (both missed cases and over-diagnosis) of BE by endoscopists and pathologists.^{30,31} As with the Cytosponge test, the sensitivity of endoscopy is better when longer segments of BE tissue are present.²⁰

Individuals diagnosed with BE will already likely be receiving drug treatment, such as with proton pump inhibitors, to treat symptoms of gastroesophageal reflux.³² Depending on the type of abnormal cells present and the size of the Barrett's segment, they may receive either surveillance endoscopy at different intervals to monitor disease progression or minimally invasive, endoscopic treatments to remove the dysplastic cells.^{9,18}

Until recently, the main treatment option for BE with high-grade dysplasia, or early esophageal cancer, was esophagectomy (removal of the esophagus) – a major surgical procedure with a high risk of complications and impact on subsequent quality of

life.^{1,32} Less invasive, endoscopic treatment options now include endoscopic resection of the dysplasia, argon plasma coagulation, spray cryotherapy, photodynamic therapy, and radiofrequency ablation.^{9,32} Radiofrequency ablation is now recommended as a preventive measure for both low-grade and high-grade dysplasia in BE.³³⁻³⁵ The availability of these less risky treatment alternatives to esophagectomy also makes screening for BE more appealing.¹

Methods

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the Grey Matters checklist (<http://www.cadth.ca/resources/grey-matters>). No methodological filters were applied. The search was limited to English-language documents published before June 5, 2015. Regular alerts were established to update the search until August 24, 2015.

The Evidence

A recent UK case-control study (BEST2) assessed the safety, acceptability to patients, and diagnostic accuracy of the Cytosponge with TFF3 biomarker testing, compared with endoscopy and biopsy for the diagnosis of BE.¹³ The study was conducted at 11 hospitals and included 1,110 participants; 463 individuals with dyspepsia (indigestion) and symptoms of gastroesophageal reflux formed the control group and 647 individuals with a previous diagnosis of BE were the case group. Participants in both groups received the Cytosponge procedure, followed by endoscopy. Participants were allowed to choose either sedation or local anaesthetic spray before their endoscopy. The test results were reviewed by two researchers and a histocytopathologist, all of whom were blinded to the patient's initial clinical status.¹³

More than 93% of the participants (n = 1,042) were able to swallow the Cytosponge. Increased body mass index (BMI) was associated with more difficulty in swallowing the device.¹³ More than 97% of the participants scored the Cytosponge experience as 3 or higher ("mildly unpleasant or better") on a 10-point scale from 0 ("worst imaginable experience") to 10 ("very enjoyable experience"), with 5 representing neutral ("neither pleasant nor unpleasant"). This rating was described as significantly higher than participants' rating of endoscopy (the equivalent

percentage for endoscopy was shown only graphically).¹³ Approximately a third of the participants rated both procedures equally, while another third preferred the Cytosponge. Patients who did not have sedation for their endoscopy were more likely to give the Cytosponge procedure a higher score. Patient scores of the Cytosponge were lower than in an earlier pilot study, where tests were conducted in a community care setting.¹ The lower acceptability score may have been because these patients were about to undergo endoscopy and were in a clinical setting.¹³

The sensitivity and specificity of the Cytosponge-TFF3 test for diagnosing BE were 79.9% and 92.4%, respectively.¹³ The false-positive rate was 7.6%, which is within the range of false-positives found with current colorectal cancer screening tests.¹³ The researchers also found an association between the false-positive tests and patients at higher risk for gastric cancer. Test sensitivity was higher when longer segments of Barrett's tissue were present (these carry a higher risk for becoming cancerous). Sensitivity was also higher in participants who underwent two Cytosponge tests.¹³ Neither sensitivity nor specificity was affected by age, sex, or BMI. Risk stratification of patients who tested positive for the TFF3 biomarker (to identify those most at risk for cancer) could be improved by screening for additional markers, such as TP53 mutations, which indicate the presence of high-grade dysplasia.¹³

Drawing from 12 UK general practices, the BEST1 study examined patient acceptability and the accuracy of the Cytosponge and TFF3 biomarker test in patients with a history of gastroesophageal reflux.¹ Of the 504 study participants, 501 were able to swallow the Cytosponge device. Compared with endoscopy, the sensitivity and specificity of the test were 73.3% and 93.8% for detecting BE of 1 cm or more in size. The measures for BE segments of 2 cm or more were 90.0% and 93.5%.¹ Scores from the completed surveys of 496 study participants (at baseline) indicated that most patients had low levels of anxiety before and after the test, although a subset (141 patients, or 24.4%) reported high anxiety both before swallowing the sponge and at follow-up.¹

In an early UK "proof-of-principle" study of the Cytosponge, 43 patients with known BE (diagnosed by endoscopy and biopsy) and 54 healthy volunteers received the Cytosponge test. The overall rating of the acceptability of this test was 4 on a 10-point scale from 0 ("worst imaginable experience") to

10 ("very enjoyable experience"), with 5 representing "neither pleasant nor unpleasant."²³ Of the patients with known BE who had already experienced endoscopy, 80% stated they would prefer to have surveillance with the Cytosponge than endoscopy. Both the sensitivity and specificity of the Cytosponge were higher than 67%, and the sensitivity was higher (76%) in patients with longer segments (> 3 cm) of BE.²³

Adverse Effects

Three serious adverse events (one case of atrial fibrillation and two cases of bleeding) were reported in the UK case-control study, but these were associated with the endoscopy or biopsy procedures. No serious adverse events associated with the Cytosponge were reported.¹³ Some patients (16.7%) experienced minor bleeding abrasions due to the Cytosponge, but these did not require treatment.¹³

Similarly, no serious adverse events were reported in the 2010 study among the 501 (from a total of 504) participants who were able to swallow the Cytosponge.¹

Administration and Cost

Across Canada, gastrointestinal endoscopy is performed by different clinical specialists, including internists, otolaryngologists, thoracic surgeons, gastroenterologists, colorectal surgeons, and family doctors.³⁶ Endoscopy can take from 15 to 30 minutes; patients are required to fast for at least eight hours before the procedure. They may request sedation.

In comparison, the Cytosponge is suitable for use in primary care and can be administered by a nurse.¹¹ The time required for the nurse to explain the process to the patient and administer the Cytosponge test is less than 10 minutes.¹³ Nurses are trained to administer the test in one training session.

Immunohistochemical staining and interpretation of Cytosponge samples may involve additional laboratory staff time and costs. If necessary, test samples can be stored (at 4°C) for several weeks.¹³ Biomarker testing can be performed in a centralized laboratory to ensure better quality control.

A 2013 UK study modelled the cost-effectiveness of no screening versus endoscopic versus non-endoscopic (i.e., Cytosponge) screening for BE.³⁷ The researchers determined that, in comparison with no screening, Cytosponge screening

of 50-year-old men with a history of gastroesophageal reflux is cost-effective, and would reduce mortality from esophageal cancer. The Cytosponge costs used in the model (converted from UK pounds to US dollars) were as follows: manufacturing cost per Cytosponge, US\$15; test administration, US\$11; and laboratory costs, US\$61.00.

The 2014 annual report of the UK's Medical Research Council's technology transfer agency, MRC Technology, noted: "Cytosponge and associated analysis could cost the NHS £50 per examination, compared to £200 per endoscopy."¹⁵ In a 2012 review, the estimated costs of standard endoscopy were considerably higher – at US\$930 and £520 per patient.³¹

Information from another UK study found that of 161 referrals for endoscopy from general practitioners, one in six patients could have received the Cytosponge test instead.³⁸ This would have reduced costs and wait-lists for endoscopy, enabled "rapid bedside testing," and provided a less invasive test option for patients unwilling to undergo endoscopy.³⁸

Concurrent Developments

Transnasal esophagoscopy (transnasal endoscopy) is another alternative to conventional endoscopy for viewing the esophagus.¹¹ The procedure is performed in the physician's office, and only topical anaesthesia is needed. A tiny, "ultrathin" endoscope is passed through one of the nasal passages and into the esophagus; the lining of the esophagus is then visible and abnormal tissue can be biopsied as needed. A UK review noted that the cost of ultrathin, transnasal endoscopes is similar to the cost of standard endoscopes (from £20,000 to £25,000), and as these also require specialist expertise, the per-patient cost of an endoscopy is similar.³¹

Capsule-based imaging of the esophagus, such as with the PillCam ESO and ESO 2 (Given/Covidien/Medtronic), is now possible via wireless, ingestible capsules that record pictures of the esophageal wall as they pass through the digestive tract. These imaging capsules do not require that patients are sedated, but, unlike endoscopy, they cannot collect specimens for analysis.¹¹ The UK review estimated that ingestible capsules cost approximately £350 per capsule, with the associated workstation equipment costing £20,000.³¹

In Europe, another sponge device, the Oesotest (Actimed SA, Switzerland) has been used for cytological sampling in patients at high risk for squamous cell esophageal cancer screening³⁹ and is also being investigated for BE.⁴⁰ In the US, Capnostics, LLC appears to be in the early stages of launching a similar sponge cytology on a string device (a "bottle brush" cellular retrieval system) for use in the detection of BE and upper gastrointestinal disorders.⁴¹

An older, string-based technology for sampling fluid and cells from the digestive tract, the Entero-Test (HDC Corporation, US), is used in the diagnosis of gastrointestinal disorders, such as giardiasis and eosinophilic esophagitis (exposure to certain food antigens that causes inflammation and strictures to form in the esophagus).⁴² The Entero-Test is also called the "string test," as the string is enclosed in a gelatin capsule and the cell samples adhere to the string itself.⁴²

Like the Entero-Test, the Cytosponge may be an alternative to endoscopy and biopsy for collecting mucosal samples in patients with eosinophilic esophagitis, and other gastrointestinal diseases, including *Helicobacter pylori*.⁴³⁻⁴⁷

Test panels that incorporate several biomarkers, rather than a single one, are also under investigation. Such panels may improve test accuracy, as well as the ability to identify those patients at the highest risk for developing esophageal cancer.^{30,31,48}

Ongoing studies of the Cytosponge are expected to provide additional evidence for the use of the technology for other potential indications, including squamous cell esophageal cancer,^{49,50} and for monitoring patients with BE after endoscopic treatments.⁵¹

Rate of Technology Diffusion

The Cytosponge device is not yet used in Canada. However, the increasing demand for endoscopy services may stimulate the adoption and diffusion of this technology. Canada's aging population is reflected in many aspects of health care, including the rising demand for gastrointestinal endoscopy services.⁵² A recent analysis of Canadian Institute for Health Information (CIHI) data found a nationwide average increase of 16.4% in the number of upper gastrointestinal endoscopies performed from 2004 to 2005 and from 2008 to 2009.⁵³

Implementation Issues

The psychological impact of screening individuals at risk for BE requires further investigation, given the uncertainty of whether BE remains a benign condition or becomes a precursor to esophageal cancer.³¹ For example, the benefits that might be gained from minimally invasive treatments that can prevent or treat esophageal cancer if it is detected at an early stage will influence the desirability of earlier screening.³¹

Additional histocytology staff may be needed for preparing and interpreting the Cytosponge samples.

Use of the Cytosponge and biomarker testing in those with multiple risk factors for BE may reduce the wait times and costs associated with endoscopy.³⁸ However, BE is currently underdiagnosed and only a small percentage of those with gastroesophageal reflux receive an endoscopy.¹³ Because patients find the Cytosponge to be a more acceptable test, it may encourage screening for BE in the at-risk population. This may increase the overall number of patients identified and treated for BE and, consequently, wait times for and costs associated with endoscopy.

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