Volumetric laser endomicroscopy for the detection of early Barrett's neoplasia

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Introduction
and outline of this thesis
INTRODUCTION

Over the last two decades the incidence of patients with esophageal adenocarcinoma has been rising steeply.\textsuperscript{1} The majority of this increase can be attributed to male patients. Esophageal cancer is among the top ten most common cancers and leading causes of cancer death worldwide, and has a low 5-year survival rate.\textsuperscript{2–4} At the time of diagnosis most patients are over 60 years old. Barrett’s esophagus is a known precursor for esophageal adenocarcinoma. It is a condition in which gastroesophageal reflux causes the normal squamous layering of the esophageal wall to be replaced by columnar-lined epithelium with intestinal metaplasia. During a gradual process, non-dysplastic Barrett’s mucosa may develop from low-grade dysplasia, through high-grade dysplasia into esophageal adenocarcinoma. The annual incidence of esophageal adenocarcinoma in patients with Barrett’s esophagus is reported to be only between 0.12% and 0.5%.\textsuperscript{1,5,6} However, the chance of developing esophageal adenocarcinoma is 30 times higher in Barrett’s patients than in the age-matched population.\textsuperscript{7} The importance of early detection of dysplasia or cancer is that when diagnosed in an early stage, patients can still be treated endoscopically. These patients have an excellent prognosis, whereas in more advanced stages, major surgery is required which is associated with comorbidity and a lower survival rate.

The stepwise development of early adenocarcinoma creates a window of opportunity to detect this disease in a pre- or early stage. Therefore, the standard of care for Barrett’s patients consists of regular surveillance with white-light endoscopy and quadrantic random biopsies every 2 cm of the Barrett’s segment. However, the current surveillance protocol is hampered by several difficulties. First, the appearance of early neoplasia on white-light endoscopy is subtle and therefore difficult to detect. For this reason, random biopsies are obtained resulting in laborious procedures and numerous biopsies requiring evaluation by a pathologist. Second, the incidence of adenocarcinoma in patients with Barrett’s esophagus is low. Therefore, relevance and cost-effectiveness of the current surveillance protocol are questioned.

Hence, new strategies are warranted to improve the detection of early neoplastic lesions in Barrett’s esophagus. Several advanced imaging techniques have been studied aiming to improve Barrett’s surveillance. Over the last 15 years the research line of imaging studies in the Academic Medical Center in Amsterdam has evaluated endoscopic techniques such as narrow band imaging and wide-field autofluorescence, and the trimodal imaging system (combination of both techniques). The performance of these modalities was compared to white light endoscopy and dye-spray chromoendoscopy. Beyond high-definition white light endoscopy, however, no technique is recommended for use at the time of writing. Therefore, the quest for an imaging technology that significantly improves the detection of early neoplasia continued.

This thesis focusses almost entirely on Volumetric laser endomicroscopy (VLE), which is a novel wide-field imaging system that displays promising characteristics. VLE incorporates second generation optical coherence tomography (OCT) technology, that utilizes near-
infrared light to create cross-sectional images in gray-shades based on differences in optical scattering of tissue structures. The balloon-based system is used through the endoscope and is capable of imaging a 6-cm long circumferential segment of Barrett’s esophagus in near-microscopic resolution, in 90 seconds. Subsurface layers are visualized till a depth of 3 mm. With VLE the detection of subtle abnormalities or subsurface irregularities that are still invisible during endoscopy could be improved. Compared to the other currently available imaging techniques, VLE has the following theoretical advantages: VLE images through the esophageal wall, providing more insight inside the superficial wall layers. In addition, the VLE imaging volume is significantly larger than what previous OCT systems were capable of. The three-dimensional near-microscopic scan provides a direct overview of the entire Barrett’s segment, which is of great benefit for use in clinical practice. VLE could thereby reduce sampling error and potentially cause a paradigm shift from the current random biopsy protocol towards VLE-targeted biopsies. Thus, VLE is a great innovation and therefore we investigated its true potential to improve early neoplasia detection during Barrett’s surveillance.

At the start of this PhD, little was known about the interpretation of VLE data. There was a large gap in the literature, both in years of publication and in knowledge. Almost a decade ago several studies utilizing the first OCT systems described OCT features of esophageal mucosal types and neoplasia. However, these systems could only image small tissue areas and the studies lacked one-to-one histological correlation of the OCT images. In the years thereafter, further technical improvements resulted in the optical frequency domain imaging technology, which is incorporated in the VLE system and is capable of fast image acquisition of large tissue volumes. In order to know what we truly see on VLE scans, comparison with the gold standard histology is essential. Therefore, we constructed one-to-one correlations of ex vivo VLE images with histology through a meticulous protocol. This unique VLE-histology image database forms the basis for all studies described in this thesis. The overarching research question was if VLE can improve early detection of Barrett’s neoplasia. A dual pathway was followed: First, qualitative studies examined which VLE features represent neoplasia. In addition to human eye detection, the second path focused on quantitative methods to detect neoplasia on VLE.

In conclusion, this thesis contributes to the field of advanced imaging techniques for the improvement of early neoplasia detection in patients with Barrett’s esophagus. VLE has great potential since it is the first system that enables examination of the subsurface layers of the esophageal wall in high resolution and over a large volume. An objective tool for automated analysis of the scan could aid the endoscopist with VLE interpretation and neoplasia detection.

The work presented in this thesis has been driven by the collaboration of several groups. The esophageal research team from the AMC led by Professor Bergman worked together with the AMC departments Pathology and Biomedical Engineering and Physics, and the Video Coding and Architectures research group at the department of Electrical Engineering from the University of Technology in Eindhoven. Overseas, we worked together with the Tearney
Laboratory at the Wellman Center for Photomedicine in Boston, and a VLE expert from the Mayo Clinic in Rochester.

OUTLINE OF THIS THESIS
Part I: Advanced imaging techniques
The review in Chapter 1 gives an overview of all current and upcoming advanced imaging techniques used during endoscopy for Barrett’s esophagus. In addition, a guide is provided for how to optimize endoscopic detection of early Barrett’s neoplasia using white light endoscopy and chromoendoscopy.

Part II: Volumetric laser endomicroscopy – Qualitative studies
Chapter 2 laid the groundwork for all other VLE studies in this thesis. We developed an approach for one-to-one correlation of ex vivo VLE images with corresponding histology. A unique VLE-histology database was constructed. Using this database, features of the different esophageal mucosal types and focal structures on VLE were described in Chapter 3. Furthermore, VLE features predictive for early Barrett’s neoplasia were identified, evaluated and scored by two VLE experts during different phases. Three VLE features were found to be significantly correlated to Barrett’s neoplasia. These features were incorporated in a VLE prediction score, which showed promising accuracy. In Chapter 4 the VLE prediction score was used to evaluate the performance of two VLE experts to identify early Barrett’s neoplasia in full ex vivo VLE scans of endoscopic resection specimens and full in vivo VLE scans. Varying results were observed, warranting further studies in larger sample size. In Chapter 5 we investigated the feasibility of VLE for the detection of buried Barrett’s glands beneath neosquamous epithelium in patients treated with radiofrequency ablation. VLE detected subsquamous glandular structures in the majority of patients, however in only one patient these structures corresponded to buried Barrett’s glands on histology. In all remaining cases, only non-pathological structures such as blood vessels and dilated ducts of (sub)mucosal glands were seen on histology.

Chapter 6 examined the feasibility of the novel VLE laser marking tool, which is capable of applying VLE-guided laser marks on the esophageal mucosa. This enables direct correlation of in vivo VLE scans with histology, which was not possible before. The VLE laser marking system was found to be feasible and safe, and targeting VLE areas of interest proved to be highly successful.

Part III: Volumetric laser endomicroscopy – Quantitative studies
Next to the qualitative studies that investigated the interpretation of VLE with the human eye, in part II we examined quantitative, objective methods to optimize VLE interpretation and Barrett’s neoplasia detection. In Chapter 7 we explored a method utilizing the scattering properties of tissue. We hypothesized that the attenuation coefficient $\mu_{VLE}$, which quantifies the decay of detected backscattered light versus depth, could potentially distinguish between non-dysplastic and neoplastic Barrett’s on VLE. In Chapter 8 we examined if
A computer algorithm could detect early neoplasia on ex vivo VLE images. The VLE prediction score was used as clinical input for the development of clinically derived algorithm features. The algorithm showed very good performance for detecting Barrett’s neoplasia, with a higher accuracy than the two VLE experts (chapter 3). Technical specifications of the development and design of the computer algorithm were extensively described in Chapter 9.
REFERENCES


