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## Current and Future Use of Esophageal Capsule Endoscopy

Junseok Park<sup>1</sup>, Young Kwan Cho<sup>2</sup> and Ji Hyun Kim<sup>3</sup>Department of Internal Medicine, <sup>1</sup>College of Medicine, Soonchunhyang University, Seoul, <sup>2</sup>Eulji University School of Medicine, Seoul, <sup>3</sup>Inje University Busan Paik Hospital, Busan, Korea

Capsule endoscopy can be a diagnostic option for patients with esophageal diseases who cannot tolerate esophagogastroduodenoscopy. Functional modifications of the capsule allow for thorough examination of the esophagus. Esophageal capsule endoscopy has so far failed to show sufficient performance to justify the replacement of traditional endoscopy for the diagnosis of esophageal diseases because the esophagus has a short transit time and common pathologies appear near the esophagogastric junction. However, technological improvements are being introduced to overcome the limitations of capsule endoscopy, which is expected to become a good alternative to conventional endoscopy. **Clin Endosc 2018;51:317-322**

**Key Words:** Esophagus; Capsule endoscopy; Barrett's esophagus; Esophageal varices

### INTRODUCTION

Esophagogastroduodenoscopy (EGD) using a flexible endoscope is generally considered to be an optimal method for examining the esophagus. However, it carries disadvantages, such as discomfort and inconvenience, which may cause patients to decline necessary endoscopic evaluation. Simpler and less invasive modalities are needed as an alternative to traditional endoscopy. Video capsule endoscopy (VCE), widely used for investigating small bowel (SB) diseases, can be an acceptable option for the diagnosis of esophageal diseases. The esophagus normally has a short transit time and common pathologies tend to occur near the gastroesophageal junction. Therefore, VCE requires certain technical modifications for esophageal examination. In addition to technological improvements, tethering on a capsule can also improve VCE's

applicability to the esophagus. These adaptations allow VCE to be valuable in advanced diagnostic studies. This review will discuss recent developments and future prospects for esophageal VCE.

A capsule endoscopy system for the esophagus has been developed and is currently commercially available. The PillCam ESO<sup>®</sup> (Given Imaging Ltd., Yoqneam, Israel) was approved by the Food and Drug Administration in November 2004. Costing around \$500, the improved PillCam ESO2<sup>®</sup> capsule has been available since 2007 (Fig. 1). The size, shape, and weight of the capsule endoscope are similar to those used in the SB (PillCam SB2) (26×11 mm and less than 3.0 g). However, several functional modifications have been incorporated to optimize the capsule for esophageal evaluation. For example, the battery life is shortened to 20 minutes (rather than the 8–12 hours of SB capsules). In addition, cameras are placed on both

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Correspondence: Ji Hyun Kim

Department of Internal Medicine, Inje University Busan Paik Hospital, 75 Bokji-ro, Busanjin-gu, Busan 47392, Korea

Tel: +82-51-890-6930, Fax: +82-51-892-0273, E-mail: zep2000@hanafos.com

ORCID: <https://orcid.org/0000-0003-0861-2792>

\*Junseok Park and Young Kwang Cho contributed to this paper equally.

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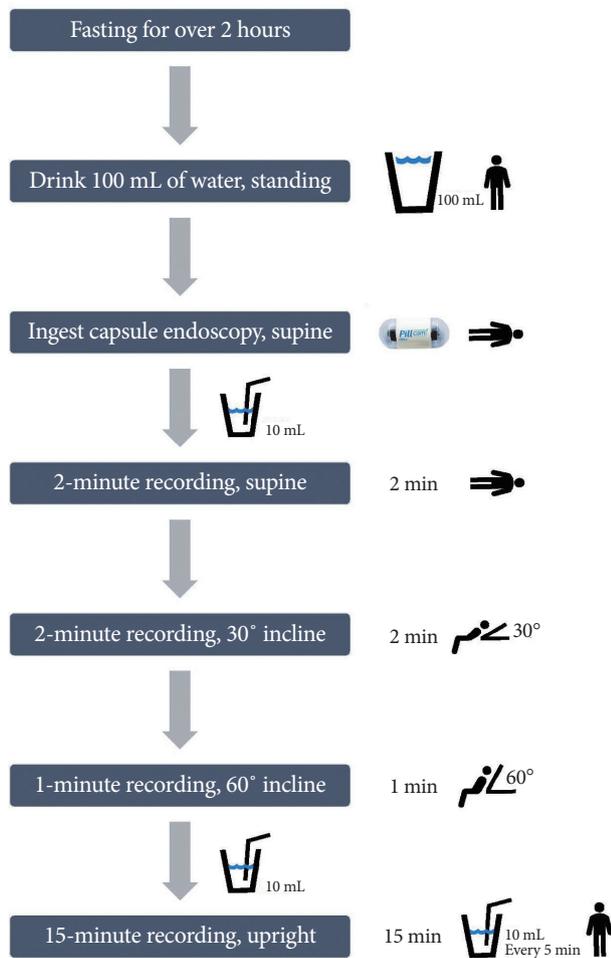


Fig. 1. PillCam ESO2<sup>®</sup> (Given Imaging Ltd., Yoqneam, Israel) capsule.

ends of the capsule and take images at 18 frames per second (fps; compared to 2–3 fps for SB capsules) with a wider angle (169°). A third-generation esophageal capsule endoscope, PillCam ESO3, with a wider angle of view (174°) and higher recording rate (35 frames/s), has already been introduced, although its practical advantage should be evaluated in a future study.

## PREPARATION AND PROCEDURES

For an appropriately thorough examination, the patient should be fasting for over 2 hours. Generally, the patient drinks 100 mL of water while standing and then ingests the capsule in the supine position (Fig. 2). Additional 10-mL sips of water can be administered through a syringe or straw. A 5-minute ingestion protocol is recommended. Two-minute recordings in the supine and 30° inclined position are followed by a 1-minute recording at 60°. A subsequent 15-minute recording is acquired in the upright position. The images ob-



**Fig. 2.** Schematic process of esophageal capsule endoscopy.

tained are transmitted via three thoracic sensors to the recorder.

## CURRENT EXPERIENCES WITH ESOPHAGEAL CAPSULE ENDOSCOPY

Several studies have demonstrated the effectiveness of esophageal capsule endoscopy (ECE) through comparisons with EGD as the reference standard. Most studies were conducted on patients with Barrett’s esophagus (BE) or esophageal varices (EV). As a minimally invasive diagnostic tool, ECE can be an option for screening patients who cannot tolerate EGD.

### ECE for gastroesophageal reflux disease and Barrett’s esophagus

Endoscopic evaluation is recommended for patients with gastroesophageal reflux disease (GERD) and its complications, especially BE, which has malignant potential.<sup>1</sup> Traditional endoscopy is limited by its cost, inconvenience, and the invasiveness of sedation.<sup>2,3</sup> Several studies have been conducted to evaluate capsule endoscopy as a less invasive and more convenient endoscopic procedure for diagnosing GERD and BE.

A capsule endoscope especially designed for esophageal examination was introduced in 2004.<sup>4</sup> The capsule was mechanically modified with two cameras located on both ends. It can obtain images at 4 fps for approximately 20–30 minutes. Using the capsule endoscope, Eliakim et al. evaluated 17 patients with positive findings on EGD in the supine position.<sup>4</sup> They achieved better detection rates, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) (70.6%, 100%, 80%, 92%, and 100%, respectively).

The increased image acquisition ability has improved the diagnostic yield of capsule endoscopy. In 2006, Koslowsky et al. investigated 2 types of capsules in 42 patients with GERD symptoms and 8 patients with confirmed BE.<sup>5</sup> Compared with EGD, the 4-fps capsule showed sensitivity, specificity, PPV, and NPV rates of 81%, 61%, 74%, and 79%, respectively, while the 14-fps capsule achieved rates of 100% ( $p < 0.02$ ), 74%, 100%, and 77%, respectively. They concluded that the 14-fps capsule has greater sensitivity and allows better visualization of the entire esophagus than the 4-fps capsule.

The diagnostic accuracy of 14-fps capsule endoscopy was assessed in patients with BE, esophagitis, and hiatal hernia.<sup>6</sup> The authors compared the results of VCE with EGD in a blinded, prospective study. The results in the 94 patients with GERD symptoms and those undergoing BE surveillance showed a higher diagnostic accuracy for BE than for erosive esophagitis. The sensitivity, specificity, PPV, and NPV for BE in GERD patients were 67%, 87%, 60%, and 90%, respectively, while those for erosive esophagitis were 50%, 90%, 56%, and

88%, respectively. However, the authors concluded that the diagnostic rates for BE were not sufficiently accurate for VCE to replace EGD as the standard diagnostic modality.

Galmiche et al. investigated the diagnostic yield of ECE in a prospective multicenter trial of patients with chronic reflux symptoms.<sup>7</sup> The study enrolled 77 patients, including 24 with esophagitis and 10 with esophageal metaplasia (ESEM), and validated the findings of ECE with EGD. The 14-fps ECE system showed sensitivity for esophagitis and ESEM of 79% and 60%, specificity of 94% and 100%, PPV of 83% and 100%, and NPV of 92% and 95%, respectively. The authors concluded that ECE can be used for screening, but its exact role in detecting esophagitis and ESEM requires further investigation.

A meta-analysis was conducted to evaluate the diagnostic accuracy of ECE for BE in patients with GERD.<sup>8</sup> Bhardwaj et al.<sup>8</sup> evaluated 618 patients from 9 studies (Table 1).<sup>5,7,9-13</sup> The pooled sensitivity and specificity of ECE for the diagnosis of BE in all studies were 77% and 86%, respectively; those of EGD, as the reference standard, were 78% and 90%, respectively. The results adjusted for publication bias demonstrated that ECE has a moderate sensitivity and specificity for the diagnosis of BE in patients with GERD. However, the authors suggested that EGD remains the modality of choice for evaluation of suspected BE.

### ECE for esophageal varices

EV are highly prevalent in cirrhotic patients, and complications from bleeding are associated with a high rate of mortality.<sup>14</sup> Endoscopic screening is recommended for patients with liver cirrhosis.<sup>15</sup> These patients are at an inherently higher risk of complications during traditional endoscopy, in addition to the common cardiopulmonary complications related to sedation and analgesia.<sup>16,17</sup> ECE was investigated as a less-invasive alternative to EGD for diagnosing EV.

Ramirez et al. reported the first study focusing on VCE for EV in 2005.<sup>18</sup> They evaluated 30 cirrhotic patients with string-capsule endoscopy. The string-attached SB capsule en-

doscope showed 96.7% accuracy in the diagnosis of EV and was preferred by the majority of patients (83.3%).

The first 2 comparative studies were published in 2006, in which ECE showed a high diagnostic yield for EV in cirrhotic patients. Eisen et al. compared the results of the 14-fps capsule endoscope with those of EGD in 32 patients.<sup>19</sup> The reported sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 100%, 89%, 9.1, and 0.0, respectively. Lapalus et al. presented the results of their comparison in 21 cirrhotic patients.<sup>20</sup> The ECE system successfully detected the EV in 85% of the cases and indicated a need for primary prophylaxis in 100%.

A large, multicenter prospective study of 120 patients was conducted and showed the sensitivity, specificity, NPV, and PPV of ECE for the detection of EV to be 77%, 86%, 69%, and 90%, respectively.<sup>21</sup> The sensitivity, specificity, NPV, and PPV for indicating primary prophylaxis were 77, 88, 90, and 75%, respectively. The authors concluded that ECE is feasible, safe, well tolerated, and accurate for the diagnosis of EV. They also suggested that ECE could be an alternative to EGD in the evaluation of EV, for the screening of cirrhotic patients, and for indicating primary prophylactic treatment.

A study performing both ECE and EGD in 50 cirrhotic patients reported that the accuracy of ECE in deciding the need for prophylaxis was 74%, with a sensitivity of 63% and specificity of 82%.<sup>22</sup> Inter-rater agreement was moderate ( $\kappa=0.56$ ). Agreement between EGD and ECE on grade of varices was also moderate ( $\kappa=0.53$ ) and inter-rater reliability was good ( $\kappa=0.77$ ). In contrast to the former study, the authors concluded that ECE has a limited role in deciding which patients would need primary prophylaxis.

The results of a large, prospective, comparative study of 300 patients undergoing EV screening using ECE and EGD were published in 2015.<sup>23</sup> The French cirrhotic patients were evaluated with ECE followed by EGD. The diagnostic indices of ECE for diagnosing and staging EV were: sensitivity, 76% and 64%; specificity, 91% and 93%; PPV, 88% and 88%; and NPV,

**Table 1.** Pooled Sensitivity and Specificity of Esophageal Capsule Endoscopy in Diagnosing Barrett's Esophagus

Author	Year	No. of patients	Reference standard	Capsule type	Sensitivity (%)	Specificity (%)
Eliakim et al. <sup>9</sup>	2005	106	EGD	PillCam ESO	97	99
Koslowsky et al. <sup>5</sup>	2006	50	EGD	PillCam ESO	75–100	100–100
Lin et al. <sup>10</sup>	2007	90	Histology	PillCam ESO	67	84
Galmiche et al. <sup>7</sup>	2008	77	EGD	PillCam ESO	60	100
Sharma et al. <sup>11</sup>	2006	94	EGD	PillCam ESO	77	95
Gralnek et al. <sup>12</sup>	2008	28	EGD	PillCam ESO2	100	74
Ramirez et al. <sup>13</sup>	2008	100	EGD	Tethered PillCam SB	78	89

EGD, esophagogastrroduodenoscopy; SB, small bowel.

81% and 78%, respectively. Patient satisfaction was assessed using the visual analog scale, and the ECE scores were significantly higher (87±22 vs. 58±5,  $p<0.0001$ ). The authors suggested that ECE specificity and PPV results indicated it can play a role in patients with contraindications for EGD or those who refuse it.

Recently, McCarty et al. evaluated ECE for the diagnosis and grading of medium to large EV in patients with portal hypertension in a systematic review and meta-analysis.<sup>24</sup> The authors collected 17 studies performed between 2005 and 2015 for a total patient pool of 1,328.<sup>18-21,23,25-31</sup> The diagnostic accuracy of ECE in the diagnosis of EV was 90% (95% confidence interval [CI], 0.88–0.93). The diagnostic pooled sensitivity and specificity were 83% (95% CI, 0.76–0.89) and 85% (95% CI, 0.75–0.91), respectively (Table 2). The diagnostic accuracy of ECE in the grading of varices was 92% (95% CI, 0.90–0.94) and the pooled sensitivity and specificity were 72% (95% CI, 0.54–0.85) and 91% (95% CI, 0.86–0.94), respectively. Based on these results, ECE was not considered capable of replacing EGD for diagnosing EV. However, it may be used in patients who are contraindicated for EGD or those who refuse it.

The diagnostic yield of ECE has proven insufficient for it to replace EGD in the evaluation of esophageal diseases. How-

ever, ECE has continuously evolved with developments in technology, and can be a reasonable option for patients who are reluctant to undergo traditional endoscopy.

## ADDITIONAL APPLICATIONS

Chen et al. introduced string ECE with real-time viewing.<sup>32</sup> They evaluated the cotton string-attached PillCam ESO capsule in 30 healthy volunteers with a real-time monitoring program. Compared with conventional ECE, the string-attached ECE showed improved Z-line visualization (at least two-quadrant visualization, 100.0% vs. 80.0%,  $p<0.001$ ; at least three-quadrant visualization, 90.0% vs. 36.7%,  $p<0.001$ ).<sup>32</sup>

A novel optomechanically-engineered device that can capture cross-sectional microscopic images has also been introduced.<sup>33</sup> This swallowable tethered capsule has been named optical coherence tomography endomicroscopy. Gora et al. presented their *in vivo* experience using tethered capsule endomicroscopy for BE screening.<sup>34,35</sup>

**Table 2.** Pooled Sensitivity and Specificity of Esophageal Capsule Endoscopy in Diagnosing Esophageal Varices

Author	Year	No. of patients	Reference standard	Capsule type	Sensitivity (%)	Specificity (%)
Ramirez et al. <sup>18</sup>	2005	30	EGD	Tethered M2A	96	100
Eisen et al. <sup>19</sup>	2006	32	EGD	PillCam ESO	100	89
Lapalus et al. <sup>20</sup>	2006	21	EGD	PillCam ESO	68	100
de Franchis et al. <sup>27</sup>	2008	288	EGD	PillCam ESO	84	88
Pena et al. <sup>29</sup>	2008	20	EGD	PillCam ESO	68	100
Lapalus et al. <sup>21</sup>	2009	120	EGD	PillCam ESO	77	86
Schreibman et al. <sup>30</sup>	2011	37	EGD	PillCam ESO	65	67
Ishiguro et al. <sup>28</sup>	2012	29	EGD	PillCam ESO	95	83
Chavalitdhamrong et al. <sup>25</sup>	2012	65	EGD	PillCam ESO	78	47
Stipho et al. <sup>31</sup>	2012	100	EGD	Tethered PillCam SB	84	72
Aoyama et al. <sup>26</sup>	2014	119	EGD	PillCam SB/SB2	72	100
Sacher-Huvelin et al. <sup>23</sup>	2015	330	EGD	PillCam ESO2	76	91

EGD, esophagogastroduodenoscopy; SB, small bowel.

**Table 3.** Comparisons of Procedural Characteristics between Esophageal Capsule Endoscopy and Traditional Esophagogastroduodenoscopy

	Capsule endoscopy	Esophagogastroduodenoscopy
Histological tissue sampling	Impracticable	Practicable
Luminal insufflation	Impracticable	Practicable
Locomotion control	Impracticable	Practicable
Therapeutic procedure	Impracticable	Practicable
Conscious sedation	Not necessary	Usually required

## LIMITATIONS AND FUTURE PROSPECTS OF ECE

In addition to the relatively low diagnostic accuracy, ECE has other limitations to its ability to diagnose esophageal diseases. For instance, it lacks the ability to obtain histological samples or perform therapeutic procedures, both of which are required during the diagnosis and surveillance of BE (Table 3). Air insufflation is not possible using capsule endoscopy and proper expansion of the esophagus is necessary to accurately diagnose and grade EV. Moreover, endoscopic treatment, including band ligation and chemical sclerotherapy, cannot be performed with ECE.

Because of these limitations, ECE is not recommended as a first-line diagnostic tool. However, continued technical improvements are being introduced to advance the diagnostic yield of capsule endoscopy. Remote magnetic control systems allow it to overcome the rapid transit time of the esophagus.<sup>36</sup> Modification of the light source with a flexible spectral imaging color enhancement system has been adopted to help diagnose esophageal malignancy.<sup>37</sup> Recent *ex vivo* research has demonstrated that targeted biopsy using magnetic capsule endoscopy and a self-folding microgripper is possible.<sup>38</sup>

## CONCLUSIONS

Capsule endoscopy has been proven to be a feasible and safe diagnostic option for patients with esophageal diseases. Several studies have reported promising results in screening for BE and EV. While the results do not support the replacement of EGD with capsule endoscopy as the gold standard diagnostic modality for esophageal diseases, the recently developed PillCam ESO3 may be used in patients who refuse or are contraindicated for EGD. Capsule endoscopy should have more diagnostic abilities to overcome the physiological and anatomical characteristics of the esophagus. Technological advances are improving the value of capsule endoscopy in conjunction with locomotion control and tissue sampling, and will provide the benefits of capsule endoscopy in the diagnosis of esophageal disease.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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