

Endoscopic Mucosal Resection versus Intensive Surveillance for the Management of High Grade Dysplasia in Barrett's Esophagus

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A. Introduction

Barrett's esophagus is a premalignant condition of the esophagus in which its normal squamous lining becomes replaced by columnar epithelium. This condition is believed to undergo transformation, usually first to low grade dysplasia (LGD), then to high grade dysplasia (HGD), and finally adenocarcinoma. The risk of progression of high grade dysplasia to adenocarcinoma in 5 years has been reported to be between 16 and 59% in two large studies^{1,2}. The 5-year survival rate of patients who develop adenocarcinoma has been reported as low as 15%. Thus, treatment of HGD before it progresses to cancer is desirable as this greatly improves survival.

The standard treatment for high grade dysplasia, however, is controversial, and involves a choice between prophylactic esophagectomy, investigational endoscopic ablative therapies, and intensive surveillance, a decision usually based on surgical candidacy and patient preference. Proponents of surgery base their stance on 2 facts; (a) about 30% - 73% of patients diagnosed with HGD who underwent esophagectomy have been found to already have adenocarcinoma, identified in their surgical specimens, which was missed by endoscopy with random biopsy^{3,4}, and (b) esophagectomy is the only modality shown thus far to have the highest likelihood for cure when neoplasia is detected at an early stage⁵.

At the other end, supporters of the "watch and wait" approach argue to defer surgery until an absolute indication for its use (i.e. cancer) arises, because (a) esophagectomy is an maximally invasive procedure with high rates of morbidity and mortality: in some reports up to 14% operative and hospital mortality have been observed⁶, and (b) studies have mostly shown that only a minority of patients with HGD will ever develop cancer⁷.

Intensive surveillance and esophagectomy are currently the only two standard approaches approved for the management of HGD. Local endoscopic ablative techniques that offer less morbidity and mortality than esophagectomy, but more definitive treatment for disease than watching and waiting, have been proposed as alternative treatments for HGD. Though multiple observational trials have shown good results with these treatments, they are still considered investigational only, and thus can only be used as treatments in the setting of a research protocol. Endoscopic mucosal resection (EMR), which involves removal of only the affected superficial layer of the esophagus, is one of such endoscopic therapies that has shown promise in preliminary studies^{8,9}, with 5-year survival rates up to 95-100% in several Japanese studies¹⁰. Some studies of EMR for HGD as well as early adenocarcinoma have shown rates of recurrent or progressive disease as low as 14%¹¹ and 5-year survival rates as high as 86% in early adenocarcinoma¹².

The purpose of this study is to propose EMR as a new standard treatment for HGD by demonstrating its efficacy in a randomized, controlled comparison with one of the current standard approaches, intensive surveillance. If EMR shows superiority to surveillance, it should then be approved as a standard of care together at the same level as both esophagectomy and surveillance for the treatment of this premalignant condition.

B. Hypothesis

The primary hypothesis of this study is that EMR is better than intensive surveillance for preventing progression of high-grade dysplasia in Barrett's esophagus to cancer.

C. Methods

a. Study Design

This will be a randomized, controlled, double-blinded study. Successive patients presenting to the gastroenterology divisions of 2 large medical centers in the northeast U.S.A. for management of Barrett's esophagus with HGD, who voluntarily defer surgery or are considered non-surgical candidates, will be randomized to either EMR or intensive surveillance as their treatment modality. In order to maintain patient blinding, patients randomized to intensive surveillance will undergo sham EMR (simple endoscopy with biopsy) as their initial "treatment". After their treatments, patients in both arms will then be followed bimonthly with upper endoscopy/biopsy (+/- endoscopic ultrasound) to evaluate for subclinical disease progression, basic laboratory tests, and semiannual radiographic imaging to evaluate for metastatic disease, for a maximum of 5 years. Patients randomized to EMR will initially receive up to 3 treatments as needed in the first 4 months of the study in attempt to treat all affected mucosa. All patients will be maintained on acid-suppressive therapy throughout the duration of the study. Patients found to have progressive disease during the follow-up period, defined as histological evidence of intramucosal or invasive adenocarcinoma, or radiographic evidence of metastatic cancer, will then exit the study and be offered the appropriate management for their specific condition according to current standards of practice.

b. Conceptual and Operational Definitions

The primary outcome to be measured in this study is progressive disease, defined as proportion of patients with histological or radiographic identification of cancer -intramucosal, invasive or metastatic. The secondary outcome to be measured is adverse events such as esophageal perforation, dysphagia, bleeding, which will be obtained by a combination of patients' reporting of symptoms on a checklist, and clinician's reporting of adverse events noted during or after any endoscopic procedure.

c. Statistical analysis

At the end of the study period, the primary outcome will be analyzed by using a two-by-two table to show the proportions of patients in each group who developed progressive disease. Cumulative incidences of disease progression as a function of time will be shown using a Kaplan-Meier curve. Secondary outcome will be displayed on a simple table showing the relative incidences of the different adverse effects between the two groups.

d. Sample size

Based on the categorical outcome of disease progression, chi-square analysis was used to determine the number of patients to be recruited into each arm, based on an effect size of 20% difference between the 2 groups. This was derived by an expectation from prior data of a likely disease progression rate of 40% in patients surveyed endoscopically, versus a progression rate of 20% with EMR treatment. Using these numbers, it was calculated that 92 patients per arm of the study would need to be enrolled to give the study 80% power to detect this difference. We will proceed to enroll 100 patients in each group.

D. Subjects

Patients will be considered for recruitment if they are between the ages of 35 and 80, have biopsy-proven evidence of high grade dysplasia, and are not surgical candidates, either due to personal choice or poor health status. Subjects will be recruited from 2 large metropolitan health centers in the northeast United States. Exclusion criteria include other malignancies, any contraindication to conscious sedation, pregnancy or any other contraindication to radiographic imaging, and HGD dysplasia involving more than 3 contiguous centimeters of esophageal mucosa. The study will attempt to include adequate amounts of women and underrepresented minorities, however, since this disease is predominantly one of

white males¹³, this group may be relatively small or non-existent. No vulnerable populations will be included in the study. Written informed consent will be obtained by face-to-face interview of potential subjects by the investigator and her assigned staff. Screening the patient populations of coinvestigators at both centers, as well as referral of patients meeting the above criteria to our study by other gastroenterologists will identify potential subjects. Potential difficulties in recruitment would include unwillingness of patients to be randomly assigned to receive either EMR or intensive surveillance as their treatment.

E. Procedures[Medical devices

Upper endoscopy with biopsy +/- endoscopic ultrasound will be performed both as part of patients' regular clinical management and to collect data **for the study**. This will be performed bimonthly, which is slightly more frequent than the 3-month interval used standardly for surveillance of patients with this condition. Endoscopic mucosal resection will be performed on those patients randomized to this arm, for up to a total of 3 treatments. This is an approximately 30-minute endoscopic procedure performed under conscious sedation, which involves removal of the superficial layer of the inner lining of the esophagus. It requires the use of a commercially available fixture, which is attached to the end of the endoscope, and consists of a combination of a suction cap and a bipolar electrical cauterization snare. Before resection, the submucosa of the affected area is injected with 15 - 20 ml of dilute epinephrine solution or normal saline to raise the mucosal layer away from the underlying submucosal and muscular layers. This significantly reduces the risk of perforation. The area is then centralized under the cap by endoscopic visualization, suctioned up into the cap, and cauterized off with the electrical snare.

F. Study questionnaire

This will consist of a checklist of symptoms known to be associated with both the disease process and the involved endoscopic procedures, such as dysphagia, odynophagia, hematemesis, and dyspepsia. Each subject will fill out this questionnaire at his or her 6-month visit.

G. Pathological Specimens

All pathologic specimens obtained from surgery, EMR, and biopsies will be reviewed by either of 2 board-certified pathologists specializing in gastrointestinal pathology, at only one of the 2 medical centers. High grade dysplasia will be defined as atypical changes in many of the mucosal epithelial cells, very abnormal growth pattern of glands, distorted or irregular rows of cells, >50% of cells having large spotted nuclei, or frequent mitotic figures, with all of any of the above abnormalities confined above the basement membrane. Adenocarcinoma will be defined as any of the above changes seen invading beyond the basement membrane, into the lamina propria or beyond. To address the possibility of differences in readings between the different observers, their prior histologic readings will have been evaluated by kappa analysis of inter-observer variability, and have shown a high correlation. All slides will remain the property of the medical center of origin.

H. Confidentiality of Study Data

The investigators will keep all consent and recruitment forms with identifying information such as name, address, and telephone numbers in a secure and separate location from study data forms. All study data forms will be labeled with a study subject number unique to each patient, and the code linking subject number to identifying information will also be stored securely by the investigators. No personal identifying information will be entered into any computerized files or programs used to analyze the data. No study participants will be identified individually by any identifying information in any initial or final report of the study, written or verbal

I. Risks and Benefits

The risks involved in this study apply mostly to patients receiving true EMR as their treatment. These include esophageal perforation, and subsequent mediastinal emphysema, stricture formation, bleeding, and dysphagia. All of these risks, with their relative incidences from the available literature, will be clearly presented to potential subjects in the consent form. In the event of occurrence of any of these events, immediate or subsequent reparative endoscopic treatment or medical therapy will be initiated free of charge to the patient. In general for both arms, the risks of upper endoscopy with biopsy include adverse reaction to sedative drugs, bleeding, perforation, and pain. As a whole, this would involve slightly more risk than that involved in standard surveillance because of the increased frequency of endoscopy in this study. Potential benefits to participants include closer monitoring, and expert medical care. There will be no monetary compensation for participation in this study.

J. Alternative Therapies

Prior to signing consent, participants will be informed of the alternative therapies for their condition, including esophagectomy and the other endoscopic ablative therapies currently in investigational use such as photodynamic therapy, laser ablation, and thermal ablation. Patients will maintain the right to withdraw from the study at any time to pursue any of these other alternatives, without compromise to their standard of care by the investigator.

K. Radiation or Radioactive Substances

Participation in this study will involve radiation exposure in the form of biannual abdomin thoracic CAT scan imaging as part of the follow-up. Within the 5 year maximum duration of this study, the radiation exposure involved should remain well within the FDA allowed total dosage. Patients will however be informed that radiation exposure is cumulative, so they will need to take into account their prior or anticipated future radiation exposure outside the setting of this study. There will be no radioactive substances used in this trial.

L. References

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