What makes an expert Barrett's pathologist?

Concordance and pathologist expertise within a digital review panel

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INTRODUCTION AND OUTLINE OF THESIS

INTRODUCTION

This thesis describes the steps taken in the set-up of the national review panel for dysplastic Barrett's esophagus (BE) in the Netherlands in 2016, called the 'LANS' ('Landelijk Adviesorgaan Neoplasie Slokdarm'). These steps range from preliminary work such as the definition of expertise, to validation of digital microscopy use and establishing benchmark criteria to which participating pathologists were required to adhere. To our knowledge, it is the first time worldwide that an expert histopathology panel is set up in such a meticulous and, most importantly, quantitative way.

BE is recognized worldwide as an independent risk factor for the development of esophageal adenocarcinoma (EAC), a type of cancer with a particularly poor prognosis and a 5-year survival rate of approximately 15%. [1] This disease develops along a spectrum of histopathological (and endoscopic) changes, from non-dysplastic BE (NDBE), to low-grade dysplasia (LGD) and finally to high-grade dysplasia and EAC. Patients with non-dysplastic Barrett's esophagus have a 0.1-0.5% chance per year to develop EAC, [2-5] while in patients with LGD, this risk substantially increases to 9-13% per year. The last diagnostic category, termed 'indefinite for dysplasia' (IND), is a diagnostic lump-category for pathologists, reserved for those cases in which for different reasons the distinction between different diagnostic categories cannot be made.

The high chances of progression associated with dysplastic BE warranted regular endoscopic and histological surveillance of these patients, in order to detect dysplastic lesions in an as early stage as possible. The cornerstone of treatment for patients with HGD or EAC used to be esophagectomy, an extensive surgical procedure associated with significant morbidity and mortality. However, with the development of endoscopic techniques over the last 15 years, all patients with confirmed LGD, HGD or even superficial EAC are endoscopically treated with an endoscopic resection (ER), with or without subsequent radiofrequent ablation of the Barrett segment.

Correct stratification of these lesions, especially of LGD, the middle of the spectrum, is therefore of the utmost importance. Unfortunately, many histopathological studies have shown that the diagnosis of LGD is hampered by significant observer agreement among general pathologists. [6-9] Within our research group, we have discovered earlier that 1) expertise of the pathologist is the most important factor for a 'correct' diagnosis, i.e. related to the follow-up of the patient, 2) that a panel of expert pathologists

are able to accurately risk-stratify patients with dysplastic BE, [4] and that 3) general pathologists tend to overdiagnose LGD. [3] The results from these studies, among others, prompted different Barrett guidelines to include review of all cases diagnosed with LGD in a community hospital setting by a 'second, preferably gastrointestinal (expert) pathologist'. [10-14] These recommendations aid diagnostic quality, but the most important important question remained, namely, how do you recognize such a pathologist-expert? An objective definition of an 'expert BE pathologist' was lacking. In addition to describing the set-up of the review panel, this thesis seeks an answer to that question.

In order to improve and centralize the care of patients with dysplastic BE, a collaboration between the endoscopists of eight different hospitals in the Netherlands was set up in 2007. They all followed an intensive endoscopic training course before forming the 'Barrett expert centers' of the Netherlands, employing common treatment protocols and research efforts. This thesis describes a similarly intensive training process for the pathologists of the Barrett expert centers in relation to the set-up of the national digital review panel for dysplastic BE.

OUTLINE OF THESIS PER CHAPTER

Part I: The role of the pathologist in diagnosis of dysplastic Barrett's esophagus – prerequisites for review

In **Chapter 1 and 2** we explored the available evidence in literature regarding expert review of dysplastic BE biopsies. Moreover, in **Chapter 2** we specifically discussed the histological pitfalls of biopsy- as well as ER specimen diagnosis. In **Chapter 3** we proved that the risk of patient progression to HGD or EAC increases as more expert BE pathologists agree on a diagnosis of LGD. In **Chapter 4** we compared digital microscopy to conventional microscopy for the assessment of BE biopsies and proved that they yield comparable intra- and interobserver agreement when used by the five expert BE pathologists that constitute the 'core' of our panel. The results of this study allowed us to proceed with the set-up of panel using digitalized slides instead of glass slides. In **Chapter 5** we proved the added value of immunohistochemical staining for the protein product of the TP53 tumor suppressor gene in a single-slide study set of mainly dysplastic BE cases. This gene is often mutated in dysplastic BE,

and can therefore be used as an adjunct to diagnosis, according to most guidelines. In this study, it increased the assessment homogeneity of a group of ten dedicated gastrointestinal (GI-)pathologists working in the Barrett's esophagus expert centers in the Netherlands. This study was the first step towards them joining the panel in addition to the five 'core' expert BE pathologists.

Part II: Setting up a national digital review panel for dysplastic Barrett's esophagus in the Netherlands – panel development and implementation

Chapters 6-9 form a timeline of the set-up of the national digital review platform for dysplastic Barrett's esophagus cases in the Netherlands, entitled 'LANS' ('Landelijk Adviesorgaan Neoplasie Slokdarm', or: national digital review platform for Barrett's neoplasia).

In **Chapter 6-8** we described the process of developing and validating objective benchmark quality criteria to assess the performance of current members of the national digital review panel, and in this way also provide a template for assessment quality to which future members ought to adhere before joining the panel. These quality criteria were developed in **Chapter 6** with the help of a study set of mainly dysplastic cases, where all slides from all levels ('whole-endoscopy') were assessed by the 5 'core' pathologists. The quality criteria for which benchmark values were established, were: the percentage of diagnoses 'indefinite for dysplasia;' the intra-observer agreement, the diagnostic accuracy and the number of significant misdiagnoses (i.e. the number of times the pathologist diagnosed NDBE when the consensus diagnosis was HGD). In **Chapter 7**, the same study set was assessed by the ten dedicated pathologists described before, and their benchmark values for the quality criteria were calculated. Because not all pathologists adhered (yet), they assessed a second study set in **Chapter 8**, for which benchmark values for the same quality criteria had also been calculated using the assessments of the five core pathologists. This study set consisted of the 80 review requests that had been sent to the national digital review panel. Finally, **Chapter 9** explored further implementation and future workability of the panel by an algorithm which deduces the minimum number of pathologists needed to assess each case in order to achieve correct patient stratification, i.e. achieve a diagnosis concordant with the gold standard diagnosis.

Chapter 10 expanded pathologist concordance to a worldwide study conducted to deduce histopathologist factors related to BE pathologist expertise. A large cohort of 51 GI pathologists worldwide, with varying levels of experience, assessed a digitalized slide set of mainly dysplastic BE cases, utilizing a web-based tool incorporating scrollable images and questionnaire that we built ourselves using the open source electronic case record form (CRF) application 'Open Clinica'. They also filled in a demographic questionnaire, with questions about their experience and working situation. Using consensus with a BE expert panel of 4 pathologists as a reference, the following factors were derived from multivariate analysis: at least 5 years of professional experience, that is commensurate with age, working at a teaching hospital or using p53 immunohistochemistry when one is not.

Finally, in **Chapter 11** we explored pathologists concordance related to the assessment of endoscopic resection (ER) specimens. All pathologists in the national digital review panel assessed four features predictive of the development of lymph node metastases (LNM), in single cross sections of endoscopic resection (ER) specimens. These features are: depth of invasion, differentiation grade, vascular invasion and radicality of the basal margin. The goal of this study was to optimize the assessment of these criteria for ER specimens, in order to incorporate review of these specimens in the digital panel in the future.

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ABBREVIATIONS USED IN THIS THESIS

BO/E; Barrett's (o)esophagus, BMI; Body Mass Index, CI; Confidence Interval, CRF; case record form, O/EAC; (o)esophageal adenocarcinoma, E(M)R; endoscopic (mucosal) resection, ESD; endoscopic submucosal dissection, GI; gastrointestinal, HGD; high-grade dysplasia, IHC; immunohistochemistry, IMC; intramucosal carcinoma, IND; indefinite for dysplasia, IQR; interquartile range, K; kappa value, LGD; low-grade dysplasia, LNM; lymph(e) node metastases, NDBO/E; non-dysplastic Barrett's (o) esophagus, OR; odd's ratio, PI; Prediction Interval, RFA; radiofrequency ablation, VLE; Volumetric Laser Endoscopy, WHO; World Health Organization, WSI; whole slide imaging.