Advanced endoscopic imaging of esophageal neoplasia; old looks and new visions

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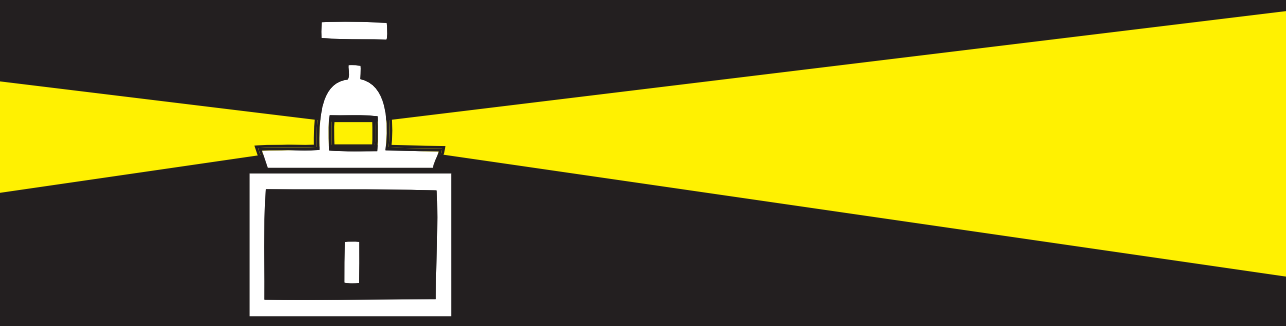
1 INTRODUCTION AND OUTLINE



Esophageal cancer is a severe disease with a dismal prognosis when detected at a symptomatic stage. Most patients diagnosed with esophageal cancer present with advanced stages of the disease and have limited curative treatment options.

There are two important types of esophageal carcinoma: squamous cell carcinoma and adenocarcinoma.

Esophageal cancer mostly derives from the normal squamous lining of the esophagus and is associated with smoking, alcohol and dietary factors. This type of cancer is highly prevalent in the middle and far East, such as Iran and China.

In the western world, most patients present with esophageal adenocarcinoma, which arises from metaplastic epithelium in the distal part of the esophagus. This precursor lesion is caused by longstanding gastro-esophageal reflux and is named after a Britisch surgeon N.R. Barrett, who first described this condition in 1950: Barrett's esophagus (BE). Due to extended irritation and inflammation caused by the acidic refluxate, the normal squamous epithelium of the distal esophagus is replaced by columnar epithelium, which resembles intestinal-type epithelium. This so called intestinal metaplasia is better suited to withstand ongoing exposure to reflux. However, intestinal metaplasia has an approximately 100x higher chance of developing into adenocarcinoma, compared to patients without Barrett's esophagus. The annual risk of progression to cancer is thought to be 0.1-0.5%.

The progression to cancer is a gradual process of intermediate steps of intraepithelial neoplasia; from low grade intraepithelial neoplasia (LGIN), through high grade intraepithelial neoplasia (HGIN) to intramucosal cancer. When confined to the upper mucosal layer these early grades of neoplasia have a virtually absent risk of lymphatic metastasis. Therefore, when detected at an early stage, esophageal carcinoma can be adequately treated with minimal invasive techniques that leave the esophagus in situ, such as endoscopic resection. Endoscopic resection has a significantly lower morbidity and mortality rate, compared to esophagectomy.

In order to intercept malignant progression at an early stage, patients with Barrett's esophagus are recommended to undergo regular surveillance endoscopy, during which the esophagus is inspected for abnormalities. However, these lesions usually present as very subtle abnormalities in otherwise unsuspicious esophageal mucosa and can be difficult to detect. In the absence of visible abnormalities, random biopsies are obtained at 2 cm intervals in four quadrants according to the Seattle protocol.

Unfortunately, random biopsies only sample approximately 5% of the surface of the Barrett's segment. In addition, The (cost-)effectiveness of surveillance endoscopy has been subject of discussion, due to the low absolute risk of progression to cancer, the laborious process of obtaining random biopsies during surveillance endoscopy, the difficulty of detecting early lesions and the complexity of the histological evaluation of biopsies.

To overcome abovementioned drawbacks, in recent years much attention has been aimed at improving the identification of patients at risk for malignant progression, advancing the detection of early lesions and increasing the yield of random biopsies. Adequate risk-stratification may improve the cost-effectiveness of surveillance endoscopy substantially. The increased yield of random biopsies may bring down the burden and costs associated with obtaining and processing large amounts of tissue samples.

In order to achieve these goals, current standards of endoscopic practice may not suffice. Improving the way we see, adjusting the way we look and realizing the way we register are imperative for high-quality patient care. All of this may benefit from advanced endoscopic imaging technologies.

Our group has been investigating various advanced imaging modalities for over a decade, mostly aimed at improving the detection rate of early neoplasia in Barrett's esophagus. Mohammed Kara was the first to describe endoscopic wide-field autofluorescence imaging (AFI) and narrow band imaging (NBI). Both techniques were extensively studied to identify the optical characteristics of early neoplasia with these modalities and their performance when compared to standard white light endoscopy (WLE) and dye-spray chromoendoscopy. Wouter Curvers followed up on these studies when both techniques were combined into one endoscopic trimodal imaging (ETMI) system. Led by our group, two (inter)national multicenter randomized cross-over studies were performed. Curvers concluded in his thesis that allthough AFI did increase the targeted detection of early neoplasia, standard WLE with random biopsies still was superior in terms of overall detection of patients with neoplasia.

Abovementioned studies led to the following research questions:

What is the true clinical relevance of autofluorescence imaging, in terms of additional diagnostic value to detect early neoplasia, and how does it impact on the therapeutic management of Barrett's patients?

With the current AFI technology being suboptimal, can an adjustment of the optical properties of the technique improve the detection of early neoplasia, or should we go back to the drawing board and start with the basics: fluorescence spectroscopy?

The strategy of Barrett's surveillance will change substantially if patients could be stratified according to individual risk profiles. Molucular biomarkers will likely play an important role in future risk stratification, yet the correct markers may be found in very subtle lesions that are hard to detect; can advanced imaging be applied to identify these markers?

This thesis focusses on recent advances in endoscopic imaging, aimed at improving the detection of early neoplastic lesions in the esophagus. We put available techniques into a new perspective by studying their clinical relevance. We investigated novel technology and developed experimental spectroscopy systems to go back to the basics. Furthermore, new insights in the genetic and optical properties of early neoplastic lesions in the esophagus have been put to the test in experimental set-ups and clinical studies.

The results of this research may impact on the current standards of care in the surveillance and work-up of patients with Barrett's esophagus and associated neoplasia.

All work presented in this thesis is a result of ongoing efforts from the esophageal research team at the Academic Medical Center (AMC) Amsterdam, in close collaboration with the Department of Biomedical Engineering and Physics of the AMC. The esophageal research team has a longstanding cooperation with partners both national and international, such as the Cancer Cell Unit in Cambridge, UK, of which this thesis is yet another fruitful product.

OUTLINE OF THE THESIS

Part One: Advanced imaging modalities in perspective

Chapter 2 gives an overview of all current imaging modalities and upcoming techniques in the field of surveillance, work-up and therapy of esophageal adenocarcinoma and squamous cell carcinoma, including chromoendoscopy, optical filter techniques and functional imaging. In **chapter 3** we have focussed on fluorescence imaging: this manuscript gives an overview of current state-of-art of (auto)fluorescence spectroscopy and endoscopy for the imaging of early Barrett's neoplasia.

After disappointing results with the second generation autofluorescence imaging (AFI) system, a third generation AFI system was developed that was aimed at targeting malignant changes in the cells themselves, rather than secondary structural alterations. The first study with this system is described in **chapter 4**.

After multiple studies performed on three generations of autofluorescence imaging systems, one important question remained: does AFI impact on the clinical management for patients with early Barrett's neoplasia. In **chapter 5** we have addressed this issue by analyzing the results of 5 previously performed studies on AFI in terms of additional diagnostic and therapeutic value.

In **chapter 6** we subsequently reviewed the clinical relevance of the most widely used commercially available endoscopic imaging techniques with regard to the diagnosis and treatment of early Barrett's neoplasia.

Part Two: Autofluorescence imaging and Biomarkers

Although AFI was shown to have a high false-positive rate, we hypothesized that AFI-positive, dysplasia-negative areas may in fact harbour early molecular changes that predict the presence of, or even progression to early neoplasia. In **chapter 7** we performed a retrospective analysis of AFI guided biopsies and correlated AFI features to a predefined panel of biomarkers. With the results of the retrospective analysis in hand, in **chapter 8** we prospectively evaluated and validated the correlation between AFI characteristics and a larger panel of biomarkers in a multicenter study with short-term follow up.

Part Three: Back to the basics; probe based fluorescence spectroscopy.

In **chapter 9** an optical biopsy system was investigated, using a 405nm induced fluorescence spectroscopy probe integrated in a standard biopsy forceps. In this study we aimed to construct an algorithm to distinguish neoplastic from non-neoplastic Barrett's mucosa and to apply this algorithm in the optical biopsy system. Given the suboptimal performance of (auto)fluorescence imaging, we hypothesized that the excitation wavelengths may be optimized. In **chapter 10** we describe a custom build multiwavelength fluorescence spectroscopy system, to assess the autofluorescence characteristics of early neoplasia at various excitation wavelengths and correlation to histology.

Furthermore, by applying a specific exogenous dye, the fluorescence contrast between normal and neoplastic tissue may be enhanced. Therefore, in **chapter 11**, the multiwavelength fluorescence spectroscopy system was used to study the optimal excitation wavelength of 5-ALA induced PpIX fluorescence in neoplastic and non-neoplastic esophageal mucosa.

Part Four: Optical Frequency Domain Interferometry

In **chapters 12** we studied optical frequency domain interferometry (OFDI). With this high-resolution scattering based technique, real-time imaging of the esophageal mucosa can be adequately assessed for the presence of neoplasia. However, prior to clinical application, one-to-one correlation between the OFDI features and histology is required. We therefore aimed to assess the relevant OFDI tissue characteristics of neoplastic and non-neoplastic BE both in- and ex-vivo in relation to histology, and develop the optimal approach for one-to-one correlation. Due to its imaging properties, OFDI may be well suited for the identification of buried Barrett's epithelium. Buried Barrett's is a controversial subject, thought to arise from glands burried below neosquamous epithelium after radiofrequency ablation (RFA). In **chapter 13** we used OFDI to evaluate subsquamous structures in neosquamous epithelium after RFA and aimed to correlate these to the histological presence of buried Barrett's glands.