Clinical Decision Support Systems for Effective Management of Patients with Barrett’s Esophagus using Optical Endomicroscopy

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INTRODUCTION

Optical endomicroscopy (OE) is a novel imaging modality that captures real-time, histology-like microscopic pictures of tissue during endoscopic procedures to allow physicians to make diagnostic and therapeutic decisions real-time. It will provide early diagnosis for patients for better clinical outcome and save healthcare cost. Because OE image video quality is low and the semantic interpretation is challenging, it has not been widely adopted in clinics. The goal of this project is to conduct a comparative effectiveness study to compare several modalities of OE and to develop a Clinical Design Support System that optimizes diagnostic models among different modality. Specifically, we will carry out this comparative effectiveness study on surveillance of Barrett’s esophagus (BE) patients, who are at high risk of developing esophageal adenocarcinoma (EAC). Using this CDSS that consists of novel algorithms for quality control, information extraction, and integration of different types of OE images with other diagnostic imaging modalities, we hope to provide final effectiveness measure of various OE modalities.

Requested Amount: $25,000 for one year

A. Proposed Research and Specific Aims

This multi-institutional translational pilot project aims to develop a clinical decision support system (CDSS) for improving the objectivity, sensitivity, and specificity of diagnosis in patients with Barrett’s esophagus (BE) using optical endomicroscopy technologies. To establish a standard clinical endomicroscopic technology, we will first acquire high-quality endomicroscopic images through techniques like image denoising, artifacts removal, then predict high-risk patients using three clinically used endomicroscopic technologies: endoscope-based confocal laser endomicroscopy (eCLE), probe-based confocal laser endomicroscopy (pCLE), and volumetric laser endomicroscopy (VLE) separately. The prediction results will also help gain insight about which technology are more accurate in different scenarios. We will also integrate these endomicroscopy images with other diagnostic imaging techniques like histopathological images, to build an even better prediction model. We expect that the decision support system will improve the sensitivity and specificity of endomicroscopic-based diagnosis in barrett’s esophagus (BE) patients. For development, validation, and clinical translation of our CDSS, this project has the following specific aims (summarized in Fig. 1):
Aim 1: To acquire high-quality endomicroscopic images from BE patients through quality control techniques. The presence of image artifacts like motion blur is one of the major obstacles to current image analysis pipelines. So how to detect such artifacts and further remove them are crucial and serve as the first step in our image analysis. In our previous study, we have explored how to automatically detect blurry regions in whole-slide images. In this study, we want to firstly adapt the previous methods to detect blur and other artifacts in endomicroscopic images. And then, based on the detection result, we want to devise a method to remove the artifacts so that we can use images with higher qualities for further analysis.

Aim 2: To develop novel image processing and machine learning methods for automated prediction of high-risk patients using one of the three sources of endomicroscopy images. Automated prediction of diseases, which is an important part of the integral advanced CDSS for medical images, provides doctors an objective and quantitative second opinion for the primary diagnosis. Recent work by researchers at Georgia Tech and others have shown that automated prediction methods can accurately predict cancer grade and cancer subtype in microscopic tumor biopsy images. These models not only provide automated predictions but also reveal informative image properties that can be used by clinicians to manually diagnose patients. These image characteristics will prove to be very useful in understanding this new imaging technology and in its translation to clinical settings. And also, the comparison between three different kinds of OE images will help us understand the advantages and disadvantages of each image modality.

Aim 3: To integrate all three kinds of endomicroscopy images as well as other diagnostic images. Automated prediction of high-risk patients using endomicroscopic images using a single source could be biased under some specific conditions. In typical clinical practice, physicians often use multiple imaging techniques, which include eCLE, pCLE, VLE, OCT, high definition white light endoscopy (HD-WLE), endovaginal sonography (EVS), pathological whole-slide images, fluoroscopy images and etc., to further confirm the subtype or the progression of a specific disease. So integrated prediction by learning from all kinds of diagnostic images is a challenging yet useful task. The integration model can not only improve the accuracy of diagnosis but also provide insight about how each source of images perform in patients under different medical conditions.

In summary, this pilot project develops innovative image analysis and visualization methods for endomicroscopic images. It compares three commonly clinical-used endomicroscopic technologies and establishes the most effective diagnostic models for BE patients. The expected outcomes from this project will include a CDSS, accurate prediction models, novel image analysis algorithms, and informative image features for high-risk BE patients. Thus, this project will greatly facilitate the translation of novel endomicroscopic technology to clinical setting.

B. Background and Significance

Barrett’s esophagus (BE) is pre-malignant condition of the esophagus defined as a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and confirmed to have intestinal metaplasia via histological analysis [1]. BE is a well-known risk factor for esophageal adenocarcinoma (EAC). The estimated incidence of EAC in the United States has increased 500% since the 1970s [2]. Furthermore, EAC remains highly lethal with a 5-year survival rate of 13 - 15% [1]. To increase survival, current guidelines recommend early detection of EAC in BE patients using a surveillance protocol based upon tissue histology. However, because of the limited mucosal sampling during this protocol, regions with neoplasia may be missed. A novel imaging modality, termed “Optical Endomicroscopy” (OE), allows physicians to capture real-time microscopic pictures of the mucosa during endoscopic procedures. Using the endomicroscope, now physicians are able to make real-time clinical diagnosis and perform treatment during the same endoscopic session.
instead of waiting a couple of days for biopsy results and performing another endoscopic session for treatment (if needed).

Clinical information systems are integral and permanent fixtures in the workflow of delivering quality clinical care in gastrointestinal unit. Automation of endoscopic procedure reporting has helped to increase clinical efficiency, improve communication, and enforce standards for documentation. However, much is to be desired in respect to imaging informatics features available for clinical decision support systems (CDSSs) designed to aid in the acquisition, storage, retrieval, display, and analysis of clinical imaging data. OE can particularly benefit from CDSSs because of the many challenges involved in obtaining optical biopsies of a high quality [3]. We propose CDSSs can facilitate OE-based diagnosis by filtering out poor diagnostically irrelevant endomicroscopic biopsies, allowing for extraction of quantitative imaging features, and optimizing clinical diagnostic models for detection of BE associated neoplasia.

C. Experimental Design and Methods

Multimodal Imaging Data Acquisition

An IRB protocol will be submitted for this investigation. Consecutive adult patients (greater than or equal to 18 years of age) scheduled to undergo an elective endoscopy with a history of BE and known or suspected BE associated high grade dysplasia or intramucosal carcinoma will be eligible for enrollment. After obtaining informed consent, each patient will be prepared for esophagogastroduodenoscopy (EGD) via standard practice and several modalities of imaging will be collected through standard protocols for further diagnosis and analysis.

Aim #1: Quality Control for Robust System

Quality control is an essential step for any imaging informatics pipeline. Image artifacts have unpredictable effects on image segmentation and other quantitative image features. Therefore, it is essential to either eliminate or correct these artifacts for robust decision support systems [4]. Most prominent image artifact in endomicroscopic images are motion artifacts, which are caused by the relative displacements between microscope and tissue during imaging. Figure 2 illustrates some good (no artifact) and bad (with motion artifacts) OE images. Published literatures on decision support systems for endomicroscopic images have not reported any automated methods for motion artifacts detection and quality control. Therefore, our first aim in this project is to develop and validate automated quality control methods for endomicroscopic images.

Motion artifacts have been widely studied in other imaging modalities but OE images may be captured randomly along the esophagus, so these methods cannot be directly applied to quality control in OE images. We propose to develop a supervised model for classifying images into good and bad quality images using image texture features such as intensity histograms, Gabor features and etc. Figure 2 illustrates some preliminary results for our supervised model in forming a 3-dimensional scatter plot, where x, y, and z dimensions are defined by three texture features. In the scatter plot, we show distribution of 119 CLE images collected from a patient in an endoscopic examination. Images are color coded based on their quality: red for bad and blue for good.

Figure 2. Quality control methods for endomicroscopic images. (A-B) low quality images with motion artifacts, (C-D) diagnostic quality images, and (E) Scatter plot showing distribution 119 OE image samples acquired from a patient in one endoscopic protocol.
After the detection of artifacts, we will then remove these artifacts through various image analysis algorithms. Image denoising method is one of the algorithms that can help remove the noise in original images. In this project, we plan to adapt this type of methods to endomicroscopic images in order to remove artifacts. With more high quality images available, the downstream analyses are expected to be more accurate. One of the most significant contributions of this method is reducing the loss of information during the diagnostic procedures.

**Aim #2: Comprehensive Information Extraction and Decision Making**

Automated prediction and decision-making using OE images rely heavily on the information extraction step. Previous works on automated analysis of OE images only used pixel-level patterns [5]. Although pixel-level patterns can be informative about certain diagnostic models, they are susceptible to noise and difficult to interpret the biological mechanisms[4]. We propose to develop comprehensive feature extraction methods that will capture both pixel-level and object-level properties from OE images.

To capture pixel-level features, we will extract texture features from a grayscale OE image. These features will quantify texture properties such as image sharpness, contrast, changes in intensity, and discontinuities or edges by measuring properties derived from gray-level intensity profiles and Gabor filter. For object-level features, we will extract shape and spatial distribution of glands in OE images. Among shape features, we will extract both contour- and region-based features [6].

To realize full potential of endomicroscopy in surveillance of high risk BE patients, we need robust detection of BE and BE associated neoplasia. We propose to develop and validate models for automated diagnosis of these endpoints from OE images.

For each prediction model, we will select informative image features using statistical feature selection methods. Feature selection in prediction modeling is beneficial for the following reasons: 1) prediction modeling after dimensionality reduction can result in simpler models with higher prediction performance and 2) dimensionality reduction can provide insights about the data by highlighting important features or dimensions [7]. We plan to apply univariate [8] and multivariate (e.g., minimum redundancy maximum correlation (mRMR) [9]) filter methods for feature selection. After feature selection, we will develop diagnostic models using various classifiers such as k-nearest neighbors (k-NN), support vector machines (SVM), and Bayesian methods. We will adopt techniques of active learning and relevant feedback, where gastroenterologist provide active feedback to the learning algorithm in order to iteratively improve its knowledge [10] (Figure 3). We hypothesize that after a relatively short training phase, our decision support systems would perform adequately for clinical applications.

**Aim #3: Integrated learning from multiple sources of images**
During patients’ treatments, physicians will use several different methods of diagnostic imaging to determine the most probable disease type for the patients. Traditional prediction modelling mostly use one single modality to provide decision support for physicians, which is sometimes biased, so we propose to utilize multiple sources of data through the techniques called Gradient Boosting Consensus (GBC)[11] to make integrated predictions for patients. Improved sensitivity and specificity are expected after taking advantage of all imaging modalities. In brief, GBC generates a set of classifiers from each of the source, and the weighted majority of these classifiers is output as the prediction result. The rationale behind our model is that patients who share similar conditions should have similar prediction outcomes across all modalities, which can be used to impose certain constraints on our classifiers. Based on our assumption, prediction from a single source should be as consistent as possible with the integration, so here we use a loss function to penalize the inconsistency. By letting the inconsistency be smaller than a fixed threshold, we can solve for a better integrated classifier. The threshold can be empirically determined by inner loop cross validation and our model accuracy will be then be evaluated using an outer loop cross validation. The workflow can be summarized in Fig. 4.

D. Timeline

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Reference