

## Role of Enhanced Visibility in Evaluating Polyposis Syndromes Using a Newly Developed Contrast Image Capsule Endoscope

Ken Hatogai\*, Naoki Hosoe<sup>†</sup>, Hiroyuki Imaeda<sup>‡</sup>, Jean-François Rey<sup>§</sup>, Sawako Okada<sup>||</sup>, Yuka Ishibashi<sup>||</sup>, Kayoko Kimura<sup>||</sup>, Kazuaki Yoneno<sup>||</sup>, Shingo Usui<sup>||</sup>, Yosuke Ida<sup>||</sup>, Nobuhiro Tsukada\*, Takanori Kanai<sup>||</sup>, Toshifumi Hibi<sup>||</sup>, and Haruhiko Ogata<sup>†</sup>

\*Tokyo Saiseikai Central Hospital, Tokyo, Japan, <sup>†</sup>Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine, Tokyo, Japan, <sup>‡</sup>Department of General Internal Medicine, Saitama Medical University, Saitama, Japan, <sup>§</sup>Institut Arnault Tzanck, St Laurent du Var, France, and <sup>||</sup>Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

**Background/Aims:** A flexible spectral imaging color enhancement system was installed in new capsule software for video capsule endoscopy. Contrast image capsule endoscopy (CICE) is a novel technology using light-emitting diodes selected for the main absorption range of hemoglobin. We assessed the feasibility and diagnostic efficacy for small bowel surveillance in patients with polyposis syndromes. **Methods:** Six patients with polyposis syndromes, four with familial adenomatous polyposis and one each with Cowden syndrome (CS) and Cronkhite-Canada syndrome (CCS) were examined using CICE. We conducted three evaluations to assess the effect on the numbers of the detected polyps; compare polyp diagnostic rates between adenoma and hamartoma; and assess polyp visibility. **Results:** The numbers of detected polyps and diagnostic accuracy did not differ significantly between pre-contrast and contrast images. However, 50% of the adenomatous polyps displayed enhanced visibility on contrast images. CICE contrast images exhibited clearly demarcated lesions and improved the visibility of minute structures of adenomatous polyps. Hamartomatous polyp micro-structures in patients with CS and CCS were more clearly visualized on contrast than pre-contrast images. **Conclusions:** CICE is an effective tool for enhancing the visibility of polyps in patients with polyposis syndrome. (*Gut Liver* 2012;6:218-222)

**Key Words:** Video capsule endoscopy; Image enhanced endoscopy; Contrast image capsule endoscopy; Polyposis syndrome

### INTRODUCTION

Video capsule endoscopy (VCE) was first reported by Iddan *et al.*<sup>1</sup> in 2000. VCE allows visualization of the small intestinal mucosa and facilitates detection of small intestinal abnormalities. Several studies have shown VCE to be extremely valuable for certain disorders, such as obscure gastrointestinal bleeding,<sup>2</sup> suspected Crohn's disease (CD),<sup>3,4</sup> small bowel tumors,<sup>5</sup> and small intestinal mucosal injury associated with the use of nonsteroidal anti-inflammatory drugs.<sup>6</sup> The efficacy of VCE for surveillance of small intestinal polyps in patients with polyposis syndromes has also been reported.<sup>7-14</sup>

In the decade since its introduction, VCE has been improved in terms of systems and protocols, such as angle of view, analysis software, pro-kinetics and bowel preparation. In conventional endoscopy, development of narrow band imaging (NBI) and flexible spectral imaging color enhancement (FICE) systems improved visualization of minute micro-vascular patterns and mucosal structures. Some reports have suggested the efficacy of magnifying endoscopy with NBI and FICE for predicting histological characteristics of polyps.<sup>15,16</sup> For VCE, a new version of RAPID software (Given Imaging Ltd., Tokyo, Japan) has been installed in the FICE system, raising the possibility of improving the contrast of vascular and mucosal patterns.<sup>17,18</sup>

Herein, we performed VCE using a capsule equipped with white-light light-emitting diodes (LED), hereinafter referred to as contrast image capsule endoscope (CICE). A specially selected white-light LED provides increased intensity of illumination in the blue range, which is the spectral range maximally absorbed by hemoglobin. The aim of this pilot study was to assess the

Correspondence to: Haruhiko Ogata

Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan

Tel: +81-3-3353-1211, Fax: +81-3-3357-2778, E-mail: hogata@z8.keio.ac.jp

Received on September 5, 2011. Accepted on October 25, 2011.

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl.2012.6.2.218>

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

feasibility and efficacy of CICE for small bowel surveillance in patients with polyposis syndromes.

## MATERIALS AND METHODS

### 1. CICE

The capsule is the same type as that of the Olympus EC Type 1 (Olympus Medical Systems, Tokyo, Japan), but is equipped with white-light LED selected specifically to increase illumination intensity in the blue light range mainly absorbed by hemoglobin (Fig. 1). Contrast images are generated employing green and blue to make the blue-enhanced white-light LED effect more visible. Pre-contrast white-light images can also be created.<sup>19</sup> Contrast images and pre-contrast white-light images cannot be created simultaneously by the workstation; however, such that contrast images must be reconstructed using another computer after downloading the video.

### 2. Patients and VCE procedure

This pilot study included 6 patients (5 men, 1 woman; mean age, 39.8 years; range, 25 to 64 years): 4 with familial adenomatous polyposis (FAP) and 1 each with Cowden syndrome (CS) and Cronkhite-Canada syndrome (CCS). All of the four patients with FAP, including a pair of brothers, were diagnosed by colonoscopy and/or duodenoscopy, their familial histories, and APC gene mutations. The case 4 was diagnosed CS by biopsy samples obtained from esophagus, stomach and colon, and also pathognomonic skin lesions. The case 5 patient was diagnosed as CCS by gastric and colonic hamartomatous polyps and typical clinical symptoms such as skin pigmentation, alopecia, and nail dystrophy. Written informed consent was obtained from all 6 patients. The VCE procedure was as follows. The patients swallowed the VCE device after a 12-hour fast with neither pre-medication nor bowel preparation. Drinking and eating were permitted after 2 and 4 hours, respectively. The recorded digital information was downloaded from the recorder into the work-

station (WS-1; Olympus Medical Systems), and the images were analyzed using the appropriate software. Images were first assessed routinely and then converted into contrast images using another computer.

For the purpose of assessing the distribution of small bowel polyps, the small bowel transit time was divided into 3 equal parts, creating tertiles (first, second, and third tertiles) as previously described.<sup>20</sup>

### 3. Evaluations of CICE images

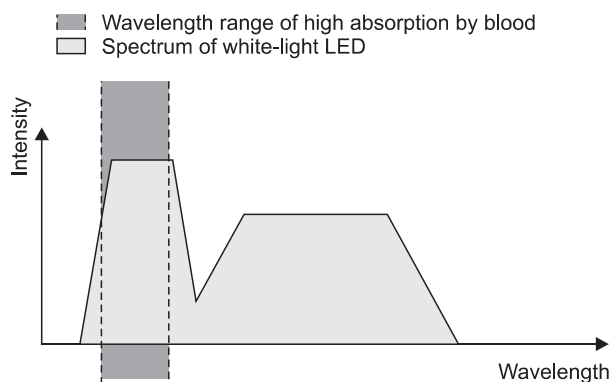
To compare the numbers of detected polyps between pre-contrast and contrast images, 2 endoscopists (K. H. and N. H.) read the same VCE record using pre-contrast and contrast images in alternate shifts. Next, to assess the additional effects of using contrast images, a 10-question, computer-based test consisting of 10 images (5 adenomatous polyps and 5 hamartomatous polyps) was conducted. The participants were 5 novice endoscopists and 5 expert endoscopists. Novices by definition had less than 3 years of experience with endoscopy. Experts by definition had more than 10 years of experience with endoscopy. All participants were blinded to the patients' clinical histories. At first, each participant judged whether polyps were adenomatous or hamartomatous based on pre-contrast images. Next, each participant judged whether polyps were adenomatous or hamartomatous polyps based on contrast images. Finally, all participants scored each contrast image in comparison with the corresponding pre-contrast image, as previously reported.<sup>18</sup> In brief, the 10 pre-contrast polyp images (5 adenomatous polyps and 5 hamartomatous polyps) were presented to each participant in random order for comparison with the contrast images. Participants scored each of the pre-contrast and contrast images for visibility of the polyp according to the following scale: +2 (improved visibility), +1 (somewhat improved visibility), 0 (visibility equivalent to that of conventional CE visibility), -1 (somewhat decreased visibility), and -2 (decreased visibility). Scores of the 5 novice and the 5 expert endoscopists for each pre-contrast and contrast image were tallied. If an image earned a total score of 5 or more, the image was considered to be improved, a score between 4 and -4 points indicated no change, and a score of -5 or less indicated decreased visibility.

### 4. Statistical analysis

Statistical analysis was performed using the Mann-Whitney U test for non-normally distributed continuous variables, and Fisher's exact test for non-continuous variables. A p-values less than 0.05 were considered significant. PASW version 17.0 software (SPSS Inc., Tokyo, Japan) was used for all statistical analyses.

## RESULTS

All capsules were excreted within 2 weeks, and no VCE-



**Fig. 1.** The principle of contrast image capsule endoscopy. A specially selected white-light light-emitting diode (LED) provides an increased intensity of illumination in the blue range, which is the spectral range maximally absorbed by hemoglobin.

**Table 1.** Patient Profiles and Polyp Distribution

Case	Age	Gender	Disease	Conventional endoscopy		Distribution of polyps		
				Stomach	Colon	First tertile	Second tertile	Third tertile
1	35	M	FAP	+	NA	+	-	-
2	38	F	FAP	+	+	+	-	-
3	25	M	FAP	+	+	+	-	-
4	28	M	FAP	+	+	+	-	-
5	49	M	CS	+	+	+	+	+
6	64	M	CCS	+	+	+	-	+

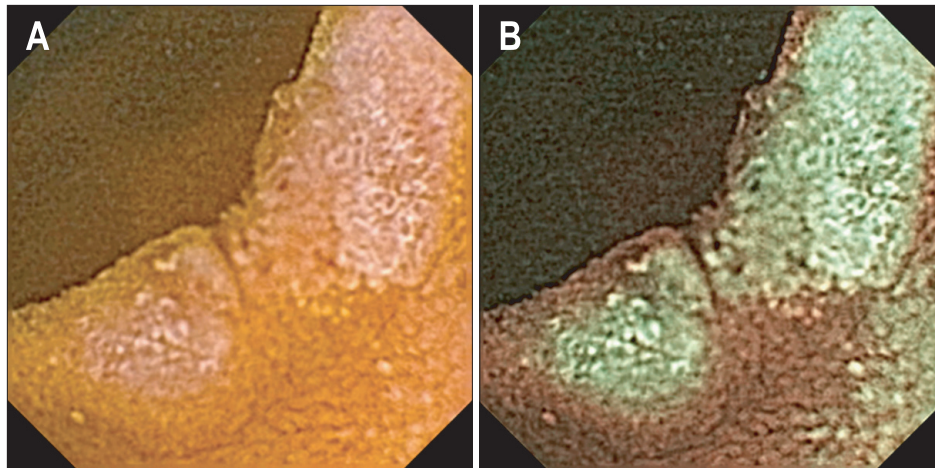
FAP, familial adenomatous polyposis; CS, Cowden syndrome; CCS, Cronkhite-Canada syndrome; NA, not available.

**Table 2.** Mean Accuracy of Polyp Discrimination

	Image type		p-value
	Pre-contrast	Contrast	
Novice endoscopist	76% (38/50)	72% (36/50)	0.82
Experienced endoscopist	80% (40/50)	82% (41/50)	1.00
Total	78% (78/100)	77% (77/100)	1.00

**Table 3.** Evaluation of Visibility Using Contrast Images

	Improved visibility	Equivalent visibility	Decreased visibility
Adenomatous polyp	50% (5/10)	50% (5/10)	0% (0/10)
Hamartomatous polyp	20% (2/10)	80% (8/10)	0% (0/10)
Total	35% (7/20)	65% (13/20)	0% (0/20)



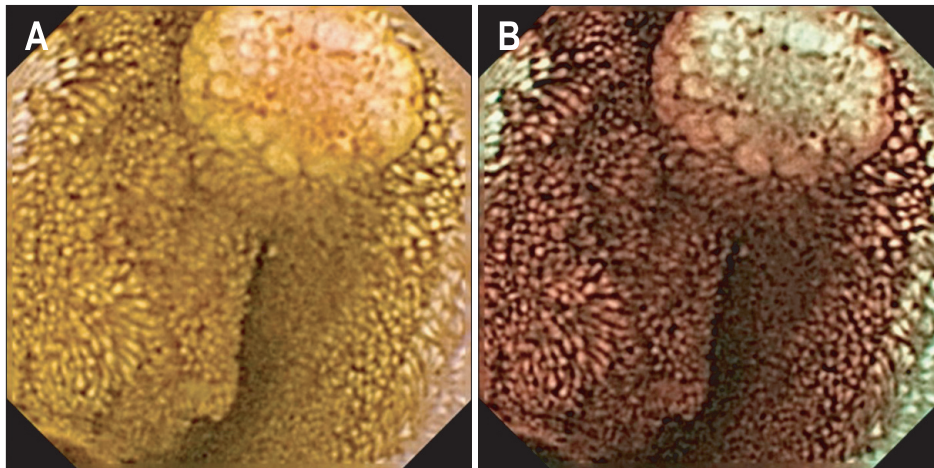
**Fig. 2.** Contrast image capsule endoscopy images (A, pre-contrast; B, contrast) of small intestinal polyps were obtained in Case 1 with familial adenomatous polyposis. Adenomatous and normal components are clearly distinguished as light greenish and brownish areas, respectively. The micro-structures of the polyps are visualized more clearly in the contrast image than pre-contrast image.

associated adverse events occurred in any of our cases. Total small intestinal surveillance was achieved in 4 of the 6 cases, but VCE did not reach the cecum during the observation period in 2 cases. All patients had gastric polyps. Though all patients with FAP had polyps only in the first tertile of the small bowel, those with CS or CCS had polyps in the first tertile as well as the second and/or third tertiles (Table 1).

Numbers of the detected polyps did not differ significantly between pre-contrast and contrast images (data was not shown). The accuracy rates of polyp diagnosis using pre-contrast and contrast images are shown in Table 2. There was no significant difference between pre-contrast and contrast images in discriminating adenomatous from hamartomatous polyps. For expert endoscopists, the accuracy rate was increased with contrast images. On the other hand, for novices, the accuracy rate was decreased. Assessment of enhanced visibility using contrast

images is shown in Table 3. All 10 polyps had equivalent or enhanced visibility on contrast images. Most notably, 50% of adenomatous polyps showed enhanced visibility on contrast images.

Representative images are shown in Figs 2 and 3. In pre-contrast images, polyps in FAP patients were visualized as whitish slightly elevated lesions with a centrally depressed area (Fig. 2A). On the other hand, in contrast images, adenomatous and normal components were clearly distinguished as light greenish and brownish areas, respectively (Fig. 2B). Polyps associated with CS and CCS were visualized as spherical elevated lesions with atrophied villi, and the colors were a mixture of white and orange shades essentially the same as the surrounding normal mucosa in pre-contrast images (Fig. 3A). On contrast images, micro-structures of the polyps were visualized more clearly than in the pre-contrast images (Fig. 3B).



**Fig. 3.** Contrast image capsule endoscopy (A, pre-contrast; B, contrast) and narrow band imaging images of small intestinal polyps were obtained in Case 5 with Cowden syndrome. The micro-structures are more clearly visualized in the contrast image.

## DISCUSSION

CICE was first reported by Aihara *et al.*<sup>19</sup> To our knowledge, this is the first pilot study to assess the feasibility of the newly developed CICE for small bowel surveillance in patients with polyposis syndromes. The major advantage of VCE is that information from the mid-gastrointestinal tract can be obtained without patient discomfort. We attempted to evaluate the distributions of polyps and to assess the efficacy of CICE for evaluating polyposis syndromes. The distributions of polyps in 3 polyposis syndromes could be evaluated by CICE, as previously reported for VCE.<sup>7-14</sup> We conducted three evaluations to 1) determine effects on numbers of the detected polyps, 2) compare polyp diagnostic rates between adenoma and hamartoma, and 3) assess polyp visibility. The numbers of the detected polyps did not differ significantly between pre-contrast and contrast images. This suggests that CICE is not appropriate as a screening procedure, such as for detecting polyps, but is suitable for investigating polyps which have already been detected. Accuracy rates of polyp diagnosis did not differ significantly between pre-contrast and contrast images for discriminating adenomatous from hamartomatous polyps. We evaluated only 10 polyps, assessed by 10 investigators. To confirm efficacy in discriminating adenomatous from hamartomatous polyps using CICE, further clinical study is necessary. Interestingly, for expert endoscopists, the accuracy rate was increased with contrast images. This was not the case for novice endoscopists. The CICE contrast images clearly demarcated lesions and improved the visibility of minute structures of adenomatous polyps in FAP cases by using a specialized white-light LED. All 10 polyps had equivalent or enhanced visibility when contrast images were employed. In particular, visibility was enhanced for 50% of adenomatous polyps on contrast images. Two major virtual chromoendoscopy techniques are now available, NBI and FICE. FICE is based on the bandwidth of the conventional endoscopic image narrowed down arithmetically using computerized spectral estimation technology.<sup>17,18</sup> NBI, on the other hand, is based on the presence

of optical filters within the light source of the endoscope, which constrains the bandwidth of spectral estimation technology.<sup>21</sup> FICE is classified as a digital image enhancement method, NBI as an optical-digital method.<sup>22</sup> Software can be installed in the FICE system without modification of the capsule, while NBI would require re-engineering of the capsule with incorporation of optical filters. As NBI is a real-time imaging technique, the capsule with optical filters can generate only NBI images. Thus, CICE was developed to obtain normal and hemoglobin enhanced images simultaneously using an LED selected to specifically increase illumination intensity in the blue light range mainly absorbed by hemoglobin. The CICE technique is classified as an optical-digital method, as noted above, making it different from FICE in terms of use of the selected LED. It also differs from NBI in that no optical filters are used. CICE has been evaluated in patients with obscure gastrointestinal bleeding and CD as well. The clinical benefit was not obvious for detection of angioma (10 patients) but in 4 patients with CD, mucosal abnormalities were clearly seen due to the CICE technology.<sup>23</sup>

This study has limitations. It was a pilot study of only 6 patients. We could not confirm that the diagnostic yield or detection rate of polyps obtained using contrast images was higher than values obtained using pre-contrast images. We found that CICE contrast images allowed clearer visualization than pre-contrast images of the demarcation between adenomatous and normal components. In addition, CICE contrast images provided more minute structural details of lesions than pre-contrast images. This new technology can be adapted to maneuverable capsule endoscopy,<sup>24,25</sup> to allow precise diagnosis, like conventional endoscopes with NBI or FICE, in the near future.

In conclusion, CICE is an effective tool for enhancing visibility of polyps in the patients with polyposis syndrome. CICE is a novel, easy-to-apply imaging tool that is equipped with LED selected specifically for the main absorption range of hemoglobin. Further clinical trials are needed to confirm the efficacy of this new device.

**CONFLICTS OF INTEREST**

Y. I. is supported by The Japanese Foundation for Research and Promotion of Endoscopy Grant. Naoki Hosoe is supported by The Research fund of Mitsukoshi Health and Welfare Foundation. No other financial relationships relevant to this publication were disclosed.

**ACKNOWLEDGEMENTS**

We are grateful to Olympus Medical Systems Co. for providing the CICE device.

**REFERENCES**

1. Iddan G, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. *Nature* 2000;405:417.
2. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. *Am J Gastroenterol* 2005;100:2407-2418.
3. Albert JG, Martiny F, Krummenerl A, et al. Diagnosis of small bowel Crohn's disease: a prospective comparison of capsule endoscopy with magnetic resonance imaging and fluoroscopic enteroclysis. *Gut* 2005;54:1721-1727.
4. Mehdizadeh S, Chen GC, Barkodar L, et al. Capsule endoscopy in patients with Crohn's disease: diagnostic yield and safety. *Gastrointest Endosc* 2010;71:121-127.
5. Trifan A, Singeap AM, Cojocariu C, Sfarti C, Stanciu C. Small bowel tumors in patients undergoing capsule endoscopy: a single center experience. *J Gastrointest Liver Dis* 2010;19:21-25.
6. Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. *Clin Gastroenterol Hepatol* 2005;3:55-59.
7. Burke CA, Santisi J, Church J, Levinthal G. The utility of capsule endoscopy small bowel surveillance in patients with polyposis. *Am J Gastroenterol* 2005;100:1498-1502.
8. Caspari R, von Falkenhausen M, Krautmacher C, Schild H, Heller J, Sauerbruch T. Comparison of capsule endoscopy and magnetic resonance imaging for the detection of polyps of the small intestine in patients with familial adenomatous polyposis or with Peutz-Jeghers' syndrome. *Endoscopy* 2004;36:1054-1059.
9. Katsinelos P, Kountouras J, Chatzimavroudis G, et al. Wireless capsule endoscopy in detecting small-intestinal polyps in familial adenomatous polyposis. *World J Gastroenterol* 2009;15:6075-6079.
10. Mata A, Llach J, Castells A, et al. A prospective trial comparing wireless capsule endoscopy and barium contrast series for small-bowel surveillance in hereditary GI polyposis syndromes. *Gastro-*

*intest Endosc* 2005;61:721-725.

11. Postgate AJ, Will OC, Fraser CH, Fitzpatrick A, Phillips RK, Clark SK. Capsule endoscopy for the small bowel in juvenile polyposis syndrome: a case series. *Endoscopy* 2009;41:1001-1004.
12. Riegler G, Esposito I, Esposito P, et al. Wireless capsule enteroscopy (Given) in a case of Cowden syndrome. *Dig Liver Dis* 2006;38:151-152.
13. Tescher P, Macrae FA, Speer T, et al. Surveillance of FAP: a prospective blinded comparison of capsule endoscopy and other GI imaging to detect small bowel polyps. *Hered Cancer Clin Pract* 2010;8:3.
14. Wong RF, Tuteja AK, Haslem DS, et al. Video capsule endoscopy compared with standard endoscopy for the evaluation of small-bowel polyps in persons with familial adenomatous polyposis (with video). *Gastrointest Endosc* 2006;64:530-537.
15. Neumann H, Fry LC, Bellutti M, Malfratherer P, Mönkemüller K. Double-balloon enteroscopy-assisted virtual chromoendoscopy for small-bowel disorders: a case series. *Endoscopy* 2009;41:468-471.
16. Uchiyama Y, Imazu H, Kakutani H, et al. New approach to diagnosing ampullary tumors by magnifying endoscopy combined with a narrow-band imaging system. *J Gastroenterol* 2006;41:483-490.
17. Pohl J, Aschmoneit I, Schuhmann S, Ell C. Computed image modification for enhancement of small-bowel surface structures at video capsule endoscopy. *Endoscopy* 2010;42:490-492.
18. Imagawa H, Oka S, Tanaka S, et al. Improved visibility of lesions of the small intestine via capsule endoscopy with computed virtual chromoendoscopy. *Gastrointest Endosc* 2011;73:299-306.
19. Aihara H, Ikeda K, Tajiri H. Image-enhanced capsule endoscopy based on the diagnosis of vascularity when using a new type of capsule. *Gastrointest Endosc* 2011;73:1274-1279.
20. Goldstein JL, Eisen GM, Lewis B, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. *Aliment Pharmacol Ther* 2007;25:1211-1222.
21. Gono K, Obi T, Yamaguchi M, et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004;9:568-577.
22. Tajiri H, Niwa H. Proposal for a consensus terminology in endoscopy: how should different endoscopic imaging techniques be grouped and defined? *Endoscopy* 2008;40:775-778.
23. Rey JF, Seitz U. How to improve video capsule image visibility? *Gastroenterology* 2010;138(5 Suppl 1):S-669.
24. Rey JF, Ogata H, Hosoe N, et al. Feasibility of stomach exploration with a guided capsule endoscope. *Endoscopy* 2010;42:541-545.
25. Swain P, Toor A, Volke F, et al. Remote magnetic manipulation of a wireless capsule endoscope in the esophagus and stomach of humans (with videos). *Gastrointest Endosc* 2010;71:1290-1293.