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

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**Publication date**  
2014

[Link to publication](#)

#### **Citation for published version (APA):**

Boerwinkel, D. F. (2014). *Advanced endoscopic imaging of esophageal neoplasia; old looks and new visions*.

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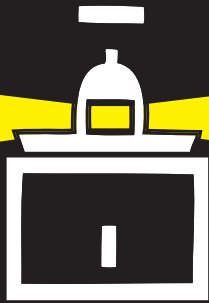
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DISCUSSION:  
OLD LOOKS  
AND NEW VISIONS







Patients with Barrett's esophagus have an increased risk of developing esophageal adenocarcinoma. By subjecting these patients to regular endoscopic surveillance, the progression towards invasive carcinoma may be intercepted at a curable stage. This endoscopic surveillance strategy may benefit from advanced endoscopic imaging techniques to increase its (cost-)effectiveness. In recent years, various advanced imaging techniques have been put to the test in experimental set-ups, in small pilot series and in large randomized trials. The major challenge to overcome has traditionally been the recognition of lesions, generally achieved by increasing the contrast between normal and abnormal tissue. This was studied by addressing wide-field detection and small-field differentiation of early neoplastic lesions. With the current developments in global economy and health-care issues, the cost-effectiveness of the surveillance strategies has come into play. Therefore much attention has also been directed at identifying patients at risk for neoplastic progression, improving the yield of Barrett's surveillance and the work-up and treatment of early esophageal carcinoma. In this thesis we have addressed the abovementioned issues.

## OLD LOOKS

We have demonstrated that autofluorescence imaging (AFI), in its current form, has limited additional value as a red-flag technique for the detection and treatment of early neoplasia in Barrett's esophagus. In addition, a newly developed third generation AFI system did not prove to outperform the commercially available technique. This costly and complex imaging modality should therefore, in our opinion, not be implemented in general endoscopic practice.

In contrast, we have shown that the apparent disadvantage of AFI – high false positive rate – can in fact be used to predict prevalent neoplasia, by assessing a panel of clinically feasible biomarkers in AFI positive areas. AFI may therefore aid in the development of a risk-stratification model that applies a combination of optical properties and genetic biomarkers to render individual patients at low- or high-risk for progression and act accordingly.

Furthermore, we developed experimental, fluorescence based spectroscopy modalities and evaluated these in pilot series. We hypothesized that by finding the optimal excitation wavelengths, the signal-to-noise ratio could be improved, thus increasing the contrast between non-dysplastic Barrett's and early neoplasia. Fluorescence based spectroscopy was incorporated into an optical biopsy system. We were able to show that such a system may increase the yield of random biopsies during surveillance endoscopy. Although fluorescence may not be the optical technique to reach optimal sensitivity and specificity, the system setup is promising and deserves further attention.

The general impression, however, is that none of the studied modalities provides the full answer to any of the abovementioned challenges.

Imaging studies on novel endoscopic modalities that aim to detect rare and subtle neoplasia in Barrett's esophagus are complex.

First, the construction of a solid endpoint for these studies is inherently difficult. Advanced imaging modalities have the purpose of detecting early neoplastic lesions that are not (easily) detected with white light endoscopy (WLE). Determining a gold standard is hampered by the subtlety of

the morphological and molecular changes in very early neoplasia. This is illustrated by the high interobserver variability among pathologists for histological evaluation of intraepithelial neoplasia (i.e. LGIN and HGIN)<sup>1-3</sup>. Biomarker studies are especially complex in this respect, since they aim to detect molecular abnormalities even before morphological changes have occurred. How can a surface imaging modality identify an abnormality if we're not even sure what we are looking for? Second, without properly validated imaging classifications, the interpretation of images (still or real-time) is unavoidably subjective. In addition, currently validated classifications, such as for NBI, show a marked interobserver variability<sup>4</sup>. This renders clinical applicability of these classifications suboptimal.

Lastly, the incidence of early neoplasia is relatively low<sup>5</sup>. Many imaging studies are performed in tertiary referral centres in patient populations with a high a-priori chance of detecting early neoplasia. In these centres, study endoscopies are carried out by expert endoscopists who have a trained eye for subtle lesions. This may introduce a bias that can either overestimate (high-risk population) or underestimate (expert endoscopist) the value of the studied imaging modality. Given the abovementioned limitations, can we not suffice with optimized white light endoscopy and random biopsies?

We have shown that neoplastic lesions within the Barrett's segment that direct the choice of therapy are virtually always found with WLE inspection only. Additional neoplasia identified in random biopsies, or in lesions detected with AFI, rarely contain stages of neoplasia that have an impact on clinical therapeutic decision making. Any visible lesion upon WLE inspection will be endoscopically resected for diagnostic and therapeutic purposes. Previous research by our group confirmed that after endoscopic resection of the most suspicious lesion primarily detected with WLE, no more severe grades of neoplasia were found<sup>6,7</sup>. Therefore, after resection of the primary visible lesion, or in the absence of a WLE detected lesion, additional flat neoplasia may be adequately treated with radiofrequency ablation (RFA). This not only decreases the clinical relevance of advanced imaging techniques, but may also make the – disputed – distinction between flat HGIN and intramucosal cancer (IMC) less relevant. Extrapolating this line of thought, even IMC found in random biopsies may thus be safely ablated.

Despite recent developments in advanced imaging, optimized white light endoscopy with systematic random biopsies currently remains the gold standard for the detection of early neoplasia in Barrett's esophagus.

We therefore should advocate a comprehensive improvement in human, training and endoscopy related factors to improve surveillance, work-up and treatment strategies. Optimizing the endoscopic circumstances – not only the technological tool – is of pivotal importance, yet raising the awareness and having a suspicious eye are equally essential<sup>8</sup>. A training program, which is currently being developed by the international workgroup for the classification of oesophagitis (IWGCO<sup>9,10</sup>), may adjust the way endoscopists look and change the way they register.

Most surveillance endoscopies are performed in community hospitals. In this setting, the prevalence of early neoplasia is low (i.e. <5%) and therefore the endoscopist is generally not very familiar with the endoscopic appearance of early Barrett's neoplasia<sup>5,11</sup>. Therefore, in our opinion, centralisation of Barrett's care is key, with special attention to expert pathological evaluation.



In addition, in the absence of visible abnormalities – which represents the majority of Barrett's patients – an improved risk-stratification model, rather than just inspection with random biopsies, is a dire necessity to ensure the effectiveness of Barrett's surveillance and treatment. Advanced imaging technologies, potentially in combination with molecular biomarkers, may aid in the development of such a model.

Future studies and guidelines should be based on abovementioned comprehensive themes, the wise selection of advanced imaging technologies just being part of the whole.

## NEW VISIONS

Since the year 2000, guidelines for Barrett's surveillance have based (cost-)effectiveness on a progression risk to carcinoma of 0.5% per year<sup>11</sup>. Recently however, new insights have demonstrated that this figure may be substantially lower, ranging from 0.12 to 0.33%<sup>5,12</sup>. This directly affects the recommendations on which the guidelines are based. Moreover, with newly emerging minimal invasive and safe treatment options such as RFA, surveillance may even become obsolete since we can now effectively eliminate the precursor lesion. Lastly, the western population is expanding, the average age rising and the incidence of Barrett's esophagus increasing. This calls for renewed attention to surveillance and treatment regimens, especially in the current economy.

### Genetic biomarkers and minimal invasive screening

The first requirement to increase the (cost-)effectiveness of surveillance is a better risk stratification of Barrett's patients. Hopes are set that a molecular biomarker, or a panel of biomarkers, may replace histology and allow better and more objective identification of patients who are at low or high risk of progression to cancer<sup>13,14</sup>. The low-risk group could potentially be discharged from endoscopic surveillance, while high-risk group may undergo intensified follow-up, or even prophylactic ablation therapy. Moreover, the limitation of histological inter-observer variability will be evaded.

Several markers have been proven to correlate with malignant progression, such as abnormalities in p53 and p16 gene (loss of heterozygosity, deletion, mutation), and chromosomal abnormalities (aneuploidy and tetraploidy)<sup>15-18</sup>. Gene silencing by promoter hypermethylation is another common event in carcinogenesis and p16, RUNX3 and HPP1 have been investigated previously and showed to correlate with dysplasia and rate of malignant progression<sup>19</sup>. Another promising approach is molecular analysis of minimally invasive obtained cytology samples using brush or sponge cytology. Histological sampling through brush cytology in itself has been shown to reach a concordance rate with histology of 80%, with a sensitivity for detecting HGIN of 80-100%<sup>20,21</sup>. Molecular studies using multicolor fluorescent in situ hybridization have assessed genetic abnormalities, such as gene losses and ploidy changes, but also mutations in p53 and p16 genes<sup>22</sup>. Initial investigations have shown good sensitivity for the identification of HGIN and IMC<sup>23</sup>. Large prospective validation studies are currently being conducted using a panel of combined genetic markers.

One established biomarker for neoplastic progression is the presence of low grade intraepithelial neoplasia (LGIN). Two studies performed by our group have demonstrated that when a histological diagnosis of LGIN was confirmed by a panel of expert pathologists, the annual risk of progression to HGIN was 13.4%<sup>3</sup>. With such figures, patients with confirmed LGIN may be eligible for prophylactic therapy. A recent prospective multicenter trial comparing surveillance versus RFA for confirmed LGIN underlined the premalignant nature of LGIN and the safe and effective characteristics of RFA<sup>24</sup>. Future guidelines are likely to adopt centralized pathology review, especially of LGIN, as well as potential treatment of this high-risk precursor lesion.

Despite these recent efforts, genetic biomarkers have not yet reached implementation into clinical practice due to technical challenges and lack of validation studies. However, the results of large validation studies can be expected in the next coming years, hopefully giving rise to individual risk stratification models that can be implemented into future surveillance guidelines. Moreover, biomarkers may be obtained using minimal invasive techniques, potentially even allowing for endoscopy-free sampling in general practices, thus increasing efficiency and decreasing costs and patient burden<sup>25</sup>.

A promising technique for less invasive imaging of Barrett's esophagus is optical frequency domain imaging (OFDI). The technique uses a balloon to centralize a rotating probe in the esophageal lumen. This enables high-speed and high-resolution image acquisition of the whole Barrett's segment<sup>26</sup>. Preliminary studies suggest that there are specific OFDI characteristics that correlate with neoplasia<sup>27</sup>. In the future, the system may be equipped with an integrated laser to allow marking of distinct areas based on OFDI features<sup>28</sup>. Theoretically, with the right algorithm, this may enable automated detection and marking of neoplastic lesions. In the more distant future, one may even imagine automated delineation and ablation of early neoplasia. The system will then operate more or less independent from its operator, thus eliminating one of the weak links in endoscopy; the subjective assessment of the endoscopist.

The last recently developed technology that may potentially increase the efficiency of surveillance on a short term, is an optical biopsy system. By integrating multiple spectroscopy techniques with a high sensitivity and negative predictive value in an optical biopsy forceps, the Seattle protocol can be expanded. In stead of 4 quadrant biopsies, the endoscopist can obtain a substantial number of (optical) biopsies. Subsequently, only those areas that are considered suspicious by both the system and the endoscopist are physically sampled. Such a system will use a black-box principle. The yield of random biopsies, especially in a low-risk surveillance setting, may therefore rise, independent of the endoscopist ability to recognize early neoplasia.

### **Advanced imaging technology and neoplastic field defect**

Recent insights have shown that prevalent neoplasia can cause remote genetic alterations and genomic instability in histologically normal tissue surrounding the site of neoplasia – a so called field defect of carcinogenesis<sup>29</sup>. A carcinogenic field defect has been demonstrated for various cancers, including Barrett's associated adenocarcinoma. Recently, the optical detection of field carcinogenesis was reported. Data on spectroscopic scanning techniques at histologically inconspicuous areas showed high accuracy in predicting the presence of distant colonic adenomas<sup>30</sup>



and squamous neoplasia elsewhere in the aerodigestive tract<sup>31</sup>. For rectal low-coherence enhanced backscattering spectroscopy in 284 patients, the area under the ROC curve showed an excellent test characteristic (0.93) for the prediction of prevalent neoplasia in the colon, irrespective of adenoma size or location<sup>32</sup>. Elastic-scattering spectroscopy has proven to predict clinically significant neoplasia throughout the colon in 18 patients with 100% sensitivity and 87% sensitivity<sup>33</sup>. Partial wave spectroscopic microscopy, which measures nuclear disorder strength on brush cytology samples, was able to detect a squamous field defect in 50 patients for esophageal adenocarcinoma (1,79 times higher disorder strength compared to controls,  $p < 0.01$ ) and high grade dysplasia ( $\times 1.63$ ,  $p < 0.01$ )<sup>34</sup>. Therefore, a second opportunity for spectroscopy next to the detection of neoplasia, is the identification of an optical marker for a carcinogenic field defect, much alike risk-stratification using molecular markers. Scanning distant, easy-to-reach areas with a spectroscopy probe may aid the endoscopist during surveillance endoscopy, and serve as a minimal invasive screening and risk stratification tool, potentially even without the need for endoscopy.

In order to pursue spectroscopy for endoscopic differentiation and optical identification of field carcinogenesis, research should focus on large, prospective cohort studies. This will involve scanning not only possible neoplastic areas, but also more distant locations, such as the proximal Barrett's segment, the more proximal squamous mucosa and even oral mucosa. The optical biopsy forceps offers an excellent tool for integrating multiple spectroscopy modalities (e.g. fluorescence, scattering or Raman spectroscopy, combined with optical frequency domain interferometry). Synchronous genetic biomarker analysis on biopsy material, combined with optical scanning and long term follow up may yield a multimodal risk-stratification model that can individualize care for Barrett's patients.

### Recommendations on imaging endoscopy in the near future

Abovementioned biomarker-based risk stratification models and minimal invasive optical strategies to identify a neoplastic field defect are far from implementation into daily clinical gastroenterologic practice.

For the next 10 years, Barrett's surveillance must therefore comply to a few endoscopic essentials: centralization of care, including pathology; proper training of endoscopists and personnel in optimized endoscopic practice and recognition of disease; and the use of the best endoscopic tools available. As for endoscopic imaging: all high-tech investigations notwithstanding, optimized white light endoscopy with random biopsies will remain the cornerstone of endoscopic surveillance for Barrett's esophagus.

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