STUDY PROTOCOL VERSION

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Pilot study for imaging of the esophagus using a tethered capsule OCT endomicroscopy in the Primary Care setting.

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A. BACKGROUND AND SIGNIFICANCE

Barrett 's esophagus and esophageal adenocarcinoma

Barrett's esophagus (BE) is a condition associated with older age, Caucasian race, and longstanding gastroesophageal reflux disease (GERD),[1] where the normal squamous epithelium is replaced by intestinal epithelium, also termed specialized intestinal metaplasia (SIM).[2] BE can undergo dysplastic progression, leading to esophageal adenocarcinoma (EAC), a cancer with a poor overall 5-year survival of 10%.[3-5] There are approximately 8,000 new cases of EAC per year in the US[6] and its incidence is growing at a higher rate than any other cancers, with a six-fold increase over the past three decades.[1]

Current management of BE. Because patients with BE carry 35-120 times higher risk of developing EAC[7,8] and treatment of early stage cancer can be curative, the American College of Gastroenterology (ACG),[9] the American Gastroenterological Association (AGA),[10] and the American Society for Gastrointestinal Endoscopy (ASGE)[11] recommend that patients with risk factors for Barrett's esophagus, such as chronic GERD, age over 50, male sex, elevated body mass index, and hiatal hernias be screened for SIM with upper endoscopy (esophagogastroduodenoscopy - EGD). For this procedure, the patient is sedated and a video endoscope is inserted transorally into the insufflated esophagus. The gastroenterologist then inspects the esophagus, stomach, and gastroesophageal junction (GEJ). If abnormal, salmon- colored mucosa is identified proximal to the diaphragmatic pinch, a biopsy is excised and sent to pathology for analysis. Patients found to have histopathologic evidence of SIM undergo regular surveillance, which consists of taking random, 4-quadrant biopsies every 1-2 cm along the longitudinal extent of the BE segment.[9,11] Surveillance intervals every 2-5 years are recommended in patients without dysplasia and every 6 months for patients with low-grade dysplasia (LGD).[9,11,12] For patients with high-grade dysplasia (HGD), either surveillance at 3 months intervals, ablation, endoscopic mucosal resection (EMR), or esophagectomy is recommended.[9,11-13]

Limitations of endoscopic screening

At present, approximately 1M patients in the US are screened with upper endoscopy for BE every year.[14] At an average of $1000 per procedure, screening for BE amounts to $1B annual expense to our health care system. Any method to lower the cost of screening today would be of great benefit to society in this time of escalating health care costs

Even though upper endoscopic screening is widely practiced, many patients with GERD are still not screened. This fact could partially explain why > 95% of patients who currently present with EAC have not had a prior diagnosis of BE.[15] However, screening the entire GERD population at risk would not be economically feasible, as there are 40-60M patients with GERD in the US[16] and an estimated 3-12M patients with BE.[17,18] Moreover, recent studies have shown that 39-44% of patients with BE[19] and EAC[20] did not report symptoms of GERD, indicating that the potential screening pool may be even larger. A recent medical decision analysis performed to assess the cost-effectiveness of endoscopic screening in patients with GERD concluded that the expense of endoscopy was one of the most important factors determining whether or not screening was cost-effective.[21] This analysis also indicated that screening for SIM could be justified.[21]

Besides cost, another limitation of upper endoscopy for screening is its low accuracy. Studies have shown that endoscopists correctly identify SIM in only approximately 40-50% of cases.[22,23] Even when endoscopy does identify abnormal mucosa, the fractional area of tissue sampled by biopsy is low and SIM or dysplasia may be missed.[24,25] A separate cost-effectiveness analysis by Inadomi *et al*. showed that screening and subsequent surveillance was cost effective only in those patients with dysplasia.[26] This study suggests that the best screening method would be capable of identifying dysplastic SIM, something that is not possible with endoscopy. The diagnostic failings of upper endoscopy, combined with its high cost make it a good target for improvement.

Finally, screening is only useful if there is a viable follow-up option that will change outcome for those patients who have a positive test. Random biopsy surveillance, the follow-up procedure for patients found to have SIM, is also subject to significant limitations. Since dysplasia and adenocarcinoma are not evident by endoscopy and are focally distributed, random biopsy is inherently prone to sampling errors. Even when using the largest biopsy forceps available (jumbo biopsy forceps), most biopsy procedures interrogate < 1% of the involved segment of BE.[24,25] The inadequacy of random biopsy is highlighted by histopathologic analyses of esophagectomy specimens that have found undetected intramucosal carcinoma (IMC) in 40% and invasive adenocarcinoma in 13% of patients with a prior diagnosis of HGD only.[27-29] A method for guiding the gastroenterologist to excise biopsies from regions that contain the most severe disease should improve the overall effectiveness of screening and surveillance of BE patients.

Cost of sedation and upper endoscopy

Sedation, via IV administration of sedatives and narcotic analgesics, is the single most important contributor to the high cost of upper endoscopy and is estimated to account for 30-50% of the total procedural cost.[30] Because of the mortality and morbidity associated with complications related to sedation, patients must undergo continuous cardiopulmonary monitoring and nursing support during the endoscopic procedure. Post-procedural recovery also contributes to the expense, as it requires additional nursing, monitoring, and patient care in a large and specialized physical space. After discharge, patients frequently need to be escorted home and lose at least a day of work.[31]

Optical Coherence Tomography (OCT)

Optical Coherence Tomography is a optical diagnostic technology that provides a high-resolution (10 μm axial resolution) cross-sectional images of tissues in noninvasive way.[32,33] We have demonstrated that OCT has the potential to provide more diagnostic information as it can distinguish BE and dysplasia with accuracies ranging from 80-90% and be less costly than upper endoscopy.[34-36]

We have utilized the high-speed version of OCT to perform three-dimensional, architectural microscopy of long segments of luminal organs using helically scanning balloon- centering catheters.[37-39] We have successfully conducted balloon-catheter esophageal OCT in over 100 patients[40] and have shown that it is a safe and rapid procedure. With this technology, however, OCT balloon catheter placement requires sedated upper endoscopy.

Tethered capsule OCT endomicroscopy

We have developed a tethered capsule OCT device intended as an inexpensive screening tool for BE.41,42 The capsule, which is attached to a thin, flexible tether, is reusable after being processed by a standard disinfection technique. Used without sedation, the capsule is swallowed by the patient and travels in the esophagus to the GEJ via peristalsis. Cross-sectional microscopic OCT images of the entire esophagus are collected during transit. The total time needed for swallowing, imaging and retrieval does not exceed 10 minutes. We have tested the feasibility and the tolerability of this new OCT screening technology in 77 procedures in healthy volunteers and patients with various esophageal disease including BE. The procedure has been safe and well tolerated. High quality microscopic images of the esophagus have been obtained in 90% of the enrolled subjects.

Tethered capsule OCT endomicroscopy for population based screening

Our previous clinical experience with tethered capsule OCT endomicroscopy has been in the setting of gastroenterology endoscopy clinics. These study procedures were conducted in GI endoscopy suites by gastroenterologists and GI nurses. While these studies have been useful to determine the safety and feasibility of capsule endomicroscopy in human subjects, the ideal setting for screening patients for BE is in the primary care office. We therefore propose to conduct a study to evaluate the feasibility and acceptability of using of our tethered capsule endomicroscopy device in the primary care office setting.

B. SPECIFIC AIMS

The goal of this research is to test the feasibility and acceptability of a tethered capsule OCT endomicroscopy as a device for population based screening in the primary care practice environment.

C. SUBJECT SELECTION

Sixty volunteer subjects scheduled for non-urgent visits to outpatient primary care practices at MGH will be enrolled in the study.

Subjects will be selected according to the following inclusion and exclusion criteria:

THE INCLUSION CRITERIA:

- Patients must be scheduled for non-urgent appointment at primary care practice including annual wellness visits and routine follow-up appointments.
- Patients must be over the age of 18
- Patient must be able to give informed consent
- Patient must have no solid food for 4 hours prior to the procedure, and only clear liquids for 2 hours prior to the procedure.

THE EXCLUSION CRITERIA:

- Subjects with current symptoms of dysphagia
- Subjects with any history of intestinal strictures, prior GI surgery, or history of intestinal Crohn's disease.
- Subjects with current symptoms of fever, nausea or sore throat at the time of the appointment.
- Pregnancy

RECRUITMENT METHODS

Potential participants will be identified from the primary care physician's schedule by reviewing the electronic clinic schedule at least 2 weeks in advance of the visit. On a regular basis, a list of potentially eligible subjects (based on reason for visit and age) will be sent to the primary care physician via Partners email to seek permission to contact each patient about the study. After the primary care physician has given permission, a letter cosigned by the primary care physician and the PI will be sent to the potential participants as well as a copy of a consent form and a short fact sheet about the study (included). Contact details will be provided in the letter for all potential subjects to call with questions or concerns regarding the research study, or to opt out in advance of the scheduled visit if they choose to do so. Subsequently, potential participants will be contacted by telephone about 3 days prior to the scheduled visit to assess if they would be interested in participating, remind them not to eat for at least 4 hours prior to the visit and answer any questions they might have.

On the day of the visit, potential participants will be approached by the study staff member. The details of the study will be reviewed and the questions from the participants about the study will be answered. The capsule operator is a designated study member trained in operating the capsule. The PCP will also be available to answer any questions about the study. The consent for this study will be obtained by a licensed physician or designated research study member. This will happen either

immediately before or after the clinic visit. Participants can change their mind at any time and withdraw from the study at any point, including after signing the consent form

D. STUDY PROCEDURES

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PROCEDURE

The procedure will take place immediately before or after the patients' Primary Care appointment in an available exam room within the primary care practice suite. As described above, patients will have received written information prior to the day of the capsule procedure and patients will have another chance to discuss the procedure with the study coordinator and clinical study staff during the consent process prior to the capsule procedure. Participation in this study is completely voluntary, and the patient can stop the procedure at any time.

According to the sterilization method in place at the MGH GI unit, the capsule and sheath will undergo a high level disinfection before each use. This protocol is identical to that of MGH GI unit endoscopes and esophageal manometry study catheters (ESMO), both of which are passed through the upper GI tract and removed. Alternatively, before each case, the capsule and sheath will be sterilized at the MGH Sterile Department using cold gas Ethylene Oxide.

For each of the consenting patients, inclusion criteria and clinical characteristics such as age, sex, body mass index (BMI), current medication regimen and GI related history will be recorded. Study subjects will be asked to verify that they have not consumed solid foods in the past 4 hours, and have had only clear liquids for the past 2 hours. Women of child-bearing age will be asked to take a urine pregnancy test and women with positive test results will be excluded from the study.

Subjects will be seated and wearing their own clothing for the procedure. They do not need to change into the hospital gown. Subjects will be asked to sip water from a straw to facilitate swallowing the capsule. Subjects will be given the option of using an over the counter throat numbing spray , which will reduce the irritation to the back of the throat by the tether. Subjects typically will use the spray few minutes before the start of the procedure. Subjects will also be given the option to use a readily available over the counter water-based lubricating spray that helps the subject swallow the capsule more easily. Subjects typically use 2-4 sprays (.3-.6 ml) before the procedure. We recognize that everyone utilizes different strategies to swallow capsules and we would like to provide them with whatever

they need to successfully swallow. This may include using food products such as applesauce, pudding, and yogurt as well as implementing additional swallowing methods. The texture and density of the food products can make it easier to swallow capsules whole. These methods are optional and entirely up to the subject. Should the study subject not be able to swallow the capsule after ten attempts, the research procedure will be terminated.

The capsule will be administered by operators trained in the procedure. With an upgraded imaging console for improved ease of use, the operator can both administer the capsule and control the system as opposed to the previous design that requires separate capsule and system operators. The compact system design will also significantly improve ease of equipment transport to and from facilities for procedures. A clinician will always be available during the procedure for consultation or advice if any problems are encountered.

The imaging procedure starts after the operator confirms that the capsule has been swallowed (about 20 cm from the subject's incisor). The distance from the incisors will be established via marks on the outer sheath of the tether. OCT images of the esophagus will be obtained as the capsule is descending between the stomach and upper esophageal sphincter. The subject may be asked to take additional sips of water during the procedure to assist in the motion of the capsule as it passes through the lower esophageal sphincter. Imaging will be performed in the same manner as in our other current IRB approved tethered capsule endomicroscopy studies. The capsule position will be controlled manually via the tether outside of the subject's mouth by the catheter operator. Recorded real time OCT images displayed on the monitor and distance marks on the tether will be used for confirmation of capsule position in the esophagus. After the imaging procedure is finalized the catheter operator will remove the capsule from the esophagus by gently pulling the tether.

The capsule may be repositioned for imaging up to 4 times up and down the esophagus. The subject may be asked to swallow a different size capsule to obtain the best distal esophageal images. It is expected that the maximum experimental time including swallowing the capsule, the imaging procedure, and removal of the capsule will take approximately 20 minutes in total. Subjects will not be asked to swallow more than 2 capsules during any procedure.

If the study subject wants to stop for any reason, at any time during the procedure or should the physician/clinical staff at any point feel that the health and well being of the subject is compromised, image acquisition will be immediately suspended, and the capsule catheter removed.

FOLLOW UP:

After the imaging procedure, the subject will be asked a set of questions regarding tolerability of the procedure before leaving the clinic.

An investigator will also assess the quality of the recorded images and movies obtained with each exam after the imaging is completed. OCT images will be analyzed at a later

time and will be used for research purposes only. They will not be used for any diagnostic purposes. After analysis of the data, the PI might alert the PCP to some findings and will discuss the relevance of those findings.

Investigators and study staff will meet with physicians and clinic staff regularly to assess study procedures and troubleshoot any issues that might have arisen regarding recruiting, consenting, the imaging procedure, or any other component of this pilot study.

E. COSTS

The experimental procedure will be done at no cost to the subject or his/her insurance company and patients will not be responsible for any costs incurred as part of participating in this study.

All subjects will be offered a gift certificate in the amount of $50 as compensation for their time.

F. BIOSTATISTICAL ANALYSIS

This is a feasibility study in order to estimate subject participation rates, study time requirements, and general participant feedback. We will use this information to design a larger, more comprehensive clinical study for general population screening.

G. RISKS AND DISCOMFORT

We have performed over 120 such procedures without any unanticipated adverse events or device malfunction.

This OCT endoscopy capsule is similar to other approved video endoscopy capsules.

Capsule endoscopy of the esophagus was approved by the FDA in November 2004. It has been offered as an alternative to EGD for screening patients with chronic reflux and those with a known history of Barrett's esophagus. Capsule endoscopy (Givens G2, OMOM Capsule Endoscope) does not require sedation and it is generally well tolerated by the majority of patients. Capsule endoscopy imaging is a safe procedure that carries few risks. Some of the risks associated with capsule endoscopy are symptomatic capsule retention and aspiration. For normal patients no cases of retention or aspiration have been reported. Retention rates have been reported as 1% and mainly in patients with strictures. Only a few cases of aspiration have been reported, mostly in older patients. In our study we will use a tethered capsule and strictures are an exclusion criteria. Retention and aspiration are highly unlikely. In the unlikely event that retention does occur, it is expected that the capsule will pass through the GI tract. In the event that the capsule does not pass through the GI tract, X-rays will be taken and the capsule will be removed via endoscopy.

It is expected that tethered capsule endomicroscopy will have risks and discomfort similar to the approved endoscopy capsules. In the unlikely event that the capsule is disconnected from the tether, it is expected that any component of the capsule will be able to pass through the GI tract since the OCT capsule's diameter and length are

comparable to those of FDA-approved, commercially available capsule endoscopes that are swallowed and allowed to pass through the GI tract.

In order to minimize risk, and as a safety precaution, the laser will only be turned on when the endomicroscope is within the esophagus. The system is operated by trained and experienced operators and the laser is only turned on once the capsule operator confirms that the capsule has been swallowed and is within the esophagus.

In order to minimize the potential risk of confidentiality, the acquired OCT data and all other patient information will be assigned a subject number unique to this study. All other patient personal information will be removed. A master log will be maintained with full names and medical record numbers, which will be secured in the research coordinator's office. This will be accessible only when deemed necessary and only to members of the study team.

It is also not anticipated that participation in this pilot study will directly pose any psychological risk.

H. POTENTIAL BENEFITS

There are no medical benefits to the study participants. Images acquired during the study are only for research purposes and will not inform clinical care. However, if there are any findings of esophageal abnormality seen on OCT, the results will be discussed with the primary care physician.

I. MONITORING AND QUALITY ASSURANCE

As the risks associated with this protocol are low, a Data and Safety Monitoring Board will not be required. Dr. Tearney, the Principal Investigator of this study will be directly responsible for the conduct of the study. Dr. Tearney will be responsible for ensuring that the study is conducted according to the IRB-approved protocol and regulations, and for protecting the rights, safety and welfare of the subjects. Dr. Tearney has regular scheduled meetings with the clinical staff. He will be responsible for monitoring the study and any adverse or unanticipated events on a regular basis. Dr. Tearney is also responsible for reporting any unexpected or adverse events to the Partners IRB".

J. REFERENCES

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