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Cellulose Sponge, the Detector of Esophageal Cancer: Innovation for Early Detection of Esophageal Cancer without Biopsy?: A Mini Review

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Abstract

Patients with esophageal cancer each year can reach 400,000 people. Inefficient screening methods and worsening symptoms, patients often come late. Squamous cell carcinoma, which is the cause of esophageal cancer, has percentage of 84% of all cancer incidences. So far, the current screening strategy is endoscopy with biopsy. This screening has the main side effect of bleeding in metaplastic area. Cellulose Sponge, the Detector of Esophageal Cancer (CaSPER), can be used for screening without a biopsy using a cellulose sponge. The method used in this mini review is an evidence-based method that focuses on evaluating pre-existing journals. The result is that CaSPER is able to provide strong cellular results of 98%, specificity of 100%, and sensitivity of 97%. Capsules made of glucose and cytosponge of cellulose will bring the metaplastic cells to the sponge. This screening is feasible, safe, comfortable, and without side effects. Using trefoil factor 3 as biomarker is able to distinguish between goblet and pseudogoblet cells. CaSPER is minimally invasive, cheaper, and easily accepted, so that in the future it is hoped that it can be mass produced, especially for areas with high esophageal cancer.

Introduction

In 2022, The American Cancer Society's estimates that about 20,640 esophageal cancers will be diagnosed in 2022. There were 16,000 deaths from esophageal cancer. Esophageal cancer squamous cell carcinoma is a fatal disease because the average initial symptoms are asymptomatic [1]. In addition, it has poor prognosis and is only symptomatic in the late stages [2]. This disease is included in one of the 10 most common cancers and the sixth cancer that causes death on a worldwide scale and ranks as the 3rd malignancy in the gastrointestinal tract after gastric-colorectal cancer and hepatocellular cancer [3].

Esophageal cancer has a geographic variation in incidence ranging from 3 per 100,000 population in Western countries to 140 events per 100,000 population in the Central Asia [4]. This disease is also one of the cancers with the lowest cure rates, with 5-year average survival of approximately 10%, this survival rate is the worst after hepatobiliary cancer and pancreatic cancer [5]. Worldwide about 30 million people die of esophageal cancer. Incidence in men is much higher than in women, the ratio between men and women is between 11 and 17:1 [6]. The older the greater chance of developing esophageal cancer, age under 35 years has a lower chance, age 35 and over has gradually increasing likelihood, age range 60–69 is the highest age for incidence esophageal cancer [7].

Barrett's esophagus estimates 3–17 million people in the US, which is a precursor to esophageal adenocarcinoma or EAC. EAC develops from non-dysplastic, low-grade, high-grade dysplastic, and invasive intestinal metaplasia. Thus, the current guidelines recommend surveillance based on Barrett's histology [8].

The gold standard used is endoscopic cytology with iodine staining. The examination so far used is through taking a biopsy sample with an endoscopic camera. Side effects of biopsy are: Infection and bleeding in neoplastic lesions. With contraindications: Infection of the lesion, impaired hemostatic function, and biopsy outside the area planned to be excised during surgery [9].

Because of this, the authors provide a strategic solution for esophageal cancer screening using Cellulose Sponge, The Detector of Esophageal Cancer (CaSPER) made from natural ingredients with higher

sensitivity and specificity also patient comfort than the current screening.

Methods

The method used in this mini review is an evidence-based method that focuses on evaluating pre-existing journals. There are several stages in this method, namely: Determining the eligibility criteria for journals, sources of information, selecting literature, collecting data, and selecting data. The author uses search engines including Nature, PubMed, Springer Google Scholar, ScienceDirect, and PlosOne with the keyword cellulose sponge, esophageal cancer, and screening.

Results

Research conducted by Middleton *et al*. proved from 102 asymptomatic patients, 50 men and 52 women aged 30–77 years. Cytosponge was swallowed by participants and then examined and the results were obtained by 98% giving an adequate cellular result or a total of 100 participants. The results showed 1% low-grade dysplasia, 6% metaplasia, 22% gastritis, 1% atypical squamous cell, and 4% inflammation [10].

Research in Iran showed that from 301 subjects were examined using a cytosponge and no complications were found, 92.7% of participants felt comfortable with the examination. The results of the sensitivity and specificity of the examination reached 97% with 100% accuracy in cytology examination and p53 staining for esophageal squamous dysplasia (ESD) detection. This sponge capsule is a very safe, feasible, and acceptable method for diagnose of precancerous lesions [11].

The results of another study in England with the randomized trial of cytosponge showed satisfactory results regarding the number of cells from analytical sample of 95%. Thus, cytosponge improved the diagnosis by 10 times. Patients with this capsule examination were diagnosed with Barrett's esophagus compared to the group without the capsule/using endoscopy. Side effect is only sore throat in some patients [12].

A total of 268 patients at Mayo Clinic were examined and results showed that cytosponge test accurately showed 92% of patients with Barrett's esophagus [13]. The samples obtained will be examined using formalin-fixed paraffin embedded. The staining used was hematoxylin and eosin. Then, it will be examined under a microscope [10].

Based on research, this method has adverse event sore throat about 4%, some feel a burning sensation when the cytosponge is pulled out of the mouth. In another research showed gastric pain 11%, nausea or vomiting 6%, voice disturbance 3%, diarrhea or upset stomach 4%, and 1% serious adverse events such as unconsciousness and detachment of the sponge on day of the procedure. The failure to make the patient swallow CaSPER again was 19%, this was because there were no distal esophageal cells when removed [14].

The results of the study data showed: 39% of these procedures were acceptable, 65% showed interest in this method, 95% of patients were able to swallow capsules and successfully obtained samples for analysis, 3% of patients were used for endoscopy. This study also revealed that CaSPER can improve diagnosis by 10 times the results obtained in positive patients with Barrett's esophagus compared to the usual care group. Side effects are also very minimal and most often just a sore throat [12].

Comparison of sensitivity and specificity is not much different from the current gold standard. Based on research related to the detection of Barrett's esophagus using endoscopic biopsy, it was found that the sensitivity was 100% and the specificity was 84.3%. This method aims to find esophageal squamous epithelium and cylindrical tissue from the stomach. From the results, 20.5% had no abnormalities and 79.5% had pathological diagnoses such as esophagitis (fungal, mild, moderate, severe, and eosinophilic) and Barrett's esophagus [15]. Meanwhile, the cytosponge with trefoil factor 3 (TFF3) from the research conducted showed a sensitivity of 79.9% and specificity of 92.4%. In another study, the cytosponge segment size of 2 cm had a sensitivity of 90% with a specificity of 93.5% [16]. This includes the factor that there is no repetition of diagnostic procedures in examinations [14].

The cost-effective cytosponge is seen from the cost incurred for one diagnostic, which is $107 with an incremental cost-effectiveness ratio (ICER) of $7184 per quality-adjusted life-years (QALY) [14]. The cost of endoscopic biopsy for esophageal cancer is ICER $52,483 per QALY and assay cost per test is $1475, endoscopy with biopsy is $2038, with a range of $760–$3750 [17]. Hence, the cost-effective for CaSPER is 90%. In addition, CaSPER does not require hardware that requires spending money, only training for health workers is needed so that nurses can practice in health services [16].

Discussion

CaSPER (cellulose sponge, the detector of esophageal cancer)

CaSPER with cytosponge is a disposable device used to collect cells in the esophagus.

When the capsule is swallowed, the cytosponge will expand into a smaller size with a harder texture. After 5–7 min, the cytosponge will be pulled out by vertical examination.

CaSPER is capable of being a screening with high sensitivity and specificity. Immunohistochemistry in the form of TFF3 as a biomarker [18]. The goal is to increase the accuracy of detection to distinguish goblet cells from pseudogoblet cells. In addition, TFF3 showed strong staining on the mucosal surface biopsy of Barrett esophagus CaSPER samples [19].

TFF3 has a trefoil characteristic which contains 40 amino acids composed of three conserved disulfides. This protein is expressed on the goblet cells of intestinal, colon, and respiratory epithelium. The exact function of this protein is still unclear, but it is hypothesized that it functions to stabilize the mucus layer, epithelial healing, and protect the mucosa [20].

Cytosponge CasPER-TFF3 was able to detect gastric intestinal metaplasia which was not detected on endoscopy [21]. Gastric IM is associated with an increased risk of adenocarcinoma [22]. The form of sampling is by swallowing a capsule that is connected with a thread from outside the patient's mouth, until the capsule is decomposed by acid, then a sponge made of cellulose will open. When the sponge is open, the general practitioner will pull it out of the patient's mouth. The sponge made of cellulose will then carry some sample cells to be examined.

In the principle of manufacture, CaSPER is made of four parts, all of which are degradable. The puller is a regular rectangular shape with a thickness of 3 cm, a length of 5 cm, a width of 5 cm made of fine wood fiber, making it easy to hold and harmless in use. Catgut thread was used for the fixation of the cellulosic sponge. Cellulose sponge in the form of a cytosponge made from polyester, a long chain of repeating PET molecules, whereas viscose is a long chain of cellulose molecules, will open when in the stomach and is more acid-resistant than glucose.

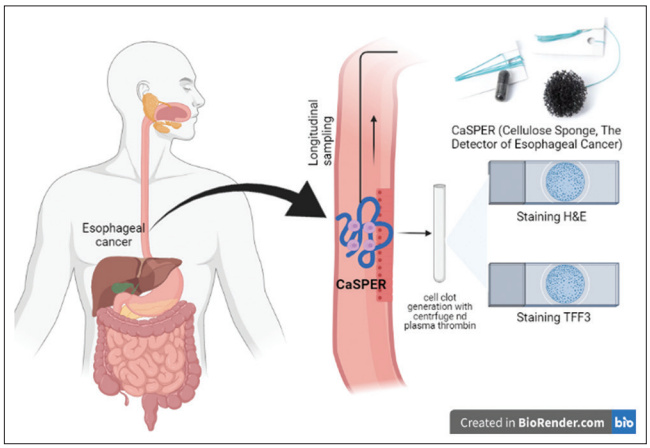

Figure 1: CaSPER (Cellulose Sponge, The Detector of Esophageal Cancer)

The capsule that coats the cytosponge is made of glucose/gelatin, it will break down more easily in an acidic environment.

Cellulose which will be the main ingredient of cytosponge is arranged as well as possible to make it easier when it expands in the stomach after the capsule breaks down. This sponge is designed to be lightweight, acid-resistant, and easy to expand to make it easier to pass through the esophagus without causing lesions or bleeding, especially cancer cells.

This device is contraindicated for patients who have dysphagia or swallowing disorders, portal hypertension or esophageal varices, esophageal/stomach abnormalities, esophageal ablation or mucosal resection, or post-invasive esophageal or gastric surgery for at least 2 months, as well as patients taking anticoagulants (Figure 1).

Sample assessment from CaSPER

The sample assessment was carried out systematically, the first thing that was excluded was clot preparations with a size of <5 mm and did not contain columnar cells which were classified as inadequate. The second is that a sample with a size >5 mm but no columnar cell is classified as negative with low confidence, while a sample >5 mm in the columnar cell group without intestinal metaplasia is categorized as negative with high confidence. If goblet cells are found, they are classified as "positive," suggestive of intestinal metaplasia, Barrett's esophagus [20], [23].

The differential diagnosis of reactive atypia was true dysplasia; hence, the sample was reported as "positive with columnar atypia" and the patient was advised to undergo endoscopic examination with biopsy to clarify the atypia detected by CaSPER.

Disadvantages of CaSPER include

Gag reflex thread breaking from the cellulose sponge due to pulling the handle from the outside which is too strong, the old capsule breaks down in the stomach, the patient has difficulty swallowing the capsule.

The potential of CasPER as an early detection of esophageal cancer

The availability of minimally invasive, acceptable, safe, and cost-effective screening has a high potential to make esophageal cancer screening, especially in patients older than 50 years with severe and chronic reflux symptoms. Furthermore, the capsule will dissolve after 5–8 min and release the sponge. Without sedation less expensive than diagnose with endoscopy, this tool just take 10 min during the procedure.

Innovative use of multigene sequencing panel aims to screen patients with BE who have dysplasia. So that not all patients with BE undergo routine examinations [24]. In a study population with a high prevalence of ESD, CaSPER had a sensitivity and specificity of 100% and 97% with a combination of p53 immunohistochemistry [11].

Conclusion

CaSPER is a screening tool that is easy to use, low in side effects, convenient, inexpensive, and especially suitable for elderly patients. The use of TFF3 immunohistochemistry plays a very important role in distinguishing the presence of goblet cells from more detailed microscopy findings. Capsule made from glucose and sponge made from cellulose that easier for longitudinal sampling with sensitivity and specificity 97% and 100%. Although endoscopic diagnostics are still the most ideal/gold standard method, this method is not easy to apply, especially in mass screening in health services.

Recommendations

Recommendation for further research is that is necessary to develop especially genetic combinations in CaSPER so that diagnostic screening is more classified. Also, more production CaSPER because this tool is very useful, especially in areas with a high prevalence of esophagogastric cancer.

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