From the Center for Digestive Diseases, Department of Medicine
Karolinska University Hospital and Karolinska Institute,
Stockholm, Sweden

ASPECTS ON ENDOSCOPIC CHARACTERIZATION AND CLINICAL MANAGEMENT OF BARRETT'S ESOPHAGUS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

To be publicly defended in föreläsningssalen B64, B2 huset,
Huddinge University Hospital
Tisdagen, den 17 januari 2017, Kl 13.00

by
Francisco Baldaque Silva
M.D

Principal Supervisor:
Professor Hanns-Ulrich Marschall
Department of Molecular and Clinical Medicine
Sahlgrenska Academy
University of Gothenburg, Gothenburg

Co-supervisor:
Professor Lars Lundell
Gastrocentrum and CLINTEC
Karolinska Institute, Stockholm

Opponent:
Professor Marco Bruno
Department of Gastroenterology and
Hepatology Erasmus University, Rotterdam,
The Netherlands

Examination Board:
Professor Jörgen Larsson
Department of Surgery Karolinska Institute,
Stockholm

Professor Michael Wirén
Department of Surgery Linköpings
University, Linköping

Docent Thomas Franzén
Department of Surgery Linköpings
University, Linköping

Stockholm 2017

ABSTRACT

Barrett's esophagus (BE) is considered to result from prolonged gastroesophageal reflux and is the only known precursor of esophageal adenocarcinoma. The clinical management of BE patients aims to control esophageal reflux to reduce mucosal injury and neoplastic progression, and to detect early neoplastic lesions in Barrett's mucosa, suitable for curative endoscopic treatment.

The first part of this thesis evaluates the effect of a stepwise increase in the dose of proton pump inhibitors (PPI), on esophageal acidic reflux, symptoms and histology in long segment BE patients (group 1, n=24). We also compare these outcomes in BE patients under PPI with the results of BE patients after clinically successful fundoplication (group 2, n=30). In all but one patient in group 1, it was possible to normalize acid reflux with PPI, resulting in improvements in symptom scores. However, symptomatic amelioration was only significant in the first step of PPI treatment. Patients with PPI or fundoplication had the same levels of symptom scores. Normalization of the acid reflux in both groups was associated with reductions of papillary length, thickness of the basal cell layers, dilation of intercellular spaces, and acute and chronic inflammation of the squamous epithelium. We did not find a significant change in markers of proliferation and differentiation in Barrett's mucosa associated with normalization of acid reflux in either group.

The second part of this thesis assesses 3 different endoscopic classification systems, Amsterdam, Kansas and Nottingham, developed for the characterization of Barrett's mucosa. These classifications use magnification endoscopy with narrow band imaging (ME-NBI) for the identification of intestinal metaplasia and dysplasia in Barrett's mucosa. We used 84 video segments from Barrett's mucosa, that were randomly selected and blindly evaluated by 9 observers with different expertise in the field. All classifications were feasibly but showed suboptimal accuracy and low inter-observer agreement, with slightly better results for the Amsterdam classification.

The last part of this thesis evaluates the role of a structured learning program for the application of the Amsterdam classification system. We used the first 70 videos from the 84 randomly selected videos from the previous study. While, during the learning process, there was a decrease in the time spent for evaluation and an increase in declared certainty of prediction, the accuracy in histological prediction did not improve. This classification system was found to be suboptimal in terms of accuracy and inter- and intra-observer agreements.

This thesis shows that, in long segment BE patients, acid reflux and symptom scores co-vary through the several steps of the PPI treatment, achieving the same level as after a successful fundoplication. If a single dose of PPI is associated with marked improvement of symptoms, higher doses may be needed for complete acid suppression. Minor changes were found among morphological markers of reflux disease, both in the glandular and in the squamous epithelium, irrespective of medical or surgical treatment. Our results underscore the questionable utility of ME-NBI classification systems for clinical routine practice in BE.

Keywords: Barrett's esophagus, anti-reflux surgery, proton pump inhibitors, narrow band imaging.