Cap Assisted Upper Endoscopy versus High Definition White Light Endoscopy and Narrow Band Imaging Alone in the Detection of Visible Lesions Barrett's Esophagus: A Randomized Tandem Study

Principal Investigator: Vladimir M. Kushnir, M.D.
Division of Gastroenterology
Washington University in St Louis School of Medicine
660 South Euclid Ave, Box 8124
St Louis MO 63110
Phone: 314 454-5960
Fax: 314 454-6006

Coordinating Center: Washington University School of Medicine

Co-Investigators: Stephen Hasak, M.D.
Dayna Early, M.D.
Daniel Mullady, M.D.
Gabriel Lang, M.D.
Koushik Das, M.D.

Study Coordinator: Thomas Hollander, RN
Statistician: Vladimir M. Kushnir, M.D.

Protocol Version: 2.5
Protocol Date: October 25, 2021

Cap Assisted Upper Endoscopy versus High Definition White Light Endoscopy and Narrow Band Imaging Alone in the Detection of Visible Lesions Barrett's Esophagus: A Randomized Tandem Study

Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

TABLE OF CONTENTS

1 Background and Rationale

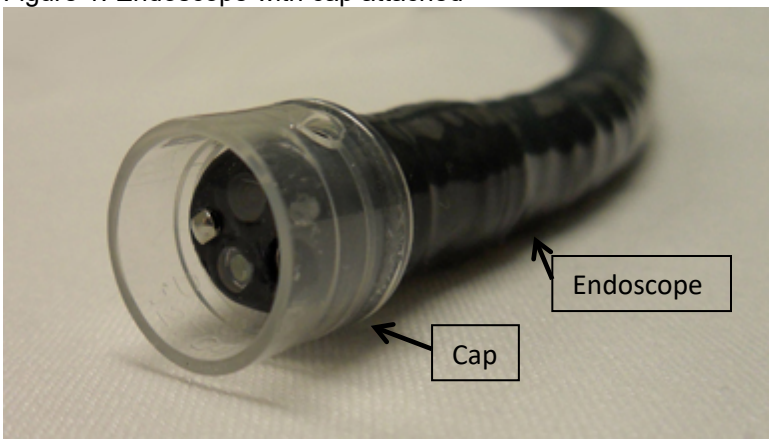
1.1 Barrett's Esophagus

Barrett's esophagus (BE) is a common premalignant condition associated with gastroesophageal reflux disease (GERD). [1, 2] About 10% of patients with chronic GERD develop BE, which has an overall estimated prevalence of 1.6% in the general population. [3, 4] BE is characterized by replacement of normal squamous epithelium by columnar epithelium with goblet cells, otherwise known as intestinal metaplasia.[5] It is associated with an increased risk of esophageal adenocarcinoma, but the rate of progression to malignancy varies depending upon histologic findings. Risk of malignant transformation is up to 10% per year in patients with high grade dysplasia. [6-7]

1.2 Endoscopic Eradication Therapy

Endoscopic eradication therapy (EET) is a term used to describe various endoscopic modalities employed to eradicate dysplastic lesions in Barrett's esophagus, including endoscopic mucosal resection (EMR), endoscopic submucosal resection (ESR), radiofrequency ablation (RFA), photodynamic therapy (PDT), and cryoablation. EET reduces the risk of disease progression to higher grade dysplasia and to adenocarcinoma in patients with BE and dysplasia. [1, 8]. EET is also cost effective when compared to surveillance alone. [9] EMR can be used alone for curative intent of dysplastic BE or prior to RFA with lesions identified on EMR. EMR followed by RFA is currently the treatment of choice for patients with BE and high grade dysplasia, as eradicated rates are improved compared with treatment with either modality alone. [10] Given these data, it is especially important to maximize the identification of all visible BE lesions.

Figure 1: Endoscope with cap attached



Transparent fitted cap endoscopy can be used to increase diagnostic and therapeutic yield in a variety of settings including screening colonoscopy, esophageal foreign body retrieval, and GI bleeding. [11-15] In screening colonoscopies for example, caps increase the diagnostic yield of detecting polyps by 5-10%. [11, 12] In the setting of this proposed study, caps may improve visualization and detection of mucosal abnormalities through a variety of mechanisms, including keeping mucosa within range of the focal depth of the endoscope, stabilizing the endoscope, and helping to align a target lesion for biopsy and/or therapy. A previous study assessing the effect of cap-assisted endoscopy in diagnosing BE in a population with suspected disease increased the probability of diagnosis from 69.4% to 83.3% when compared to conventional endoscopy. [15] However to date, the utility of cap assisted endoscopy in detecting visible and dysplastic lesions in BE has not been evaluated.

1.3 Rationale

Our hypothesis is that the addition of a transparent cap to the end of the endoscope will increase the detection and diagnostic yield of visible lesions in Barrett's esophagus. Thus, the goal of this tandem design trial is to compare the diagnostic yield (DY) of cap assisted endoscopy with that of conventional endoscopy using high definition-white light endoscopy (HD-WLE) and narrow band imaging (NBI) in patients with Barrett's esophagus.

2 Objectives

2.1 Primary Objective

To compare the diagnostic yield of esophagogastroduodenoscopy (EGD), a test to examine the lining of the esophagus, stomach, and first part of the small intestine, with HD-WLE and NBI with the diagnostic yield of cap-assisted EGD with HD-WLE and NBI. "Diagnostic yield" is defined as the proportion of EGD in which visible BE lesions were identified and confirmed histologically as low grade dysplasia, high grade dysplasia, intramucosal cancer, or invasive adenocarcinoma

2.2 Secondary Objectives

1. To determine the number of visible lesions detected per person in EGD with vs without cap.
2. To evaluation the detection of high grade dysplasia and esophageal adenocarcinoma in EGD with vs without cap
3. To determine the total procedure duration in minutes
4. To assess safety by recording procedure-related adverse events.

3 Eligibility Criteria

3.1 Inclusion Criteria

1. Must be at least 18 years of age.
2. Must be patients undergoing standard of care EGD for the confirmation of dysplasia in BE or EET for dysplasia in BE.
3. Must be able to understand and willing to sign an IRB-approved written informed consent document.

3.2 Exclusion Criteria

1. Pregnant or breastfeeding.
2. Prior endoscopic treatment for BE.
3. Unable to tolerate sedation due to medical comorbidities.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Current approved protocol version date
6. Planned date of enrollment
7. Completed eligibility checklist, signed and dated by a member of the study team
8. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

4.4 Randomization

Consenting and eligible participants will be randomized to one of two arms. Participants in the first arm will undergo EGD with cap first, followed by EGD without cap. Participants in the second arm will undergo EGD without cap first, followed by EGD with cap. All participants will have EGD with and without cap; the randomization affects the order in which the procedures take place. The order of cap placement will be determined by a preprinted randomization sequence kept in an opaque envelope that will be opened after enrollment.

5 Study Procedures

This is a tandem design trial comparing the diagnostic yield of HD-WLE and NBI with and without the use of an Olympus Disposable Distal Attachment cap.

5.1 Recruitment

Adult patients scheduled to undergo esophagogastroduodenoscopy (EGD) will be screened for the study. Patients will be identified as candidates for the study from the BJH Surgery Schedule the day before they come in. If they present for the evaluation and/or treatment of dysplastic lesions in BE, one of the investigators or a research assistant will discuss the study with potential participants in the pre-endoscopy area. Those subjects who qualify for the study based on inclusion/ exclusion criteria will be invited to participate. The consent process will take place in the pre-endoscopy area. Those patients who wish to participate will sign the informed consent document and proceed to EGD; randomization will take place after the patient is consented and before the procedure starts.

5.2 Intervention

After randomization, the endoscopist will then perform exam with or without cap using HD-WLE and NBI and identify visible lesions. Identified lesions will be recorded on the case report form using a blank clock face divided in four quadrants and with distance from the incisors in cm. The endoscope will then be withdrawn. A second endoscopist will then perform a second EGD with a cap if none was used on initial exam or without a cap if one was used on initial exam. The second endoscopist will be blinded to the results of the initial exam. If there is no physician available to perform second endoscopy then the patient will not be considered for the study. Visible lesions will be recorded in same format as initial exam. Finally, the endoscopist of record will biopsy or perform EMR of all noted lesions, which will be sent for pathological review, the results of which will be captured from the medical record. All procedures will be performed by a gastroenterologist experienced in EET or by a fellow under direct supervision. Patients will be contacted in 48 hours by phone by clinical staff to monitor for AEs

6 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

6.1 Definitions

6.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and

Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

Risks associated with this study include risk of breach of confidentiality and having to be under sedation for an additional 2-5 minutes while the second exam of the study is being performed.

6.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

6.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

6.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

6.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

6.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

6.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

6.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

6.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

6.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 6.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

6.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

6.6 Timeframe for Reporting Required Events

Adverse events will be tracked for 48 hours after EGD.

7 Data and Safety Monitoring Plan

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months following the activation of the first secondary site. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites and separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

8 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

9 Statistical Considerations

9.1 Sample Size Calculations

Based on prior studies of diagnostic yield of HD-WLE and NBI in detecting abnormalities in BE we assume that using a cap during BAE will increase the diagnostic yield by 15%. With this assumption in mind and requiring a power of 80% and alpha of 0.05 (two tailed) we would need a total of 170 patients.

9.2 Analysis methods

This study will collect both categorical and quantitative demographic variables and endoscopy procedural details: procedure duration, diagnostic finidngs, and procedure complications. Pathology results will be recorded and the electronic medical record will be reviewed to extract any relevant clinical information. All complications will be noted. All information will be transferred into a database. The categorical variables will be summarized using frequencies and percents, while the quantitative variables will be summarized using means and standard deviations. Chi square test will be used for categorical variables while student's t test will be used for quantitative variables to test the difference between the study groups. Additionally, multivariable analysis will be used in order to identify factors associated with success increasing diagnostic yield. Continuous variables with a non-normal distribution will be compared using the Wilcoxon rank-sum test. The statistical software program SPSS will be used for analysis. A two sided p value of < 0.05 will be considered significant.

10 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

11 References

1. Winters C, SPurling TJ, Chobanian SJ, et al. (1987) Barrett's esophagus: A prevalent occult complication of gastroesophageal reflux disease. Gastroenterology 92: 118-24.
2. Shaheen NJ, Sharma P, Overholt BF, et al. (2009) Radiofrequency ablation in Barrett's esophagus with dysplasia. NEJM 360 (22): 2277-88. 19.
3. Abrams JA, Fields S, Lightdale CJ, Neugut AI. (2008) Racial and ethnic disparities in the prevalence of Barrett's esophagus among patients who undergo upperendoscopy. Clin Gastroenterol Hepatol 6: 30-4.
4. Ronkainene J, Aro P, Storskrubb T, et al. (2005) Prevalence of Barrett's esophagus in the genreral population: an endoscopic study. Gastroenterology 129: 1825-31.
5. Spechler SJ. (2002) Barrett's esophagus. NEJM 346: 836-42.
6.Bhat S, Coleman HG, Yousef F, et al. (2011) Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst 103: 1049-57.
7. Rastogi A, Puli S, El-Serag HB, et al. (2008) Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high grade dysplaisa: a meta-analysis. GAstrointest Endosc 67: 394-8.
8. Phoa KN, van Viltsteren FG, Weusten BL, et al. (2014) Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia. JAMA 311 (12): 1209-17.
9. Filby A, Taylor M, Lipman G, et al. (2017) Cost-effectiveness analysis of endoscopic eradication therapy for treatment of high-grade dysplasia in Barrett's esophagus. Journal of Comparative Effectiveness Research Epub.
10. Wani S., et al (2013) Management of high-grade dysplasia and intramucosal adenocarcinoma in Barrett's esophagus. Clin Gastro and Hep 10(7):704-11.
11. Rastogi A (2013) Cap-assisted colonoscopy. Gastroenterol Clin North Am 42: 479-489.
12. Westwood DA, Alexakis N, Connor SJ (2012) Transparent cap-assisted colonoscopy versus standard adult colonoscopy: a systematic review and meta-analysis. Dis Colon Rectum 55: 218-225.
13. Yap CK, Ng HS (2001) Cap-fitted gastroscopy improves visualization and targeting of lesions. Gastrointest Endosc 53: 93-95.
14. Kim JI, Kim SS, Park S, Han J, Kim JK, et al. (2003) Endoscopic hemoclipping using a transparent cap in technically difficult cases. Endoscopy 35: 659-662.
15. Chen BI, Xing XB, Wang JH, et al. (2014) Improved biopsy accuracy in Barrett's esophagus with a transparent cap. WJG 20(16): 4718- 22.