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Brief comments on Rapid Response (RR) report from Healthcare Improvement Scotland on Cytosponge™ for the detection of pre-malignant or early curable oesophageal cancer; published 4 September 2020

The main conclusion of the RR report **[1]** is (page 1):

> *"Endoscopy with biopsy is likely to remain the modality of choice [in Scotland] for patients with alarm symptoms".*

The primary basis for this conclusion is as follows (page 1):

> "*Based on the low volume and quality of published studies it is not possible to reliably determine the value of Cytosponge for the detection of pre-malignant or early curable oesophageal cancer, nor to assess the suitability of using Cytosponge as a substitute for endoscopy in Scotland."*

An important reference used in the RR report is a systematic review by Iqbal *et al.* of the safety and efficacy of Cytosponge in the diagnosis of oesophageal pathology, published in November 2018 in the *European Journal of Gastroenterology & Hepatology* **[2]**. The RR report describes this review by Iqbal *et al.* as follows (page 4):

> *"A well-conducted systematic review from 2018 assessed the efficacy of Cytosponge, compared with the gold standard of endoscopic biopsy (assumed 100% accuracy), for detection of oesophageal pathologies including Barrett's oesophagus, dysplasia, and carcinoma."*

Iqbal *et al.* stated their main conclusions in the Abstract of their review as follows (page 1):

> *"With the major limitation that most studies were performed by a single investigative group that developed the technology, the device yielded overall impressive results against the endoscopy/biopsy gold standard. Patient acceptability was high. If these promising early results are validated by other investigators in other populations, the Cytosponge represents an important new advance in the detection of oesophageal pathology that could potentially decrease the burden of endoscopic oesophageal sampling."*

Table 1 in the RR report summarises the findings from six studies that reported diagnostic accuracy of Cytosponge for the detection of Barrett's oesophagus. (The literature provides insufficient data to assess the diagnostic accuracy of Cytosponge for the detection of oesophageal carcinoma.) Based on these studies, Iqbal *et al.* calculated the pooled sensitivity and specificity of Cytosponge as 81% and 91%, respectively.

The RR report comments as follows (page 2):

> *"In other words, using pooled sensitivity and specificity, 19% of patients tested for Barrett's oesophagus using Cytosponge would receive a false negative result and 9% a false positive result."*

A false positive result would lead to an unnecessary referral for endoscopy with biopsy, with the consequent use of scarce resources and risk of complications. The implications of a false negative result are that potential cases of Barrett's oesophagus and, even more seriously, pre-malignant or early curable oesophageal cancer are missed at that stage of the diagnostic pathway.

However, even the presumed gold standard of endoscopy plus biopsy is not 100% reliable in practice. A systematic review conducted by Visrodia *et al.* **[3]**, published in March 2016 in *Gastroenterology*, concluded that up to 25% of oesophageal adenocarcinomas are missed at index endoscopy for Barrett's oesophagus. A more recent paper by Van Putten *et al.* **[4]**, published in May 2018 in the *United European Gastroenterology Journal*, investigated the rate of missed cases of high-grade dysplasia or oesophageal adenocarcinomas among 13,159 patients from the Northern Ireland Barrett's oesophagus register who had been diagnosed between 1993 and 2010. Van Putten *et al.* concluded (page 519):

> *"Approximately one on 10 high-grade dysplasia or oesophageal adenocarcinomas cases are missed at incident Barrett's oesophagus diagnosis, which is significant but lower than previous reports [in particular, Visrodia et al. 2016]."*

When we are comparing the sensitivity of Cytosponge with that of endoscopy plus biopsy, are we making a like for like comparison? As acknowledged in the RR report (page 3):

> *"During the COVID-19 pandemic all endoscopy services were cancelled, with the exception of emergency cases. Consequently there is a large backlog of patients in Scotland waiting for diagnostic upper gastrointestinal endoscopy."*

In any attempt to substantially reduce this waiting list, a diagnostic and prevention strategy for oesophageal adenocarcinomas that relies solely on endoscopy plus biopsy would appear less than feasible given the high strain that endoscopy puts on scarce hospital resources (even more so if patients request sedation). Instead, many patients would get endoscopies at a later time than originally planned. In contrast, widespread use of Cytosponge would enable substantially more patients (50% or more depending on COVID-19 and other factors) to be seen in any given period.

This implies that a fairer comparison would be between an endoscopy procedure that is likely delayed (and for which any false negative result may not be reconsidered until an even later stage) and the use of Cytosponge closer to the originally planned time (and for which any negative result could be reconsidered within a reasonable period of time should the patient's symptoms persist or worsen).

The above arguments are proper topics for the two health economics / cost effectiveness studies (by Benaglia *et al.* 2013 **[5]** and Heberle *et al.* 2017 **[6]**, respectively) discussed in the RR report. A more recent study, published after the RR report came out, should be added to this list; namely, the economic evaluation by Swart *et al.* of Cytosponge screening for Barrett's oesophagus versus usual care using data from the BEST3 randomised controlled trial, published in June 2021 in *EClinicalMedicine* **[7]**.

The BEST3 findings were presented in an August 2020 paper by Fitzgerald *et al.* in the *Lancet* **[8]**; they were discussed in some detail in the RR report, in the course of which some methodological flaws were noted. A key finding from BEST 3 was as follows (page 333):

> *"Nine (<1%) of 6834 participants were diagnosed with dysplastic Barrett's oesophagus (n=4) or stage I oesophago-gastric cancer (n=5) in the intervention group, whereas no participants were diagnosed with dysplastic Barrett's oesophagus or stage I gastro-oesophageal junction cancer in the usual care group."*

Developing an appropriate Markov model based on BEST3 data, Swart *et al.* drew the following implications (page 2):

> *"The published evidence suggests that the Cytosponge-TFF3 procedure is cost-effective and affordable if provided as a triage test for people with gastro-oesophageal reflux disease to increase detection of Barrett's oesophagus. Although systematic Cytosponge-TFF3 testing for individuals on medication for reflux incurs higher costs per person than usual care, and involves additional diagnostic endoscopy in a minority, Cytosponge-TFF3 also generates additional quality-adjusted life years due to earlier cancer diagnosis and curative treatment."*

In conclusion, it can be argued that the question of capacity – in particular, the current (and quite possibly prolonged) lack of hospital resources to conduct planned endoscopy procedures in a timely manner – has received insufficient attention in the RR report. As already noted, widespread use of Cytosponge would enable substantially more patients (50% or more depending on COVID-19 and other factors) to be seen in any given period. Although endoscopy plus biopsy appear to have superior sensitivity (although still less than 100%) and specificity than Cytosponge, this advantage can be negated by a lack of effective capacity to perform these resource-intensive procedures in a timely manner. Instead, using Cytosponge for suitable patients would allow them to be seen and diagnosed closer to the originally planned time, leading where necessary to faster treatments with associated gains in quality-adjusted life years. Any (potentially false) negative results from the Cytosponge test could be reconsidered within a reasonable period of time should the patient's symptoms persist or worsen.

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