Acceptability and accuracy of a non-endoscopic screening test for Barrett’s oesophagus in primary care: cohort study

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ABSTRACT
Objectives To determine the accuracy and acceptability to patients of non-endoscopic screening for Barrett’s oesophagus, using an ingestible oesophageal sampling device (Cytosponge) coupled with immunocytochemistry for trefoil factor 3.
Design Prospective cohort study.
Setting 12 UK general practices, with gastroscopies carried out in one hospital endoscopy unit.
Participants 504 of 2696 eligible patients (18.7%) aged 50 to 70 years with a previous prescription for an acid suppressant (H2 receptor antagonist or proton pump inhibitor) for more than three months in the past five years.
Main outcome measures Sensitivity and specificity estimates for detecting Barrett’s oesophagus compared with gastroscopy as the ideal method, and patient anxiety (short form Spielberger state trait anxiety inventory, impact of events scale) and acceptability (visual analogue scale) of the test.
Results 501 of 504 (99%) participants (median age 62, male to female ratio 1:1.2) successfully swallowed the Cytosponge. No serious adverse events occurred. In total, 3.0% (15/501) had an endoscopic diagnosis of Barrett’s oesophagus, using an excess of 80% mortality at five years unless detected early (also called intraepithelial neoplasia).3 Oesophagectomy has formed the basis for curative treatment even in patients with surveillance detected asymptomatic disease. However, because of the 5% mortality and significant morbidity associated with this highly invasive surgery, little enthusiasm has been shown for diagnosing Barrett’s oesophagus at a population level. The treatments for intraepithelial neoplasia in Barrett’s oesophagus have recently undergone a paradigm shift with the rapid development of outpatient endoscopic technologies, such as mucosal resection and radiofrequency ablation.4,6 The feasibility for endoscopic treatment now means that more systematic screening for Barrett’s oesophagus merits further consideration.

Conclusions The performance of the Cytosponge test was promising and the procedure was well tolerated. These data bring screening for Barrett’s oesophagus into the realm of possibility. Further evaluation is recommended.

INTRODUCTION

The incidence of oesophageal adenocarcinoma, for which Barrett’s oesophagus is the main risk factor, has increased sixfold in the Western world since the 1990s.1 Meta-analyses suggest that the risk for conversion from Barrett’s oesophagus to adenocarcinoma is 0.5% per year and this conversion is thought to occur up to 15 years after diagnosis.2 This cancer has in excess of 80% mortality at five years unless detected early (also called intraepithelial neoplasia).3 Oesophagectomy has formed the basis for curative treatment even in patients with surveillance detected asymptomatic disease. However, because of the 5% mortality and significant morbidity associated with this highly invasive surgery, little enthusiasm has been shown for diagnosing Barrett’s oesophagus at a population level. The treatments for intraepithelial neoplasia in Barrett’s oesophagus have recently undergone a paradigm shift with the rapid development of outpatient endoscopic technologies, such as mucosal resection and radiofrequency ablation.4,6 The feasibility for endoscopic treatment now means that more systematic screening for Barrett’s oesophagus merits further consideration.

The ideal method for diagnosing Barrett’s oesophagus is white light gastroscopy and biopsy, despite limitations such as the invasiveness of the procedure, the need for great expertise, the high cost, and the subjective nature of the diagnosis. However, limited endoscopy and fiscal resources may restrict the use of this procedure in large, population based screening programmes, and many people may be reluctant to undergo hospital based gastroscopy because of its inconvenience and discomfort.8,9

The perfect screening test should be simple, rapid, non-invasive, inexpensive, and acceptable to the patient. Multiple endoscopic screening methods have been developed, including brush cytology, electronic devices, and biopsies, but their sensitivity is low and patient acceptability is poor.1,5,10-12

The Cytosponge test for Barrett’s oesophagus compared with gastroscopy at a population level. The treatments for intraepithelial neoplasia in Barrett’s oesophagus have recently undergone a paradigm shift with the rapid development of outpatient endoscopic technologies, such as mucosal resection and radiofrequency ablation.4,6 The feasibility for endoscopic treatment now means that more systematic screening for Barrett’s oesophagus merits further consideration.

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As highlighted by the chief medical officer, Sir Liam Donaldson, in his 2008 report, a need exists for a safe, minimally invasive, cheap, and easily administered method aimed at the primary care setting to diagnose Barrett’s oesophagus.\(^7\)\(^{10}\) We have shown that non-endoscopic screening is feasible and safe using a new device called the capsule sponge, or Cytosponge.\(^{12}\) To distinguish Barrett’s cells from a mixed cell population, including gastric cardia and squamous epithelium, we have coupled the device with an immunohistochemical biomarker, trefoil factor 3.\(^{11}\) We determined the accuracy and acceptability of using the Cytosponge combined with trefoil factor 3 as a non-endoscopic procedure for the detection of Barrett’s oesophagus in primary care.

**METHODS**

This prospective cohort study was undertaken in 12 general practices in the United Kingdom. The outcome measures were sensitivity and specificity estimates for detecting Barrett’s oesophagus compared with gastroscopy as the ideal method to inform a future study, and patient anxiety and acceptability of undergoing the test.

**Setting and recruitment**

We identified eligible patients by searching the prescribing database of the 12 primary care practices for adults aged 50 to 70 with a previous prescription for an acid suppressant (H\(_2\) receptor antagonist or proton pump inhibitor) for more than three months in the past five years. Exclusion criteria were a previous diagnosis of Barrett’s oesophagus, gastroscopy within the past year, dysphagia, known portal hypertension, drug or pathophysiological abnormality of coagulation, important physical or psychological comorbidity precluding gastroscopy, or the inability to provide informed consent. The number of general practices was based on previous studies based in primary care reporting that 16.3\% of patients with reflux symptoms agreed to endoscopy.\(^{12}\) The general practices sent eligible participants an invitation letter. Responders who agreed to take part were sent an appointment for the Cytosponge test at the general practice. Recruitment continued until more than 500 people had participated.

**Study procedures**

*Appointment in general practice and questionnaire follow-up*

After written informed consent had been obtained the participants completed a sociodemographic and clinical questionnaire and an assessment of symptoms (gastro-oesophageal reflux disease impact score\(^{13}\)).

The research nurse or research fellow (gastroenterologist in specialist training) administered the Cytosponge, an ingestible gelatine capsule containing a compressed mesh attached to a string. The Cytosponge was approved by the UK Medical Health Regulatory Agency in 2008 (fig 1). Briefly, the capsule and bunched up string are swallowed with water. The string is held without any tension to allow the capsule to move into the stomach. The patient holds onto the string for five minutes after ingestion to allow the capsule to dissolve in the proximal stomach, where a spherical mesh of 3 cm diameter is released. The back of the throat is then sprayed with 1\% lidocaine (lignocaine) and the expanded mesh withdrawn by pulling on the string with the patient’s head in an extended position. After retrieval the string is cut and the Cytosponge containing the cytological specimen placed in preservative fluid (gift from Surepath; BD Diagnostics, Durham, NC, USA) and kept at room temperature until transportation to the laboratory. The whole process of administering the Cytosponge, including instructing the patient, takes less than 10 minutes.

Within 30 minutes of the procedure the participants completed a questionnaire including the short form Spielberger state trait anxiety inventory,\(^{14}\) the impact of events scale,\(^{15}\) and a visual analogue scale to measure acceptability.\(^{16}\) The short form Spielberger state trait anxiety inventory has been extensively used in studies of disease screening. We prorated the scores as per developers’ guidelines, with a score of 40 or more considered to represent clinically significant anxiety.\(^{17}\) To measure the effect of the Cytosponge on anxiety and distress we used the impact of events scale. The scale yields two scores assessing intrusive and avoidance thoughts. Final scores range between 0 and 35 for intrusion and 0 and 40 for avoidance (total score between 0 and 75), with values of more than 19 for each subscore (38 for total score) representing high test induced distress and values below 8.5 for each subscore (17 for total score) representing low distress.\(^{18}\) We calculated scores for participants who completed a minimum of 75\% of questions on each subscore. The visual analogue scale assessed acceptability of the procedure, where 0 represented the “worst experience” and 10 the “best experience.” Similar questionnaires were posted to all participants seven and 90 days later. Non-responders were sent one postal reminder and if that failed one telephone reminder.

**Laboratory processing of samples**

To provide the patient with a prompt result we stored the Cytosponge samples at room temperature and...
processed them within 48 hours; the samples can be stored in the refrigerator at 4°C before processing without affecting the assay result. Samples were processed to paraffin blocks. Immunostaining was carried out for trefoil factor 3, which we identified to be a diagnostic marker of Barrett’s oesophagus from a systematic gene expression profiling experiment. Two independent researchers, one with expertise in pathology (SK) and a gastrointestinal cytopathologist (MO’D), reported the findings. Sections stained for trefoil factor 3 were scored in a binary fashion as either positive or negative. Any glandular cells with trefoil factor 3 staining were considered as positive and to make the result as robust and objective as possible we used no intensity cut offs. The κ statistic between the two scorers was 0.74, indicating substantial agreement.

**Gastroscopy: the ideal method**

We invited those participants who had swallowed the Cytosponge to attend for a gastroscopy within three weeks of the screening test. The gastroscopies were carried out at a single specialist unit by one of three endoscopists, who adhered to a strict diagnostic protocol. To check for confounding by intestinal metaplasia of the stomach we assessed samples from the cardia and 2 cm above the squamocolumnar junction in all participants. If Barrett’s oesophagus was present, we collected additional four biopsies every 2 cm according to surveillance guidelines, which were reviewed by a gastrointestinal pathologist (MO’D) with extensive experience in Barrett’s oesophagus. Endoscopists and histopathologists were blinded to the result of the Cytosponge.

**Statistical analysis**

Based on assumed sensitivity and specificity of 75% and 85% and a prevalence of Barrett’s oesophagus of 3%, power calculations indicated that to obtain an estimate with a 95% confidence interval plus or minus 15% we required 500 participants. Statistics for continuous variables were expressed as medians and interquartile ranges. We used a Mann-Whitney test to compare continuous or ordinal variables between groups and a χ² test to compare categorical variables. Accuracy of the test was reported using Pearson Clopper exact 95% confidence intervals. All reported P values were two sided. Statistical analyses were carried out using Prism V5.01.

**RESULTS**

Twelve general practices covering a population of 100 668 were recruited over 20 months from May 2008 to December 2009 (fig 2). In total, 2696 patients identified from the practice prescribing databases were eligible and invited to take part in the study; 504 (18.7%) agreed. The Cytosponge was successfully swallowed by 501 (99%; three were unable to swallow). Two Cytosponges failed to fully expand and the corresponding samples had a low cell yield. All 501 participants were included in the analysis and those who did not attend for gastroscopy (n=32) were considered not to have Barrett’s oesophagus. Two Cytosponges were successfully swallowed by 501 (99%; three were unable to swallow). The Cytosponge was successfully swallowed by 501 (99%; three were unable to swallow). Two Cytosponges failed to fully expand and the corresponding samples had a low cell yield. All 501 participants were included in the analysis and those who did not attend for gastroscopy (n=32) were considered not to have Barrett’s oesophagus. No serious adverse events were associated with swallowing.
the Cytosponge, in particular no bleeding or aspiration. No failures took place in the sample processing or staining for trefoil factor 3.

Personal and clinical characteristics of participants

Table 1 shows the personal and clinical characteristics of the study population. The numbers of men and women were almost equal (male to female ratio 1:1.2) with a median age of 62 years (interquartile range 56-66 years) in both sexes. The male to female ratio (1:1.1) and median age (63 years, 58-67) of the non-responders did not differ significantly from that of the responders. The median waist to hip ratio for men was 0.96 (interquartile range 0.92-1.00), which falls within the range considered to be a medium health risk, and for women 0.86 (0.82-0.91), which is associated with a high health risk. The median body mass index of 29.4 (26.2-32.9) indicated that most participants were overweight, with more than 45% in the obese range. Overall, participants consumed less alcohol than the national average, but the proportion of smokers (past and present) was 10% higher for each sex than the national UK averages. Only 68% of participants (344/501) were currently taking prescribed acid suppressants, but all met the inclusion criteria of such therapy at some time in the past five years. Overall, 73% (367/501) of participants reported uncontrolled to very poorly controlled reflux symptoms according to the impact scores for gastro-oesophageal reflux disease (table 1).

Accuracy of the test

Based on standard gastroscopy the prevalence of Barrett’s oesophagus was 3.0% (15/501) for segments of circumferential length 1 cm or more and 2.2% (10/501) for segments of 2 cm or more, with a median length of C4M5 (interquartile range C1M2-C9M9) (table 2). Table 3 shows the characteristics of the patients with a diagnosis of Barrett’s oesophagus categorised according to the circumferential length of segment (≥1 cm or ≥2 cm) compared with those without Bar-
rett’s oesophagus. No statistical differences were observed between the patients with Barrett’s oesophagus (≥1 cm) and those without. If a cut off of 2 cm or more was used, there was a higher prevalence of tobacco smoking in patients with Barrett’s oesophagus \( (P = 0.03) \). The small sample size, however, precludes definitive conclusions.

Figure 3 shows haematoxylin and eosin and trefoil factor 3 staining of the Cytosponge specimen from a representative segment of tissue from a patient with Barrett’s oesophagus. For a cut off of 1 cm or more, 11 of 15 segments were detected with the Cytosponge, giving a sensitivity of 73.3% (95% confidence interval 44.9% to 92.2%). For a cut off of 2 cm or more, nine of 10 segments were detected, giving a sensitivity of 90.0% (55.5% to 99.7%). The specificity was 93.8% (91.3% to 95.8%) and 93.5% (90.9% to 95.5%) for segments of 1 cm or more and 2 cm or more, respectively. The likelihood of being positive for trefoil factor 3 was statistically associated with the length of the segment affected by Barrett’s oesophagus \( (P = 0.009 \text{ for circumferential length and } P = 0.02 \text{ for maximal length; table 2}) \). Thirty false positives occurred, of which six had some evidence of columnar lined epithelium (<1 cm) that did not fulfil the diagnostic criteria for this study. Hence, for segments of 1 cm or more, trefoil factor 3 yielded a sensitivity of 73.3% (44.9% to 92.2%), a specificity of 93.8% (91.3% to 95.8%), a positive predictive value of 26.8% (14.2% to 42.9%), and a negative predictive value of 99.1% (97.8% to 99.8%). Presence of intestinal metaplasia at the cardia, hiatus hernia, or oesophagitis was not associated with the likelihood of being positive for trefoil factor 3 \( (\text{data not shown}) \).

Table 2 | Characteristics of patients with diagnosed Barrett’s oesophagus

| Practice | Patient | Sex | Age | Body mass index | Waist to hip ratio | Highest educational attainment | Smoking (pack years) | Alcohol (units/week) | Symptom control | Drugs | Barrett’s oesophagus or adenocarcinoma in first degree relative | Circumferential length (cm) | Maximal length (cm) | Cytosponge test result |
|----------|---------|-----|-----|-----------------|-------------------|-------------------------------|----------------------|---------------------|-----------------|-------|---------------------------------------------------------------|-----------------------------|------------------------|-------------------------|
| Practice A: | Patient 1 | Male | 69 | 27.5 | 1.00 | School to 16 | 0 | 14 | Poor | Antacids | No | 1 | 3 | Positive |
| Practice B: | Patient 1 | Male | 70 | 31.6 | 1.03 | School to 16 | 0 | 10 | Uncontrolled | Proton pump inhibitors | No | 4 | 6 | Positive |
| Practice C: | Patient 1 | Female | 54 | 39.8 | 0.86 | School to 16 | 0 | 2 | Poor | Antacids+proton pump inhibitors | No | 1 | 2 | Positive |
| Practice D: | Patient 1 | Male | 52 | 29.0 | 0.96 | School to 18 | 8 | 10 | Very well | Antacids | No | 6 | 6 | Positive |
| Practice E: | Patient 1 | Female | 66 | 37.2 | 0.95 | School to 16 | 37 | 0 | Fair | Antacids+proton pump inhibitors | No | 2 | 5 | Negative |
| Practice F: | Patient 1 | Male | 61 | 31.7 | 1.02 | School to 16 | 32 | 10 | Uncontrolled | Antacids | No | 8 | 8 | Positive |
| Practice G: | Patient 1 | Male | 66 | 32.4 | 1.10 | School to 16 | 31 | 2 | Poor | Proton pump inhibitors | No | 5 | 7 | Positive |
| Practice H: | Patient 1 | Male | 64 | 24.8 | 0.86 | School to 18 | 0 | 6 | Fair | Proton pump inhibitors | No | 1 | 2 | Negative |
| Practice I: | Patient 1 | Female | 63 | 33.5 | 0.85 | School to 16 | 0 | 0 | Poor | Proton pump inhibitors | No | 9 | 9 | Positive |
| Practice J: | Patient 1 | Female | 70 | 32.0 | 0.83 | School to 16 | 0 | 4 | Poor | None | No | 1 | 2 | Negative |
Participant anxiety and test experience

Response rates were high for all questionnaires at all time points: 496 (99%) at baseline, 466 (93%) at day 7, and 415 (83%) at day 90. Anxiety levels were low in most patients before and after the test. A subset (141/496) of patients (28.4%, 95% confidence interval 24.4% to 31.6%) reported high anxiety scores before swallowing the sponge that remained high during follow-up. The median scores for all participants were 33.1 (interquartile range 26.6-43.3) at day 0, 30.0 (20.0-40.0) at day 7, and 26.6 (20.0-36.6) at day 90 (fig 4). The scores on the impact of event scale remained constant at days 7 and 90 after the Cytosponge test, with less than 4.5% (95% confidence interval 2.8% to 6.1%) of participants displaying significant distress for any subscore at any time point (fig 4). The median (interquartile range) scores for the visual analogue scale were 7.0 (5.0-8.0) at the time of the test, 6.0 (5.0-8.0) at day 7, and 6.0 (4.0-7.0) at day 90 (fig 4).

DISCUSSION

The Cytosponge test is a safe and well tolerated method to screen for Barrett’s oesophagus that can be carried out in a primary care setting. In this population with a history of reflux disease the prevalence of Barrett’s oesophagus for a circumferential length of 1 cm or more was 3.0%, for which trefoil factor 3 had a sensitivity and specificity of 73.3% and 93.8%, respectively. The sensitivity increased to 90.0% for segments of 2 cm or more. This study was not, however, designed to estimate test characteristics with high precision, and the estimate of sensitivity has wide confidence limits. Further evaluation in a larger cohort is now warranted.

Strengths and weaknesses of the study

The attendance rate of 504 (18.7%) is consistent with the 16.3% reported in a previous endoscopic study in the primary care setting.23 This should be considered in the context of a study that involved two procedures, including a hospital visit for gastroscopy. Recruitment rates for this study should not be seen as surrogate for uptake of this test if it were rolled out in a nationwide screening programme, which would be accompanied with major consumer awareness campaigns. This response bias may have resulted in people with more significant symptoms presenting or people with more positive attitudes towards receiving a screening test. Based on sex and age distribution, the non-responders and responders originated from a homogeneous population. Our preliminary data suggest that the test was useful in the primary care setting. However, the sensitivity and specificity need to be confirmed in a larger study.

Table 3 | Comparison between patients with and without Barrett’s oesophagus stratified per circumferential length cut-off point of affected segment. Data are medians (interquartile ranges) unless stated otherwise

| Characteristics | Circumferential length ≥1 cm | Circumferential length ≥2 cm |
|-----------------|----------------------------|----------------------------|
|                  | Barrett’s oesophagus (n=15) | No Barrett’s oesophagus (n=486) | P value |
| Male to female ratio | 1:5:1 | 0.86:1 | 0.26 |
| Age | 64.0 (59.0-67.0) | 62.0 (56.0-66.0) | 0.18 |
| Body mass index | 31.6 (27.5 to 33.5) | 29.4 (26.2 to 32.9) | 0.55 |
| Waist to hip ratio | 0.91 (0.85 to 0.96) | 0.91 (0.85 to 0.96) | 0.16 |
| Smoking (pack years) | 8.0 (6.0-10.0) | 6.0 (4.0-8.0) | 0.30 |
| Alcohol consumption (units/week) | 4.0 (2.0 to 6.0) | 4.0 (2.0 to 6.5) | 0.24 |
| Symptoms (GERD score) | 4.0 (2.0 to 6.0) | 4.0 (2.0 to 6.5) | 0.67 |
| Acid suppressants (%) | 73.3 | 66.2 | 0.36 |

GERD=gastro-oesophageal reflux disease.
*Proton pump inhibitors or H2 receptor antagonists, or both.
Although emerging imaging techniques may be more applicable to primary care than endoscopic techniques are the ideal methods for diagnosis but not easily applicable to mass screening in the primary care setting and is well tolerated. The Cytosponge, a novel oesophageal sampling device, can be applied safely in the primary care setting and is well tolerated. The trefoil factor 3 biomarker when applied to the Cytosponge specimen had encouraging sensitivity and specificity for detecting Barrett’s oesophagus.

WHAT THIS STUDY ADDS

The Cytosponge, a novel oesophageal sampling device, can be applied safely in the primary care setting and is well tolerated.

The trefoil factor 3 biomarker when applied to the Cytosponge specimen had encouraging sensitivity and specificity for detecting Barrett’s oesophagus.

Screening for Barrett’s oesophagus using this device warrants further evaluation.

acceptable to most of those who participated in the study. Although we did not find evidence of significant psychological distress associated with the screening test in most of the participants, a subpopulation seemed to have high levels of anxiety at baseline, which persisted at day 90: this high level of anxiety may therefore have little to do with the test.

Competing technologies currently undergoing evaluation include ultrathin transnasal endoscopy and video capsule endoscopy, which remain expensive and limited to specialist centres; furthermore, endoscopy using a video capsule does not permit cell sampling, which remains a critical component for diagnosis.20 21 The sensitivity and specificity for the diagnosis of Barrett’s oesophagus, even for the video capsule, remain relatively low, with values of 78% and 88%, respectively.28

Comparison with other studies

The 3.0% prevalence of Barrett’s oesophagus reported here is in keeping with previous published studies. In Europe and the United States, a prevalence of 2.3-2.6% was reported for any length of Barrett’s oesophagus in patients with reflux and 0.2-0.5% for segments greater than 2 cm.25 29 30 The possibility that those who agreed to take part had more severe symptoms of reflux may explain the slightly higher prevalence reported here. Much debate has been about the clinical significance of “short segments” of Barrett’s oesophagus and the presence of gastric versus intestinal metaplasia, and while carrying out this study the diagnostic criteria have continued to alter.31 However, for both circumferential length criteria (≥1 cm and ≥2 cm), the sensitivity, specificity, and negative predictive value of our Cytosponge test compared favourably with data from screening tests using mammography for breast cancer screening, prostate serum antigen testing for prostate cancer, and faecal occult blood testing for colorectal cancer.32 33 Since screening detected cases will result in endoscopic confirmation and surveillance, changes to drugs, and treatment such as radiofrequency ablation,34 35 we believe that the test should be designed to detect clinically significant patients who would most likely benefit from surveillance or endoscopic treatment. A screening test for Barrett’s oesophagus should have high specificity to avoid unnecessary confirmatory endoscopies or interventions. Barrett’s oesophagus meets many of the established criteria for population screening.36

Implications for clinicians and policy makers

Barrett’s oesophagus is an important public health problem in the West and the metaplasia-dysplasia-adenocarcinoma sequence is well described.37 This study has shown the Cytosponge to be simple, safe, and acceptable to the population considered to be at risk (patients with reflux) and seems reasonably accurate. Furthermore, the binary scoring for trefoil factor 3 makes the test amenable to automation. Further application of risk models may be required to determine the optimal target population (symptoms only, men or both sexes, obese only).38 In the current environment endoscopic screening for Barrett’s oesophagus followed by surveillance is not deemed to be cost effective.39 However, the Cytosponge might prove a more cost effective approach to screening as no hardware needs to be purchased and only minimal training is required, such that the test could be carried out by a practice nurse in the primary care setting. We are planning an in-depth cost effectiveness analysis as part of a future screening study. Furthermore, samples from the Cytosponge have the potential to be adapted for surveillance, with the application of suitable risk stratification biomarkers.40 41

Conclusions

In summary, in this study we have shown that the Cytosponge coupled with a single immunomarker is a promising tool to screen for Barrett’s oesophagus in the primary care setting and that further evaluation is warranted. Our data are specific to a predominantly white population in the United Kingdom. Generalisation to other communities requires a multicentre study and this would also provide more robust estimates of diagnostic accuracy. The results presented here bring screening for Barrett’s oesophagus into the realm of possibility.

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Contributors: SRK ran the study and collected the data. PLS designed the study, analysed the data, and wrote the manuscript. MJD reviewed the pathology and reviewed the Cytosponge samples. ID ran the study. MD prepared and stained the samples. JMB, JE, AB, HM, FW, and RHH designed the study and reviewed the manuscript. PP overviewed the statistics. RCF designed the study and wrote the manuscript. RCF is guarantor for the study.

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