Towards patient tailored management for Barrett's related neoplasia

Nieuwenhuis, E.A.

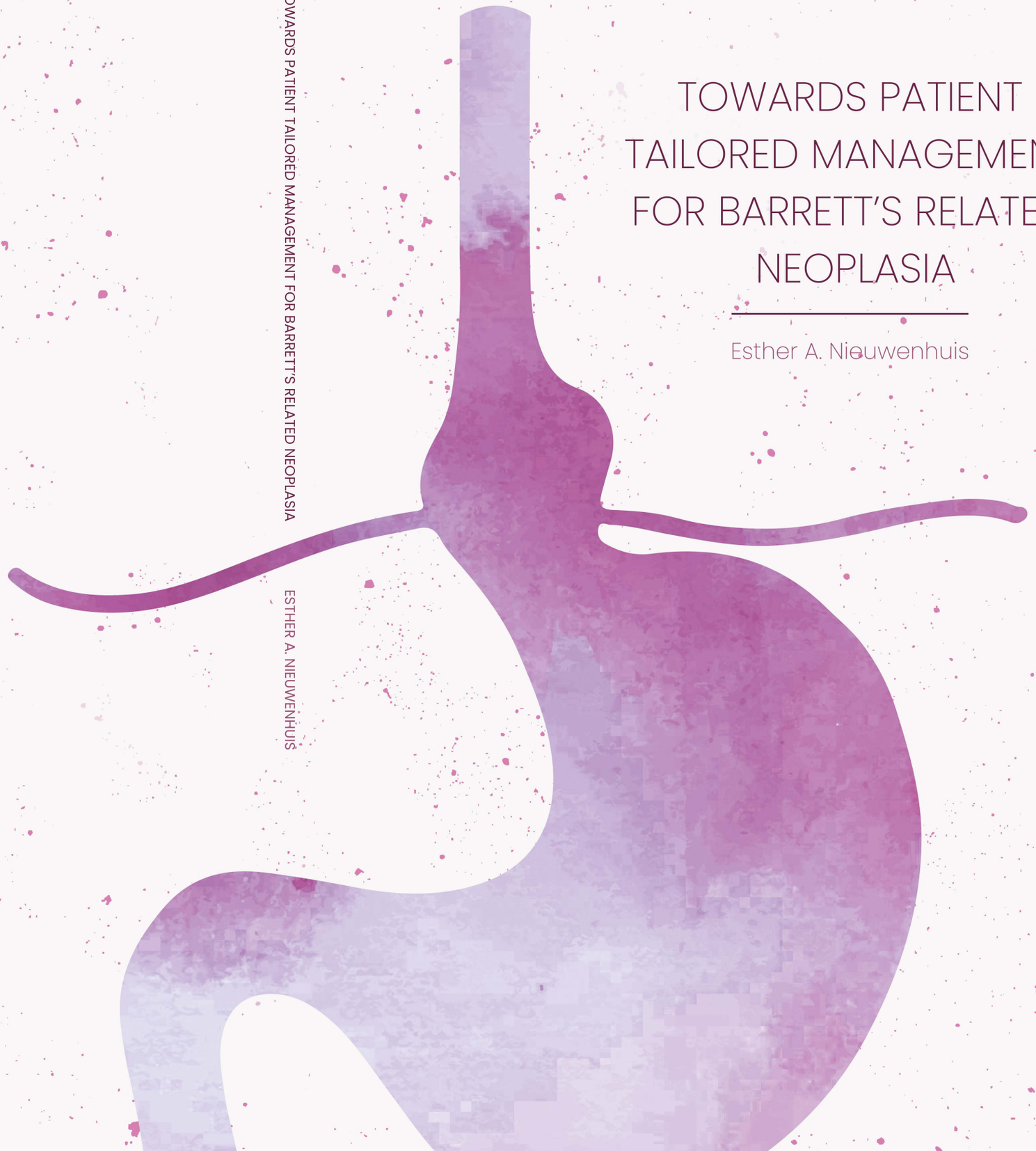
Publication date
2022
Document Version
Final published version

TOWARDS PATIENT TAILORED MANAGEMENT FOR BARRETT'S RELATED NEOPLASIA

ESTHER A. NIEUWENHUIS

TOWARDS PATIENT TAILORED MANAGEMENT FOR BARRETT'S RELATED NEOPLASIA

Esther A. Nieuwenhuis



Towards patient tailored management for Barrett's related neoplasia

Esther A. Nieuwenhuis

Towards patient tailored management for Barrett's related neoplasia
Esther A. Nieuwenhuis

ISBN	978-94-6419-603-0
Cover	Marilou Maes, persoonlijkproefschrift.nl
Design	Marilou Maes, persoonlijkproefschrift.nl
Printing	Gildeprint Enschede, gildeprint.nl

Financial support for printing this thesis was kindly provided by Nederlandse Vereniging voor Gastroenterologie, Pentax Medical, Erbe Nederland B.V., ChipSoft, Micro-Tech Nederland, Maatschap interne geneeskunde en maag- darm- leverziekten St. Antonius Ziekenhuis.

Towards patient tailored management for Barrett's related neoplasia

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 9 december 2022, te 16.00 uur

door Esther Anita Nieuwenhuis
geboren te AMSTERDAM

Promotiecommissie

Promotor:	prof. dr. J.J.G.H.M. Bergman	AMC-UvA
Copromotor:	dr. R.E. Pouw	AMC-UvA
Overige leden:	prof. dr. A.J. Bredenoord	AMC-UvA
	prof. dr. J.E. van Hooft	Universiteit Leiden
	prof. dr. H.W.M. van Laarhoven	AMC-UvA
	prof. dr. S. Seewald	Universität Bonn
	dr. W.J. Eshuis	AMC-UvA
	dr. S.L. Meijer	AMC-UvA

Faculteit der Geneeskunde

TABLE OF CONTENTS

General introduction and outline of this thesis

GENERAL INTRODUCTION

Barrett's esophagus (BE) is a condition in which the normal squamous epithelial lining of the distal esophagus is replaced by columnar epithelium containing intestinal metaplasia due to chronic gastro-esophageal reflux. BE is known to be the most important risk factor for esophageal adenocarcinoma (EAC) (1). The worldwide incidence of EAC has increased six-fold over the past decades, and is predominant in the Western World (2,3). In advanced stages, EAC is associated with a poor survival; the 5-year survival rate has reported to be varying between 5-25% (4). Nevertheless, the development to advanced cancer occurs gradually from non-dysplastic intestinal metaplasia, to low-grade dysplasia (LGD), high-grade dysplasia (HGD), early carcinoma, and eventually invasive carcinoma (5). This stepwise process allows for early endoscopic identification of abnormalities by performing high quality visualization, targeted biopsies of visible lesions, and random biopsies of normal appearing Barrett's epithelium, and allows endoscopic treatment to prevent progression to advanced disease.

The past two decades minimally invasive endoscopic resection (ER) has replaced surgical esophagectomy as first-choice therapy for the treatment of early neoplastic lesions in Barrett's esophagus. ER enables both potential complete resection of an early neoplastic lesion and accurate histopathological assessment, which is important to determine further management. Multiple ER techniques have been described for visible lesions in a BE segment, which are discussed in more detail in chapter 1 of this thesis. After removal of visible lesions, the residual Barrett's mucosa remains at risk for developing malignant metachronous lesions. This risk is thought to be 11-30% within 3 years of follow-up (6,7). Therefore, the second step in endoscopic treatment consists of eradicating the entire BE segment by means of ablation therapy, generally using radiofrequency ablation (RFA). This 2-step treatment approach has been studied extensively in multiple high-quality studies, and has demonstrated its safety and effectivity for the treatment of early BE neoplasia (8–11). Because of its success, the "BE treatment spectrum" is quite broad nowadays. Next to ablation of residual BE mucosa after ER, RFA may also be considered in patients with a repeated, confirmed diagnosis of LGD, since RFA significantly decreases progression to HGD/EAC (9)). Moreover, for flat type BE harboring HGD without visible lesions requiring ER, RFA is indisputably advised to prevent progression to cancer.

Still, risks and benefits must be considered when deciding to initiate endoscopic treatment, since the ultimate aim remains preventing progression to symptomatic disease, and this decision is dependent on patient's age and comorbidity. For early EAC, the decision between local endoscopic treatment with low adverse event risk,

and invasive esophagectomy with high morbidity (up to 65%) and mortality (0-4%) rates is guided by the risk for lymph node metastasis (12). The risk for early carcinoma without histopathological high-risk features (i.e., tumor invasion depth <500µm, good to moderate differentiation grade of tumor cells, without lymphovascular invasion (LVI), which was radically resected) is negligible (<2%) (13–15). For these tumors, local treatment is considered sufficient. Traditionally, the lymph node metastasis risk for tumors invading deeper into the submucosa (i.e. ≥500µm), is considered too high (±45%) to offer these patients curative endoscopic treatment (16,17). Only in elderly patients with comorbidity, more often a less invasive endoscopic protocol is chosen. However, the risk of lymph node metastasis associated with more advanced stages of Barrett's carcinoma is mainly based on old surgical studies. In these studies, the invasion depth and other risk features might be underestimated, because the deepest part of infiltration might not have been included in cut slides, and accurate assessment of differentiation grade and LVI was considered less relevant. A number of more recent endoscopy-based studies, also considering poor differentiation and LVI, showed lower lymph node metastasis risk than previously assumed (0-30%), making an invasive esophagectomy possibly unnecessary in a subset of patients (13,18,19).

The threshold to start treatment was much higher when only esophagectomy was available, and now that a less invasive modality is at hand, lower and upper boundaries regarding indications for treatment have been shifting at both sides of the spectrum. On one side, we nowadays treat patients with confirmed LGD and on the other side, we are pushing boundaries of endoscopic treatment towards more advanced stages of early EAC.

In this thesis, we evaluated different aspects to optimize management for early esophageal adenocarcinoma arising from Barrett's esophagus and explored whether endoscopic management could be an option in more advanced stages of early cancer.

OUTLINE OF THIS THESIS

Part I of this thesis evaluates endoscopic combination therapy as the preferred treatment for early neoplasia in Barrett's esophagus. Therefore, in chapter 1 and 2, we elaborate on multiple endoscopic resection- and radiofrequency ablation techniques. That both techniques are safe and effective for treatment of Barrett's related neoplasia is already known. However, long-term outcomes are lacking. Chapter 3 describes short- and long-term outcomes of all patients who underwent endoscopic treatment with RFA in the Netherlands, from the introduction of this technique in 2008.

Part II focuses on improving personalization of Barrett's neoplasia management. In chapter 4, we assess if confirmed LGD is an indicator for prevalence of higher grades of synchronous dysplasia or visible lesions in the BE segment in an expert center. Chapter 5 analyses whether endoscopic surveillance instead of RFA, after ER for early neoplasia, would be a valid alternative in older patients with limited life expectancy. In chapter 6, we report the development and external validation of a prediction model for recurrence after successful treatment, to personalize post-treatment surveillance. Chapter 7 describes the complicated course of a small subset of Barrett patients not healing with squamous epithelium after RFA. Evidence-based advices are provided as well. In chapter 8, we describe the development and external validation of a prognostic model to predict which patient will experience such a complicated treatment course.

Part III evaluates if endoscopic management is also a safe option for patients with esophageal adenocarcinoma containing high-risk histopathological features, instead of surgery. High lymph node metastasis rates are reported in current literature for these patients, however, we hypothesize that the rates are overestimated due to differences in specimen preparation for histological assessment. Surgical specimens are cut in wider slices than ER specimens, which could lead to underestimation of tumor invasion depth in surgical specimen if the deepest part of infiltration was not included. This underestimation might result in overestimating associated metastases rates. We test this hypothesis in chapter 9, and in chapter 10, we report lymph node metastasis rates and EAC-related deaths during endoscopic follow-up after endoscopic resection of high-risk early esophageal adenocarcinoma in 120 patients treated in one of the Dutch Barrett Expert Centers.

In the final chapter, 'Thesis summary, general discussion and future perspectives' the main findings of this thesis are reviewed and recommendations for further research are discussed.

REFERENCES

1. Spechler SJ. Barrett's esophagus and esophageal adenocarcinoma: pathogenesis, diagnosis, and therapy. Med Clin North Am. 2002 Nov;86(6):1423–45, vii.
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005 Jan 19;97(2):142–6.
3. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet (London, England). 2013 Feb 2;381(9864):400–12.
4. Cancer Facts and Figures. Am Cancer Soc. 2021;(Atlanta, United States).
5. Shaheen NJ, Richter JE. Barrett ' s oesophagus. Lancet [Internet]. 2009;373(9666):850–61. Available from: http://dx.doi.org/10.1016/S0140-6736(09)60487-6
6. Peters FP, Kara MA, Rosmolen WD, Aalders MCG, Ten Kate FJW, Bultje BC, et al. Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. Gastrointest Endosc. 2005;61(4):506–14.
7. May A, Gossner L, Pech O, Fritz A, Günter E, Mayer G, et al. Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: Acute-phase and intermediate results of a new treatment approach. Eur J Gastroenterol Hepatol. 2002;14(10):1085–91.
8. Phoa KN, Pouw RE, Bisschops R, Pech O, Ragunath K, Weusten BLAM, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: Results of an European multicentre study (EURO-II). Gut. 2016;65(4):555–62.
9. Phoa KN, van Vilsteren FGI, Weusten BLAM, Bisschops R, Schoon EJ, Ragunath K, et al. Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia. Jama [Internet]. 2014;311(12):1209. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.2511
10. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med [Internet]. 2009 May 28;360(22):2277–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19474425
11. Desai M, Saligram S, Gupta N, Vennalaganti P, Bansal A, Choudhary A, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointest Endosc. 2017 Mar;85(3):482-495.e4.
12. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg. 2012 May;16(5):1055–63.
13. Schölvinck D, Künzli H, Meijer S, Seldenrijk K, van Berge Henegouwen M, Bergman J, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surg Endosc. 2016;30(9):4102–13.
14. Alvarez Herrero L, Pouw RE, van Vilsteren FG, ten Kate FJW, Visser M, van Berge Henegouwen MI, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy. 2010 Dec;42(12):1030–6.

15. Pech O, May A, Manner H, Behrens A, Pohl J, Weferling M, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology. 2014 Mar;146(3):652-660.e1.

16. Buskens CJ, Westerterp M, Lagarde SM, Bergman JJGHM, ten Kate FJW, van Lanschot JJB. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc. 2004 Nov;60(5):703–10.

17. Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJW, Bergman JJHGM, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch. 2005 May;446(5):497–504.

18. Manner H, Pech O, Heldmann Y, May A, Pauthner M, Lorenz D, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc. 2015 Jul;29(7):1888–96.

19. Künzli HT, Belghazi K, Pouw RE, Meijer SL, Seldenrijk CA, Weusten B, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United Eur Gastroenterol J. 2018 Jun;6(5):669–77.

PART I

The cornerstone of successful endoscopic treatment for early Barrett's neoplasia

CHAPTER 1

Role of Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection in the Management of Barrett's Related Neoplasia

Esther A. Nieuwenhuis, Oliver Pech,
Jacques J.G.H.M. Bergman, Roos E. Pouw

Gastrointest Endosc Clin N Am. 2021 Jan;31(1):171-182.
doi: 10.1016/j.giec.2020.09.001

INTRODUCTION

Barrett's esophagus (BE) is defined as a metaplastic change of the normal squamous lining of the distal esophagus, with replacement of squamous epithelium by an intestinal-type epithelium caused by longstanding gastroesophageal reflux disease. BE has malignant potential through the sequence of no dysplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and eventually early esophageal adenocarcinoma (EAC) [1,2]. BE patients have a 30- to 40-fold higher risk of EAC compared with the general population [3]. Therefore, endoscopic surveillance is recommended to detect dysplasia before it progresses to EAC, and to detect EAC at a curable stage. Surgical esophagectomy has traditionally been recommended for patients found to have early neoplasia arising in BE. However, esophagectomy is associated with high morbidity (up to 65%) and significant mortality rates even in high-volume centers (2%– 4%) [4]. For the past 2 decades, much research has focused on development of endoscopic imaging techniques to detect EAC at an early stage, and on endoscopic treatment techniques to create less-invasive treatment modalities for early BE-related neoplasia. The endoscopic resection (ER) technique for the treatment of neoplastic lesions was first developed in Japan for the treatment of early gastric cancer [5]. The technique has been adapted by Western endoscopists in subsequent years for various indications, including Barrett's neoplasia. ER has proven to be a safe, effective, and minimally invasive alternative to surgery for treatment of early neoplastic lesions in BE, and is considered to be the cornerstone of endoscopic treatment. ER is an endoscopic approach in which the neoplastic epithelium is excised, providing adequate tissue specimens, enabling accurate histologic staging of a lesion while also potentially being curative. Staging consists of assessing invasion depth, differentiation grade, presence of lymphovascular invasion, and radicality of the resection, and is important to determine further management [6–9]. There are 2 common methods to perform ER: cap-based ER and endoscopic submucosal dissection (ESD). Both methods will be discussed in this article.

INDICATIONS FOR ENDOSCOPIC RESECTION

Because ER only allows for local therapy of suspicious visible lesions arising from BE, it is essential to adequately select patients for whom the risk of lymph node involvement or hematogenous dissemination is low enough to justify performing local ER instead of esophagectomy with lymph node dissection. This risk should also be balanced against the high morbidity and mortality rates of esophagectomy, and the clinician should take the patient's wish and performance status into account.

Mucosal Cancer

ER for the treatment of BE with HGD or EAC limited to the mucosa (i.e., T1m1-m3) has been established as first-choice treatment, with excellent efficacy and safety, also in long-term analyses. In one of the largest published studies in which data from 1000 patients with endoscopically resected mucosal EAC were collected, 96.3% of patients had achieved a complete response shortly after ER. After 5 years of follow-up, the long-term complete remission rate was 93.8%, and only 2 patients died of BE-associated cancer [10]. Furthermore, several studies have shown that the risk of lymph node involvement is minimal (1%) in patients with mucosal EAC [10,11]. Therefore, ER is considered the treatment of choice for this indication. Nevertheless, data for patients with a mucosal EAC containing high-risk features (i.e., poor differentiation and/or lymphovascular invasion) are not available in the current literature. Therefore, the risk of lymph node metastases in these specific patients is currently unknown.

Submucosal Cancer

In the last few years, the indication for endoscopic therapy has extended to tumors invading the submucosa superficially (i.e., invasion depth <500 µm) without any other histopathological risk factors for lymph node metastasis (i.e., good-to-moderate differentiation [G1-G2], no presence of lymphovascular invasion [LVI], and negative vertical resection margins [R0]), since the risk to develop lymph node metastasis appears to be less than 2% [12,13]. This is lower than the mortality risk of esophagectomy. Therefore, endoscopic treatment and follow-up seem to be valid alternatives to surgical resection for this indication. Patients with high risk submucosal cancer (i.e., deep submucosal infiltration ≥500 µm, and/or poor differentiation [G3], and/or presence of LVI, and/or R1 resection) are considered surgical candidates, as the risk of lymph node metastasis is thought to be much higher (16%–44%) [14,15]. However, these numbers are mainly based on old surgical series. These numbers may also be overestimated, as these studies often did not differentiate between various submucosal infiltration depths, and this was not required for patient management. Furthermore, surgical resection specimens are cut in larger slices than ER specimens,

which may lead to underestimation of the presence of histologic risk factors associated with higher risk of lymph node metastasis, and the deepest infiltrating part of a tumor, poor differentiation, or presence of LVI may have been missed. Recently, several studies, which only included patients who underwent ER for high-risk submucosal cancer, were published indicating that the risk of metastases may be lower than generally assumed (0%–30%) [13,16,17]. Nevertheless, it does exceed the mortality rate of surgical resection. Therefore, endoscopic management after ER of high-risk submucosal cancer is not advised by current guidelines. However, in selected patients, a strict endoscopic follow-up protocol with regular endoscopic and endosonographic follow-up to detect lymph node metastases at a curable stage can be considered.

ENDOSCOPIC WORK-UP

Patients with HGD or cancer found on biopsies, and all patients with a visible abnormality, regardless of the pathology outcome, should be referred to a center with high expertise in endoscopic evaluation and treatment of BE-related neoplasia to confirm these findings. Repeating endoscopy at an expert center with experienced endoscopists and pathologists provides a more reliable final diagnosis. More importantly, patients referred with flat HGD or cancer in random biopsies are likely to actually have a visible abnormality that was missed during the first endoscopy. A study comparing the detection rate of neoplastic BE lesions between community and expert endoscopists showed that 76% of patients who were referred for evaluation of HGD or cancer in random biopsies without a visible abnormality reported, did have a visible abnormality detected by an expert endoscopist [18]. Furthermore, repeat endoscopy assures the detection of other abnormalities elsewhere in the BE segment that otherwise might be left untreated. Contrarily, if a visible abnormality is detected but biopsies do not show dysplasia or cancer, one should keep the possibility of a false-negative histopathological diagnosis in mind with a low threshold to refer for a diagnostic ER or at least perform repeat endoscopy with biopsies. Moreover, high-quality documentation during endoscopy by taking multiple photos and recording videos can be used while consulting an expert center.

Detection of Early Neoplasia

Thorough endoscopic inspection of the entire BE segment is necessary to detect early neoplastic lesions, as they often present as subtle mucosal irregularities. It is preferred to use high-resolution endoscopy, complemented with virtual chromoendoscopy (i.e., narrow-band imaging, blue-laser imaging, i-scan) to delineate the extent of a lesion. Other than using the best available equipment and having familiarity with the endoscopic appearance of BE-related early neoplasia, it is also important to perform a

systematic procedure, such as cleaning, pull back, inspection of the gastroesophageal junction in the inverted position, endoscopic classification by macroscopic appearance of visible lesions, and biopsies. Cleaning After inflation of the esophagus, adequate cleaning of the esophageal wall by rinsing with water to remove all mucus contributes to better sight and therefore less chance of missing subtle abnormalities. Suctioning of fluids should be done in the stomach and hernia to avoid suction lesions within the Barrett's segment. Pull back Using white light, the endoscope should be carefully withdrawn in a continuous way to examine the BE segment for mucosal abnormalities and to describe the extent of the BE according to the validated Prague C & M criteria [19]. Special attention to the area between 12 o'clock and 6 o'clock in the endoscopic view is recommended. Several studies have shown that early cancer in BE is most commonly found in the right hemisphere of the esophagus, with the highest rate in the 12 o'clock to 3 o'clock quadrant [20,21].

Inspection of the gastroesophageal junction in the inverted position

Lesions in this area are easily missed when only looking antegrade. Endoscopic classification by macroscopic appearance of visible lesions The macroscopic appearance of a lesion in BE should be classified according to the Paris classification, a classification based on earlier Japanese classifications, which was developed to allow morphologic classification of early and/or superficial lesions in the gastrointestinal (GI) tract [22,23]. The classification divides lesions into 3 major types: protruded, flat, and excavated. Protruded lesions (Paris type 0-Ip and 0-Is) are defined as having more than double the amount of mucosal thickness in a histologic specimen [24]. In clinical practice, a biopsy forceps placed longitudinally next to the lesion is a helpful reference value, where the height of protruded lesions is defined as being higher than a closed biopsy forceps (2.5 mm). Flat lesions are divided into 3 subtypes: slightly elevated lesions (Paris type 0-IIa), which are defined as less than double the amount of mucosal thickness in a histologic specimen or as less high than a closed biopsy forceps; completely flat lesions (Paris type 0-IIb); and slightly depressed lesions (Paris type 0-IIc), which are defined as less deep than 1 cup of an open biopsy forceps. Excavated lesions (Paris type 0-III) are predominantly ulcerative and are defined as deeper than half the cup of an open biopsy forceps. The macroscopic appearance of a lesion is associated with infiltration depth and therefore indirectly with the risk of metastatic lymph nodes. A retrospective study evaluating the histopathology of specimens obtained from 296 ER procedures in correlation with endoscopic characteristics showed that Paris type 0-I and 0-IIc lesions were more likely to infiltrate into the submucosa (26% and 25%) compared with types 0-IIa, 0-IIa-IIb, and 0-IIa-IIc (9%, 8% and 10%, respectively) (P=.009). None of the type 0-IIb lesions showed submucosal invasion. However, a limitation to this study was that not all resection specimens were reassessed in this retrospective setting

[25]. Pech and colleagues [21] did overcome this limitation by prospectively assessing macroscopic types of 380 early neoplastic lesions in BE and their histopathological outcomes. The study showed that slightly depressed lesions (Paris type 0-IIc) infiltrated into the submucosa more often (25%) than elevated (11%) and slightly elevated lesions (Paris type 0-I and 0-IIa) (14%) or flat lesions (Paris type 0-IIb) (4%). Type 0-IIb neoplasia was significantly more frequently associated with early local tumor stage and a good differentiation grade than all other types. However, none of the Paris type 0-I or type 0-II lesions were associated with a very high risk of submucosal invasion. Diagnostic ER therefore is considered indicated and safe for these lesions. No sufficient data are available on the rate of submucosal invasion in excavated lesions, but these types of lesions tend to include invasive tumors and are also less suitable for treatment with ER given the ulceration.

Biopsies

Targeted biopsies can be obtained from visible abnormalities. However, when the lesion is evidently present and diagnostic ER already planned, targeted biopsies of the lesion are optional. Nevertheless, whether visible lesions are found or not, tissue sampling is still required for mapping the (residual) BE. In inexperienced hands, 10% to 20% of lesions are missed with targeted biopsies alone [26]. The Seattle biopsy protocol is recommended for mapping the whole BE segment by randomly taking 4- quadrant biopsies. This biopsy protocol starts from the top of the gastric folds moving upwards up to the most proximal extent of the BE segment, while sampling at 2 cm intervals [27]. The reason for working in the proximal direction is to minimize bleeding obscuring the endoscopic view.

Diagnostic Endoscopic Resection for Visible Lesions as a Staging Procedure

When a visible lesion is first identified upon endoscopic inspection, it needs to be accurately evaluated by classifying the lesion using the previously described Paris classification to determine whether it is suitable for ER. When the appearance does not raise suspicion for deep submucosal infiltration, which is most important for determining the chances of radicality and lymph node metastases, the lesion may be removed by ER. This is a valuable diagnostic step, because the pathologist will be able to accurately assess risk factors for lymph node metastases such as infiltration depth, differentiation grade, and lymphovascular invasion. As described earlier, mucosal cancer and low-risk submucosal cancers are indications for further endoscopic management.

Other Staging Procedures

Because the risk of LNM is considered low among patients diagnosed with mucosal or low-risk submucosal tumors (1% and <2%, respectively), additional staging

procedures such as endoscopic ultrasound (EUS) and positron emission tomography (PET) computed tomography (CT) scan are not necessarily required. For patients with suspicion on a deeper submucosal invading lesion, or presence of poor differentiation of LVI in biopsies, baseline staging may be helpful before deciding on performing ER. EUS is the most accurate technique for locoregional staging of esophageal cancer and has a high negative predictive value (>95%) for the absence of local lymph nodes. However, EUS is more reliable in patients with more advanced cancer than in patients with early EAC. Moreover, accuracy is affected by the experience of the endosonographer [28,29]. Just as for EUS, PET-CT is only advised for baseline staging in patients with a high-risk EAC, as the value mainly lies in the detection of distant metastasis. There is no evidence in the literature that PET-CT is better for detection of distant metastasis in submucosal EAC compared with CT [30-32].

PERFORMING ENDOSCOPIC RESECTION

Expertise and experience are required to resect esophageal lesions in a safe and effective way. First of all, the endoscopist needs to decide whether a lesion will be removed by en bloc or piecemeal resection, depending on the size and the macroscopic appearance of the lesion. The most commonly used ER technique in the Western world is a cap-based technique named multiband mucosectomy (MBM), which allows for en bloc resection of lesions up to 20 mm in diameter. Larger lesions require multiple resections in the same endoscopic treatment session, a so-called piecemeal procedure, or ESD. Different established techniques will be described. One of the disadvantages of the piecemeal procedure is that the radicality of the resection at the lateral margins is impossible to assess for the evaluating pathologist. Endoscopic assessment of the radicality of a resection is therefore important. Other downsides of piecemeal resections are that they tend to be more technically demanding to perform, have a higher complication risk, and are more time consuming [10]. After detection of the visible lesion, it is essential to mark the lesion by delineating the lateral borders by placing coagulation marks. Without these markings, it may be difficult to recognize the lateral margins of the lesion during the endoscopic resection because of reduced visibility due to bleeding or coagulation effects. By placing markers beforehand, one ensures the macroscopic lateral radicality when all coagulation markers are removed after the resection.

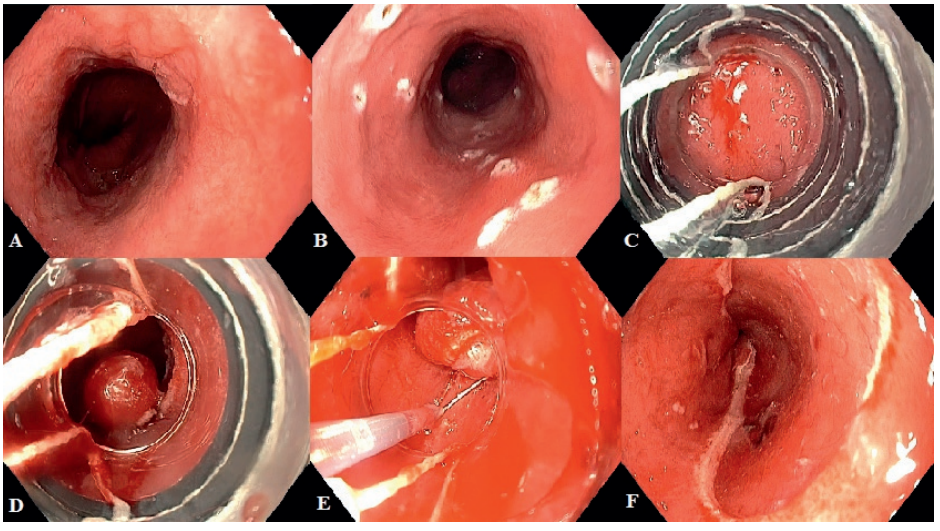
Different Endoscopic Resection Techniques

There are currently 2 common methods to perform an endoscopic resection: cap-based endoscopic resection and ESD.

Cap-based endoscopic resection techniques:
These techniques include the MBM technique (Fig. 1, Video 1) and the endoscopic resection-cap technique.

Multiband mucosectomy technique: The most commonly used ER technique nowadays is the MBM technique, which uses a modified variceal band ligator with a transparent cap and a polypectomy snare. First, the neoplastic lesion is sucked into the cap. Subsequently, by triggering the releasing handle, a rubber band is released, which only captures the mucosa. The rubber band is not strong enough to hold on to the deeper layers of the esophageal wall. Therefore, the target mucosa can be resected by using the polypectomy snare with a minimal risk of damaging the deeper muscle layer, even without prior submucosal lifting. The MBM technique can be performed by using the Duette System (Cook, Limerick, Ireland), or the Captivator device (Boston Scientific).

Figure 1. Multiband mucosectomy



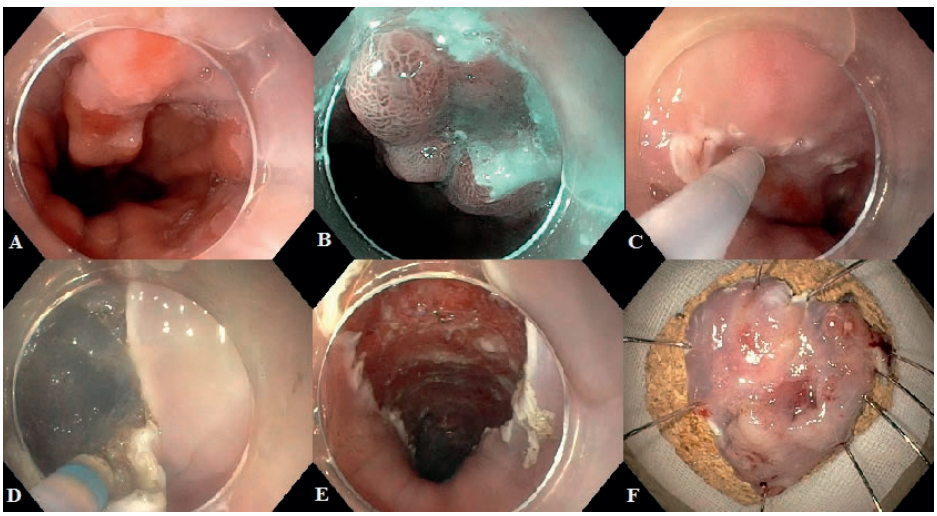
Multiband mucosectomy using the Duette System (Cook, Limerick, Ireland). **A and B,** Endoscopic view of Barrett's neoplasia which is delineated with electrocoagulation markers before starting the endoscopic resection procedure. **C and D,** Endoscopic view through the Duette cap: a pseudopolyp is created by suctioning the mucosa into the ligation cap and releasing a rubber band. **E,** Pseudopolyp resection by hexagonal snare. **F,** View on the resection wound after removal of the cap.

Endoscopic resection-cap technique: Another technique for ER of BE lesions is the ER-cap technique, which involves the use of a specifically designed transparent oblique cap with a distal ridge, which allows for the placement of an asymmetrical crescent-shaped electrocoagulation snare. This technique is performed by lifting the lesion with

fluid that is injected into the submucosal layer. Subsequently, the snare is prelooped in the ridge of the cap, whereafter the lesion is sucked into the cap, and the snare is tightened. The created pseudopolyp can then be resected.

Several studies have shown that both cap-based techniques are safe and effective for the removal of visible lesions in a BE segment [33-35]. The overall complication rate mentioned in a large trial including 1000 BE patients with mucosal EAC was 1.5% (n=15). Major complications were bleeding (n=14) and perforation (n=1), but these could all be managed conservatively. The complete eradication rate of neoplasia was 96% [10]. As already mentioned, the MBM technique is currently the most commonly used in all Barrett's expert centers. A randomized-controlled trial comparing both techniques for piecemeal ER showed that MBM and ER-cap achieve comparable success and safety rates. However, MBM was cheaper and quicker compared to ER-cap, and most endoscopists consider MBM easier to learn [36]. Furthermore, the indication to perform an ER-cap resection is mostly replaced by ESD (Fig. 2, Videos 2 and 3).

Figure 2. Endoscopic submucosal dissection



Endoscopic submucosal dissection. **A and B,** Endoscopic view of Barrett's neoplasia using white-light and narrow-band imaging. **C,** View on the delineated lesion that is being lifted by submucosal fluid injection. **D,** Dissection of the submucosal layer using the Dual knife **E,** View on the resection wound through the cap. **F,** Resection specimen pinned on a corkboard

Endoscopic submucosal dissection:

ESD allows for en bloc resection of early neoplasia irrespective of the lesion's size and therefore overcomes the problem of piecemeal ER, which is required for lesions

larger than 2 cm. The procedure starts with delineation of the lateral margins and lifting of the submucosal layer with injection fluid. The mucosal incision alongside the coagulation markers is performed using an electrosurgical knife. After completing the incision, the submucosa is dissected step by step, while repeating submucosal lesion to ensure a safety margin toward the muscle layer. Indications for ESD are strong suspicion of submucosal invasion and the resection of lesions with a large intraluminal component (i.e., very bulky lesions). Because ESD appears to be a technically demanding procedure and is time consuming, ESD is, in the Western world, still only applied in selected cases by experienced endoscopists. Furthermore, ESD has not been shown to be superior to ER for excision of mucosal cancer. A trial directly comparing cap-based ER and ESD in patients with early Barrett's neoplasia randomized 40 patients (cap-based ER technique, n=20 vs. ESD, n=20). The study did not show any difference in complete remission of neoplasia at 3 months (cap-based ER 16 of 17 vs. ESD 15 of 16, P=1.0). During a mean follow-up of 23 months, cancer recurrence was observed in 1 patient treated with ESD. Two adverse events were seen, both perforations during ESD. Although the study was underpowered, this may confirm that there is only little clinical relevance to perform ESD in most BE patients with early neoplasia [37-39]. Nevertheless, larger studies on ESD for Barrett's neoplasia in the Western world are yet to be performed.

Post-Treatment Management

Maintenance therapy with high-dose proton pump inhibitors (PPIs) is recommended for all patients with BE containing neoplasia. Besides PPIs, extra acid suppression during 2 weeks directly after ER is advisable to allow the ER wound to heal adequately with neosquamous epithelium (e.g., with sucralfate suspension). Adherence to a liquid diet until 24 hours after ER is advisable, after which the diet can gradually be advanced to a soft and then a normal diet guided by the patients' symptoms. Most common symptoms after ER are chest discomfort, sore throat, and pain when swallowing. If necessary, patients can use painkillers such as acetaminophen or if necessary nonsteroidal anti-inflammatory drug suppositories. The wound generally is healed in 3 to 6 weeks after the procedure, depending on the extent of resection.

HISTOPATHOLOGICAL EVALUATION ENDOSCOPIC RESECTION SPECIMENS

Esophageal neoplasia is classified according to the Vienna classification, which divides neoplasia into 5 categories [40]: 1: no dysplasia; 2: indefinite for dysplasia; 3: low-grade dysplasia; 4: high-grade dysplasia; 5: invasive carcinoma. Category 5 is subdivided based upon whether there is invasion into the lamina propria or muscularis mucosae (category

5.1, also referred to as intramucosal cancer) or into the submucosa (category 5.2, also referred to as submucosal cancer). In case invasive carcinoma is found, the infiltration depth, differentiation grade (good, moderate, poor, or undifferentiated), presence of LVI, and radicality of the resection should be assessed. Infiltration depth is divided into mucosal and submucosal invasion. T1m2: infiltration into the lamina propria; T1m3: infiltration into the muscularis mucosae. For submucosal infiltration, measuring and reporting the depth in mm are preferred over subdividing the submucosa in 3 equal parts, because not the entire submucosal layer is present in the ER specimen. T1sm1: infiltration of no more than 500 µm, T1sm2: infiltration greater than 500 to no more than 1000 µm, T1sm3: infiltration greater than 1000 µm. Radicality is assessed at the vertical (deep) resection margin. In case of en bloc resection, the radicality of the lateral margins is assessed also. There exists interobserver reliability among pathologists. As a result, it may be helpful to achieve a consensus among more than 1 pathologist in categorizing such specimens.

EFFICACY OF ENDOSCOPIC RESECTION IN MANAGEMENT OF BARRETT'S-RELATED NEOPLASIA

Available evidence shows that ER is a successful diagnostic tool and treatment modality in patients with mucosal or low-risk submucosal Barrett's cancer. ER provides accurate histopathological assessment of the tumor and is therefore considered as the key step in the work-up of early Barrett's neoplasia. Several large prospective studies analyzing the efficacy and safety of ER have been performed in the past 10 to 15 years. Studies have consistently demonstrated ER success rates between 91% and 99%, with major complication rates (i.e., bleeding, perforation, or stricture after ER) ranging from only 1.5% to 4% [33,41,42]. One of these series contains an international, single-arm, prospective international, multicenter registry primarily examining the success rate of ER using MBM. Successful ER was reached in 322 of 332 lesions (97%; 95% confidence interval [CI], 94.6%-98.4%). A perforation occurred in 3 patients (0.9%); all could be managed endoscopically, and patients were admitted for several days with intravenous antibiotics. Late bleeding requiring intervention occurred in 5 patients (1.5%), and dysphagia requiring dilatation occurred in 11 patients (3.8%) [42]. In one of the largest retrospective studies analyzing the long-term follow-up results of 1000 BE patients treated with ER for HGD or mucosal EAC, 96% achieved complete remission of neoplasia. Recurrent or metachronous lesions developed in 15% of patients and were successfully endoscopically re-treated in 82% of patients. Only 0.2% died because of metastatic EAC during follow-up. The overall long-term complete remission rate was 94% [10]. Therefore, ER is considered as the cornerstone of endoscopic therapy in BE-related neoplasia. Nevertheless, the optimal strategy for patients with a high-risk

submucosal lesion is yet to be defined and should therefore be discussed during a multidisciplinary team meeting, including a gastroenterologist, oncologist, and surgeon.

SUMMARY

ER is a safe and effective diagnostic tool and treatment modality in patients with early Barrett's neoplasia. ER offers multiple advantages, such as enabling accurate histopathological assessment, high success rates, and low complication rates. Multiple techniques have been reviewed in this article. In summary, MBM is the most commonly used ER technique; however, ESD is currently upcoming in the Western world. Evidence shows that ER for low risk-lesions is justifiable; however, future studies should assess whether ER is also justified in selected patients with high-risk submucosal lesions.

CLINICS CARE POINTS

ER is justified in mucosal and low-risk submucosal cancer because of the low risk of lymph node metastasis. In selected patients a strict endoscopic follow-up protocol can be considered after radical removal of a high-risk submucosal lesion.

REFERENCES

1. Shaheen NJ, Richter JE. Barrett's oesophagus. Lancet 2009;373(9666):850–61.
2. Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med 2014;371(8):36–45.
3. Solanky D, Krishnamoorthi R, Crews N, Johnson M, Wang K, Wolfsen H, Fleischer D, Ramirez FC, Katzka D, Buttar N, Iyer PG. Barrett Esophagus Length, Nodularity, and Low-grade Dysplasia are Predictive of Progression to Esophageal Adenocarcinoma. J Clin Gastroenterol 2019 May/Jun;53(5):361–5. https://doi.org/10.1097/MCG.0000000000001027. PMID: 29608452.
4. Markar SR, Karthikesalingam A, Thrumurthy S, et al. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg 2012;16(5):1055–63.
5. Inoue H, Endo M. Endoscopic esophageal mucosal resection using a transparent tube. Surg Endosc 1990;4(4):198–201.
6. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 2000;118(4): 670–7.
7. Nijhawan PK, Wang KK. Endoscopic mucosal resection for lesions with endoscopic features suggestive of malignancy and high-grade dysplasia within Barrett's esophagus. Gastrointest Endosc 2000;52(3):328–32.
8. Vieth M, Ell C, Gossner L, et al. Histological analysis of endoscopic resection specimens from 326 patients with Barrett's esophagus and early neoplasia. Endoscopy 2004;36(9):776–81.
9. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008;57(9):1200–6.
10. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014;146(3):652–60.e1.
11. Alvarez Herrero L, Pouw RE, van Vilsteren FG, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 2010;42(12):1030–6.
12. Manner H, May A, Pech O, et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008;103(10):2589–97.
13. Schölvinck D, Künzli H, Meijer S, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surg Endosc 2016;30(9):4102–13.
14. Buskens CJ, Westerterp M, Lagarde SM, et al. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc 2004;60(5):703–10.
15. Westerterp M, Koppert LB, Buskens CJ, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005;446(5):497–504.

16. Manner H, Pech O, Heldmann Y, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc 2015; 29(7):1888–96.
17. Künzli HT, Belghazi K, Pouw RE, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United European Gastroenterol J 2018;6(5):669–77.
18. Schölvinck DW, van der Meulen K, Bergman JJGHM, et al. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy 2017;49(2):113–20.
19. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: The Prague C & M criteria. Gastroenterology 2006;131(5):1392–9.
20. Enestvedt BK, Lugo R, Guarner-Argente C, et al. Location, location, location: does early cancer in Barrett's esophagus have a preference? Gastrointest Endosc 2013;78(3):462–7.
21. Pech O, Gossner L, Manner H, et al. Prospective evaluation of the macroscopic types and location of early Barrett's neoplasia in 380 lesions. Endoscopy 2007; 39(7):588–93.
22. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. Available at: https://www.worldendo.org/wp-content/uploads/ 2016/03/ ParisClassification2000.pdf.
23. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37(6):570–8.
24. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20(1):1–19.
25. Peters FP, Brakenhoff KPM, Curvers WL, et al. Histologic evaluation of resection specimens obtained at 293 endoscopic resections in Barrett's esophagus. Gastrointest Endosc 2008;67(4):604–9.
26. Curvers WL, Bergman JJGHM. Multimodality imaging in Barrett's esophagus: looking longer, seeing better, and recognizing more. Gastroenterology 2008; 135(1):297–9.
27. Levine DS, Blount PL, Rudolph RE, et al. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. Am J Gastroenterol 2000; 95(5):1152–7.
28. Bergman JJ, Fockens P. Endoscopic ultrasonography in patients with gastroesophageal cancer. Eur J Ultrasound 1999;10(2–3):127–38.
29. Fockens P, Van den Brande JH, van Dullemen HM, et al. Endosonographic T-staging of esophageal carcinoma: a learning curve. Gastrointest Endosc 1996;44(1):58–62.
30. van Westreenen HL, Westerterp M, Sloof GW, et al. Limited additional value of positron emission tomography in staging oesophageal cancer. Br J Surg 2007; 94(12):1515–20.
31. Noble F, Bailey D, SWCIS Upper Gastrointestinal Tumour Panel, et al. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. Clin Radiol 2009 Jul;64(7):699–705.
32. Cuellar SLB, Carter BW, Macapinlac HA, et al. Clinical staging of patients with early esophageal adenocarcinoma: does FDG-PET/CT have a role? J Thorac Oncol 2014;9(8):1202–6.
33. Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007;65(1):3–10.

34. Behrens A, May A, Gossner L, et al. Curative treatment for high-grade intraepithelial neoplasia in Barrett's esophagus. Endoscopy 2005;37(10):999–1005.

35. Larghi A, Lightdale CJ, Ross AS, et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. Endoscopy 2007;39(12):1086–91.

36. Pouw RE, van Vilsteren FGI, Peters FP, et al. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. Gastrointest Endosc 2011;74(1):35–43.

37. Terheggen G, Horn EM, Vieth M, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut 2017;66(5):783–93.

38. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47(9):829–54.

39. Bourke MJ, Neuhaus H, Bergman JJ. Endoscopic submucosal dissection: indications and application in Western endoscopy practice. Gastroenterology 2018; 154(7):1887–900.e5.

40. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47(2):251–5.

41. Alvarez Herrero L, Pouw RE, van Vilsteren FGI, et al. Safety and efficacy of multiband mucosectomy in 1060 resections in Barrett's esophagus. Endoscopy 2011; 43(3):177–83.

42. Pouw RE, Beyna T, Belghazi K, et al. A prospective multicenter study using a new multiband mucosectomy device for endoscopic resection of early neoplasia in Barrett's esophagus. Gastrointest Endosc 2018;88(4):647–54.

SUPPLEMENTARY MATERIAL

To access the video material accompanying this article, visit the online version at www.giendo.theclinics.com, and at https://doi.org/10.1016/j.giec.2020.09.001.

CHAPTER 2

Radiofrequency Ablation of Barrett's Epithelium

E.A. Nieuwenhuis, J.J.G.H.M. Bergman, R.E. Pouw

Gastrointestinal and Pancreatico-Biliary Diseases: Advanced Diagnostic and Therapeutic Endoscopy. Springer, Cham. https://doi.org/10.1007/978-3-030-56993-8_6

ABSTRACT

Radiofrequency ablation (RFA) is an endoscopic treatment modality for Barrett's esophagus (BE). RFA has proven safe and highly effective for endoscopic eradication of Barrett's mucosa containing dysplasia and for residual Barrett's mucosa after focal endoscopic resection (ER) of visible lesions. This endoscopic treatment strategy is standard of care for Barrett's associated early neoplasia in all current guidelines. This chapter will evaluate the use of circumferential and focal RFA for the treatment of BE. The indications and technical aspects will be discussed, and we will review follow-up intervals after successful treatment with RFA. In addition, we will discuss the efficacy and safety outcomes of RFA.

INTRODUCTION

Barrett's esophagus (BE) is defined as a metaplastic change of the esophageal lining, with replacement of the squamous epithelium by an intestinal-type epithelium. The condition develops as a consequence of long-standing gastroesophageal reflux disease and may lead to neoplastic progression through the sequence of no dysplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and eventually early esophageal adenocarcinoma (EAC) [1, 2]. BE patients have a 30 to 40-fold higher risk of EAC compared to the general population [3].

In the past, the management of HGD and EAC arising in BE consisted of surgical esophagectomy, associated with high morbidity (up to 65%) and mortality rates even in high-volume centers (2–4%) [4]. Therefore, much research has focused on endoscopic imaging to detect EAC at an early stage and on endoscopic treatment techniques to develop less invasive endoscopic treatment modalities for early BE related neoplasia.

In the past two decades, minimally invasive endoscopic resection (ER) has replaced surgical esophagectomy as first-choice therapy for the treatment of early neoplastic lesions in Barrett's esophagus. ER provides adequate tissue specimens, allowing for accurate histopathological staging of a lesion, by the assessment of invasion depth, differentiation grade, presence of lymphovascular invasion, and radicality of the resection. Endoscopic resection thus similarly fulfills a diagnostic and therapeutic role in the management of Barrett's neoplasia [5, 6].

After ER of a neoplastic lesion within a BE, the residual Barrett's mucosa remains at risk for developing malignant metachronous lesions. This risk is thought to be 30% within 3 years of follow-up [6,7]. Therefore, endoscopic treatment of the complete Barrett's segment after focal removal of neoplasia is advised, preferably using radiofrequency ablation (RFA) [8–10]. Also, for flat-type BE harboring LGD or HGD without visible lesions requiring ER, RFA is advised to prevent progression to cancer.

Before RFA became the preferred ablation technique for dysplastic BE and residual BE mucosa after focal ER, other techniques have been studied for this purpose, such as photodynamic therapy (PDT), stepwise radical endoscopic resection (SRER) of the whole BE, and argon plasma coagulation (APC). PDT showed disappointing results. Most patients had residual IM, and it did not seem to prevent recurrence during follow-up. Furthermore, it was associated with photosensitivity as an unpleasant side effect [11]. SRER proved to be highly effective in the eradication of the residual BE segment with eradication rates up to 98% for neoplasia and 85% for IM. However, SRER was

associated with a high rate of symptomatic stenosis in more than 50% of patients [12]. The effectiveness of APC has shown to be variable. In a number of published studies, complete eradication of BE by treatment with APC varied widely, between 38% and 98.6% [13].

In 2005, RFA became available as a new treatment modality. RFA has proven safe and highly effective for endoscopic eradication of Barrett's with dysplasia and for residual BE mucosa after focal ER. RFA results in complete eradication rates of dysplasia and intestinal metaplasia in 80–100% and 54–100% of patients, respectively, with a complication rate less than 10% [5, 14–26]. Therefore, RFA is considered the treatment of choice for the eradication of flat dysplastic BE or residual BE after ER of visible lesions [9, 10, 27].

INDICATIONS FOR RADIOFREQUENCY ABLATION

Barrett's Esophagus with Macroscopically Visible Neoplastic Lesions

Patients with a macroscopically visible neoplastic lesion in their Barrett's segment may be treated with RFA but only after endoscopic resection of all visible abnormalities to allow for accurate histological staging. If the ER specimen confirms that the neoplasia is confined to the mucosa (LGD, HGD, T1a), and in case if cancer shows good-to-moderate differentiation, without signs of lymphovascular invasion, and if the lesion is radically resected with tumor-free vertical margins, the patient is suited for further endoscopic management. Several studies have shown that the risk of lymph node involvement is minimal (1%) in these patients [28, 29]. In the last couple of years, the indication for endoscopic therapy has extended to tumors invading the submucosa but with low-risk characteristics, since the risk of lymph node metastasis in this groups also is very low (<2%) [30, 31]. These characteristics are maximum tumor invasion depth into the submucosa of <500μm, good-to- moderate differentiation, no lymphovascular invasion, and negative vertical resection margins (R0)). In patients with high-risk submucosal cancer (i.e., invasion depth into the submucosa ≥500 μm, and/or poor differentiation, and/or presence of lymphovascular invasion), the risk of lymph node metastasis is thought to be much higher (16–44%) [31–33]. These numbers are mainly based on old surgical series. Recently, however, a number of studies including endoscopically treated patients with T1b cancer were published indicating that the risk of lymph node metastasis may be lower than generally assumed. Endoscopic management after endoscopic resection of a high-risk T1b cancer is not advised by current guidelines; however, in selected patients a strict endoscopic follow-up protocol with regular endoscopic and endosonographic follow-up to detect lymph node metastases at a curable stage can be considered [31, 34, 35].

Next to removing and staging neoplastic lesions, ER of visible lesions is also required to render the mucosa flat for subsequent ablation therapy, ensuring that the RF energy can reach until the muscularis mucosae.

As described previously, additional RFA of all remaining Barrett's tissue after focal ER of neoplasia is currently advised to prevent the development of metachronous lesions in the residual Barrett's mucosa after ER. The chance of developing such a lesion is approximately 11–30% in 3 years [6,7], although these numbers include synchronous neoplasia and the true risk of metachronous lesions may be lower.

Barrett's Esophagus with Flat High-Grade Dysplasia

Since HGD is a serious risk factor for the development of cancer (19% progression within 1 year), this is a strong indication for treatment. Several studies showed that RFA is a highly effective and safe treatment method to eradicate high-grade dysplasia and thus to prevent progression to cancer. Nevertheless, proper patient selection and adequate endoscopic work-up are necessary to ensure that only patients with true flat HGD are being treated with RFA monotherapy, without prior ER [22].

Barrett's with Low-Grade Dysplasia

If LGD in BE is confirmed by an expert pathologist, the risk of progression to HGD/EAC is 9.1% per patient-year. However, if the LGD is downstaged to NDBE or indefinite for dysplasia, the risk of malignant progression is much lower with 0.6% and 0.9% per patient-year, respectively [36]. This knowledge led to a number of studies evaluating if RFA could result in a decrease of progression to HGD/EAC compared to endoscopic surveillance. A prospective randomized trial from Europe demonstrated that RFA in patients with confirmed LGD resulted in a 25% absolute risk reduction of progressing to HGD/EAC when compared to surveillance (1.5% in the RFA group vs. 26.5% in the surveillance group) after a median follow-up of 36 months [14]. Another randomized, sham-controlled, study from the USA showed progression from LGD to HGD in 5% in the RFA group and in 14% in the sham group after 1 month (RR 0.3, 95% CI 0.1–1.9) [22]. A retrospective study performed in routine clinical practice in the USA, comparing progression rates in BE patients with LGD treated with RFA versus patients kept under surveillance, showed annual rates of progression to HGD or EAC of 6.6% in the surveillance group and 0.77% in the RFA group [37].

The abovementioned literature suggests that a consensus diagnosis of LGD by an expert pathologist correlates with a significant risk of progression and that RFA significantly reduces this risk.

In the European study, however, the diagnosis of LGD was not reconfirmed in 28% of patients in the surveillance arm during follow-up [14]. To avoid over-treatment with RFA, current Barrett's esophagus guidelines advise to consider RFA as alternative to surveillance in patients with a confirmed and repeated diagnosis of LGD. Factors that might influence the decision whether or not to perform RFA for confirmed LGD include patient's age, comorbidity, pre-existing fibrosis or stenosis of the esophagus, and patient's preference [38].

Non-dysplastic Barrett's Esophagus

Whether to offer RFA treatment to patients with non-dysplastic BE is controversial since the annual risk of progression to EAC is low, estimated at about 0.3% per year [39]. Unfortunately, there are no objective markers available yet to identify patients with an increased risk of progression. In addition, the majority of BE patients are elderly with significant comorbidities and limited life expectancy. Therefore, BE guidelines agree that ablative therapy cannot be recommended in patients with non- dysplastic BE. On average, the health benefit of RFA may be too low to give a justification for its use. Whether RFA could be offered to patients with BE diagnosis at a young age (<50 years old), a positive family history of esophageal adenocarcinoma or a very long Barrett's segment is unclear and is yet to be decided per case.

ABLATION PROCEDURES AND TECHNICAL ASPECTS

RFA commonly starts with circumferential ablation of the Barrett's segment, followed by focal ablation to treat the residual Barrett's mucosa. Next to the Barrx FLEX generator, a number of distinct ablation catheters are available: Barrx360 Express for circumferential RFA and the Barrx90, Barrx Ultra Long, Barrx60, and Channel RFA device to treat smaller areas with focal ablation. The ablation catheters contain bipolar electrodes, which are tightly spaced (250 μm) and deliver controlled radiofrequency pulses to the esophageal wall at a preset energy setting, power density, and time, allowing a uniform ablation depth into the mucosal layer of the esophagus, causing thermal injury and destruction of tissue. Since RFA at the right settings only penetrates the mucosa, the risk of developing an esophageal stenosis due to damage to and subsequent scarring of the submucosa is limited [19].

Circumferential Ablation

In the past couple of years, the Barrx360 balloon catheter was widely used to perform circumferential ablation of the BE segment. Performing RFA with the Barrx360 device consisted of esophageal sizing with a sizing catheter, followed by selection of an ablation catheter with an appropriate diameter, and then ablation treatment.

Recently, the Barrx360 system was replaced by the Barrx360 Express system, which consists of a self-sizing balloon catheter that is adjustable to the esophageal inner diameter.

Indications for circumferential RFA are:

- Presence of flat dysplastic circumferential BE ≥2 cm in length.
- Presence of residual circumferential BE ≥2 cm in length after prior ER for a visible lesion.
- In case of multiple BE islands or tongues.

The balloon catheter of the Barrx360 Express contains a 4-cm-long bipolar electrode, which is wrapped around an inflatable self-sizing balloon. The device features the ability to self-adjust to the esophageal lumen, which leads to a couple of advantages. First, the sizing step is no longer necessary, which reduces the number of intubations with the endoscope. This may be more comfortable for the patient. Second, the balloon is self-sized at each ablation zone, which may allow for more uniform ablation and reduces the impact of varying esophageal inner diameter. In addition, due to the 1 cm extra length compared to the older Barrx360 catheter, a potentially longer BE-segment can be treated with fewer ablations.

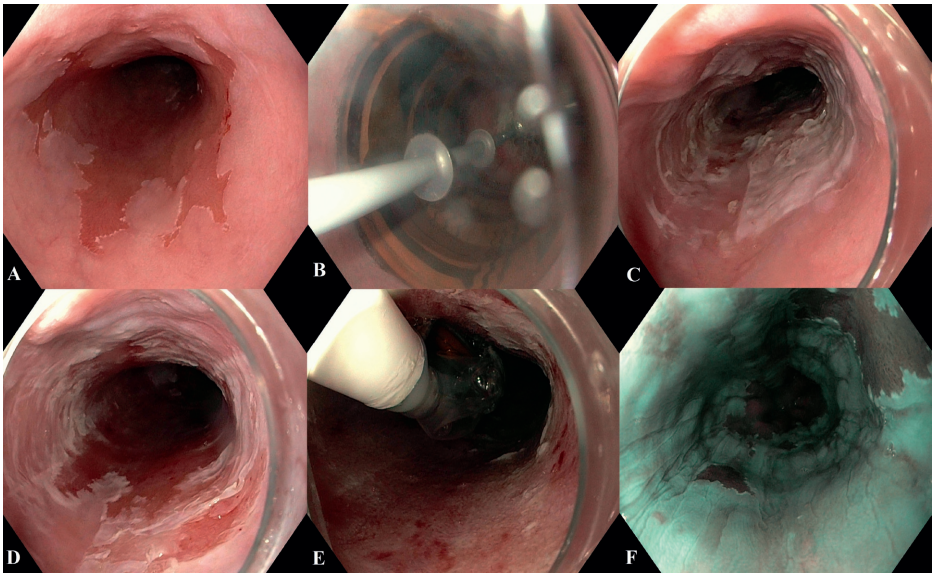
In a randomized trial, three different ablation regimens for the Barrx360 Express were prospectively evaluated [40]. Patients were randomly assigned to the standard (1x10J/cm2-clean-1x10J/cm2), simple-double (2x10J/cm2-no-clean), or simple-single ablation regimen (1x10J/cm2-no-clean). The primary outcome was endoscopically visible BE regression (%). Secondary outcomes were procedure time, adverse events, and patients' discomfort. The simple-double ablation arm was closed pre- maturely because of a 21% stenosis rate, where after the trial continued with the standard and simple-single arm. Performing circumferential RFA with the Barrx360 Express using the simple-single regimen resulted in inferior BE regression at 3 months compared to the standard regimen (simple-single arm 73% vs. 85% in the standard arm (mean difference 13% (95% CI, 5–23%)). Although the procedure time was significantly longer in the standard arm (31 vs. 17 min, $p < 0.001$), using the standard ablation regimen was advised for the treatment of BE using the Barrx360 Express. This standard regimen is as follows (Fig. 1):

- Circumferential RFA starts with cleaning of the esophageal wall. Previously, the cleaning was performed by using 1% acetylcysteine and flushing with water to

remove excessive mucus, but a randomized trial suggested that just rinsing with water is sufficient [41].

- A stiff guidewire is introduced, and the endoscope is removed. Hereafter, the Barrx360 Express catheter is introduced over the guidewire, followed by the endoscope.
- Under endoscopic visualization, the balloon is positioned at the proximal end of the Barrett's segment allowing 1–2 cm overlap with the normal squamous esophageal tissue. The catheter is inflated by pressing the foot pedal, and once adequate mucosal contact is made, the foot pedal can be used to activate the electrode and ablate the mucosa. After the ablation, the balloon deflates and curls up again so it can be moved distally. The catheter is repositioned distal from the prior ablation zone, allowing an overlap of ±5 mm with the previous ablation zone, and a subsequent ablation can be performed. This way, working from proximal to distal, the entire Barrett's segment can be ablated.

Figure 1. Endoscopic images of primary circumferential ablation using the Barrx360 Express system



(A) C8M9 Barrett's segment after prior endoscopic resection for early adenocarcinoma; (B) the Barrx360 Express catheter is introduced and inflated at the proximal end of the Barrett's segment; (C) whitish coagulum resulting from the first ablation pass (10 J/cm2); (D) after the first ablation pass and cleaning of the ablation zone, most of the coagulum is removed; (E), after cleaning the ablation zone, the catheter is reintroduced for a second ablation pass. The second pass results in a tan colored ablation zone; F, treatment effect 4 months after the first circumferential RFA treatment using the Barrx360 Express system. Regression of Barrett's epithelium was estimated to be 80%.

- As discussed above, a regimen with two subsequent ablations was found to result in an unacceptable high risk of severe esophageal strictures. It is thus advised to treat the whole BE segment from proximal to distal once and then to repeat this a second time. The cleaning step in between the two ablations passes is necessary to remove the coagulated tissue. Without this cleaning step, it is impossible to distinguish the edges of the ablation zone made during the second pass. These edges need to be identified for correct replacement of the ablation catheter when moving from proximal to distal, to avoid unnecessary overlap. For this cleaning step, the endoscope and balloon catheter are removed from the patient after the first ablation pass. The balloon can then be cleaned outside the patient with a wet gauze. The endoscope, with a distal attachment cap at its tip, is reintroduced to clean the esophageal wall by rinsing water and scraping off the coagulum using the rim of the cap. Then, the guidewire is reintroduced, the endoscope removed, the catheter reintroduced, and then followed by reintroduction of the endoscope, after which a second ablation pass moving from proximal to distal is performed.
- After the second ablation pass, the catheter and endoscope can be removed, and the procedure is finished. No additional cleaning of the esophagus is required.

Approximately 3 months after the first circumferential ablation treatment, patients undergo follow-up endoscopy. Additional circumferential RFA is performed in case of residual circumferential BE ≥2 cm in length or in case there are still multiple islands or long tongues of BE. In case the residual BE segment measures <2 cm, the presence of small BE tongues, scattered BE islands, or circular treatment of the gastroesophageal junction, focal ablation using a focal ablation catheter (mostly the Barrx90) is performed.

Focal ablation

The Barrx90 device is used to ablate smaller areas of BE and is an "over-the-scope device." It consists of an electrode array (20 mm x 13 mm) that is attached to the tip of the endoscope using a flexible strap. The electrode is assembled on a platform allowing the device to move front, back, right, and left, ensuring optimal tissue contact. Focal ablation with the Barrx90 catheter is performed as follows (Fig. 2):

- The endoscope is introduced after the electrode is placed on its tip at the 12 o'clock position in the endoscopic view.
- Focal ablation should be started distal at the gastroesophageal junction, since this is the area most at risk for neoplastic recurrence and since endoscopic differentiation of residual Barrett's mucosa from the cardia mucosa is impossible [42]. This area should therefore be treated at least once using the focal ablation catheter. The whole circumference of the junction should be ablated by repositioning the electrode after

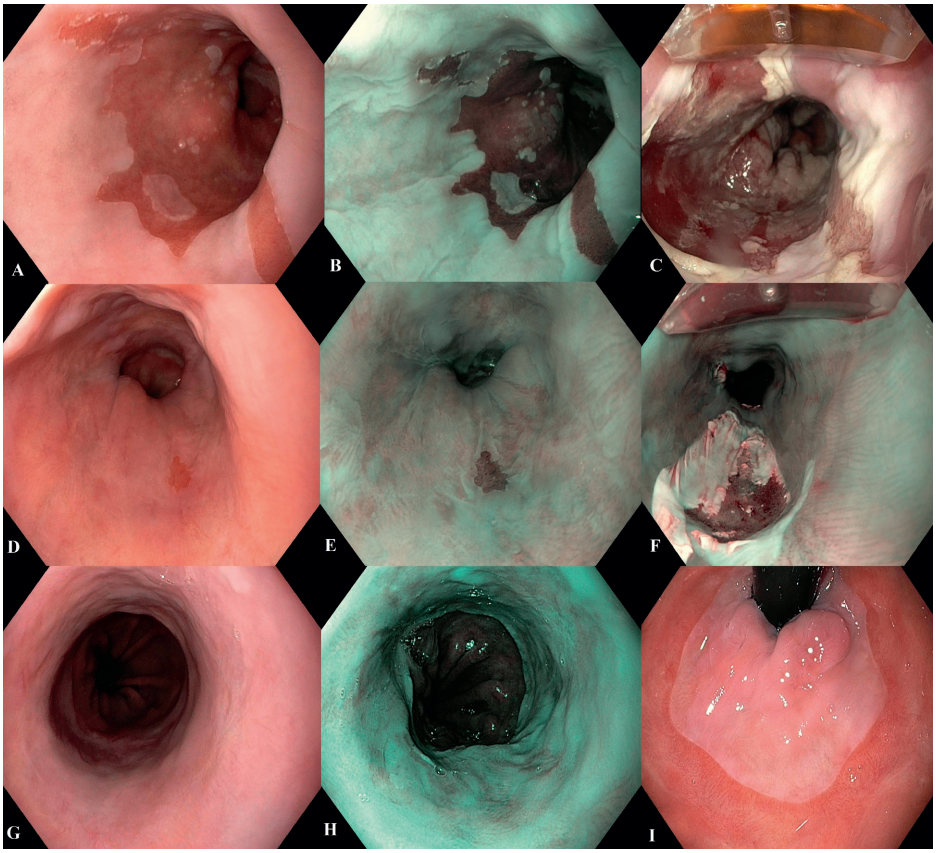
each ablation, using a torqueing maneuver. A small overlap between ablation zones is allowed.

- After ablation of the gastroesophageal junction, the catheter can be moved proximally to ablate residual tongues of islands of Barrett's mucosa. Since the distal end of the catheter is within the endoscopic view (the proximal end is located on the endoscope shaft), moving from distal to proximal allows for optimal endoscopic repositioning of the electrode.
- The advised ablation regimen for focal RFA is to perform three subsequent ablations at 12 J/cm2, without the need for cleaning the ablation zone or electrode. This regimen is based on a multicenter randomized non-inferiority trial comparing this simplified regimen to a double-double regimen at 15 J/cm2, with a cleaning step in between ablations. The study showed that the 3 x 12J/cm2 regimen was non-inferior to the 2 x 15J/cm2-clean-2 x 15J/cm2 regimen and did not result in more complications.

Three alternative focal ablation devices are available for focal ablation of Barrett's mucosa, the Barrx Ultra Long catheter, the Barrx60 catheter, and the Channel RFA device. The latter is a "through-the-scope" device instead of an "over-the-scope" device. None of these catheters have yet been evaluated in clinical studies; therefore, the use of these catheters is based on previous experiences with the Barrx90 device. The Barrx Ultra Long device has an electrode array of 40 mm long and 13 mm wide, resulting in a 200% larger electrode surface area as compared with the Barrx90 device. The device can be used if there are large tongues of residual Barrett's. The Barrx60 device has an electrode surface area of 60% of the surface area of the Barrx90 device and is used in patients with small islands of Barrett's mucosa in the presence of a stenosis. The RFA channel device fits through the working channel of an endoscope with a recommended diameter of 2.8 mm or larger and has the same active electrode surface area as the Barrx60 device.

Ablation can be repeated every 12 weeks until all Barrett's mucosa has been eradicated both visually and histologically. A maximum number of two circumferential and three focal ablation sessions are advisable and in most cases also sufficient to achieve complete eradication. In case of detection of small residual Barrett's islands (<5 mm), these can be treated with argon plasma coagulation (APC). In case of larger areas of residual BE mucosa, or in case of visible lesions arising during the treatment period, endoscopic resection can safely be performed as an escape treatment after RFA [43].

Figure 2. Endoscopic images of a focal ablation procedure using the Barrx90 system.



(A) Antegrade view of an esophagus after prior endoscopic resection for early adenocarcinoma in a C0M3 Barrett's esophagus; (B) corresponding image with narrowband imaging; (C) ablation effect immediately after ablation with the Barrx90 system (three times 12 J/cm2 without cleaning). The distal end of the catheter is visible at the 12 o'clock position in the endoscopic view; (D) ablation effect 3 months after the first focal RFA treatment. Residual island at 6 o'clock; (E) corresponding image with narrowband imaging; (F) ablation effect immediately after the second focal RFA treatment of the neo-squamocolumnar junction and the residual island; (G) again 3 months later, no residual Barrett's mucosa is seen, and the esophagus is regenerated with neosquamous epithelium; (H), corresponding image with narrowband imaging; (I) View of cardia and neo-squamocolumnar junction in the retroflexed position.

POST-TREATMENT MANAGEMENT

Two studies have investigated the association between acid-suppressive therapy and efficacy of radiofrequency ablation. Both studies showed that acidic reflux increased the risk of persisting IM after RFA in patients with BE [44, 45]. Besides, acid- suppressive therapy contributes to patient comfort. Therefore, it is important that all patients

receive high-dose proton pump inhibitors (PPI) as maintenance therapy. Furthermore, extra acid suppression next to the PPI after each ablation session is advisable, for example, sucralfate suspension for 2 weeks.

Adherence to a liquid diet until 24h after RFA is advisable, after which the diet can gradually be advanced to a soft and then a normal diet guided by the patients' symptoms. The most common symptoms after RFA are nausea, chest discomfort, sore throat, and pain with swallowing. If necessary, patients can use painkillers such as acetaminophen or if necessary NSAID suppositories and/or antiemetic.

Follow-up after endoscopic eradication therapy

Twelve weeks after the last RFA treatment, the absence of residual Barrett's mucosa is confirmed by endoscopic inspection. If no residual Barrett's epithelium is detected, biopsies from just distal (<5 mm) to the neo-squamocolumnar junction are obtained to evaluate for residual IM. In case IM is found, focal ablation of this area can be performed once more in case the maximum advised amount of ablation sessions is not reached yet. Obtaining biopsies from the junction remains important, since the risk for recurrence in this area is high [46–48]. Furthermore, there are no endoscopic techniques to help the endoscopist differentiate between gastric mucosa and IM. Limited data are available on the clinical relevance of recurrent IM at the level of the squamocolumnar junction. It may reflect insufficient treatment or recurrent disease, or it is an irrelevant finding. For now, the biopsies just distal to the neo-squamocolumnar junction are used as an objective endpoint for complete eradication of Barrett's mucosa. Furthermore, these biopsies could be helpful during further follow-up to detect recurrent disease in hospitals less experienced in following these patients. However, the cornerstone of endoscopic follow-up should consist of careful endoscopic inspection of the neosquamous epithelium and the neo-squamocolumnar junction to rule out the presence of residual or recurrent Barrett's epithelium or neoplasia. The techniques used for inspection are high-definition white light endoscopy (WLE) and narrowband imaging (NBI) (or comparable imaging technologies such as FICE and i-scan).

The need to perform strict endoscopic follow-up after complete eradication is still unclear, because sufficient long-term follow-up data is lacking. On the other hand, studies showed that over 90% of patients remain free of dysplasia after successful ablation therapy [20].

Since clear data is absent, follow-up intervals and methods after endoscopic therapy are based on expert opinion and may differ between international guidelines. Advised follow-up intervals depend on the initial grade of dysplasia:

- In the Netherlands, patients who were treated for HGD or EAC and reached complete eradication of dysplasia and IM undergo follow-up endoscopy annually during the first 5 years of follow-up. If there is sustained eradication, surveillance can be stopped or continued every 2–3 years, depending on the patient's age, comorbidity, and patient's preference [8]. Others perform follow-up endoscopies every 3 months during the first year after successful treatment and annually thereafter [9], while yet others again increase the interval more gradually by performing two endoscopies during the second year [10, 49].
- Follow-up strategies for patients who were treated for LGD and achieved complete eradication vary as well. In the Netherlands, these patients undergo follow-up endoscopy at 1 year and 3 years after treatment. If there is sustained eradication of IM at that point, follow-up will be stopped because the risk of progression seems to be low in these patients [20]. Other guidelines suggest to perform follow-up every year for 2 years and every 3 years thereafter [10] or to perform follow-up twice in the first year and annually thereafter [49].

In case of persisting intestinal metaplasia with or without dysplasia after treatment, it may be decided to further follow the patient endoscopically. Intervals should depend on histological outcome and should be considered on a case-by-case basis.

Hence, future studies should focus on optimal follow-up intervals and biopsy strategies after successful endoscopic eradication of BE with dysplasia.

EFFICACY OUTCOMES OF RADIOFREQUENCY ABLATION

Short-term and long-term outcomes

Several studies have shown that RFA is a highly effective and safe treatment modality for the eradication of all Barrett's mucosa, endoscopically as well as histologically. These studies report the rates of complete eradication of IM (CE- IM) of 54–100% and complete eradication of dysplasia (CE-D) of 80–100% [5, 14– 26]. The prospective studies using a strict treatment protocol of prior ER of any visible lesions, a combination of circumferential and focal RFA and standard RFA treatment of the gastroesophageal junction, demonstrate higher eradication rates than retrospective studies without a clear treatment protocol.

The limited 5-year follow-up data that is available also show diverging results for long-term efficacy of RFA.

In 2013, a cohort study from the Netherlands followed 54 patients with HGD and/ or EAC who were treated with RFA every 3 months with or without a prior endoscopic resection. When complete eradication was achieved, patients underwent follow-up endoscopies at 6 months, 12 months, and annually thereafter during 5 years. The results showed sustained complete eradication of neoplasia and IM in 90% of patients. All recurrences were managed endoscopically [17].

In a US study treating non-dysplastic BE patients with RFA, CR-IM was achieved in 98% of patients. At 5-year follow-up, CR-IM was maintained in the majority of patients (92%). 8% of patients showed recurrent NDBE. Focal RFA converted all these to CR-IM. None of the patients showed progression to dysplastic disease [50]. In a cohort study using data from prospectively maintained databases of five (three USA and two UK) tertiary referral centers where RFA was performed for non- dysplastic BE or dysplastic BE, including standard treatment of the GEJ, RFA was performed until CR-IM was confirmed at two consecutive endoscopies at least 3 months apart, confirming the eradication of IM on biopsies from both the GEJ and tubular esophagus. The study aimed to assess the timeline, location, and patterns of recurrence following CR-IM. 594 patients achieved CR-IM after treatment, and the calculated cumulative recurrence risk of any BE within 2 years was 19%. 74% of BE recurrences developed at the GEJ, of which 24% were dysplastic [51].

Another study assessed the anatomic locations and histology of recurrences after successful endoscopic eradication therapy in a large multicenter database of 443 patients who reached CR-IM. Fifty patients (23%) had recurrent disease, of which 74% without dysplasia. Overall, 49 of 50 recurrences (98%) occurred either within 2 cm of the GEJ or at the site of a visible lesion. Moreover, late recurrences (>1 year after treatment) were more likely to be visible than early recurrences (<1 year). In this study, there was variation in endoscopic treatment techniques and surveillance protocols. It remains unclear whether standard treatment of the GEJ was performed. Furthermore, CR-IM was defined as eradication of IM on all surveillance biopsy samples in the tubular esophagus or at the GEJ, which implies that the definition of CR-IM did not include absence of IM in the GEJ. This could explain the relatively high recurrence rates [52].

Since the majority of recurrences in all studies were non-dysplastic, the clinical relevance remains unclear. Additional long-term data is lacking; thus, for stronger conclusions and potential widening of the follow-up intervals, more studies analyzing long-term outcomes of RFA for the treatment of Barrett's need to be performed.

ADVERSE EVENTS

The most common adverse events mentioned after RFA treatment include esophageal strictures, chest pain, and late bleeding (>48 h). Stricture rates up to 12% are reported, which can generally be resolved with endoscopic dilatation(s). Late bleedings are reported in a maximum 3% of patients. None of the studies reported a serious acute bleeding, perforation, or death. Thus, severe adverse events due to RFA treatment are very uncommon [5, 14, 16, 18, 21–26].

The extent of prior ER may be associated with an increased risk for adverse events, especially for stricture formation and mucosal laceration. In a study performed by Pouw et al. with 65 included patients, there were no complications in patients who did not previously undergo an ER. Five cases of stricture formation occurred; all in patients whose ER involved more than 50% of the circumference and was longer than 2 cm in length [5, 25].

CONCLUSION

RFA has proven to be effective and safe for patients with flat Barrett's containing dysplasia and for treatment of the residual Barrett's segment after endoscopic resection for early esophageal adenocarcinoma. Future perspectives may lie in biomarkers predicting which BE patients have an increased risk of progressing to HGD/EAC and may thus benefit from prophylactic RFA treatment. Furthermore, optimal follow-up frequency and intervals after successful RFA eradication therapy are yet to be determined. Considering the low risk of recurrence of mainly non-dysplastic BE mucosa after RFA, one may question the relevance of strict endoscopic follow-up and the long-term benefit on quality of life and life expectancy of such strict surveillance for patients.

REFERENCES

1. Spechler SJ, Souza RF (2014) Barrett's esophagus. N Engl J Med 371(8):36–45
2. Shaheen NJ, Richter JE (2009) Barrett' s oesophagus. Lancet [Internet] 373(9666):850–861. https://doi.org/10.1016/S0140-6736(09)60487-6
3. Solanky D, Krishnamoorthi R, Crews N, Johnson M, Wang K, Wolfsen H, et al. Low-grade Dysplasia are Predictive of Progression to Esophageal Adenocarcinoma. 2018; 00(00):1–5
4. Markar SR, Karthikesalingam A, Thrumurthy S, Low DE (2012) Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg 16(5):1055–1063
5. Pouw RE, Wirths K, Eisendrath P, Sondermeijer CM, Ten Kate FJ, Fockens P et al (2010) Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol. [Internet 8(1):23–29. https://doi.org/10.1016/j.cgh.2009.07.003
6. Peters FP, Kara MA, Rosmolen WD, Aalders MCG, Ten Kate FJW, Bultje BC et al (2005) Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. Gastrointest Endosc 61(4):506–514
7. May A, Gossner L, Pech O, Fritz A, Günter E, Mayer G et al (2002) Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. Eur J Gastroenterol Hepatol 14(10):1085–1091
8. Nederlandse Vereniging van Maag-Darm-Leverartsen (2018) Richtlijn Barrett-oesofagus
9. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang J-Y, Watson P et al (2014) British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 63(1):7–42
10. Association AG (2011) American gastroenterological association medical position statement on the management of Barrett'S esophagus. Gastroenterology. [Internet 140(3):1084–1091. https:// doi.org/10.1053/j.gastro.2011.01.030
11. Peters F, Kara M, Rosmolen W, Aalders M, Ten Kate F, Krishnadath K et al (2005) Poor results of 5-aminolevulinic acid-photodynamic therapy for residual high-grade dysplasia and early cancer in Barrett esophagus after endoscopic resection. Endoscopy 37(5):418–424
12. Belghazi K, van Vilsteren FGI, Weusten BLAM, Meijer SL, Bergman JJGHM, Pouw RE (2018) Long-term follow-up results of stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia. Gastrointest Endosc 87(1):77–84
13. Kahaleh M, Van Laethem J-L, Nagy N, Cremer M, Devière J (2002) Long-term follow-up and factors predictive of recurrence in Barrett's esophagus treated by argon plasma coagulation and acid suppression. Endoscopy 34(12):950–955
14. Phoa KN, van Vilsteren FGI, Weusten BLAM, Bisschops R, Schoon EJ, Ragunath K et al (2014) Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and Low-grade dysplasia. JAMA [Internet] 311(12):1209. https://doi.org/10.1001/jama.2014.2511

15. Gondrie JJ, Pouw RE, Sondermeijer CMT, Peters FP, Curvers WL, Rosmolen WD et al (2008) Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. Endoscopy 40(5):359–369
16. Kim HP, Bulsiewicz WJ, Cotton CC, Dellon ES, Spacek MB, Chen X et al (2012) Focal endoscopic mucosal resection before radiofrequency ablation is equally effective and safe compared with radiofrequency ablation alone for the eradication of Barrett's esophagus with advanced neoplasia. Gastrointest Endosc 76(4):733–739
17. Phoa KN, Pouw RE, Van Vilsteren FGI, Sondermeijer CMT, Ten Kate FJW, Visser M et al (2013) Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. Gastroenterology. [Internet 145 (1):96–104. https://doi.org/10.1053/j.gastro.2013.03.046
18. Fleischer DE, Overholt BF, Sharma VK, Reymunde A, Kimmey MB, Chuttani R et al (2008) Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. Gastrointest Endosc. [Internet 68(5):867–876. https://doi.org/10.1016/j.gie.2008.03.008
19. Ganz RA, Utley DS, Stern RA, Jackson J, Batts KP, Termin P (2004) Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus. Gastrointest Endosc 60(6):1002–1010
20. Orman ES, Li N, Shaheen NJ (2013) Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol 11 (10):1245–1255
21. Ganz RA, Overholt BF, Sharma VK, Fleischer DE, Shaheen NJ, Lightdale CJ et al (2008) Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicenter registry. Gastrointest Endosc 68(1):35–40
22. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK et al (2009) Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med [Internet] 360 (22):2277–2288. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19474425
23. Lyday W, Corbett FS, Kuperman DA, Kalvaria I, Mavrelis PG, Pruitt RE (2009) Endoscopic radiofrequency ablation of Barrett's esophagus: safety and efficacy outcomes in 429 patients treated in a multi-center community practice registry. Gastrointest Endosc 69(5):AB114
24. Haidry RJ, Butt MA, Dunn JM, Gupta A, Lipman G, Smart HL et al (2015) Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. Gut 64 (8):1192–1199
25. Phoa KN, Pouw RE, Bisschops R, Pech O, Ragunath K, Weusten BLAM et al (2016) Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut 65(4):555–562
26. Gondrie JJ, Pouw RE, Sondermeijer CMT, Peters FP, Curvers WL, Rosmolen WD et al (2008) Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. Endoscopy 40(5):370–379
27. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau J-M, Esteban J-M et al (2017) Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endos- copy (ESGE) position statement. Endoscopy [Internet] 49(02):191–198. https://doi.org/ 10.1055/s-0042-122140

28. Alvarez Herrero L, Pouw RE, van Vilsteren FG, ten Kate FJW, Visser M, van Berge Henegouwen MI et al (2010) Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 42(12):1030–1036

29. Pech O, May A, Manner H, Behrens A, Pohl J, Weferling M et al (2014) Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 146(3):652–660.e1

30. Manner H, May A, Pech O, Gossner L, Rabenstein T, Günter E et al (2008) Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 103(10):2589–2597

31. Schölvinck D, Künzli H, Meijer S, Seldenrijk K, van Berge Henegouwen M, Bergman J et al (2016) Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surg Endosc 30(9):4102–4113

32. Buskens CJ, Westerterp M, Lagarde SM, Bergman JJGHM, ten Kate FJW, van Lanschot JJB (2004) Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc 60(5):703– 710

33. Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJW, Bergman JJHGM et al (2005) Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro- esophageal junction. Virchows Arch 446(5):497–504

34. Manner H, Pech O, Heldmann Y, May A, Pauthner M, Lorenz D et al (2015) The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submu- cosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc 29(7):1888– 1896

35. Künzli HT, Belghazi K, Pouw RE, Meijer SL, Seldenrijk CA, Weusten B et al (2018) Endoscopic management and follow-up of patients with a submucosal esophageal adenocarci- noma. United Eur Gastroenterol J 6(5):669–677

36. Duits LC, Phoa KN, Curvers WL, Ten Kate FJW, Meijer GA, Seldenrijk CA et al (2015) Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut 64(5):700–706

37. Small AJ, Araujo JL, Leggett CL, Mendelson AH, Agarwalla A, Abrams JA et al (2015) Radiofrequency ablation is associated with decreased neoplastic progression in patients with Barrett's esophagus and confirmed Low-grade dysplasia. Gastroenterology 149(3):567–576. e3; quiz e13-4

38. Wani S, Rubenstein JH, Vieth M, Bergman J (2016) Diagnosis and Management of Low-Grade Dysplasia in Barrett's esophagus: expert review from the clinical practice updates Committee of the American Gastroenterological Association. Gastroenterology 151(5):822–835

39. Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S et al (2012) The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut 61 (7):970–976

40. Belghazi K, Pouw RE, Koch AD, Weusten BLAM, Schoon EJ, Curvers WL et al (2019) Self-sizing radiofrequency ablation balloon for eradication of Barrett's esophagus: results of an international multicenter randomized trial comparing 3 different treatment regimens. Gastrointest Endosc 90(3):415–423

41. van Vilsteren FGI, Phoa KN, Alvarez Herrero L, Pouw RE, Sondermeijer CMT, van Lijnschoten I et al (2013) Circumferential balloon-based radiofrequency ablation of Barrett's esophagus with dysplasia can be simplified, yet efficacy maintained, by omitting the cleaning phase. Clin Gastroenterol Hepatol 11(5):491–98.e1

42. Alvarez Herrero L, Curvers WL, Bisschops R, Kara MA, Schoon EJ, ten Kate FJW et al (2014) Narrow band imaging does not reliably predict residual intestinal metaplasia after radiofrequency ablation at the neo-squamo columnar junction. Endoscopy 46(2):98–104

43. Pouw RE, Gondrie JJ, Rygiel AM, Sondermeijer CM, ten Kate FJ, Odze RD et al (2009) Properties of the neosquamous epithelium after radiofrequency ablation of Barrett's esophagus containing neoplasia. Am J Gastroenterol 104(6):1366–1373

44. Akiyama J, Marcus SN, Triadafilopoulos G (2012) Effective intra-esophageal acid control is associated with improved radiofrequency ablation outcomes in Barrett's esophagus. Dig Dis Sci 57(10):2625–2632

45. Krishnan K, Pandolfino JE, Kahrilas PJ, Keefer L, Boris L, Komanduri S (2012) Increased risk for persistent intestinal metaplasia in patients with Barrett's esophagus and uncontrolled reflux exposure before radiofrequency ablation. Gastroenterology 143(3):576–581

46. Weston AP, Sharma P, Banerjee S, Mitreva D, Mathur S (2005) Visible endoscopic and histologic changes in the cardia, before and after complete Barrett's esophagus ablation. Gastrointest Endosc 61(4):515–521

47. Sampliner RE, Camargo E, Prasad AR (2006) Association of ablation of Barrett's esophagus with high grade dysplasia and adenocarcinoma of the gastric cardia. Dis esophagus Off J Int Soc Dis Esophagus 19(4):277–279

48. Pouw RE, Peters FP, Sempoux C, Piessevaux H, Deprez PH (2008) Stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia: report on a Brussels' cohort. Endoscopy 40(11):892–898

49. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG clinical guideline: diagnosis and Management of Barrett's esophagus. Am J Gastroenterol [Internet] 2016; 111(1):30–50. Available from: https://doi.org/10.1038/ajg.2015.322

50. Fleischer DE, Overholt BF, Sharma VK et al (2010) Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy 42:781

51. Sami SS, Ravindran A, Kahn A, Snyder D, Santiago J, Ortiz-Fernandez-Sordo J et al (2019) Timeline and location of recurrence following successful ablation in Barrett's oesophagus: an international multicentre study. Gut 68(8):1379–1385

52. Omar M, Thaker AM, Wani S, Simon V, Ezekwe E, Boniface M et al (2019) Anatomic location of Barrett's esophagus recurrence after endoscopic eradication therapy: development of a simplified surveillance biopsy strategy. Gastrointest Endosc 90(3):395–403

CHAPTER 3

Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period

Sanne van Munster, Esther Nieuwenhuis, Bas L A M Weusten, Lorenza Alvarez Herrero, Auke Bogte, Alaa Alkhalaf, Ed Schenk, Erik J Schoon, Wouter Curvers, Arjun D Koch, Steffi Elisabeth Maria van de Ven, Pieter Jan Floris de Jonge, Tjon J Tang, Wouter B Nagengast, Frans T M Peters, Jessie Westerhof, Martin H M G Houben, Jacques JGHM Bergman, Roos E Pouw

Gut. 2022 Feb;71(2):265-276. doi: 10.1136

ABSTRACT

Objective

Radiofrequency ablation (RFA) ± endoscopic resection (ER) is the preferred treatment for early neoplasia in Barrett's oesophagus (BE). We aimed to report short-term and long-term outcomes for all 1384 patients treated in the Netherlands (NL) from 2008 to 2018, with uniform treatment and follow-up (FU) in a centralised setting.

Design

Endoscopic therapy for early BE neoplasia in NL is centralised in nine expert centres with specifically trained endoscopists and pathologists that adhere to a joint protocol. Prospectively collected data are registered in a uniform database. Patients with low/high-grade dysplasia or low-risk cancer, were treated by ER of visible lesions followed by trimonthly RFA sessions of any residual BE until complete eradication of BE (CE-BE). Patients with ER alone were not included.

Results

After ER (62% of cases; 43% low-risk cancers) and median 1 circumferential and 2 focal RFA (p25-p75 0–1; 1–2) per patient, CE-BE was achieved in 94% (1270/1348). Adverse events occurred in 21% (268/1386), most commonly oesophageal stenosis (15%), all were managed endoscopically. A total of 1154 patients with CE-BE were analysed for long-term outcomes. During median 43 months (22–69) and 4 endoscopies (1–5), 38 patients developed dysplastic recurrence (3%, annual recurrence risk 1%), all were detected as endoscopically visible abnormalities. Random biopsies from a normal appearing cardia showed intestinal metaplasia (IM) in 14% and neoplasia in 0%. A finding of IM in the cardia was reproduced during further FU in only 33%, none progressed to neoplasia. Frequent FU visits in the first year of FU were not associated with recurrence risk.

Conclusion

In a setting of centralised care, RFA±ER is effective for eradication of Barrett's related neoplasia and has remarkably low rates of dysplastic recurrence. Our data support more lenient FU intervals, with emphasis on careful endoscopic inspection. Random biopsies from neosquamous epithelium and cardia are of questionable value.

INTRODUCTION

Endoscopic eradication treatment (EET) is an established treatment approach for eradicating Barrett's oesophagus (BE) with early neoplasia. EET is generally a multimodal treatment consisting of endoscopic resection (ER) in case of visible lesions, followed by eradication of the residual flat BE segment, to minimise the risk of metachronous dysplasia. For the latter, radiofrequency ablation (RFA) is the most commonly used technique. Current clinical guidelines unanimously recommend this effective and safe two-step approach as standard of care [1–3].

Landmark studies consistently report excellent efficacy, with complete eradication of all neoplasia as well as complete eradication of all BE in 74%–98% of patients [4–7]. However, the long-term durability remains poorly characterised. Some studies have reported long-term outcomes, but were limited by small sample size, heterogeneous treatment and follow-up (FU) protocols, and/or different definitions for recurrence. Consequently, reported rates for dysplastic recurrence vary widely from 1% to 20% per person year [4,5, 8–13].

EET for BE related dysplasia and early cancer in the Netherlands is uniquely organised, with centralisation of care in Barrett Expert Centers (BECs). All patients are referred to a BEC, where care is provided by experienced endoscopists and pathologists, all of whom participated in joint training programmes. All centres adhere to a joint treatment and FU protocol and difficult cases are discussed in regular interdisciplinary meetings. Data on treatment and outcomes of all patients treated in the BECs are registered in a uniform database. A joint research network has been established for studies in the field of pathology [14–17], imaging [18–20], and treatment [4, 5, 9, 21–26] for early BE neoplasia. The aim of the current study was to report the short-term and long- term outcomes for all patients treated for BE with dysplasia and/ or early cancer in the Netherlands, according to a uniform EET protocol including RFA.

METHODS

The BEC registry is an ongoing, multicentre initiative designed to establish outcomes of patients undergoing EET for early BE neoplasia in a setting of centralised care (Netherlands Trial Register, NL7039, online supplemental table S1). The registry includes data for all patients who underwent endoscopic treatment for early BE neoplasia in the Netherlands since 2008, when RFA was introduced into regular clinical practice. The Dutch patient federation for cancer of the digestive tract ('Stichting voor patiënten met kanker aan het spijsverteringskanaal') was involved in the design, reporting and dissemination plans of our study.

Study population

For the current study, all patients with BE and confirmed low-grade dysplasia (LGD), high-grade dysplasia (HGD) or low-risk oesophageal adenocarcinoma (LR EAC) (mucosal or superficial submucosal (sm1) cancer, well to moderately differentiated, without lymphovascular invasion, no tumour invasion (R0) in the vertical resection margin), who underwent at least 1 RFA treatment between 1 January 2008 and 31 December 2018, were included in the 'RFA treatment cohort' (figure 1). Non-dysplastic Barrett's oesophagus (NDBE) is not an accepted indication for RFA in our country and these patients were not included in our cohort.

The 'RFA durability cohort' (figure 1) was defined as all patients with successful EET, defined as complete endoscopic eradication of BE (CE-BE), with at least 1-year FU at the moment of data collection.

We excluded 255 cases (figure 1) with high-risk EAC in their ER specimen (i.e., deep submucosal invasion (sm2-3), poor differentiation, lymphovascular invasion or invasion of cancer (R1) in the vertical resection margin).

We also excluded cases (n=94; figure 1) in whom—after the ER—no further attempts were at CE-BE for various reasons, mainly limited life expectancy [27]. Finally, we excluded 224 patients (figure 1) in whom other techniques than RFA were used to achieve CE-BE, either stepwise radical endoscopic resec- tion (SRER; n=149), hybrid-APC (n=43), endorotor (n=20), cryoballoon ablation (n=9) or other techniques (n=3).

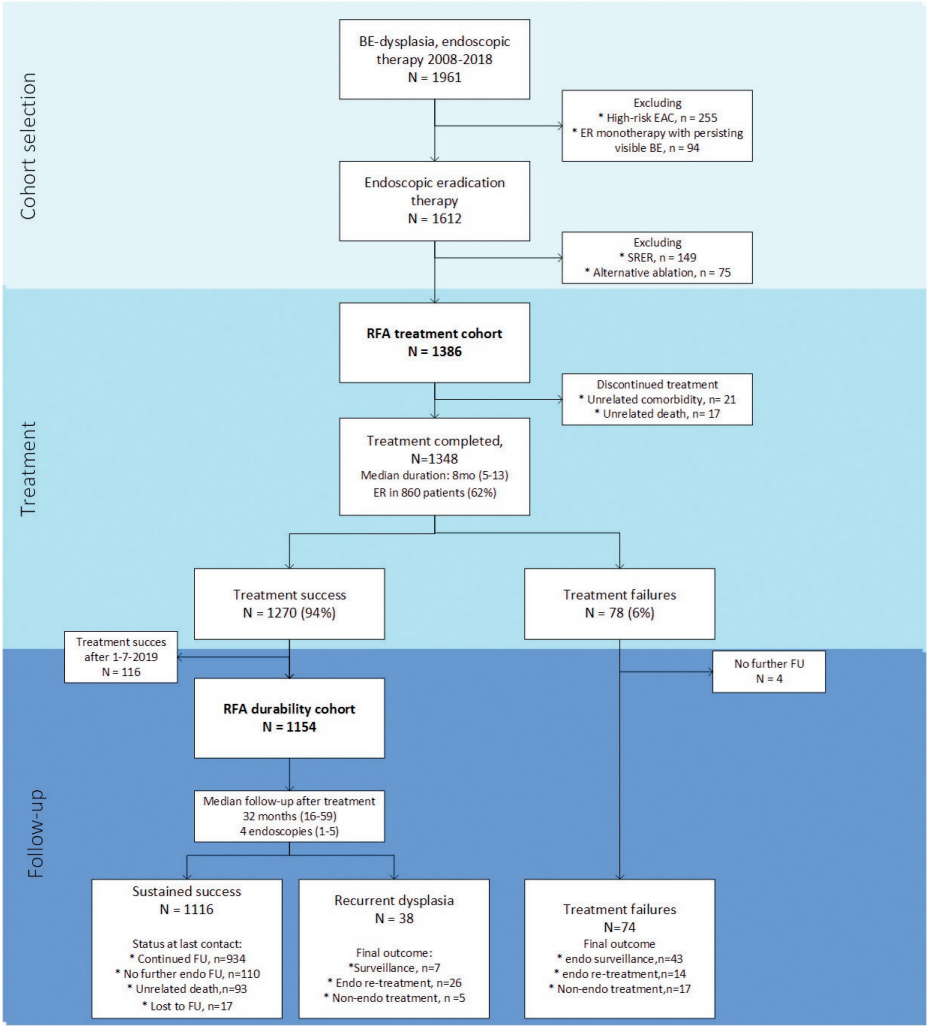
Part of the patients included in the current study have been treated in context of a prospective clinical trial and were there- fore mentioned in prior published work [4, 5, 9, 24, 28, 29].

Treatment protocol

Patients who were referred with histologically confirmed LGD, HGD or LR-EAC underwent a dedicated imaging endoscopy using high-definition endoscopy. The oesophagus was carefully inspected with documentation of the Prague C&M criteria [30], presence of visible lesions or other abnormalities such as oesophagitis or stenosis. Visible lesions were removed with ER, per default using cap-based ER and endoscopic submucosal dissection was used for special indications, that is, bulky lesions that could not be sucked in the ER cap, or lesions with a suspicion of submucosal invasion. Patients with limited life expectancy underwent ER monotherapy and no RFA, with surveillance of the remaining BE segment. For all other patients, RFA (Barrx system, Medtronic, Minneapolis, Minnesota, USA) was performed at 3–4 month intervals to eradicate flat

BE as described previously [4] (figure 2). Touch-up treatment for any residual flat, non-neoplastic BE areas that persisted after RFA treatment (including at least 1 focal RFA of the GE-junction) was allowed, using ER (for areas>5 mm) or a maximum of two APC sessions for areas <5 mm. If biopsies from the GE-junction showed persisting IM after RFA, one additional focal RFA of the GE junction was allowed. Residual BE could also be kept under endoscopic surveillance, at the discretion of the endoscopist.

Figure 1. Patient flow



BE, Barrett's oesophagus; EAC, oesophageal adenocarcinoma; ER, endoscopic resection; FU, follow-up; RFA, radiofrequency ablation; SRER, stepwise radical endoscopic resection.

When complete endoscopic eradication of all visible BE was achieved, the oesophagus was sampled to confirm eradication of IM. Initially, biopsies were obtained from neosquamous epithelium (NSE) over the length of the initial BE segment (4 quadrants every 2 cm) and from the cardia (ie, <5 mm distally from the neosquamocolumnar junction). From 2013, the NSE biopsies were abandoned due to low diagnostic yield and emerging evidence that adequate endoscopic inspection provided more clinically relevant information than random NSE biopsies [31].

Follow-up protocol

Endoscopic FU consisted of high-definition endoscopy with optical chromoendoscopy, with changing intervals and sampling methods over time. Initially, FU endoscopies were performed every 3 months in the first year, followed by annual endoscopies in years 2–5, and then one endoscopy in every 2–3 years. However, from 2015, we abandoned the quarterly endoscopies in the first year, due to low yield of clinically relevant findings.

From 2008 till 2013, 4 quadrant random biopsies were obtained from the entire NSE at 2 cm intervals and from the cardia during every FU endoscopy. In 2013, we abandoned the NSE biopsies and in 2016 we abandoned the random biopsies from the cardia, due to low yield of clinically relevant findings. Residual BE including an irregular Z-line, visible lesions, or other abnormalities always remained an indication for histological sampling.

Treatment for recurrent non-dysplastic BE was per endoscopist's discretion and based on the estimated risk for progression, and a patient's age and comorbidity. Recurrent (or persisting) BE islands were treated with re-APC.

During treatment and FU, all patients were prescribed high- dose proton-pump inhibitor therapy twice daily, supplemented with sucralfate suspension after every meal for 2 weeks after each therapeutic endoscopy.

Histological analysis

Histological evaluation of all ER specimens and biopsies obtained at baseline, during treatment and at least the first FU endoscopy was performed by a dedicated BE expert pathologist. The training of the BEC pathologists has been described in detail elsewhere [15, 17, 32].

Endpoints RFA treatment cohort

Primary effectiveness endpoint:

1. Proportion of patients with CE-BE at the first endoscopy after the treatment phase. A patient was considered a failure for this endpoint if residual endoscopically visible BE persisted after completing the treatment protocol including touch-up treatment, and/or if dysplasia persisted, including dysplasia in cardia biopsies without visible BE. IM in cardia biopsies in the absence of endoscopically visible BE was not considered a treatment failure [4]. All patients in the treatment cohort who completed the treatment protocol were included for this analysis ('per protocol population'). We divided treatment failures into two groups: (a) real treatment failures in whom>20% of the initial BE persisted and/or in whom neoplasia persisted; and (b) patients with >80% of the initial BE removed and complete eradication of neoplasia, in whom an elective decision was made to withhold further treatment.

Secondary effectiveness endpoints:

1. Differences in outcomes over time.
2. Progression to advanced EAC that exceeded boundaries for curative endoscopic treatment.
3. Complications (oesophageal stenosis, bleeding, perforation, death).

Endpoints RFA durability cohort

Primary durability endpoint:

1. Proportion of patients with sustained eradication of LGD, HGD and EAC during long-term endoscopic FU. A patient was considered a failure for this endpoint if recurrent LGD, HGD or EAC was detected in the oesophagus or cardia, or if lymph node or distant metastasis from EAC were found during FU. Failure for this endpoint was categorised into three groups according to the severity of recurrent disease: (a) LGD in a normal appearing cardia without recurrent BE; (b) recurrent BE with LGD/HGD/EAC amendable for curative endoscopic treatment; and (c) advanced EAC that exceeded boundaries for curative endoscopic treatment.

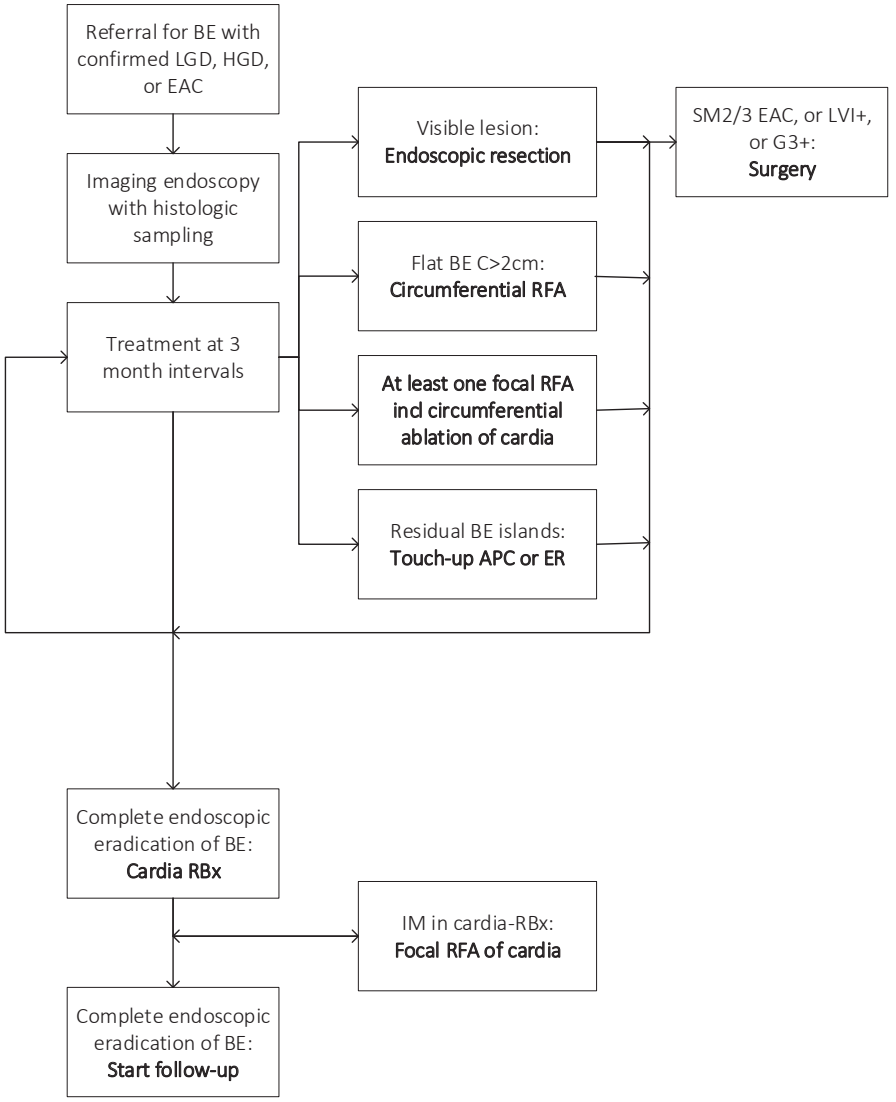
Secondary durability endpoints:

1. Sustained eradication of HGD and EAC (recurrent LGD was considered as success).
2. Progression to advanced EAC that exceeded boundaries for curative endoscopic treatment.
3. Recurrence of non-dysplastic BE.
4. Diagnostic yield for FU endoscopies and random biopsies.
5. Association between frequent endoscopies in the first FU year and recurrence.

6. Association between IM in the cardia and recurrence.
7. Unrelated mortality rates and causes of death.

Detailed definitions for our endpoints are provided in online supplemental table S2.

Figure 2. Treatment protocol



Treatment protocol followed by all Barrett Expert Centers in the Netherlands. APC, argon plasma coagulation; BE, Barrett's oesophagus; ER, endoscopic resection; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; IM, intestinal metaplasia; RFA, radiofrequency ablation.

Data collection

The BEC registry, a joint database that includes all treated patients in the Netherlands, was initiated in 2016. Patients were identified from the prospective annual registrations of treatment outcomes, prospective databases and/or patient lists at each centre. All relevant data regarding baseline characteristics, imaging, treatment and FU were retrospectively recorded from the endoscopy and pathology reports in the electronic patient files that were kept in each individual centre, and which were standardised from the beginning of the joint treatment protocol in 2008. All data were coded and merged in a joint, online data- base (Castor EDC), with a separately kept patient identification file.

The BEC registry was merged with the non-public microdata from Statistics Netherlands for survival outcomes, including date and cause of death.

Data management

Medical students in the final year of their degree reviewed all endoscopy and pathology reports for data collection under frequent supervision and after standardised training in the subject and the database. A second, independent assessment by a dedicated research fellow (MD) was done for a random 50% of the patient population. Additionally, all patients meeting primary or secondary endpoints had source data verified by a research fellow (MD) and were discussed during meetings with the study team (SvM, EN, RP, JB). All fields were examined for missing data, strange values or outliers, and these were completed or corrected where possible. All authors had access to the study data and reviewed and approved the final manuscript.

Statistics

Results of the descriptive analyses are presented as counts and proportions for categorical variables and median and ranges between the 25th and 75th percentile, or mean and SD for continues variables with skewed or normal distribution, respectively. CIs (2.5th; 97.5th percentile) were obtained using boot- strapping. Categorical variables were compared using a X2 test or Fisher's exact test, and continuous variables with a Student's t-test or Mann-Whitney U test.

The durability of eradication of dysplasia was estimated with the use of the Kaplan-Meier method. The HR for recurrent dysplasia was estimated with the use of a Cox proportional hazards model. Data for patients were censored at the last endoscopic FU. To assess causal associations, cox proportional hazard models were adjusted for age, gender, length of BE, worst histology at baseline, presence of a reflux stenosis, and presence of incident lesions during RFA treatment.

Median overall survival was estimated with use of the Kaplan- Meier. Patients were censored at the date patient was last known to be alive. Recurrence and survival were combined with the use of a cumulative incidence curve. Statistical analysis were performed using Rstudio for windows (V.3.6.1).

RESULTS

Baseline characteristics

A total of 1386 patients underwent at least one RFA treatment between 2008 and 2018 and were analysed for safety and effectiveness ('RFA treatment cohort") (figure 1). Patient characteristics are shown in table 1.

Table 1. Baseline characteristics

	RFA treatment cohort N=1386	**RFA durability cohort N=1154**
Demographics		
Male gender, n (%)	1122 (81)	947 (82)
Age, years, mean (±SD)	65 (10)	64 (9)
BMI, kg/m^2, mean (±SD)	28 (4)	28 (4)
BE history		
Prior fundoplication, n (%)	23 (2)	21 (2)
Surveillance history, n (%) In years, median (P25–P75)	892 (64) 4 (2–8)	759 (66) 3 (0–8)
Imaging		
Hiatal hernia, n (%) In cm, mean (±SD)	1321 (95) 3 (2–4)	1099 (95) 3 (2–4)
Oesophagitis, n (%)	49 (4)	38 (3)
Stenosis, n (%)	49 (4)	42 (4)
Circumferential BE, median (P25–P75)	2 (1–6)	2 (0–5)
Maximum BE, median (P25–P75)	5 (3–8)	4 (3–7)
Visible lesion, n (%)	860 (62)	718 (62)
Primary Paris type, n (%)		
0-Ip/s	81 (11)	63 (9)
0-IIa	490 (69)	419 (58)
0-IIb	111 (16)	90 (13)
0-IIc	29 (4)	22 (3)
	149 missing	124 missing

Table 1. (Continued)

	RFA treatment cohort N=1386	RFA durability cohort N=1154
Size, mm, median (P25–P75)	15 (10–20)	15 (10–20)
Pathology		
Worst overall histology, n (%)		
LGD	375 (27)	306 (27)
HGD	422 (30)	362 (31)
LR-EAC	589 (43)	486 (42)
Treatment		
Endoscopic resection, n (%)	860 (62)	718 (62)
Cap-based ER, n (%)	839 (61)	688 (60)
ESD, n (%)	31 (2)	20 (2)
RFA treatment		
C-RFA, median (P25–P75)	1 (0–1)	1 (0–1)
F-RFA, median (P25–P75)	2 (1–2)	2 (1–2)
Total RFA, median (P25–P75)	2 (1–3)	2 (1–3)
Patients with >2 C-RFA, n (%)	9 (0.6)	6 (0.5)
Patients with >4 total RFA, n (%)	57 (4)	44 (4)
Touch-up APC, n (%)	519 (37)	462 (40)
Touch-up ER, n (%)	80 (6)	74 (6)
ER for incident lesion, n (%)	69 (5)	44 (4)

APC, argon plasma coagulation; BE, Barrett's oesophagus; BMI, body mass index; C-RFA, circumferential RFA; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ER, endoscopic resection; ESD, endoscopic submucosal dissection; F-RFA, focal RFA; GEJ, gastroesophageal junction; HGD, high-grade dysplasia; LGD, low-grade dysplasia; LR-EAC, Low-risk esophageal adenocarcinoma.

Treatment cohort and outcomes

CE-BE (ie, a complete endoscopic eradication of all visible BE) at the end of the treatment phase was achieved in 94% of patients who completed the treatment protocol (95% CI 93 to 95) (1270/1348). This proportion was constant over time (online supplemental figure S1). Of the 1270 patients with CE-BE, 85 (7%) had persisting IM in biopsies obtained from a normal appearing cardia.

In 62% of patients, a visible lesion was removed with ER before RFA. This proportion differed along with the worst histological diagnosis at baseline: 17% of patients with LGD underwent baseline ER (62/375), compared with 53% of HGD patients (225/422) and

99% of patients with EAC (583/589). Six patients had EAC in a random biopsy, without visible lesions, and underwent RFA monotherapy, all were treated before 2015. For HGD patients, this proportion showed a significant increase over the years (47% before 2013 and 59% thereafter, p0.01; online supplemental figure S1).

A total of 68 (5%) patients were noted to have a neoplastic lesion after RFA was started ('incident lesion') that was removed with ER and showed HGD (n=26) or EAC (n=42). Baseline histology for these patients was HGD (n=27), or EAC (n=41). The incident lesion harboured a worse diagnosis than at baseline in 20 patients (20/1386; 1%).

Treatment consisted of median 1 circumferential (p25–p75 0–1) and two focal (p25–p75 1–2) RFA treatments per patient and was followed by touch-up ER (80/1386; 6%) and/or APC (519/1386; 37%) for residual BE areas.

Treatment failures

Seventy-eight patients (78/1348; 6%) had remaining Barrett's mucosa and/or dysplasia, and were defined as failures after median 10 (p25–p75 5–22) months of treatment. In 34 failures (34/78; 44%), over 80% of the initial BE had been removed, and an elective decision was made to withhold further treatment. These patients had median C1M2 residual BE with non- dysplastic IM (n=21) or LGD (n=13) (online supplemental table S3). During mean surveillance of 49 months with 3 endoscopies per patient after treatment was stopped, 6 (18%) developed a visible lesion. All were detected at early stages and were curatively treated endoscopically with ER for HGD (n=4) or mucosal EAC (n=2).

The other 44 failures (44/78; 56%) were real treatment failures in whom CE-BE could not be achieved, due to poor squamous regeneration (n=27) or progression to disease that exceeded boundaries for curative endoscopic treatment (n=17). These patients had median C5M7 residual BE with non-dysplastic IM (n=16), LGD (n=8), HGD (n=11), or EAC (n=9) (online supplemental table S3). The 17 patients (17/1386; 1%) who progressed to disease that exceeded the curative indication of endoscopic treatment developed high-risk EAC (n=7, all diagnosed after ER for an incident lesion) or new visible abnormalities that could not be removed with ER due to multifocality (n=9) or a persisting visible lesion that could not be removed with ER due to post-treatment fibrosis (n=1). Nine patients underwent esophagectomy and remained free of disease up to the moment of data collection (n=7) or died due to unrelated causes (n=2). The other eight patients were unfit for major surgery and had EAC-related death (n=4); unrelated death (n=2); or were alive at the moment of data collection (n=2). Twelve of these 17 cases were identified at baseline as complicated cases due to BE segment >10 cm, severe reflux oesophagitis, and/or multifocal neoplasia (online supplemental table S4).

The majority of the real treatment failures was identified early in the treatment phase. The median time between first treatment and decision to stop further treatment was 8 months. In two-thirds (29/44, 67%), treatment was stopped within the first 12 months, in 10 (23%) between 12 and 18 months, and in 4 (9%) after 18 months.

Complications

Oesophageal stenosis requiring endoscopic dilatation was the most common complication and occurred in 15% of patients (95% CI 13 to 17) (210/1386) (table 2). In 170 cases (170/1386; 12%), stenosis was resolved after 5 or less dilatations (median 2), but 40 patients (40/1386; 3%) developed a severe stenosis that required median 9 endoscopic dilatations. Additional incision therapy was required in 10 patients and esophageal stent placement in 4. All stenosis were managed endoscopically. Most severe stenosis occurred after extensive ER followed by RFA, but 12 patients (12/1386; 0.9%) developed a severe stenosis after a single circumferential RFA. Increasing BE length, prior ER and more extensive prior ER were risk factors for stenosis (online supplemental table S5).

The bleeding rate for RFA was 2% per procedure (95% CI 1 to 2) or 4% per patient (95% CI 3 to 5). No perforations occurred after RFA. Perforations occurred in 11 patients (1% (95% CI 0 to 1)) after ER (n=6) or endoscopic dilatation for oesophageal stenosis (n=5), all were managed conservatively or with endoscopic intervention.

There were no procedure related deaths.

Durability cohort outcomes

One thousand one hundred fifty-four patients who had a complete eradication of BE (CE-BE) on RFA, were analysed for long-term outcomes. The median duration of endoscopic FU (ie, until the last FU endoscopy) was 43 (p25–p75 22–69, minimum 8) months after baseline and 32 (16–59) months after the last treatment (total time at risk 3706 person years) with median 4 (1–5) FU endoscopies per patient. A substantial number of patients had long-term FU: 317 patients had FU ≥5 years and 148 patients had FU ≥7 years after achieving CE-BE. The majority of patients was still under endoscopic surveillance at the moment of data collection (n=934). In 203 patients, endoscopic FU was stopped due to age, comorbidity or death, median 37 months after the last treatment. Seventeen patients (1%) were lost to FU after mean 34 months of endoscopic surveillance with median 3 FU endoscopies.

Table 2. Safety outcomes

		Total patients N=1,386
At least 1 complication, n (% [95% CI])		**268 (21 [19-23])**
Stenosis	Incidence, n (% [95% CI])	210 (15 [13-17])
	Severity*, n (% [95% CI])	
	Mild/moderate	170 (12 [11-14)
	Severe	40 (3 [2-4])
Post-procedural bleed	Incidence, n (% [95% CI])	52 (4 [3-5])
	Severity*, n (% [95% CI])	
	Mild	19 (1 [1-2])
	Moderate	25 (2 [1-3])
	Severe	8 (0.5 [0.3-1])
	Cause, n	
	ER	29
	RFA	23
Perforation	Incidence, n (% [95% CI])	11 (0.8 [0.4-1])
	Severity*, n (% [95% CI])	
	Mild	5 (0.4 [0.1-0.9])
	Moderate	6 (0.4 [0.2-1)
	Severe	–
	Cause, n	
	ER	6
	Endoscopic dilatation	5

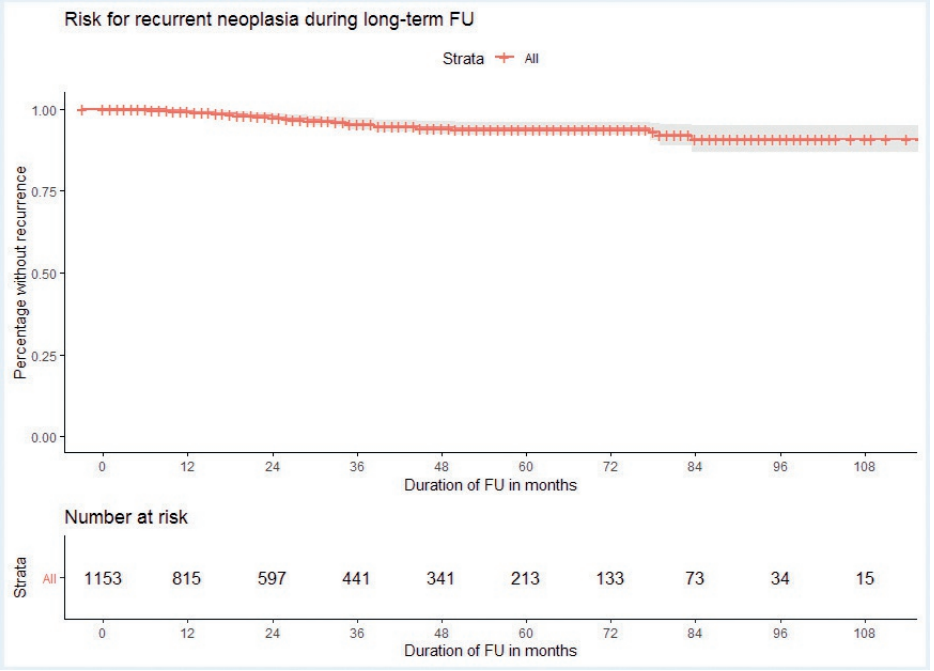
*Adverse events were graded as 'mild' (unplanned hospital admission, hospitalisation <3 days, haemoglobin drop <3 g, no transfusion), 'moderate' (4–10 days hospitalisation,<4 units blood transfusion, repeat endoscopic intervention, radiological intervention), 'severe' (hospitalisation >10 days, intensive care unit (ICU) admission, need for surgery, >4 units blood transfusion, in the case of stenosis: >5 dilatations, stent placement or incision therapy) or 'fatal' (death attributable to procedure <30 days or longer with continuous hospitalisation). See online supplemental table S2 for more definitions. ER, Endoscopic resection; RFA, Radiofrequency ablation.

During FU, recurrence of LGD, HGD or EAC occurred in 38 (38/1154; 3%) patients (annual risk 1.0% (95% CI 0.8 to 1.4)) (figure 3). A total of 24 patients had recurrent HGD/EAC (24/1154; 2%; annual risk 0.7 (95% CI 0.4 to 1.0)).

Recurrences were categorised in three grades: (1) LGD in a normal appearing cardia (9/38; 24%); (2) recurrent BE with dysplasia/EAC (24/38; 63%); and (3) advanced EAC that exceeded boundaries for curative endoscopic treatment (5/38; 13%) (table 3, online supplemental figure S2). Patients in cate- gory 1 underwent treatment (n=1) or surveillance without progression (n=8). All patients in category 2 underwent successful endoscopic treatment and CE-BE was re-established in all. Of the five patients with progression to advanced EAC (5/1154, 0.4%, annual risk 0.1% (95% CI 0.1 to 0.3)), four patients underwent surgery (T1bN1; T1bN1, T1N2, T1bN0), of which three patients later died from metastasised disease. A single patient had metastasised disease without intraluminal recurrence at the moment recurrence was diagnosed. Three of the five patients were identified at baseline as complicated cases with BE segment >10 cm, severe reflux oesophagitis and/ or multifocal neoplasia (online supplemental table S4). In total, 8 patients (8/1154; 0.7%) had a worse disease stage during FU than at baseline staging.

Recurrence occurred median 31 months (19–43) after CE-BE (figure 3). The majority of recurrences developed in the tubular oesophagus (24/38; 62%); either in short segment BE (median C1M2) or in small BE islands, always within the extent of the initial BE segment (online supplemental figure S3). The remaining 38% (14/38) occurred at the cardia. All recurrences in categories 2 and 3 were detected as endoscopic abnormalities (recurrent BE and/or visible lesion). No recurrent HGD/EAC was diagnosed solely on random biopsies.

Figure 3. Long-term outcomes



Kaplan-Meier curve for the risk for recurrent dysplasia during follow-up (FU) based on the 'RFA durability cohort'. A patient was considered a failure for the endpoint if recurrent dysplasia was found, irrespective of whether curative endoscopic retreatment was performed. Patients were censored at the last FU endoscopy at the moment of data collection.

Table 3. Recurrences

	LGD at GEJ N=9	Recurrent dysplasia/EAC N=24	Advanced EAC N=5
Initial BE			
Length, median (P25–P75)	C6M7 (4–9; 5–9)	C3M5 (1–7; 3–9)	C8M10 (5–11; 7–12)
Histology, n (%)			
LGD	1 (11)	3 (13)	–
HGD	6 (67)	5 (21)	2 (40)
LR-EAC	2 (22)	16 (67)	3 (60)
Severe reflux, n (%)	3 (33)	1 (4)	3 (60)
Treatment			
Baseline ER, n (%)	5 (56)	19 (79)	4 (80)
N C-RFA, median (P25–P75)	1 (1–2)	1 (0–1)	1 (1–2)
N F-RFA, median (P25–P75)	2 (2–3)	2 (1–2)	2 (1–3)
FU			
Prior IM in cardia, n (%)	2 (22)	1 (4)	0
N FU endoscopies before recurrence, median (P25–P75)	3 (1–5)	4 (2–5)	2 (2–3)
Months between last treatment and recurrence, median (P25–P75)	31 (17–45)	31 (23–47)	25 (18–39)
Months between last FU endsoscopy and recurrence, median (P25–P75)	11 (9–13)	12 (10–15)	12 (7–17)
Recurrence			
Location, n (%)			
Cardia	9 (100)	4 (17)	1 (25)*
Tubular	–	20 (83)	3 (75)
Detection	Cardia RBx	Visible BE a/o lesion	Visible BE a/o lesion*
Histology, n (%)			
LGD	9 (100)	5 (21)	
HGD		7 (29)†	
LR-EAC		12 (50)†	
HR-EAC			5 (100)†

*A single patient developed symptomatic, metastasized disease without abnormalities in the oesophagus.
†A worst histological grade during FU as compared with baseline, was found in eight patients in total. Three patients with baseline LGD who developed HGD (n=1) or LR-EAC (n=2) and in all five patients who developed HR-EAC during FU.
BE, Barrett's oesophagus; C-RFA, circumferential RFA; EAC, oesophageal adenocarcinoma; ER, endoscopic resection; F-RFA, focal RFA; FU, follow-up; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia; RBx, Random biopsies.

Recurrent non-dysplastic BE
During FU, recurrent NDBE occurred in 109 patients (9% (8–11)), the majority of which had diminutive BE islands (84/1154; 7%). Twenty-seven patients (27/1154; 2%) developed recurrent BE tongues of limited size (median C0M2), in all cases of lesser extent than the initial BE (online supplemental table S6). One patient (1/109; 1%) progressed to LGD in a recurrent C1M2 BE. No patient with recurrent BE progressed to HGD/EAC during a median FU of 24 months with median 2 endoscopies.

Recurrent BE tongues were detected after median 38 months, whereas BE islands were detected significantly shortly after treatment (median 15 months, P0.02). The annual risk for BE islands was 3% (2–4) in years 1–2 and 1% (1–1) in the years thereafter. The risk for recurrent BE tongues was 0.4% (95% CI 0.2% to 0.8%) in the first 2 years and 1% (95% CI 1% to 2%) in the years thereafter (online supplemental figure S4 and S5).

Diagnostic yield of FU endoscopies
Overall, a total of 3889 FU endoscopies was performed in 1154 patients. The diagnostic yield for detection of recurrent LGD/ HGD/EAC was 1.0% (95% CI 0.7% to 1.3%) (38/3889) per endoscopy and 0.6% (95% CI 0.4 to 0.9) for recurrent HGD/ EAC (24/3889).

Patients in whom CE-BE was achieved before 2015 (n=393) underwent 3-monthly endoscopies in the first year of FU (ie, FU at 0–3–6–9–12 months from CE-BE), whereas the remaining 761 patients had the first FU endoscopy performed after 1 year (ie, at 0–12 months from CE-BE). In multivariate cox analysis, no significant association was found between the frequency of FU in year 1 and dysplastic recurrence during the first 30 months (adjusted HR 1.6 (95% CI 0.6 to 4.1)). During long-term FU, no significant association was found between the frequency of FU in year 1 and progression to advanced neoplasia (adjusted HR 0.8 (95% CI 0.1 to 5.8)) (online supplemental table S7).

Random sampling from neosquamous epithelium
A total of 8588 random biopsies were obtained from the NSE in 376 patients during 924 FU endoscopies. Buried BE was found in 10 biopsies; in 1% of all endoscopies (95% CI 1 to 2) and 0.1% of all biopsies (95% CI 0.1 to 0.2) (table 4). None of the buried BE samples showed signs of dysplasia and during a median FU of 4 years and a median of 4 endoscopies after buried BE was noted, the finding was not reproduced and none of the patients showed dysplastic progression.

In 2013, we stopped obtaining random NSE biopsies. Outcomes before 2013 (annual recurrence risk 1.3 (95% CI 0.5 to 2.1)) did not differ significantly from those after 2013 (annual recurrence risk 1.0 (95% CI 0.6 to 1.3)) (p 0.56).

Random sampling from the cardia

Random biopsies from a normal appearing cardia were obtained during 2733 FU endoscopies in 1121 patients (table 4). Non- dysplastic IM was found in 14% of patients (95% CI 12% to 16%), either as persisting IM after treatment (n=78) or recurrent IM during FU (n=72). During median 3 endoscopies2–4 after the first IM finding, IM was reproduced in 33% of patients (95% CI 26% to 42%) during one (n=11) or more (n=32) endoscopies (table 4). Three patients (2% (95% CI 0% to 7%)) subsequently developed LGD: 2 developed LGD in the cardia without visible BE 12 months after IM was found and 1 developed a BE island in the tubular oesophagus with LGD 36 months after IM was noted in the cardia. None of the patients with IM progressed to HGD or EAC. In multivariate cox analysis adjusted for potential confounders (age, gender, BE length, worst baseline histology, reflux stenosis, incident lesion), no statistically significant association was found between a finding of non-dysplastic IM in the cardia and the risk for recurrence (adjusted HR 0.5 (95% CI 0.2 to 1.7)).

Random biopsies from the cardia were noted to contain LGD in 9 patients (9/11121; 0.8%) and 23 endoscopies (20/2733; 0.9%) (all defined as 'recurrences', table 3). A single patient underwent additional RFA, while the other eight underwent surveillance and during median 2 years FU with two endoscopies, none of these patients progressed to HGD/EAC.

In 2016, we stopped obtaining random cardia biopsies. Outcomes before 2016 (annual recurrence risk 1.0 (95% CI 0.6 to 1.5)) did not differ significantly from those after 2016 (annual recurrence risk 1.0 (95% CI 0.6 to 1.5) (p 0.96)).

All-cause mortality

During a median FU for vital status of 60 months (p25–p75 38–86) after baseline or 49 months (p25–p75 26–72) after the last treatment, 96 patients died, of which 92 due to unrelated causes (8.0% (6.5% to 9.7%)) and 4 due to metastasised EAC (0.3% (0.0% to 0.7%)). Most common causes of death were neoplasms other than EAC (35/92; 38%), followed by cardiovascular disease (24/93; 26%) and respiratory disease (13/93; 14%). Online supplemental figure S6 shows the cumulative incidence of unrelated death and recurrence during FU.

Progression to EAC exceeding the boundaries for endoscopic treatment

Overall, 22 patients (22/1386; 1.6% (95% CI 1.1% to 2.4%)) progressed to disease that exceeded guideline boundaries for curative endoscopic treatment, either during treatment (n=17) or during FU after CE-BE was established (n=5). The individual case histories of all these 22 patients are presented in online supplemental table S4.

Table 4. Diagnostic yield and relevance of random biopsies during follow-up (FU)

	Finding	Incidence			Relevance				
		Patient-rate % [95% CI] n/N[1]	**Endoscopy-rate % [95% CI] n/N[2]**	**Biopsy-rate % [95% CI] n/N**	**FU[3]; Years Median (IQR)**	**FU[3], N endoscopies Median (IQR)**	**Reproduced % [95% CI] n/N**	**Progression to dysplasia % [95% CI] n/N**	**Progression to neoplasia % [95% CI] n/N**
NSE random biopsies	Buried IM	2.7 [1.5-4.8] (10/376)	1.1 [0.6-2.0] (10/924)	0.1 [0.1-0.2] (10/8,588)	4 (4-5)	4 (4-5)	0 [0-3.4] (0/10)	0 [0-3.4] (0/10)	0 [0-3.4] (0/10)
Cardia random biopsies	IM	13.8 [11.5-15.5] (150/1,121)	7.2 [6.3-8.3] (198/2,733)	NA	3 (2-4)	3 (2-4)	33.3 [25.8-41.8] (43/129)[4]	2.3 [0.1-7.2] (3/129)	0 [0-2.9] (0/129)
	LGD	0.81 [0.42-1.5] (9/1,1121)	0.73 [0.46-1.15] (20/2,733)	NA	2 (2-5)	2 (2-4)	75.0 [35.6-95.6] (6/8)	NA	0 [0-40.2] (0/8)

The diagnostic yield of random biopsies from NSE and cardia and long-term follow-up of abnormal findings.

*N = patients with at least 1 endoscopy with sampling from NSE or cardia.

†N = Endoscopies with sampling from NSE or cardia.

‡Median FU after detection of buried BE; IM; of LGD.

§N=patients with IM in the cardia; either at end of treatment (n=78) or during FU (n=72). Patients with treatment (n=9) or no FU (n=12) were excluded.

¶A single patient underwent additional RFA and was not included for the FU analysis.

**Adjusted for potential confounders age, gender, length of BE, worst pathology at baseline, reflux stenosis, incident lesion.

BE, Barrett's oesophagus; IM, intestinal metaplasia; LGD, low-grade dysplasia; NSE, neosquamous epithelium; RBx, random biopsies; RFA, radiofrequency ablation

DISCUSSION

We report treatment outcomes and long-term FU for all 1386 patients with BE-related neoplasia (ie, LGD, HGD and low-risk EAC) who underwent endoscopic treatment with RFA since 2008, based on a nationwide cohort with treatment provided exclusively in expert centres. Treatment was effective in eradicating all BE in 94% of patients. Most failures had achieved a complete eradication of HGD/EAC, yet 1% of patients progressed to disease stages that exceeded the boundaries for curative endoscopic treatment. The majority of these patients (68%) underwent curative surgery or was unfit for major surgery and had died of unrelated causes or was alive at the moment of data collection.

Long-term effects were analysed over median 43 months with median 4 endoscopies and showed sustained eradication of dysplasia in 97%. The majority of the recurrences underwent curative endoscopic treatment, yet only 0.4% of all patients progressed to advanced EAC. Frequent FU visits in the first year did not contribute to detection of recurrences, nor did random biopsies from NSE or the cardia. Our data suggest that in expert centres, FU intervals after CE-BE may be extended, 3-monthly endoscopies in the first year may be omitted and random biopsies from NSE and cardia abandoned.

Successful treatment has previously been reported in 74%–98% of patients [4–7] with subsequent annual dysplastic recurrence risks of 1%–20% per patient year [4, 8–13], in varying cohort studies and registries from USA and Europe. Our outcome for CE-BE (94%) lies at the upper end of this spectrum and our annual recurrence risk at the lower end (1%). Our beneficial rates might partially be explained by the stringent quality control in our study: treatment was only performed in expert centres with dedicated pathologists and endoscopists who had participated in joint training programmes. Baseline ER for visible lesions was performed in 53% of HGD patients (ie, 47% of HGD patients had flat BE with HGD in random biopsies and underwent RFA) and 99% of patients with EAC, as compared with 47% and 77%, respectively, of patients in the UK cohort [33]. An important difference with RFA studies from the USA is that we incorporated ablation of the gastro-oesophageal junction during each focal RFA procedure, to guarantee optimal treatment of this area [6, 34, 35]. In addition, our treatment protocol allowed for additional, low- threshold touch-up ER or APC for remaining BE islands after RFA and for additional focal RFA for persisting IM in the GEJ post-RFA. Finally, persisting IM in a normal appearing GEJ after treatment was included in our definition for success, and treatment success was assessed during a single endoscopy.

The stenosis rate of 15% is relatively high as compared with other studies [4, 6, 33]. Most prospective clinical trials have restrictions in BE length (ie, less than 8–10 cm) and in extent of prior ER (ie, <2 cm in length and/or <50% of the circumference). However, in current registry, we included all patients independent of BE length or extent of ER. Since these factors had an association with stenosis in our analysis, this may have contributed to the high stenosis rate in the current study.

Our data stress the importance of careful inspection prior to each RFA treatment. Although baseline ER was performed for 62% of patients, incident lesions were found in 5% of patients after RFA was initiated. All patients who progressed to advanced disease were identified as an incident lesion. If visible abnormalities are not recognised and removed with ER but inadvertently treated with RFA, this may lead to incomplete treatment, resulting in progression that remains undetected during the treatment course. Such occurrence may place the patient outside the window of opportunity for curative endoscopic treatment and even for curative surgery.

Although the majority of patients with an incident lesion had curative ER, 10% had progressed to high-risk cancer and required esophagectomy. Overall, 1% of patients had progressed to advanced EAC that exceeded boundaries for curative endoscopic treatment. The majority of progressors were identified at baseline as 'complicated' cases with BE neoplasia, due to ultralong BE segments, multifocal neoplasia and/or severe reflux disease. Extra caution is therefore recommended for these patients.

Our data show that post-RFA recurrences are rare. The annual incidence was 1% for recurrent LGD/HGD/EAC and 0.8% for recurrent HGD/EAC, which indicates that if one would follow 200 patients for 5 year, only 8 will develop HGD/EAC. These rates are comparable to a non-dysplastic BE population under endoscopic surveillance, where FU is performed every 3–5 years [1].

Prior FU studies suggested that most recurrences occurred in the first year after treatment [12, 36] and guidelines therefore suggest to perform 3-monthly endoscopies during the first year of FU, identical to the preablation era when visible lesions were removed with ER and the remaining flat BE was left untreated. The aforementioned studies included recurrent non-dysplastic BE and even IM in the cardia in the definition of recurrence. In our study, we also found more non-dysplastic BE, specifically diminutive islands, during the first 2 years after treatment as compared with the years thereafter. In our opinion, these small areas of non-dysplastic BE could very likely be residual tiny BE islands rather than recurrent BE. Either way, these small islands were

easily treated with a single APC treatment and were found to be of low clinical relevance. In our opinion, these findings do therefore not justify more frequent FU visits.

Our cohort could be considered as a natural experiment for the effects of 3-monthly endoscopies during the first year of FU. Until 2014, this frequent FU schedule was default while FU was performed on an annual basis from 2015 onwards. Although the cumulative incidence of LGD/HGD/EAC was slightly higher in the patients with 3-monhtly endoscopies FU (2.8 vs 1.4%), this difference was not statistically significant and was mainly based on an increased detection of LGD in the cardia, which given the absence of progression to HGD/EAC during FU, was of dubious clinical relevance. Since the reason to perform frequent FU is to prevent progression to advanced neoplasia, this should be the most important outcome in our natural experiment. Although numbers are very low, the risk appeared comparable (0.7% for frequent FU and 0.4% for annual FU, P0.4). Overall, our data suggest that frequent FU in the first year is not associated with clinically relevant recurrence during FU and can be loosened.

Furthermore, background mortality is significant in the post-treatment BE population and we recommend that this may be taken into account when defining of the need for and frequency of post-RFA FU. We are currently developing an evidence based post-RFA FU regimen based on a balance between the risk for recurrent, clinically relevant Barrett's neoplasia and a patient's overall life expectancy and risk to die of other causes.

Our data suggest that there is no need for random biopsies in post-RFA FU when treatment is performed in expert centres. All HGD/EAC recurrences appeared as endoscopically visible abnormalities and none were detected through random biopsies alone. Careful inspection of the NSE along the length of the initial BE, with targeted biopsies of any visible abnormality, is therefore the most essential part of FU. Crucial part of the inspection is careful retroflexed inspection of the cardia, since 18% of the HGD/EAC recurrences in this study occurred in this area, and these can easily be overlooked during inspection with the endoscope in antegrade position.

NSE random biopsies showed buried BE in 3% of patients, a finding that was neither reproduced nor associated with neoplastic progression during median 4 years of FU and a median of 4 endoscopies. Our findings are in line with other studies12 and supports our decision to change in our FU strategy in 2013 by abandoning random NSE biopsies.

Cardia random biopsies were noted to contain IM in 14% of patients or 7% of endoscopies. Our data suggest that this is no clinically relevant disease and no indication

for treatment: during median 3 years of FU with a median of 3 endoscopies, the finding was reproduced in only 33% of the patients and none progressed to neoplasia. This is in line with prior studies that showed reproduction of IM in 11%–33% during median 3–5 FU endoscopies [4, 9, 37]. A recent study showed no increased risk for dysplasia among patients with recurrent IM of the cardia [38]. These outcomes are comparable to those reported for a healthy, asymptomatic population without BE. IM can occur in 4%–15% of the normal population [39–44], and a study from the Mayo Clinic followed 86 patients with a diagnosis of IM of the cardia for 8 years, during which none progressed to neoplasia [45]. Accordingly, Krajciova et al showed in their retrospective analysis of 136 patients with successful ablation, that persisting IM after treated or recurrent IM during FU, detected in random biopsies from a normal appearing cardia, was not associated with an increased risk for dysplastic recurrence [45].

Apart from IM, an endoscopically normal cardia was found to contain LGD in 0.8% of patients or 0.7% of endoscopies. Although we defined this as a recurrence, the clinical relevance of this finding was negligible. None of the patients progressed to HGD/EAC and this is in line with the aforementioned study from the Mayo Clinic, which showed no progression in eight patients with LGD of the cardia [45]. Since we have stopped obtaining random biopsies from the cardia in 2016, this entity of 'invisible' LGD in the cardia will no longer be detected and, based on the low risk for progression, this appears justified. Moreover, since patients are kept under endoscopic surveillance, potential progression to HGD or worse may still be identified and treated at early stages.

Long-term endpoints for treatment of BE neoplasia have undergone significant transformation over the years. Initially, esophagectomy was the standard therapy and success was defined as 5-year tumor-free survival. Currently, endoscopic treatment is treatment of choice and given the extremely low mortality rates, EAC-related death has no longer been an appropriate endpoint. Instead, increasingly more stringent definitions have been used over time and nowadays, some studies report sustained eradication of all BE including invisible IM in the cardia [12]. Although a complete eradication of BE reflects an appropriate treatment outcome for RFA, it does not express the outcome of interest during FU. CE-BE after treatment may in fact be considered as an intermediate endpoint for the outcome of interest and the main motive to initiate RFA, that is, a reduction in the risk for future (advanced) neoplasia. Therefore, we suggest that recurrent neoplasia and not BE or IM should be the primary endpoint for assessment of long-term outcomes.

This study has important strengths. This is the first report of a nationwide cohort of patients with BE with long-term FU after centralised treatment in expert centres. Our

data are homogeneous: all endoscopists and pathologists participated in a specific and joint training programme and all centres followed a uniform treatment and FU protocol. We included all patients in the Netherlands who underwent EET. We provide high-quality data that were collected by dedicated researchers and with central discussion of all patients with endpoints. A rigorous treatment and FU protocol in all BECs and meticulous data collection resulted in only 1% of our patients that were lost to FU.

We have to address some limitations as well. Although our patients were registered prospectively, most of the actual data collection was done retrospectively with a risk for bias, specifically selection and information bias. All patients in the current study underwent at least one RFA treatment and results are therefore only applicable to patients undergoing RFA treatment. As shown in figure 1, 94 patients under- went ER monotherapy with surveillance of the remaining BE instead of RFA. Although in a majority of patients RFA was not initiated due to limited life expectancy, this decision may have (partially) been based on expected poor response after RFA, for example, due to BE regeneration of the ER wound. Long-term outcomes of these 94 patients have been described separately [27]. During median 21 months FU with 4 endoscopies per patient, 17 patients (18%) progressed to HGD/EAC. No patient progressed to advanced EAC. Endoscopic surveillance of a remaining BE segment after ER, instead of RFA, may be the preferred treatment strategy in selected patients.

Furthermore, 27% of our patients had LGD at baseline, and comparisons with HGD/EAC cohorts should therefore be made with caution. Information bias may have been present due to data collection by different persons, although random checks were performed by a second person for 50% of patients. Still, we had only few missing data due to standardised endoscopy and pathology reports in all centres. Furthermore, the assessment whether the cardia appears abnormal or normal, and thus whether biopsies should be obtained or not, may be operator dependent. Our study included only patients in the Netherlands, which limits the generalisability. All patients underwent endoscopic workup and treatment at expert centres and the results of this study can therefore not automatically be extrapolated to general practice. Current guidelines however recommend centralisation of EET for patients with Barrett's neoplasia in dedicated centres with multidisciplinary experience in this field (ie, experience in endoscopic imaging and treatment, sufficient case volumes, expert GI-pathology, and access to oesophageal surgery). Finally, although all centres followed the central treatment protocol that advised on which regimen should be used, we have no data on RFA regimen.

In conclusion, this large cohort of all Dutch patients treated with RFA±ER for BE with dysplasia or low-risk EAC, according to a uniform treatment protocol in a centralised setting, demonstrates that this approach successfully eradicates the BE segment in 94% of patients. Post-RFA recurrences are rare. Clinically relevant recurrences are detected as endoscopic abnormalities and at stages generally amend- able for curative endoscopic treatment. Our data suggest that post-RFA FU can be simplified: we may abandon 3-monthly endoscopies in the first year of FU and we may stop random sampling of NSE and cardia. Instead, dedicated endoscopic inspection, and if needed target biopsies are the most important steps to detect post-RFA recurrences.

REFERENCES

1 Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of gastrointestinal endoscopy (ESGE) position statement. Endoscopy 2017;49:191–8.

2 Gastroenterologists DSo. Richtlijn Barrett-Oesofagus, 2017.

3 Sharma P, Shaheen NJ, Katzka D, et al. AGA clinical practice update on endoscopic treatment of Barrett's esophagus with dysplasia and/or early cancer: expert review. Gastroenterology 2020;158:760–9.

4 Phoa KN, Pouw RE, Bisschops R, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut 2016;65:555–62.

5 Phoa KN, van Vilsteren FGI, Weusten BLAM, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA 2014;311:1209–17.

6 Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277–88.

7 Desai M, Saligram S, Gupta N, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointest Endosc 2017;85:482–95.

8 Wani S, Puli SR, Shaheen NJ, et al. Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. Am J Gastroenterol 2009;104:502–13.

9 Phoa KN, Pouw RE, van Vilsteren FGI, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. Gastroenterology 2013;145:96–104.

10 Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. Clin Gastroenterol Hepatol 2014;12:1840–7.

11 Cotton CC, Haidry R, Thrift AP, et al. Development of evidence-based surveillance intervals after radiofrequency ablation of Barrett's esophagus. Gastroenterology 2018;155:316–26.

12 Sami SS, Ravindran A, Kahn A, et al. Timeline and location of recurrence following successful ablation in Barrett's oesophagus: an international multicentre study. Gut 2019;68:1379–85.

13 Pouw RE, Klaver E, Phoa KN, et al. Radiofrequency ablation for low-grade dysplasia in Barrett's esophagus: long-term outcome of a randomized trial. Gastrointest Endosc 2020.

14 Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-Grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol 2010;105:1523–30.

15 Duits LC, Phoa KN, Curvers WL, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut 2015;64:700–6.

16 Duits LC, van der Wel MJ, Cotton CC, et al. Patients With Barrett's Esophagus and Confirmed Persistent Low-Grade Dysplasia Are at Increased Risk for Progression to Neoplasia. Gastroenterology 2017;152:993–1001.

17 van der Wel MJ, Klaver E, Duits LC, et al. Adherence to pre-set benchmark quality criteria to qualify as expert assessor of dysplasia in Barrett's esophagus biopsies - towards digital review of Barrett's esophagus. United European Gastroenterol J 2019;7:889–96.

18 Bergman JJGHM, de Groof AJ, Pech O, et al. An interactive web-based educational tool improves detection and delineation of Barrett's Esophagus-Related neoplasia. Gastroenterology 2019;156:1299–308.

19 Curvers WL, van Vilsteren FG, Baak LC, et al. Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multicenter, randomized, crossover study in general practice. Gastrointest Endosc 2011;73:195–203.

20 de Groof J, van der Sommen F, van der Putten J, et al. The argos project: the development of a computer-aided detection system to improve detection of Barrett's neoplasia on white light endoscopy. United European Gastroenterol J 2019;7:538–47.

21 Barret M, Belghazi K, Weusten BLAM, et al. Single-session endoscopic resection and focal radiofrequency ablation for short-segment Barrett's esophagus with early neoplasia. Gastrointest Endosc 2016;84:29–36.

22 Belghazi K, Marcon N, Teshima C, et al. Risk factors for serious adverse events associated with multiband mucosectomy in Barrett's esophagus: an international multicenter analysis of 3827 endoscopic resection procedures. Gastrointest Endosc 2020;92:259–68.

23 Belghazi K, Pouw RE, Koch AD, et al. Self-sizing radiofrequency ablation balloon for eradication of Barrett's esophagus: results of an international multicenter randomized trial comparing 3 different treatment regimens. Gastrointest Endosc 2019;90:415–23.

24 Pouw RE, Künzli HT, Bisschops R, et al. Simplified versus standard regimen for focal radiofrequency ablation of dysplastic Barrett's oesophagus: a multicentre randomised controlled trial. Lancet Gastroenterol Hepatol 2018;3:566–74.

25 Pouw RE, van Vilsteren FGI, Peters FP, et al. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. Gastrointest Endosc 2011;74:35–43.

26 van Vilsteren FGI, Alvarez Herrero L, Pouw RE, et al. Predictive factors for initial treatment response after circumferential radiofrequency ablation for Barrett's esophagus with early neoplasia: a prospective multicenter study. Endoscopy 2013;45:516–25.

27 van Munster SN, Nieuwenhuis EA, Weusten BLAM, et al. Endoscopic resection without subsequent ablation therapy for early Barrett's neoplasia: endoscopic findings and long-term mortality. J Gastrointest Surg 2021;25:67–76.

28 Künzli HT, Schölvinck DW, Phoa KN, et al. Simplified protocol for focal radiofrequency ablation using the HALO90 device: short-term efficacy and safety in patients with dysplastic Barrett's esophagus. Endoscopy 2015;47:592–7.

29 Alvarez Herrero L, van Vilsteren FGI, Pouw RE, et al. Endoscopic radiofrequency ablation combined with endoscopic resection for early neoplasia in Barrett's esophagus longer than 10 cm. Gastrointest Endosc 2011;73:682–90.

30 Alvarez Herrero L, Curvers WL, van Vilsteren FGI, et al. Validation of the Prague C&M classification of Barrett's esophagus in clinical practice. Endoscopy 2013;45:876–82.

31 Pouw RE, Visser M, Odze RD, et al. Pseudo-buried Barrett's post radiofrequency ablation for Barrett's esophagus, with or without prior endoscopic resection. Endoscopy 2014;46:105–9.

32 van der Wel MJ, Duits LC, Klaver E, et al. Development of benchmark quality criteria for assessing whole-endoscopy Barrett's esophagus biopsy cases. United European Gastroenterol J 2018;6:830–7.

33 Haidry RJ, Lipman G, Banks MR, et al. Comparing outcome of radiofrequency ablation in Barrett's with high grade dysplasia and intramucosal carcinoma: a prospective multicenter UK registry. Endoscopy 2015;47:980–7.

34 Lyday WD, Corbett FS, Kuperman DA, et al. Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. Endoscopy 2010;42:272–8.

35 Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy 2010;42:781–9.

36 Vliebergh JH, Deprez PH, de Looze D, et al. Efficacy and safety of radiofrequency ablation of Barrett's esophagus in the absence of reimbursement: a multicenter prospective Belgian registry. Endoscopy 2019;51:317–25.

37 Pouw RE, Klaver E, Phoa KN, et al. Radiofrequency ablation for low-grade dysplasia in Barrett's esophagus: long-term outcome of a randomized trial. Gastrointest Endosc 2020;92:569–74.

38 Solfisburg QS, Sami SS, Gabre J, et al. Clinical significance of recurrent gastroesophageal junction intestinal metaplasia after endoscopic eradication of Barrett's esophagus. Gastrointest Endosc 2020. doi:10.1016/j.gie.2020.10.027. [Epub ahead of print: 02 Nov 2020].

39 Siddiki HA, Lam-Himlin DM, Kahn A, et al. Intestinal metaplasia of the gastric cardia: findings in patients with versus without Barrett's esophagus. Gastrointest Endosc 2019;89:759–68.

40 Byrne JP, Bhatnagar S, Hamid B, et al. Comparative study of intestinal metaplasia and mucin staining at the cardia and esophagogastric junction in 225 symptomatic patients presenting for diagnostic open-access gastroscopy. Am J Gastroenterol 1999;94:98–103.

41 Zaninotto G, Avellini C, Barbazza R, et al. Prevalence of intestinal metaplasia in the distal oesophagus, oesophagogastric junction and gastric cardia in symptomatic patients in north-east Italy: a prospective, descriptive survey. The Italian Ulcer Study Group "GISU". Dig Liver Dis 2001;33:316–21.

42 Spechler SJ, Zeroogian JM, Antonioli DA, et al. Prevalence of metaplasia at the gastro- oesophageal junction. Lancet 1994;344:1533–6.

43 Peck-Radosavljevic M, Püspök A, Pötzi R, et al. Histological findings after routine biopsy at the gastro-oesophageal junction. Eur J Gastroenterol Hepatol 1999;11:1265–70.

44 Hirota WK, Loughney TM, Lazas DJ, et al. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. Gastroenterology 1999;116:277–85.

45 Jung KW, Talley NJ, Romero Y, et al. Epidemiology and natural history of intestinal metaplasia of the gastroesophageal junction and Barrett's esophagus: a population- based study. Am J Gastroenterol 2011;106:1447–55.

SUPPLEMENTARY MATERIAL

To access the supplementary material accompanying this article, visit the online version of Gut at www.gut.bmj.com, and at http://doi.org/10.1136/gutjnl-2020-322615

PART II

Improving patient tailored endoscopic management for Barrett's neoplasia

CHAPTER 4

Impact of Expert Center endoscopic assessment of confirmed LGD diagnosed in community hospitals

Esther A Nieuwenhuis*, Sanne N van Munster*, Wouter L Curvers, Bas L A M Weusten, Lorenza Alvarez Herrero, Auke Bogte, Alaa Alkhalaf, B Ed Schenk, Arjun D Koch, Manon C W Spaander, Thjon J Tang, Wouter B Nagengast, Jessie Westerhof, Martin H M G Houben, Jacques J G H M Bergman, Erik J Schoon, Roos E Pouw

***Authors contributed equally**

Endoscopy. 2022 Jan 28. doi: 10.1055/a-1754-7309

ABSTRACT

Background

The optimal management for patients with low grade dysplasia (LGD) in Barrett's esophagus (BE) is unclear. According to the Dutch national guideline, all patients with LGD with histological confirmation of the diagnosis by an expert pathologist (i. e. "confirmed LGD"), are referred for a dedicated re-staging endoscopy at an expert center. We aimed to assess the diagnostic value of re-staging endoscopy by an expert endoscopist for patients with confirmed LGD.

Methods

This retrospective cohort study included all patients with flat BE diagnosed in a community hospital who had confirmed LGD and were referred to one of the nine Barrett Expert Centers (BECs) in the Netherlands. The primary outcome was the proportion of patients with prevalent high grade dysplasia (HGD) or cancer during re-staging in a BEC.

Results

Of the 248 patients with confirmed LGD, re-staging in the BEC revealed HGD or cancer in 23 % (57/248). In 79 % (45/57), HGD or cancer in a newly detected visible lesion was diagnosed. Of the remaining patients, re-staging in the BEC showed a second diagnosis of confirmed LGD in 68 % (168/248), while the remaining 9 % (23/248) had non-dysplastic BE.

Conclusion

One quarter of patients with apparent flat BE with confirmed LGD diagnosed in a community hospital had prevalent HGD or cancer after re-staging at an expert center. This endorses the advice to refer patients with confirmed LGD, including in the absence of visible lesions, to an expert center for re-staging endoscopy.

INTRODUCTION

Barrett's esophagus (BE) is the most important risk factor for development of esophageal adenocarcinoma (EAC). The malignant degeneration occurs through a stepwise process of phenotypic cellular changes: from nondysplastic BE (NDBE), intestinal metaplasia, to low grade dysplasia (LGD), high grade dysplasia (HGD), and eventually EAC [1]. In advanced stages, EAC is a disease with a poor prognosis. Adequate surveillance strategies of patients with BE are therefore essential to detect neoplasia at an early stage when it is amenable to curative endoscopic treatment [2, 3].

The strongest predictor of progression to HGD/EAC in BE is a diagnosis of LGD confirmed by an expert pathologist (i. e. "confirmed LGD"). The histological diagnosis of LGD is challenging because the distinction between dysplastic changes and reactive atypia of reflux-induced inflammation is difficult. Two prior studies demonstrated that LGD diagnosed by a community pathologist, was downgraded to NDBE in 73 %–85 % after review by a BE expert pathologist. After downstaging to NDBE, the risk of progression to HGD/EAC was < 1% per patient-year [4, 5]. In contrast, for confirmed LGD, the risk of malignant progression increased to 9 %–13 % per patient-year [6, 7]. Therefore, current guidelines advise that a community diagnosis of LGD is reviewed, and if necessary revised, by an experienced pathologist [8–11].

In the Netherlands, BE treatment is centralized. While BE surveillance endoscopies are performed in community hospitals, endoscopic treatment is restricted to nine Barrett Expert Centers (BECs). Patients with visible lesions, HGD, and/or cancer are directly referred to a BEC for endoscopic treatment. Since 2017, the Dutch guideline has recommended that patients with confirmed LGD are also referred to an expert center for a dedicated re-staging endoscopy [8]. This is based on the idea that LGD is a predictor for progression to HGD or cancer and that patients may benefit from dedicated re-staging endoscopies with the option for early intervention if there are visible lesions. Furthermore, several trials have demonstrated significant risk reduction of progression from LGD to HGD/EAC after radiofrequency ablation (RFA) of the BE when compared with surveillance alone [12–14]. Most guidelines therefore state that prophylactic ablation should be considered for BE with repetitive diagnoses of LGD [8, 9].

In the current study we evaluated the diagnostic value of re-staging endoscopy performed in an expert center for patients with confirmed LGD.

METHODS

The BEC registry

All patients referred to a BEC in the Netherlands are registered in a uniform database, (i. e. the BEC registry), which has been described in detail previously [15]. For the current study, we retrospectively reviewed this database. To ensure completeness of data, an additional search of the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (i.e. PALGA foundation) was performed. The PALGA database includes all pathology reports in the Netherlands. We selected all patients with confirmed LGD and referral to a BEC from the PALGA database.

Surveillance for NDBE

Regular surveillance endoscopies for patients with NDBE are performed in community hospitals. Surveillance endoscopies consist of imaging followed by random biopsies according to the Seattle protocol (i. e. 4-quadrant biopsies at every 2 cm) [10], and targeted biopsies from visible lesions. These biopsy specimens are read by the community hospital pathologist.

Patients with direct indications for treatment (i. e. HGD or worse, and/or a visible lesion) are referred to a BEC. For patients with a diagnosis of LGD assessed by the local pathologist, expert histological review is recommended, and referral to a BEC is advised for cases in which the diagnosis of LGD is confirmed by the expert pathologist.

Expert panel histopathology revision

A central expert histopathology panel facilitates review of LGD diagnoses. The panel consists of five core pathologists who have been dedicated in the field of BE for at least 15 years and have a median case load of seven cases per week, of which ≥ 25 % are dysplastic [16, 17]. Furthermore, all pathologists had participated in the Dutch Barrett Advisory Committee for many years and participated in multiple training programs for endoscopists and pathologists (www.best-acedemia.eu). Nine other BE expert pathologists working in expert centers joined the panel more recently, following quality assessment of 80 indefinite for dysplasia and LGD digital biopsy cases followed by group discussions with the core pathologists [4]. The performance of histopathology revision has been described extensively in a previous publication [16].

For LGD diagnosed in the Netherlands, biopsy specimens are digitally transferred for review by the panel. The expert panel diagnosis is sent to the endoscopist or pathologist who requested the review.

Upon confirmation of LGD or upstaging to HGD/EAC, the advice is to refer patients to a BEC for a dedicated re-staging endoscopy. Upon downstaging of LGD to indefinite for dysplasia or no dysplasia, patients remain under endoscopic surveillance at the community hospital.

Barrett expert centers

As per the national guideline, within 3–6 months of the diagnosis of LGD, patients are scheduled for a re-staging endoscopy at a BEC [8]. There are nine BECs in the Netherlands, where care is provided by 1–2 experienced pathologists and endoscopists per center; pathologists and endoscopists have participated in joint and specific training programs. Centers adhere to a joint treatment protocol and participate in quarterly meetings to guarantee homogeneity. This infrastructure has been established since 2008, when RFA was adopted for regular clinical care.

Re-staging consists of careful imaging endoscopy with high definition endoscopes with virtual chromoendoscopy. Patients are generally under sedation and most centers schedule dedicated timeslots for BE endoscopies. The Barrett's segment is described using the Prague C&M classification [18]. Visible lesions are described using the Paris classification [19] and either biopsied or endoscopically resected directly. In addition, random biopsies following the Seattle protocol are taken from the flat Barrett's segment [20].

Endoscopic management

Visible lesions are removed with endoscopic resection techniques. If the specimen shows dysplasia or early cancer, RFA of the remaining BE is generally advised. For flat BE, a diagnosis of HGD or a repeated diagnosis of confirmed LGD during two separate endoscopies (i. e. twice LGD) are indications for prophylactic RFA [12].

When the re-staging endoscopy shows flat BE with indefinite for dysplasia or no dysplasia, patients are scheduled for surveillance endoscopies in the BEC after 12 months. If no dysplasia is found at these endoscopies, patients are referred to the community hospital and followed up according to the regular NDBE surveillance protocols.

Study population

We included cases that fulfilled all of the following criteria: 1) flat BE in the absence of visible lesions with LGD detected in a community hospital; 2) confirmed LGD upon expert pathologist review; 3) referral to a BEC between January 2017 and October 2019.

Since 2017, guidelines have advised expert histopathology review including referral to a BEC in cases of confirmation or up- staging to HGD/EAC. Cases with visible lesions assessed in the community hospital were excluded for this study cohort.

Study endpoints

We defined several endpoints:

- Proportion of patients with HGD/cancer or with visible lesions during re-staging in the BEC
- proportion of patients with high risk EAC during re-staging at the BEC, defined as cancer with deep submucosal invasion (i. e. sm2/3), and/or poor differentiation grade, and/or presence of lymphovascular invasion; in contrast, low-risk EAC was defined as any mucosal or superficial submucosal EAC (i.e. ≤ sm1) in the absence of poor differentiation and absence of lymphovascular invasion
- proportion of patients with an indication for (prophylactic) endoscopic treatment upon re-staging; indications for treatment consisted of confirmed LGD at two separate endoscopies, HGD or EAC [8].

Statistics

Statistical analysis was performed using the Statistical Software Package IBM SPSS Statistics version 24.0.0.1 for Windows (IBM Corp. Armonk, New York, USA) and R version 3.4.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org). Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR) for normally distributed or skewed data, respectively. Categorical variables were presented as counts with percentages. Adjusted 95% confidence intervals (CIs) were obtained using simple bootstrapping with 10000 samples. The chi-squared test was performed to compare binary, unpaired results.

Ethics

The Institutional Review Board of the Amsterdam University Medical Centers declared that the registry was not subject to the Medical Research Involving Human Subjects Act and waived the need for formal ethical review and patient-informed consent. However, written informed consent was obtained for all patients who underwent endoscopic treatment [15]. Patients who had not undergone endoscopic treatment were approached through an opt-out card with the option of declining participation in the study.

RESULTS

We identified 258 patients with confirmed LGD. In total, 248/ 258 patients (96 %) were referred to a BEC for a re-staging endoscopy between January 2017 and October 2019 and were included in the analysis. The remaining 10 patients remained in the care of the community hospital and were not referred for varying reasons, including limited life expectancy and/or patient preference.

Baseline characteristics are shown in Table 1. The majority of patients were male (78 %) and the median age of patients was 69 years (IQR 64–75). A total of 149 patients (60 %) had a history of Barrett's surveillance at a community hospital for a median duration of 7 years.

Table 1. Baseline characteristics

			All (n=248)
Demographics	Age, years, Median (IQR)		69 (64-75)
	Male, n (%)		194 (78)
	BMI Mean ± SD		27 ± 4
	Smokers*, n (%)		
	Current		25 (10)
	Former		84 (34)
History	History of surveillance prior to referral, n (%)		149 (60)
	Duration of prior surveillance, Median (IQR)		7 (3-12)
	History of LGD prior to referral, n (%)		31 (13)
Endoscopic BE characteristics	Prague classification for Length BE segment, cm, Median (IQR)		
	Circumferential		3 (0-6)
	Maximum		5 (3-8)
	Hiatal hernia, n (%)		235 (95)
	Esophagitis, n (%)		15 (6)
			Visible lesions (n=58)
	Paris classification of visible lesions (primary component)**, n (%)		
		Type 0-IIa	40 (69)
		Type 0-IIb	8 (14)
		Type 0-IIc	3 (5)
		Type 0-Is	1 (2)

**73 (29%) missings*
***6 (10%) missings*
Abbreviations: IQR – interquartile range; SD – standard deviation; PPI – proton pump inhibitors; LGD – low-grade dysplasia; BE – Barrett esophagus.

Re-staging endoscopy in the BEC was performed at a median of 3 months (IQR 0–3) after the community hospital endoscopy from which confirmed LGD was diagnosed.

HGD or cancer screening during re-staging

In total, 57 patients (23 %) had HGD or cancer during re-staging in the BEC. This included a diagnosis of HGD (32 patients; 13 % [95 %CI 9–18]), low risk EAC (23 patients; 9 % [95 %CI 6–14]), or high risk EAC (2 patients; 1 % [95 %CI 0.01–2]) (Table 2).

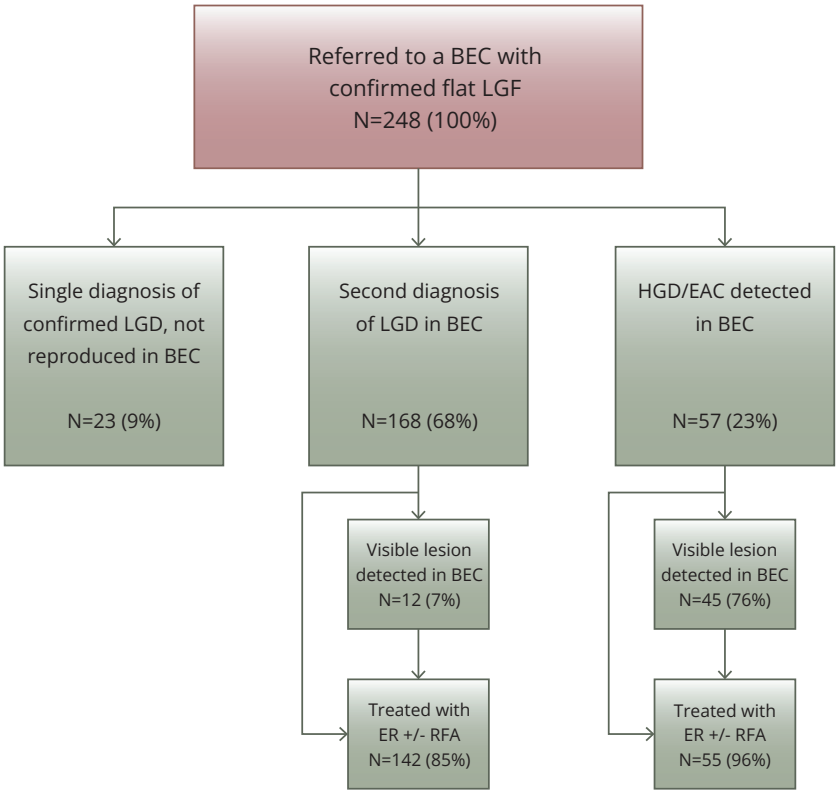
Table 2. Histopathology findings during re-staging in the BEC

Diagnosis during re-staging in BEC	Total cohort (N=248)	No visible lesion detected in BEC (histology based on random biopsies)	Visible lesion detected in BEC
Dysplasia not reproduced, n (%)	23 (9)	22 (96)	1 (4)
New diagnosis of confirmed LGD, n (%)	168 (68)	156 (93)	12 (7)
HGD, n (%)	32 (13)	12 (37)	20 (63)
EAC, n (%)	25 (10)	-	25 (100)
LR-EAC	*23 (9)*		
HR-EAC	*2 (1,0)*		

Abbreviations: BEC – Barrett Expert Center; y – year; LGD – low-grade dysplasia; HGD – high-grade dysplasia; EAC – esophageal adenocarcinoma; LR – low-risk; HR – high-risk

In 168/248 patients (68 %; [95 %CI 62–74]) a second diagnosis of confirmed LGD was found during re-staging at the BEC. In the remaining 23 patients (9 % [95 %CI 6–14]), the initial finding of dysplasia was not reproduced (Fig. 1).

Figure 1. Expert center endoscopic assessment of confirmed low-grade dysplasia – patient flow

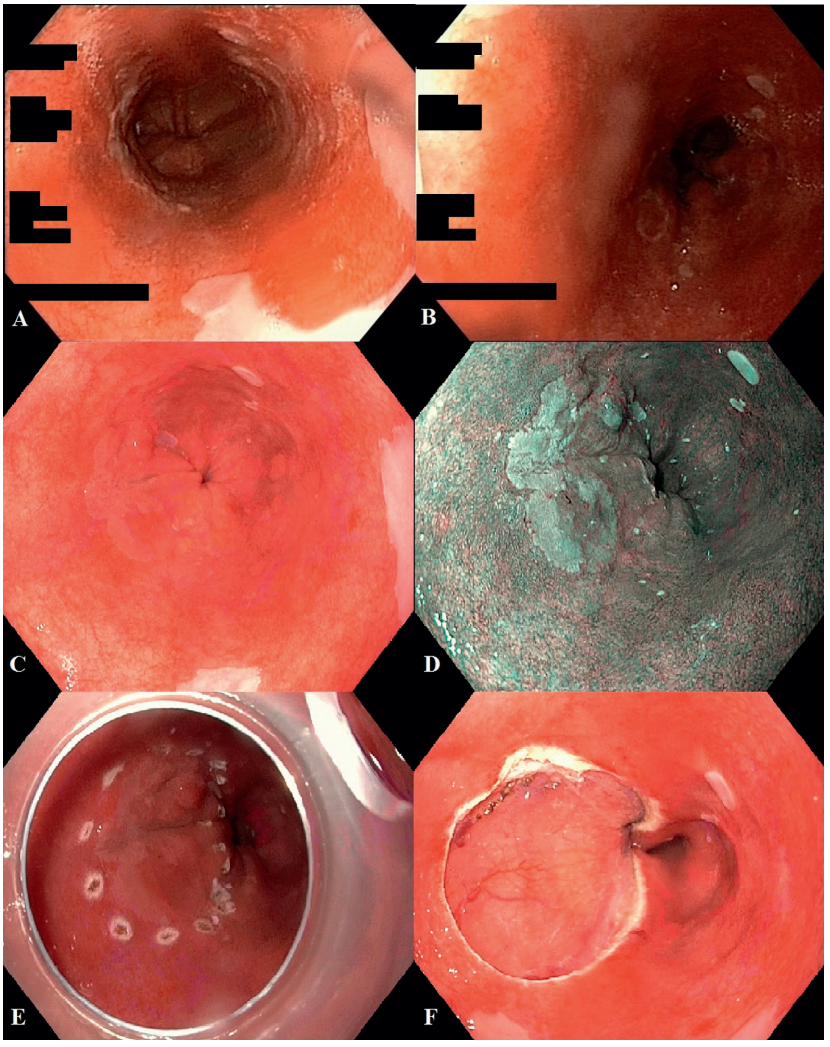


Visible lesions during re-staging

Overall, re-staging in the BEC resulted in detection of a visible lesion in 58/248 patients (23%). Fig. 2 shows a composite image from a patient with a visible lesion detected at a BEC. Stratified for worst pathology found during re-staging, all 25 patients with EAC were diagnosed with a visible lesion (100 % [95%CI 86–100]) (Table 2). For patients diagnosed with HGD, a visible lesion was found in 20/32 (63 %; [95 %CI 44–79]). Among patients with a second diagnosis of confirmed LGD, 12/168 patients (7 %; [95 %CI 4–12]) had a visible lesion. Finally, one patient (4% [95 %CI 0.1–2]) with NDBE was found to have a visible lesion that appeared suspicious for neoplasia during endoscopy and was removed with endoscopic resection, but the final pathology reading showed no dysplasia.

Overall, 51 /58 patients (88 %) had a flat-type lesion (i. e. type 0-II) according to the Paris classification, most commonly type 0-IIa (Table 1).

Figure 2. Endoscopic images of a patient referred with confirmed low-grade dysplasia (LGD) in random biopsies; no visible lesions were detected at the referring hospital.



Images from the community hospital (a, b) and the Barrett Expert Center (BEC) (c–f). a, b Images in white-light endoscopy (WLE) of a C4M5 Barrett's segment without signs of reflux esophagitis. The endoscopist reported no visible abnormalities and took random biopsies at three levels (i.e. unclear whether these were taken by following the Seattle protocol). Histopathology analysis showed LGD in all three levels, with p53 expression. Panel review confirmed the diagnosis. c, d Images in WLE and narrow-band imaging of the same patient with a Barrett's segment containing a Paris type 0-IIa visible lesion of 25 mm in diameter, 2 cm above the gastroesophageal junction, at the 7–11 o'clock neutral position. e Endoscopic view through the Duette cap: lesion delineated with electrocoagulation markers before starting the endoscopic resection procedure. f View of the wound after re- section and removal of the cap. Histopathology analysis showed esophageal adenocarcinoma invading the submucosa, with good differentiation, without signs of lymphovascular invasion.

High risk cancer during re-staging

Two patients (2/248; 1 %) were diagnosed with a high risk EAC during re-staging. One patient was found to have a visible lesion upon re-staging in the BEC. The patient had no history of surveillance for BE in the community hospital. The time between the first community hospital endoscopy and re-staging endoscopy in the BEC was 3 months. The endoscopic resection specimen showed a deep submucosal cancer (≥ 500 µm), with lymphovascular invasion and moderate differentiation, with negative deep resection margins. Additional baseline examinations showed lymph node and distant metastasis.

The second patient, also without BE surveillance history, was found to have a visible lesion upon re-staging and endoscopic submucosal dissection was initiated but prematurely aborted due to deep invasion of the proper muscle layer. Additional baseline examinations showed bone metastasis. Time between first community hospital endoscopy and re-staging was 3 weeks.

Indication for endoscopic treatment

After re-staging in the BEC, 91 % of patients (225/248; [95 %CI 86–94]) had an indication for endoscopic treatment according to current guidelines. Treatment indications consisted of EAC (n = 25), HGD (n = 32), or two diagnoses of confirmed LGD (n = 168).

Follow-up after re-staging

Endoscopic treatment

All patients with HGD (n = 32) and low risk cancer (n = 23) underwent direct endoscopic treatment. Treatment was also initiated in 142/168 patients with a second diagnosis of confirmed LGD. Complete endoscopic eradication was achieved in the majority of patients with a second diagnosis of confirmed LGD, HGD, or cancer (i. e. 94 % vs. 100 % vs. 86 %, respectively). Treatment outcomes have been described in detail in a separate article [15].

Endoscopic surveillance after a second diagnosis of confirmed LGD

Despite a repeat diagnosis of confirmed LGD, 26/168 patients (15 %) underwent endoscopic surveillance instead of prophylactic RFA owing to limited life expectancy and/or patient preference. Median BE length in this group was C5M6 (IQR C1–8; M4–10). Patients were followed for a median of 15 months (IQR 10– 23) with a median of 2 follow-up endoscopies (IQR 1–2).

Two patients progressed to HGD (2/26; 8 %; annual risk 6 %). One patient had HGD at the first follow-up after 6 months. The second patient developed HGD at 42 months

after baseline staging, with LGD reproduced during each of the three prior follow-up endoscopies. At the moment of progression to HGD, endoscopic treatment was initiated for both patients, with outcomes pending.

Endoscopic treatment after a single confirmed LGD diagnosis
A finding of dysplasia was not reproduced during re-staging in 23 patients. Patients were followed for a median of 19 months (IQR 12–25) with a median of 1 (IQR 1–2) follow-up endoscopy after restaging. Two patients (2/23; 9 %; annual progression risk 6 %) developed HGD, one after 6 months and the other after 30 months after several diagnoses of confirmed LGD.

Overall, when comparing results from all nine BECs, there was no significant difference between the centers.

DISCUSSION

We assessed the impact of a dedicated re-staging endoscopy by an expert endoscopist upon a diagnosis of flat BE with LGD confirmed by an expert pathologist. To that end, we included 248 patients who were referred to a BEC in the Netherlands with flat BE and a confirmed LGD diagnosis. In 23 % of patients, prevalent HGD or cancer was found during re-staging. This was diagnosed through targeted sampling from a visible lesion in the majority of patients. Overall, 91% of patients had an indication for endoscopic treatment after the re-staging endoscopy. Our results suggest that patients with confirmed LGD should undergo a re-staging endoscopy by an expert endoscopist.

It is well known that LGD is a challenging diagnosis and guidelines therefore recommend expert pathologist review for each LGD diagnosis [8–11]. The differentiation between reactive inflammatory changes and early dysplasia is complex. Prior studies have shown that up to 85 % of LGD diagnoses made in a community hospital, are downstaged to NDBE after expert re- view [6, 7]. Most importantly, LGD that was downstaged to NDBE progressed at an annual rate of < 1%, comparable to “normal” NDBE, whereas LGD that was confirmed had an annual progression risk of 9 %–13 % [6, 7]. Of note, in the current study we selectively included patients with LGD that was confirmed by an expert pathologist.

“Expert pathologists” in the current study were defined as pathologists dedicated in the field of BE with a median case load of seven cases a week, of which ≥ 25 % are dysplastic [16, 17]. Moreover, pathologists participated in multiple joint training programs with quality assessments followed by group discussions [4].

Some comparisons with prior studies can be drawn. The aforementioned two studies that assessed progression risks after confirmed LGD did not report a proportion of HGD/EAC and/or visible lesions detected at re-staging [6, 7]. However, steep Kaplan–Meier curves during the first 6 months suggest that HGD/EAC was already present at referral to the expert center [6, 7]. In the screening cohort of the SURF study, a randomized intervention study comparing RFA with surveillance for patients with LGD, 20/247 patients (8 %) initially diagnosed with confirmed LGD were found to have HGD or cancer during first re-staging in a BEC [12]. In addition, in a recently published retrospective study, the authors aimed to determine the proportion of prevalent HGD or EAC detected by BE referral units in patients referred from the community with a recent expert- confirmed diagnosis of LGD [21]. Similarly to our study, the authors concluded that worse grades of dysplasia (HGD/EAC) are found in a Barrett's referral unit after referral for confirmed LGD in approximately a quarter (20/75, 27 %) of patients, plausibly representing prevalent HGD/EAC [21]. We may speculate about several explanations for our findings. First, the quality of the endoscopy in the community hospital is likely to play an important role. This is mainly determined by the quality of imaging and the quality of histological sampling. It is well known that detection of visible lesions in BE is challenging. This is especially the case when exposure to visible lesions is low, as in a surveillance setting, partly due to the subtle appearance of early neoplasia, but mainly because general endoscopists are unfamiliar with the endoscopic appearance of neoplasia, as progression to neoplasia is rare (< 1 % annual risk) [22–24]. A prior study compared detection rates of visible lesions in community hospitals and after referral in BECs, and showed that expert endoscopists detected a visible lesion in 87 %, compared with 60 % in the community hospitals ($P < 0.01$) [25]. However, this study selectively included patients with HGD/EAC. The endoscopists at the expert center may therefore have been biased and were looking for a lesion, knowing that the patient had HGD/EAC.

An American study showed that nearly 25 % of endoscopies performed in patients with BE were not adherent to the Seattle protocol [26]. This finding was confirmed in a recent systematic review showing poor adherence to the Seattle protocol, especially in nonexpert centers and in longer BE segments [27]. Adherence may be low due to increased procedure time or incorrect perception of an individual patient's risk of neoplastic progression.

A second explanation reflects the quality of the endoscopy at the expert center. Endoscopic examination consists of high definition endoscopy with optical chromoendoscopy by an experienced endoscopist under optimal circumstances, with the majority of patients under sedation and with the use of dedicated timeslots for BE endoscopies.

However, if imaging and sampling may be less accurate in a community hospital, why were these patients with a visible lesion containing HGD or cancer then diagnosed with LGD? It seems unlikely that random biopsies with confirmed LGD in the community hospital were accidentally obtained from the visible lesion, and that these biopsies were then read as LGD but not as HGD or cancer. From a pathophysiological perspective, it may be that patients with HGD or cancer have a larger field defect with dysplastic changes. This large field defect with more widespread dysplastic changes may be easier to pick up with random biopsies than a solitary visible lesion. The cur- rent study shows that detection of confirmed LGD, even if the BE is deemed completely flat in a community hospital, defines a cohort with a substantial risk for more advanced histology.

Based on our results, we recommend that patients with con- firmed LGD in flat BE diagnosed in a community hospital are referred to an expert center for a dedicated re-staging endos- copy. Most importantly, one quarter of these patients may have a visible lesion with HGD or cancer, and 1 % were even found to have a high risk cancer. If these patients had been treated with RFA in a community hospital due to apparent "flat BE," this would have been inadequate therapy and the risk for progression to advance disease would be substantial.

On the other hand, if these patients with confirmed LGD had not been referred for re-staging at an expert center, surveillance would have been done after 6 months, with a risk of progression in patients with prevalent HGD/EAC. Moreover, a subtle lesion may also have been missed during the second endos- copy, with additional delay and risk for progression. The Dutch and European BE guidelines recommend that patients with confirmed LGD are referred to an expert center for re-staging within 3 months, whereas US guidelines advise re-staging after 3–6 months with high definition and (optical) chromoendoscopy, not necessarily at an expert center [8–10, 28, 29]. Considering the high rates of worse histopathology found at the expert endoscopy, we would advocate for re-staging within 3–6 months upon referral in an expert center as advised by the Dutch and European guideline.

This study has important strengths. This is the first report of a nationwide cohort of BE patients with confirmed LGD who were referred to expert centers for re-staging; the findings have direct implications for clinical care. Our data are homogeneous: all endoscopists and pathologists participated in a specific and joint training program, and all centers followed a uniform treatment and follow-up protocol. We included all patients in the Netherlands who underwent endoscopic re-staging upon confirmed

LGD in one of the BECs. We provide high quality data that were collected by dedicated researchers.

We have to address some limitations as well. This was a retrospective study with a risk for selection bias. Most importantly, we could have missed patients with confirmed LGD who were not included in our database. In order to minimize this risk and to ensure complete data, we performed an additional search of the national pathology database, in addition to the BEC registry search. There is also a risk that not all patients with confirmed LGD were referred to an expert center, but only the patients with anticipated high risk for neoplasia, such as those with long BE segments. This would result in an overestimation of the proportion of prevalent HGD in our study. However, as only 10 patients with confirmed LGD were not referred, the effect would be minimal. Finally, although guidelines recommend confirmation of each LGD diagnosis, some endoscopists may have chosen not to apply for pathology review. If specifically those patients with an assumed low risk for prevalent HGD, such as patients with short segment BE, were not referred for pathology review, then again the reported rate for prevalent HGD would overestimate the actual rate. However, our study outcomes do reflect current clinical care and therefore recommendations still hold.

In a minority of community hospital LGD cases (15 %), pathological review was performed by one local expert pathologist instead of review by the panel upon referral, because panel review is advisable, but not mandatory, according to the Dutch guideline [8]. As the endoscopists in the BEC were informed about the presence of LGD in advance, inspection may have been even more meticulous and the threshold to resect visible lesions may have been lower. However, instead of this being a limitation or bias, we feel that this reflects real-life clinical practice and only supports the advice to refer patients with confirmed LGD to an expert center for re-inspection. Unfortunately, we have no data on adherence to the Seattle protocol in the community hospitals. Therefore, we could not draw any conclusions regarding adherence to the Seattle biopsy protocol or possible sampling error. Follow-up data for confirmed LGD that was not treated in our study may be prone to confounding by indication. Downstaging to NDBE during re-staging may either indicate actual downstaging, but more likely reflects sampling error of focal LGD area(s), but it is impossible to differentiate between these two scenarios for patients in the cur- rent study. Unfortunately, we had no data on type of endoscope and use of optical chromoendoscopy. Finally, data may be less generalizable worldwide, owing to our homogeneous care set- ting in the Netherlands.

Our study shows that re-staging by an expert endoscopist upon confirmed LGD is valuable, as a quarter of the patients had prevalent HGD or cancer. Furthermore,

91 % of these patients had an indication for endoscopic treatment upon re-staging. Confirmed LGD entails a high risk of synchronous worse histopathology that can easily be overlooked by inexperienced endoscopists. We advocate for expert endoscopy for all patients with confirmed LGD.

REFERENCES

1 Shaheen NJ, Richter JE. Barrett's oesophagus. Lancet 2009; 373: 850– 861

2 Crane LMA, Schaapveld M, Visser O et al. Oesophageal cancer in The Netherlands: increasing incidence and mortality but improving survival. Eur J Cancer 2007; 43: 1445–1451

3 Solanky D, Krishnamoorthi R, Crews N et al. Barrett esophagus length, nodularity, and low-grade dysplasia are predictive of progression to esophageal adenocarcinoma. J Clin Gastroenterol 2019; 53: 361–365

4 Klaver E, van der Wel M, Duits L et al. Performance of gastrointestinal pathologists within a national digital review panel for Barrett's oesophagus in the Netherlands: results of 80 prospective biopsy re- views. J Clin Pathol 2021; 74: 48–52

5 Klaver E, Bureo Gonzalez A, Mostafavi N et al. Barrett's esophagus surveillance in a prospective Dutch multi-centre community-based cohort of 985 patients demonstrates low risk of neoplastic progres- sion. United Eur Gastroenterol J 2021; 9: 929–937

6 Duits LC, Phoa KN, Curvers WL et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut 2015; 64: 700–706

7 Curvers WL, ten Kate FJ, Krishnadath KK et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol 2010; 105: 1523–1530

8 Nederlandse Vereniging van Maag-Darm-Leverartsen. Richtlijn Barrett-oesofagus. In Dutch. IKNL; 2018: 1–71https://www.mdl.nl/sites/ www.mdl.nl/files/richlijnen/Richtlijnen%20Barrett%20oesofagus%20-%20jan%202018%20-%20tbv%20website.pdf

9 Weusten B, Bisschops R, Coron E et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2017; 49: 191–198

10 Shaheen NJ, Falk GW, Iyer PG et al. ACG Clinical Guideline: Diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016; 111: 30–50

11 Evans JA, Early DS. ASGE Standards of Practice Committee. et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc 2012; 76: 1087– 1094

12 Phoa KN, van Vilsteren FGI, Weusten BLAM et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia. JAMA 2014; 311: 1209

13 Shaheen NJ, Sharma P, Overholt BF et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009; 360: 2277– 2288

14 Small AJ, Araujo JL, Leggett CL et al. Radiofrequency ablation is associated with decreased neoplastic progression in patients with Bar- rett's esophagus and confirmed low-grade dysplasia. Gastroenterology 2015; 149: 567–576

15 van Munster S, Nieuwenhuis E, Weusten BLAM et al. Long-term out- comes after endoscopic treatment for Barrett's neoplasia with radio- frequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period. Gut 2022; 71: 265–276

16 van der Wel MJ, Duits LC, Klaver E et al. Development of benchmark quality criteria for assessing whole-endoscopy Barrett's esophagus biopsy cases. United Eur Gastroenterol J 2018; 6: 830–837

17 van der Wel MJ, Klaver E, Duits LC et al. Adherence to pre-set bench- mark quality criteria to qualify as expert assessor of dysplasia in Bar- rett's esophagus biopsies – towards digital review of Barrett's esophagus. United Eur Gastroenterol J 2019; 7: 889–896

18 Sharma P, Dent J, Armstrong D et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology 2006; 131: 1392–1399

19 The Paris endoscopic classification of superficial neoplastic lesions. Esophagus, stomach, and colon. November 30 to December 1, 2002. Gastrointest Endosc 2003; 58: (Suppl. 06): S3–43

20 Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1998; 93: 1028–1032

21 Tsoi EH, Mahindra P, Cameron G et al. Barrett's esophagus with low- grade dysplasia: high rate of upstaging at Barrett's esophagus referral units suggests progression rates may be overestimated. Gastrointest Endosc 2021; 94: 902–908

22 Bergman JJGHM, de Groof AJ, Pech O et al. An interactive web-based educational tool improves detection and delineation of Barrett's esophagus-related neoplasia. Gastroenterology 2019; 156: 1299– 1308

23 de Groof AJ, Struyvenberg MR, van der Putten J et al. Deep-learning system detects neoplasia in patients with Barrett's esophagus with higher accuracy than endoscopists in a multistep training and valida- tion study with benchmarking. Gastroenterology 2020; 158: 915–929

24 Hvid-Jensen F, Pedersen L, Drewes AM et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011; 365: 1375–1383

25 Schölvinck DW, van der Meulen K, Bergman JJGHM et al. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy 2017; 49: 113–120

26 Wani S, Williams JL, Komanduri S et al. Endoscopists systematically undersample patients with long-segment Barrett's esophagus: an analysis of biopsy sampling practices from a quality improvement registry. Gastrointest Endosc 2019; 90: 732–741

27 Roumans CAM, van der Bogt RD, Steyerberg EW et al. Adherence to recommendations of Barrett's esophagus surveillance guidelines: a systematic review and meta-analysis. Endoscopy 2020; 52: 17–28

28 Sharma P, Shaheen NJ, Katzka D et al. AGA clinical practice update on endoscopic treatment of Barrett's esophagus with dysplasia and/or early cancer: expert review. Gastroenterology 2020; 158: 760–769

29 Wani S, Qumseya B. Standards of Practice Committee. et al. Endoscopic eradication therapy for patients with Barrett's esophagus- associated dysplasia and intramucosal cancer. Gastrointest Endos 2018; 87: 907–931

CHAPTER 5

Endoscopic resection without subsequent ablation therapy for early Barrett's neoplasia: endoscopic findings and long-term mortality

S. N. van Munster, E. A. Nieuwenhuis, B. L. A. M. Weusten, L. Alvarez Herrero, A. Bogte, A. Alkhalaf, B. E. Schenk, E. J. Schoon, MD, W. Curvers, MD, A. D. Koch, MD, S. E. M. van de Ven, P. J. F. de Jonge, MD, T. Tang, W. B. Nagengast, F. T. M. Peters, J. Westerhof, M. H. M. G. Houben, Jacques J. G. H. M. Bergman, R. E. Pouw

Gastrointest Surg. 2021 Jan;25(1):67-76. doi: 10.1007/s11605-020-04836-8

ABSTRACT

Introduction

After endoscopic resection (ER) of neoplasia in Barrett's esophagus (BE), it is recommended to ablate the remaining BE to minimize the risk for metachronous disease. However, we report long-term outcomes for a nationwide cohort of all patients who did not undergo ablation of the remaining BE after ER for early BE neoplasia, due to clinical reasons or performance status.

Methods

Endoscopic therapy for BE neoplasia in the Netherlands is centralized in 8 expert centers with specifically trained endoscopists and pathologists. Uniformity is ensured by a joint protocol and regular group meetings. We report all patients who underwent ER for a neoplastic lesion between 2008 and 2018, without further ablation therapy. Outcomes include progression during endoscopic FU and all-cause mortality.

Results

Ninety-four patients were included with mean age 74 (± 10) years. ER was performed for low-grade dysplasia (LGD) (10%), high-grade dysplasia (HGD) (25%), or low-risk esophageal adenocarcinoma (EAC) (65%). No additional ablation was performed for several reasons; in 73 patients (78%), the main argument was expected limited life expectancy. Median C2M5 BE persisted after ER, and during median 21 months (IQR 11–51) with 4 endoscopies per patient, no patient progressed to advanced cancer. Seventeen patients (18%) developed HGD/EAC: all were curatively treated endoscopically. In total, 29/73 patients (40%) with expected limited life expectancy died due to unrelated causes during FU, none of EAC.

Conclusion

In selected patients, ER monotherapy with endoscopic surveillance of the residual BE is a valid alternative to eradication therapy with ablation.

INTRODUCTION

Barrett's esophagus (BE) is the most important risk factor for esophageal adenocarcinoma (EAC), which has a poor prognosis. Identifying EAC at an early stage allows for endoscopic treatment with an excellent prognosis. The first step in endoscopic treatment for BE-related neoplasia is removal of all visible lesions with endoscopic resection (ER) techniques, which serves both diagnostic and therapeutic purposes. It has been reported that the remaining flat BE that persists after ER of a neoplastic lesion has a risk of developing metachronous HGD/EAC between 15 and 30% in 3–5 years [1–3]. Based on these data, most international guidelines advise additional ablation therapy after ER to eradicate the entire BE segment [4–7]. Given the large amount of high-quality data supporting radiofrequency ablation (RFA), this is recommended as first-choice ablation technique [4, 8–10].

Although RFA therapy is highly effective for eradication of flat BE, the choice to continue with ablation requires balanced decision-making, taking into account patient's age, comorbidity, and life expectancy [6]. The aforementioned FU studies have also shown that metachronous lesions were always detected at early stages that allowed curative endoscopic treatment [1–3]. Moreover, the majority of patients will never develop metachronous neoplasia. Performing RFA for all post-ER patients may thus be associated with overtreatment.

Although severe complications due to RFA treatment are very rare, complications do occur, most commonly esophageal strictures in up to 10–14% [11]. Furthermore, RFA treatment to eradicate all residual BE requires on average 3 additional therapeutic endoscopies. Patients may experience post- procedural pain, discomfort, or dysphagia. Therefore, after ER for early neoplasia, endoscopic surveillance ("ER monotherapy") may be an acceptable alternative to RFA, especially in patients with older age and/or severe comorbidities.

In the Netherlands, endoscopic treatment for BE is centralized in 8 Barrett Expert Centers (BECs), with a uniform treatment and follow-up protocol. Since the introduction of RFA in 2008, these centers adhered to the ER monotherapy strategy in selected patients. In the current study, we report the long-term outcomes of "ER monotherapy" as an alternative to additional ablation therapy in patients with limited life expectancy.

METHODS

This study was based on the Barrett Expert Center registry (BEC registry) (Netherlands Trial Register, NL7039), which has been described in detail earlier [12]. In short, this registry captures outcomes for all patients with Barrett's neoplasia in the Netherlands who underwent endoscopic treatment since 2008. Care for BE neoplasia in the Netherlands is centralized in 8 Barrett Expert Centers (BECs), with the implication that every patient in the Netherlands is treated in one of these expert centers. This centralized organization of care was established in 2007. At that moment, a joint training program was launched for endoscopists and pathologists, one of both from each center. All BE care in the Netherlands since then has been provided by the specifically trained endoscopists and pathologists. The BECs adhered to a common treatment and follow-up protocol, and several meetings a year were held to further guarantee homogeneity. Apart from this close collaboration for clinical care, a solid joint research infrastructure was founded and resulted in multiple publications in the field of pathology [13–16], imaging [17–19], and treatment [8, 9, 20–26] of early BE neoplasia.

The centers have a minimum annual case load of 10 new patients with neoplasia per year, and all new cases are registered in a database.

Treatment protocol

Patients were referred to a BEC for careful work-up and staging after being diagnosed with low-grade dysplasia (LGD), HGD, or EAC. During an upper gastrointestinal endoscopy (UGE), the esophagus was carefully inspected with documentation of the Prague C&M criteria and presence of visible lesions or other abnormalities such as esophagitis or esophageal stenosis.

If a visible abnormality was detected, endoscopic resection (ER) was performed for histologic staging using the ER-cap technique, multiband mucosectomy (MBM), or endoscopic submucosal dissection (ESD) per physician's discretion. Four-quadrant random biopsies were obtained from the (residual) flat BE segment according to the Seattle protocol [27]. If the ER specimen showed LGD, HGD, or low-risk (LR) EAC (defined as ≤sm1 invasion with good to moderate differentiation, without lymphovascular invasion and with radical vertical resection margin), a balanced decision was made between further endoscopic treatment or surveillance. In the vast majority of patients, additional ablation therapy was offered to achieve a complete eradication of the entire Barrett's segment. However, in patients with limited life expectancy, for example, due to older age and/or severe comorbidity, surveillance of the remaining BE was preferred with endoscopic intervention in case of recurrent neoplasia and/or visible lesions.

All patients were prescribed bi-daily high-dose protonpump inhibitors.

Follow-up Protocol

FU for persisting non-dysplastic BE (NDBE)/LGD after ER consisted of yearly surveillance endoscopies in year 1 to 5, and then once per 2–3 years. FU was performed every 3–6 months for persisting HGD. The decision to stop further surveillance was made per physician's discretion in agreement with the patient.

Study Population

For the current study, we included all patients from the BEC registry who underwent ER monotherapy for LGD, HGD, or LR-EAC with residual flat BE before January 1, 2018.

Study Endpoints

The first primary endpoint was progression to HGD/EAC in the remaining BE. For patients with remaining NDBE or LGD, detection of HGD/EAC was considered to be progression. For patients with persisting flat HGD, new EAC was progression as was a new visible lesion containing HGD. All patients were included for this analysis. This endpoint was stratified for residual grade of dysplasia.

The second primary endpoint was all-cause mortality. This endpoint reflects whether the decision to prefer surveillance over ablation was justified for patients with expected limited life expectancy. Therefore, only the patients in whom the decision for ER monotherapy was based on age and/or comorbidity were included for this analysis.

Secondary endpoints included symptomatic EAC and/or EAC-related death and predictors for progression. All patients were included for these analyses. We also assessed progression risk to HGD/EAC in the remaining BE among only patients who had at least 18 months of endoscopic FU.

Data Collection and Data Management

Endoscopy and pathology data were collected in standardized form in all BECs, by medical students in the final year of their degree. Additionally, all patients with endpoints and an additional 50% of the remaining patients were double-checked by dedicated research fellows (all MDs). All fields were examined for missing data, unlogical values, or outliers, with data being completed or corrected where possible.

The BEC registry was merged with the non-public microdata from Statistics Netherlands for date and cause of death.

Statistics

Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR) for normally distributed or skewed data, respectively. Categorical variables were presented as numbers with percentages, and 95% confidence intervals (CI) were obtained using internal bootstrapping.

Progression risks were plotted using the cumulative incidence curve (CII), taking competing risks of unrelated death into account. Annual progression rates were calculated as the number of progressors divided by the total follow-up duration in years. Predictors for progression were assessed using Cox regression and Fine and Gray competing risk analysis, the latter considered unrelated death as competing risk.

Statistical analysis was performed using Rstudio for Windows (version 3.6.1) and packages: survival, survminer, cmprsk, ggplot2, and Hmisc.

Ethics

The Institutional Review Board of the Amsterdam University Medical Centers declared that the registry was not subject to the Medical Research Involving Human Subjects Act ("wet op medisch-wetenschappelijk onderzoek met mensen" in Dutch) and waived the need for formal ethical review and patient-informed consent. Patients were approached through an opt-out card with the possibility to object against participation in the registry.

RESULTS

Patient Description

Between 2008 and 2018, a total of 1962 patients with early BE neoplasia were referred to a BEC. A visible abnormality was detected in 1395 patients (71%) and removed with ER (Fig. 1). After ER for LGD, HGD, or LR-EAC (n = 1140), a flat BE segment remained in 1034 patients. The vast majority of these patients (91%) underwent additional ablation aimed at eradication of the entire BE segment. Ninety-four patients (9%) had ER monotherapy for LGD (n = 9), HGD (n = 23), T1a EAC (n = 47), or T1bsm1 EAC (n = 15), with remaining BE, and were included for this study.

Patients had a mean age of 74 (± 10) years and ASA classification II (67%) or III/IV (23/2%), with ER performed for LGD (10%), HGD (25%), or LR-EAC (66%) (Table 1).

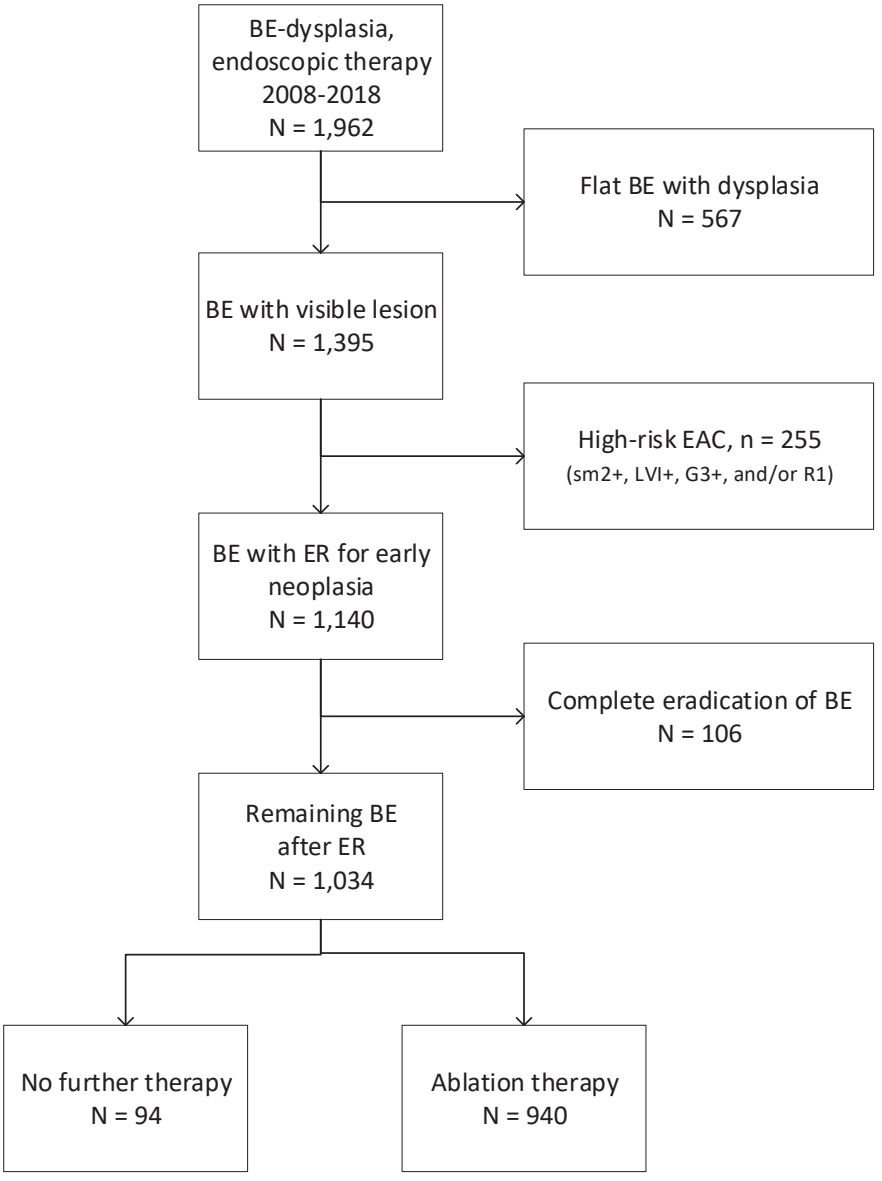
Table 1. Demographics

	All *N* = 1034	ER monotherapy *N* = 94	ER + ablation *N* = 940
Male gender, *n* (%)	803 (80)	64 (86)	766 (82)
Age, years (mean (± SD))	66 (10)	74 (10)	65 (9)
BMI, kg/m^2 (mean (± SD))	28 (5)	27 (10)	27 (5)
ASA classification, *n* (%)			
I		7 (7)	
II		63 (67)	
III		22 (23)	
IV		2 (2)	
Smoking, *n* (%)			
Current	169 (23)	12 (18)	157 (23)
Former	338 (46)	37 (56)	301 (45)
Never	232 (31)	17 (26)	215 (32)
Esophagitis, *n* (%)	36 (4)	2 (2)	34 (4)
BE segment, cm (median (IQR))	C2M5 (1–5; 3–7)	C4M6 (1–7; 3–9)	C2M5 (1–5; 3–7)
Lesion, Paris-type, *n* (%)			
0-Ip/s	107 (13)	17 (24)	90 (12)
0-IIa	563 (67)	35 (50)	528 (69)
0-IIb	131 (16)	15 (21)	116 (15)
0-IIc	35 (4)	3 (4)	32 (4)
Lesion, size, mm (mean (± SD))	25 (15)	27 (21)	25 (15)
Lesion, circ extent, % (mean (± SD))	39 (21)	39 (21)	39 (21)
ER type, *n* (%)			
EMR	983 (95)	85 (90)	898 (96)
ESD	49 (5%)	7 (7)	42 (5)
Both	2 (0.2%)	2 (2)	0
Specimen ER, *N* (median (IQR))	2 (1–3)	2 (1–3)	2 (1–3)
< 50% squamous regression of ER-site, *n* (%)	53 (5)	12 (13)	41 (5)
Worst ER pathology, *n* (%)			
LGD	69 (7)	9 (10)	60 (6)
HGD	263 (25)	23 (25)	240 (26)
EAC	702 (68)	62 (66)	640 (68)

*Missing values existed for the following variables (*n* = missing in total cohort/missing in ER monotherapy cohort): BMI (*n* = 164/25), ASA (*n* = 700/0), smoking (*n* = 295/28), Paris classification (*n* = 198/24), and regeneration of ER site (*n* = 56/0)

ASA American Society of Anesthesiologists, *BE* Barrett esophagus, *circ* circumferential, *EAC(-m/sm)* esophageal adenocarcinoma (mucosal/submucosal), *EMR* endoscopic mucosal resection, *ER* endoscopic resection, *ESD* endoscopic submucosal dissection, *HGD* high-grade dysplasia, *IQR* interquartile range, *LGD* low-grade dyspla- sia, *SD* standard deviation

Figure 1. Flowchart



Patient flow in the Barrett Expert Center Registry. All patients with remaining flat BE after ER for which no ablation was performed were included in the current study (*n* = 94)

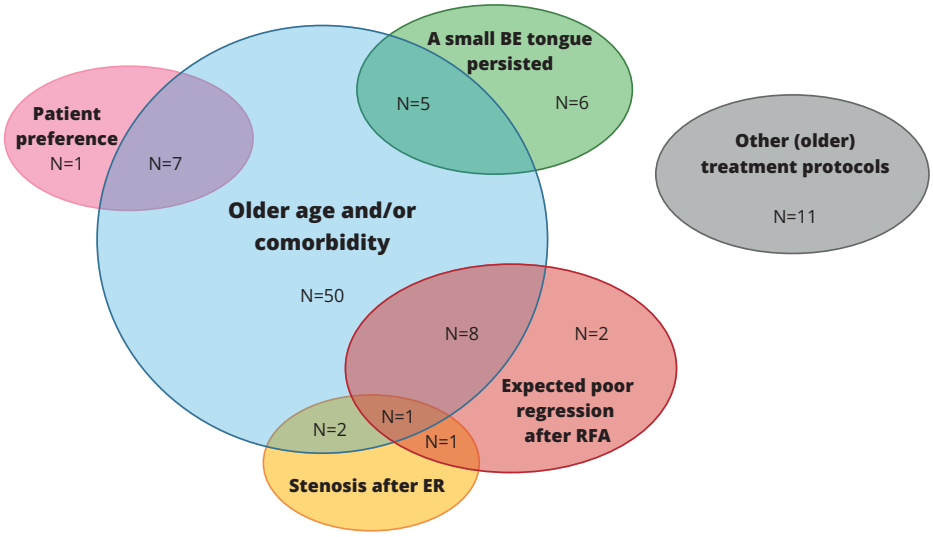
Decision-Making after ER

After ER for all visible abnormalities, a flat BE segment of median C2M5 (0–5; 3–8) remained with NDBE (n = 48, 51%), LGD (n = 29, 32%), or HGD (n = 6, 6%). In 11 patients (12%), no biopsies were obtained since this was considered not to change clinical decision-making.

In 73 patients (78%), additional ablation was not started due to age and/or comorbidity. Concomitant reasons in this group were as follows: expected poor regression after RFA due to regeneration with BE after ER (n = 8, 11%); patient preference (n = 7, 10%); persistence of a small BE tongue only (n = 5, 7%); and/or complications after ER (n = 3, 4%) (Fig. 2).

In the remaining 21 patients (22%) in whom age and co-morbidity played no role, reasons not to continue with ablation therapy were as follows: other treatment protocols (e.g., in the pre-RFA era) (n = 11, 52%); persistence of a small BE tongue only (n = 6, 29%); expected poor regression after RFA due to BE regeneration after ER (n = 3, 14%); complications after ER (n = 1, 5%); and/or patient preference (n = 1, 5%).

Figure 2. Reasons not to continue with ablation therapy after ER.



Several reasons were reported why RFA was not initiated; age and/or comorbidity constituted the most common reasons

Progression During Follow-Up

During a median endoscopic FU of 21 months (11–51) with a median of 4 endoscopies 3–5 per patient, no patient progressed to advanced cancer. Overall, 17 patients (18%, annual progression risk 8.0% [95% CI 5.1–12.5]) progressed to HGD (n = 10) or LR-EAC (n = 7) (Table 2). The median time to progression was 26 months (23–47), and the first progression was detected 18 months after ER. All patients who progressed had undergone at least 2 FU endoscopies without abnormalities after ER.

Sixteen out of seventeen progressors were successfully treated endoscopically, either with ER for a visible lesion containing LR-EAC (n = 7) or HGD (n = 6) or with ablation therapy for flat HGD (n = 3). A single patient who progressed from LGD to HGD had no further treatment, and the patient died shortly after due to an unrelated cause. Six progressors had developed a worse histological grade during FU, than the initial histology after baseline ER. This included baseline LGD to m-EAC in FU (n = 1), baseline HGD with m-EAC in FU (n = 4), and baseline m-EAC with sm-EAC during FU (n = 1).

The annual risk for progression was 6.4% for residual NDBE and 6.7% for LGD, as compared to 14.5% for residual HGD (Table 2).

In total, 55 patients had an endoscopic FU > 18 months with an annual risk for progression of 8.6% per person year [95% CI 5.4–13.3]. The median FU in this subgroup of patients was 31 months after ER (IQR 17–53).

In the majority (27/39; 69%) of the patients with FU < 18 months, endoscopic FU was discontinued at median 3 months (IQR 0–9) after ER, due to limited life expectancy. Of these 27 patients, 15 had unrelated death median 18 months after ER, whereas the remaining 12 were alive and asymptomatic at median 55 months after ER. The remaining 12/39 patients with short FU were recently treated with ER and were still under endoscopic surveillance (median 12 months).

All-Cause Mortality

Our second aim was to asses all-cause mortality during long- term follow-up in the subgroup of patients with older age and/ or comorbidity, to verify whether ER monotherapy was justified in this group of patients.

Table 2. Progression rates per histologic stage in the remaining BE after ER

Histology in residual BE after ER	Total patients (N)	Median FU duration (months)	Median N endoscopies	Worst histology during FU					Annual progression rate [95% CI]
				No FU performed	NDBE	LGD	HGD	LREAC	
No biopsies	11	17 (8–65)	3 (1–6)	5	5	1	0	0	-
NDBE	48	20 (10–48)	3 (1–5)	0	37	3	3	5	6.4% [3.3–12.1]
LGD	29	22 (14–60)	3 (1–5)	1	13	9 (4*)	5	1	6.7% [3.1–13.9]
HGD	6	41 (14–62)	7 (2–10)	0	0	0	5 (2**)	1	14.5% [5.0–34.6]
Total	94	21 (11–51)	3 (1–5)	6	54	13	13	7	8.0% [5.1–12.5]

Risk for progression to HGD/EAC during endoscopic FU, stratified for histology of the flat BE that remained after ER
*4 with persisting LGD were treated with RFA
**2 with HGD developed a lesion during FU and were treated with ER and counted as progression

As reported, in 73 patients, age and/or comorbidity played an important role in the decision not to continue with ablation therapy after ER. In 37 patients, endoscopic surveillance was stopped early at median 20 months (5–59) after ER (Fig. 3). Unrelated death occurred in 16 of these patients median 10 months after FU was stopped. The remaining 21 patients were still alive and asymptomatic median 24 months after FU was stopped.

In the remaining 36 patients, endoscopic FU was not stopped early. A total of 13 patients died from unrelated causes while being under surveillance, median 50 months after ER. The remaining 23 patients were still under surveillance at the moment of data collection, median 21 months after ER. Overall, 29 of 73 patients (40%) died due to unrelated causes median 28 months after ER at a median age of 80 (72–85) years. The remaining 44 of 73 patients were still alive at the moment of data collection median 42 months after ER. Figure 4 shows the cumulative incidence curves for progression and unrelated death. Neoplasms other than EAC (n = 11, 38%) and cardiovascular disease (n = 11, 38%) contributed the most common causes of death.

EAC-related Death

None of the 94 patients progressed to disease stages that exceeded boundaries for curative endoscopic treatment, developed symptomatic EAC, or died from EAC.

Predictors

In univariable analysis, length of the residual BE was significantly associated with risk for progression during FU (Table 3). For patients with a remaining circumferential BE of 0–1 cm, 2– 5, or > 5 cm, the annual progression risks were 1.8%, 7.0%, and 15.9%, respectively. The risk increased with 11% for every centimeter increase in BE length. The hazard ratio for persisting HGD versus LGD or NDBE was considerable, but did not reach the level of statistical significance. Estimated hazard ratios for Fine and Gray and Cox analysis were comparable.

Table 3. Univariable analysis for progression

		No progression *N* = 77	Progression *N* = 17	FG HR [95% CI]	Cox HR [95% CI]
Demographics	Age, years (mean (± SD))	75 (9)	71 (11)	1.01 [0.94; 1.04]	1.01 [0.95; 1.04]
	Male gender, *n* (%)	52 (68)	12 (71)	0.82 [0.43;3.47]	0.91 [0.32; 2.60]
Baseline BE	Worst ER histology, *n* (%)				
	LGD	8 (10)	1 (6)	2.53 [0.29; 22.3]	1.90 [0.25; 14.67]
	HGD/EAC	69 (90)	16 (94)		
	N ER specimen	2 (1–3)	2 (1–3)	0.94 [0.67; 1.30]	0.99 [0.72; 1.36]
Residual BE	Circumferential extent, cm (median (IQR))	2 (0–5)	5 (2–6)	1.11 [1; 1.23]	1.22 [1.08; 1.40]
	Maximum extent, cm (median (IQR))	5 (2–8)	6 (5–8)	1.09 [0.98; 1.21]	1.13 [0.98; 1.30]
	Worst histology, n (%) NDBE/LGD	63 (82)	14 (82)	2.17 [0.77; 6.18]	2.47 [0.68; 8.99]
	HGD	3 (4)	3 (18)		
	No histology	11 (14)	–		

Univariable analysis for demographic and treatment characteristics for prediction or progression to HGD or EAC during endoscopic FU, assessed with Cox analysis and Fine and Gray estimation

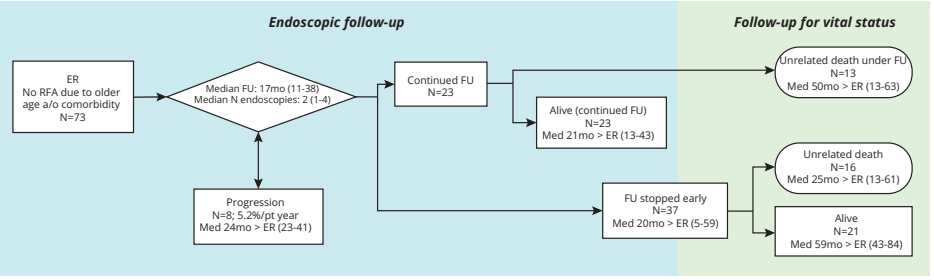
EAC esophageal adenocarcinoma, *ER* endoscopic resection, *ER* endoscopic resection, *FG* Fine and Gray, *HGD* high-grade dysplasia, *IQR* interquartile range, *LGD* low-grade dysplasia, *NDBE* non-dysplastic Barrett esophagus, *SD* standard deviation

DISCUSSION

We report endoscopic and long-term all-cause mortality out- comes for all patients with ER monotherapy in the Netherlands between 2008 and 2018, to assess whether this is a justified treatment strategy in selected patients with early BE neoplasia, for example, in case of older age and/or significant comorbidity. The risk for progression to HGD or EAC was 8% per year. In all cases, progression was detected at early stages and curatively treated endoscopically. No patient developed advanced EAC, and no patient died due to EAC, even though endoscopic surveillance was stopped early in half of the patients. Overall, 40% of patients died due to EAC unrelated causes at median 28 months after ER. These data suggest that ER monotherapy with endoscopic surveillance of the residual BE is a valid alternative to prophylactic ablation therapy in selected patients.

Data from the current study comport well with older studies from the pre-ablation era, reporting progression rates in remaining flat BE after ER varying from 15 during 5 years to 30% in 3 years [1–3]. These data have generally been used to justify initiating ablation therapy after ER, but one could also look at it from a different point of view. During every year of FU after ER, only 8% of patients develop progression, and this was always curatively treated with a single ER. RFA is effective and can achieve complete eradication of all BE (CE-BE) in 90–95% of patients. However, RFA is associated with multiple hospital visits and a risk of complications. Patients with baseline ER have the highest risk for post-RFA stenosis [28]. Apart from RFA-related complications, a recent study showed that the risk for cardiovascular complications due to sedation increases with age [29]. Unfortunately, we could not evaluate these endpoints in the current study given its retrospective nature with a risk for underreporting of these complications.

Figure 3. Long-term outcomes for 73 patients with no ablation due to older age and/or comorbidity



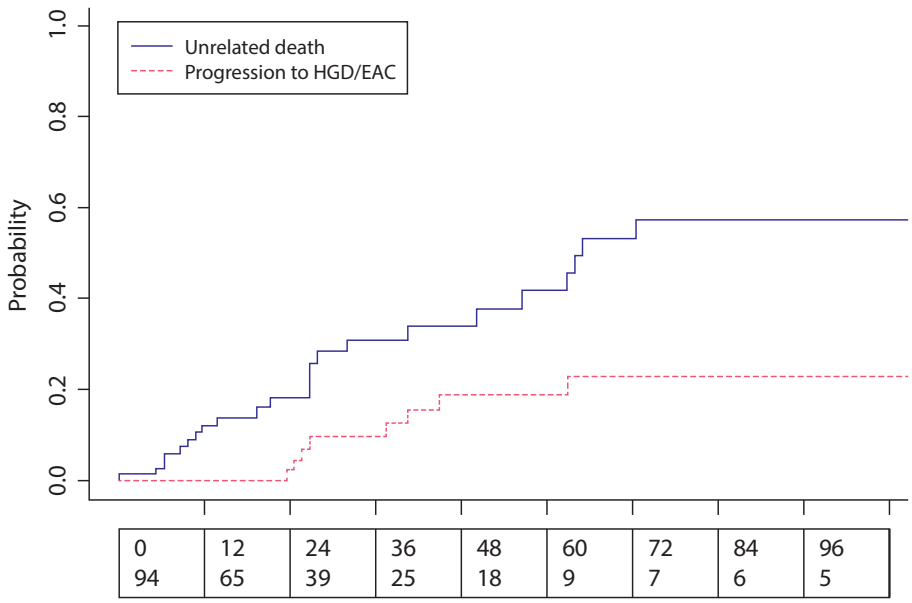
The outcomes during endoscopic follow-up, and long- term follow-up for vital status, among the 73 patients where RFA was not initiated due to older age and/or comorbidity

The decision to initiate prophylactic ablation therapy of residual BE after ER of neoplasia should be based on the answers to the following three questions:

1. What is the risk for this patient to develop recurrent neoplasia, with or without ablation therapy?

A substantial proportion of patients will never develop neoplasia in the remaining BE after ER. If the remaining BE after ER contains NDBE or LGD, the annual progression risk was only 6.4–6.7%. The median BE length in the current study was C2M5, and for shorter BE lengths, this annual risk will be even lower 1. Apart from the annual risk, we should also consider the cumulative risk for progression. Assume we continue surveillance until the age of 80 years, then the cumulative risk for a 50-year-old patient will be much higher as compared to a 78-year-old patient. Furthermore, if RFA treatment is initiated, it is important to realize that the risk for future neoplasia is lowered, but not reduced to zero. RFA generally fails to achieve CE-BE in 5–10% of patients, and the annual risk for recurrent neoplasia after CE-BE is 0.8% [12].

Figure 4. Risk for progression to HGD/EAC and unrelated death after ER monotherapy.

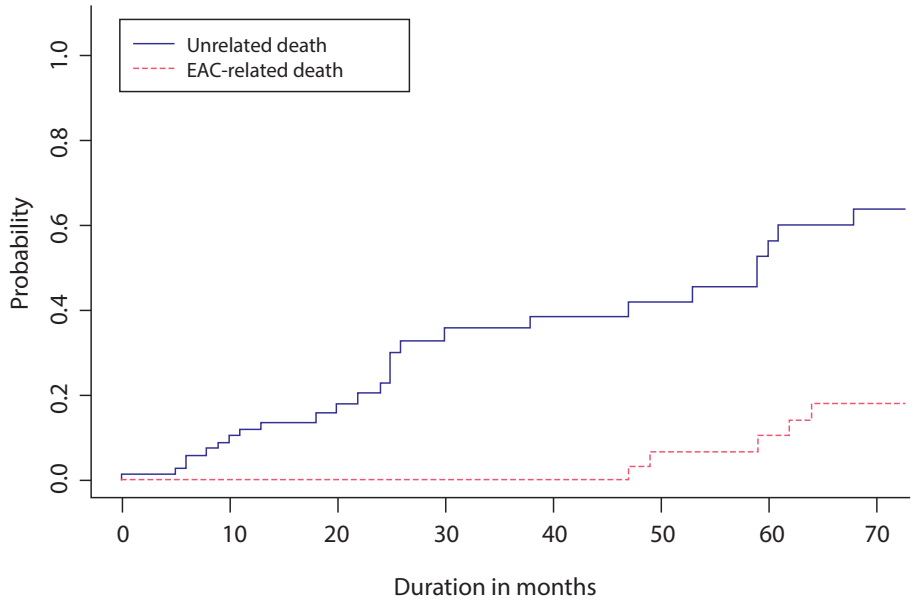


Cumulative incidence curves for progression to HGD/EAC and unrelated death during long-term FU after ER monotherapy, among the 73 patients in which RFA was not initiated due to older age and/or comorbidity.

2. If this patient develops progression, what is the risk of dying from EAC?
Second, the clinically relevant endpoint that should be prevented is progression to advanced, symptomatic EAC and/or EAC-related death. Most endoscopic studies define recurrent HGD or worse as an endpoint, or even recurrent LGD. Although this might be a logic endpoint for some studies, this is not the relevant endpoint that matters to a patient.

Proper data describing the natural history of HGD or early EAC is lacking, but older studies report incidence rates of HGD to advanced EAC of 6.6% per patient year with 2- to 5-year duration between detection of HGD and development of advanced EAC [30, 31]. Based on a worst-case scenario in which all patients would have died due to advanced EAC 2 years after progression was detected but not treated, we adapted the factual curve for progression from our study by horizontally shifting it two years to the right (Fig. 5). This new curve now represents the imaginary incidence for EAC- related death in the study population. This plot is based on numerous assumptions and should not be adopted for truth, but merely provides insight in the differences of occurrence and timing for varying endpoints used.

Figure 5. Hypothetical risks for EAC-related death and unrelated death in the situation where we would not have treated progression



Imaginary cumulative incidence curves for EAC-related death and unrelated death. The incidence curve for EAC-related was derived from the assumption that progression that was left untreated, would cause EAC-related death 2 years later.

3. How does the risk for EAC-related death relate to the risk of death due to other causes?
Finally, the benefits of eradication of all BE over removal of neoplasia should be balanced against the assumed life expectancy of a patient. Differences in life expectancy would not only change the cumulative risk for recurrence as described above but would also change the curve for unrelated death in Fig 5. For young and fit patients, this curve would shift downwards, whereas it would be steeper along with increasing age and/or comorbidity. The actual decision to eradicate the remaining BE after ER should be based on a balance between the risk of future progression to advanced EAC versus the risk for death due to other causes.

What is an acceptable surveillance interval after ER monotherapy? We detected all progressors at early stages, and we found no progression within the first 18 months post-ER. This suggests that annual surveillance is an accepted strategy and that we can safely perform the first FU endoscopy 1 year after confirmation of a completely flat BE post-ER. On the other hand, in older patients with a short remaining BE segment, we may stop endoscopic FU directly after ER, based on the aforementioned considerations.

Finally, if a patient has predictors for a low success chance after RFA, such as BE regeneration of the ER scar or a long BE without any squamous islands [26], one may decide not to start RFA but perform surveillance instead, independent of a patient's life expectancy.

This is the first study that provides long-term FU data for an alternative treatment strategy in older patients with BE- related neoplasia. In our cohort of patients treated in a centralized setting by experienced endoscopists, this constituted 10% of the population that qualified for RFA after ER according to current guidelines. The suggested ER monotherapy strategy is advised in patients with a life expectancy of < 5–10 years and should be considered for a life expectancy of < 15–20 years. We suggest to consider and discuss this strategy in patients aged > 70 years and those with severe comorbidity.

Some limitations need to be addressed. The median duration of endoscopic FU was 21 months, while the median time to progression was 26 months, and all progressors occurred at minimal 18 months after ER. In light of this, we performed analysis that only included patients with FU over 18 months, which showed a minimally increased annual progression risk (i.e., 8.0% for all patients and 8.6% for patients with FU > 18 months). Still, if we would have had longer endoscopic FU, the annual progression risk might potentially have increased with a peak after longer FU, suggesting that the progression risk is not constant over time but increased over the years. Unfortunately, our data are too limited for solid analysis of this aspect. On the other hand, we report results for

patients with limited life expectancy, and ultra-long-term FU data therefore have no clinical consequences. This is reflected by the fact that only one-third of patients was still under endoscopic surveillance at the moment of data collection. The others had already died of other causes (one-third) or were alive after endoscopic FU was already stopped (one-third). Therefore, extended FU with a potentially higher progression rate would not have changed the long-term outcomes, mortality rates, or our conclusions and recommendations.

Other limitations include the low number of events to assess predictive factors, which limited us to perform univariable analysis only. The FU duration for vital status may have been too short to detect recurrent, symptomatic disease among those patients whose FU was stopped early. A total of 7 patients had no endoscopic FU and were only assessed for vital status.

We are currently working on clinical prediction tools to provide individualized, evidence-based advices on optimal FU strategy after ER and/or RFA, taking account of the risk for progression and EAC-related death on the one hand, and patient age, comorbidity, and risk for unrelated death on the other. These data might help in defining the optimal strategy after ER monotherapy in the future.

In conclusion, ER monotherapy with endoscopic surveil- lance of the residual flat BE is a valid alternative to prophylactic ablation therapy of residual BE, in selected patients.

REFERENCES

1. Pech O, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut. 2008;57(9):1200-6.
2. May A, Gossner L, Pech O, Fritz A, Gunter E, Mayer G, et al. Local endoscopic therapy for intraepithelial high-grade neoplasia and ear- ly adenocarcinoma in Barrett's oesophagus: acute-phase and inter- mediate results of a new treatment approach. Eur J Gastroenterol Hepatol. 2002;14(10):1085-91.
3. Ell C, May A, Pech O, Gossner L, Guenter E, Behrens A, et al. Curative endoscopic resection of early esophageal adenocarci- nomas (Barrett's cancer). Gastrointest Endosc. 2007;65(1):3-10.
4. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau JM, Esteban JM, et al. Endoscopic management of Barrett's esoph- agus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2017;49(2):191-8.
5. Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of Gastroenterology guidelines on the diag- nosis and management of Barrett's oesophagus. Gut. 2014;63(1):7- 42.
6. Gastroenterologists DSo. Richtlijn Barrett-Oesofagus. 2017.
7. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of G. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016;111(1):30-50; quiz 1.
8. Phoa KN, Pouw RE, Bisschops R, Pech O, Ragunath K, Weusten BL, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut. 2016;65(4):555-62.
9. Phoa KN, Pouw RE, van Vilsteren FGI, Sondermeijer CMT, Ten Kate FJW, Visser M, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endo- scopic resection: a Netherlands cohort study. Gastroenterology. 2013;145(1):96-104.
10. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009;360(22):2277-88.
11. Desai M, Saligram S, Gupta N, Vennalaganti P, Bansal A, Choudhary A, et al. Efficacy and safety outcomes of multimodal endoscopic eradication therapy in Barrett's esophagus-related neo- plasia: a systematic review and pooled analysis. Gastrointest Endosc. 2017;85(3):482-95 e4.
12. SN van Munster EN, Blam Weusten, et al. 1083 Recurrent neopla- sia after endoscopic treatment for Barrett's neoplasia is rare and random biopsies do not contribute to its detection: Results from a nationwide cohort including all 1,154 patients treated in The Netherlands between 2008 and 2018. Gastroenterology. 2020;158:S-210 - S-1.
13. Curvers WL, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. 2010;105(7):1523-30.

14. Duits LC, Phoa KN, Curvers WL, Ten Kate FJ, Meijer GA, Seldenrijk CA, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. 2015;64(5):700-6.

15. Duits LC, van der Wel MJ, Cotton CC, Phoa KN, Ten Kate FJW, Seldenrijk CA, et al. Patients With Barrett's Esophagus and Confirmed Persistent Low-Grade Dysplasia Are at Increased Risk for Progression to Neoplasia. Gastroenterology. 2017;152(5):993- 1001 e1.

16. van der Wel MJ, Klaver E, Duits LC, Pouw RE, Seldenrijk CA, Offerhaus G, et al. Adherence to pre-set benchmark quality criteria to qualify as expert assessor of dysplasia in Barrett's esophagus biopsies - towards digital review of Barrett's esophagus. United European Gastroenterol J. 2019;7(7):889-96.

17. Bergman J, de Groof AJ, Pech O, Ragunath K, Armstrong D, Mostafavi N, et al. An Interactive Web-Based Educational Tool Improves Detection and Delineation of Barrett's Esophagus-Related Neoplasia. Gastroenterology. 2019;156(5):1299-308 e3.

18. Curvers WL, van Vilsteren FG, Baak LC, Bohmer C, Mallant-Hent RC, Naber AH, et al. Endoscopic trimodal imaging versus standard video endoscopy for detection of early Barrett's neoplasia: a multi- center, randomized, crossover study in general practice. Gastrointest Endosc. 2011;73(2):195-203.

19. de Groof J, van der Sommen F, van der Putten J, Struyvenberg MR, Zinger S, Curvers WL, et al. The Argos project: The development of a computer-aided detection system to improve detection of Barrett's neoplasia on white light endoscopy. United European Gastroenterol J. 2019;7(4):538-47.

20. Barret M, Belghazi K, Weusten BL, Bergman JJ, Pouw RE. Single- session endoscopic resection and focal radiofrequency ablation for short-segment Barrett's esophagus with early neoplasia. Gastrointest Endosc. 2016;84(1):29-36.

21. Belghazi K, Marcon N, Teshima C, Wang KK, Milano RV, Mostafavi N, et al. Risk factors for serious adverse events associ- ated with multiband mucosectomy in Barrett's esophagus: an inter- national multicenter analysis of 3827 endoscopic resection proce- dures. Gastrointest Endosc. 2020.

22. Belghazi K, Pouw RE, Koch AD, Weusten B, Schoon EJ, Curvers WL, et al. Self-sizing radiofrequency ablation balloon for eradica- tion of Barrett's esophagus: results of an international multicenter randomized trial comparing 3 different treatment regimens. Gastrointest Endosc. 2019;90(3):415-23.

23. Phoa KN, van Vilsteren FG, Weusten BL, Bisschops R, Schoon EJ, Ragunath K, et al. Radiofrequency ablation vs endoscopic surveil- lance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311(12):1209-17.

24. Pouw RE, Kunzli HT, Bisschops R, Sondermeijer CM, Koch AD, Didden P, et al. Simplified versus standard regimen for focal radio- frequency ablation of dysplastic Barrett's oesophagus: a multicentre randomised controlled trial. Lancet Gastroenterol Hepatol. 2018;3(8):566-74.

25. Pouw RE, van Vilsteren FG, Peters FP, Alvarez Herrero L, Ten Kate FJ, Visser M, et al. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endo- scopic resection of early Barrett's neoplasia. Gastrointest Endosc. 2011;74(1):35-43.

26. van Vilsteren FG, Alvarez Herrero L, Pouw RE, Schrijnders D, Sondermeijer CM, Bisschops R, et al. Predictive factors for initial treatment response after circumferential radiofrequency ablation for Barrett's esophagus with early neoplasia: a prospective multicenter study. Endoscopy. 2013;45(7):516-25.
27. Levine DS, Blount PL, Rudolph RE, Reid BJ. Safety of a system- atic endoscopic biopsy protocol in patients with Barrett's esopha- gus. Am J Gastroenterol. 2000;95(5):1152-7.
28. Haidry RJ, Butt MA, Dunn J, Banks M, Gupta A, Smart H, et al. Radiofrequency ablation for early oesophageal squamous neopla- sia: outcomes form United Kingdom registry. World J Gastroenterol. 2013;19(36):6011-9.
29. Sang Yoon Kim CMM, et al. The impacts of age and sedation on cardio-cerebrovascular adverse events after diagnostic GI endosco- py: a nationwide population-based cohort study. Gastrointest Endosc. 2020.
30. Miros M, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. Gut. 1991;32(12): 1441-6.
31. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adeno- carcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc. 2008;67(3):394-8.

CHAPTER 6

Dysplastic recurrence after successful treatment for early Barrett's neoplasia: development and validation of a penalized prediction model

Esther Nieuwenhuis*, Sanne N. van Munster*, Raf Bisschops, Hilde Willekens, Bas L. A. M. Weusten, Lorenza Alvarez Herrero, Auke Bogte, Alaa Alkhalaf, Ed B. E. Schenk, Erik J. Schoon, Wouter Curvers, Arjun D. Koch, Pieter Jan F. de Jonge, Tjon J. Tang, Wouter B. Nagengast, Jessie Westerhof, Martin H. M. G. Houben, Stefan Seewald, Martinus J. C. Eijkemans, Jacques J. G. H. M. Bergman, Roos E. Pouw

***Authors contributed equally**

Gastroenterology. 2022 Jul;163(1):285-294. doi: 10.1053/j.gastro.2022.03.020. Epub 2022 Mar 16. PMID: 35306024

ABSTRACT

Background and Aims

The combination of endoscopic resection and radiofrequency ablation is the treatment of choice for eradication of Barrett's esophagus (BE) with dysplasia and/or early cancer. Currently, there are no evidence-based recommendations on how to survey patients after successful treatment, and most patients undergo frequent follow- up endoscopies. We aimed to develop and externally validate a prediction model for visible dysplastic recurrence, which can be used to personalize surveillance after treatment.

Methods

We collected data from the Dutch Barrett Expert Center Registry, a nationwide registry that captures outcomes from all patients with BE undergoing endoscopic treatment in the Netherlands in a centralized care setting. We used predictors related to demographics, severity of reflux, histologic status at baseline, and treatment characteristics. We built a Fine and Gray survival model with least absolute shrinkage and selection operator penalization to predict the incidence of visible dysplastic recurrence after initial successful treatment. The model was validated externally in patients with BE treated in Switzerland and Belgium.

Results

A total of 1154 patients with complete BE eradication were included for model building. During a mean endoscopic follow-up of 4 years, 38 patients developed recurrent disease (1.0%/person-year). The following characteristics were independently associated with recurrence (strongest to weakest predictor): a new visible lesion during treatment phase, higher number of endoscopic resection treatments, male sex, increasing BE length, high-grade dysplasia or cancer at baseline, and younger age. External validation showed a C-statistic of 0.91 (95% confidence interval, 0.86–0.94) with good calibration.

Conclusions

This is the first externally validated model to predict visible dysplastic recurrence after successful endoscopic eradication treatment of BE with dysplasia or early cancer. On external validation, our model has good discrimination and calibration. This model can help clinicians and patients to determine a personalized follow-up strategy.

INTRODUCTION

A combination of endoscopic resection (ER) for any visible abnormalities followed by endoscopic radiofrequency ablation (RFA) for the remaining flat Barrett's esophagus (BE) is the treatment of choice for BE with dysplasia and/or early cancer [1]. This combination has been found to be safe and effective for eradicating dysplasia and/ or early BE cancer and allows for complete eradication of BE. It has been reported that 90%–95% of patients achieve complete eradication of all visible Barrett's epithelium (complete eradication of BE [CE-BE]) [1–4].

Because of the risk of recurrence after CE-BE, endoscopic follow-up is performed to identify and treat recurrences at early stages to prevent progression to advanced cancer. Reported recurrence risks vary widely, from 1% to 20% per person-year [5–8]. These differences can be partially explained by heterogeneous definitions for CE-BE and for recurrence. Centralization of BE treatment may play a role as well, with lower recurrence rates reported for patients treated in expert centers [9]. Most studies published to date are limited by small sample size and short duration of follow-up [6,7].

With the lack of reliable data on the risk of recurrence, recommendations for follow-up after CE-BE are based on expert opinion. The strategies derive from the pre-ablation era, when, after ER for visible abnormalities, endoscopic follow-up was initiated of the remaining BE. With RFA, eradication of the residual BE can be accomplished in the vast majority of patients. Hence, it is reasonable to assume that this should reduce recurrence rates and that surveillance intervals can be widened.

Understanding the clinical and treatment determinants of recurrent disease may have important implications for development of follow-up regimens. The objective of the current study was to develop and externally validate a prognostic model to predict visible recurrent dysplasia after CE-BE to further develop personalized post-RFA surveillance strategies.

METHODS

The model was built using data from the Barrett Expert Center (BEC) registry (Netherlands Trial Register, NL7039) [10]. This registry captures outcomes for all patients with early Barrett's neoplasia in the Netherlands since 2008 who underwent endoscopic treatment. Treatment for early BE neoplasia in the Netherlands is centralized in 9 BECs, which means that every patient in the Netherlands is treated in one of these tertiary referral centers. All BECs follow a joint treatment and follow-up protocol; the

endoscopists and pathologists (1–2 per center, depending on the volume) participated in a joint training program and the minimum caseload is 10 new patients with high-grade dysplasia (HGD)/esophageal adenocarcinoma (EAC) per center per year.

The model was validated on 2 external, separate databases (Supplementary Material). The Zurich database is a prospective database including all patients with BE treated in Hirslanden Klinik, Zurich, Switzerland. The Leuven database is a prospective database that included all patients treated at the University Hospital Leuven, Belgium [11]. Both centers have a tertiary referral function for treatment of BE neoplasia. Endoscopists working in these centers were jointly trained with the endoscopists from the Dutch expert centers and participated in jointly organized European training programs since 2010.

Treatment and follow-up protocol

All patients underwent endoscopic workup and staging at baseline using high-definition white light endoscopy and optical chromoscopy, with careful inspection and documentation of the Prague C&M criteria [12]; presence of visible lesions; esophagitis; esophageal stenosis; or other abnormalities.

Visible abnormalities, that is, nonflat lesions and/or lesions with irregular mucosal patterns with a suspicion for neoplasia, were removed with ER for histologic staging, followed by 3-monthly RFA until all BE was eradicated endoscopically. Random 4-quadrant biopsies were then performed <1 cm below the neosquamocolumnar junction. Successful treatment was defined as CE-BE. A failure for CE-BE had either persisting visible BE endoscopically or persisting dysplasia in biopsies just below the cardia. In line with prior studies, patients with complete endoscopic eradication of BE yet with persisting focal intestinal metaplasia (IM) in the biopsies distal to the neosquamocolumnar junction were defined as CE-BE [2].

All CE-BE patients entered follow-up. All follow-up endoscopies were performed with high-definition white light endoscopy and optical chromoscopy. The Dutch regimen changed over time in terms of surveillance intervals and histologic sampling (Supplementary Table 1). In 2008, surveillance was performed 3-monthly in year 1, annually from year 2 to year 5, and every 2–3 years afterwards. In 2015, we abandoned the extra 3-month endoscopies in year 1 due to low clinical relevance.

In 2008, we started with random biopsies from the neosquamous epithelium along the length of the initial BE, and from the cardia <1 cm below the neosquamocolumnar junction. In 2013, we abandoned the random neosquamous epithelium biopsies and in

2016, we abandoned the random cardia biopsies during follow-up endoscopies. From 2016 onward, we only performed histologic sampling from endoscopic abnormalities.

Data Collection and Data Management

Information regarding baseline characteristics, the treatment phase and long-term follow-up was collected in a joint database. Follow-up data were collected until January 1, 2020. Database quality control was performed by checking data against source documents for all patients who reached a primary end point and for 50% of the remaining patients. Data and/or images for all patients who reached a primary end point were discussed in interactive meetings with the research study group. All fields were examined for missing data, nonlogical values, and outliers, which were completed or corrected.

The BEC registry was merged with the nonpublic microdata from Statistics Netherlands for survival outcomes, including date and cause of death.

Study Population

For the current study, we included all patients from the BEC, Leuven, and Zurich registries who underwent at least 1 RFA treatment and achieved CE-BE before December 31, 2018, to ensure sufficient duration of follow-up. For the BEC registry, this is the same cohort of patients as published recently with the aim to report long-term outcomes [10].

Study End Points

The primary end point was recurrent disease, defined as a histologic finding of low-grade dysplasia (LGD), HGD, or EAC in the esophagus or cardia during follow-up. This diagnosis could be established either on biopsy samples or on endoscopic resection specimens. Progression to advanced EAC (>T1 EAC and/or lymph node and/or distant metastasis) was included in this definition.

To assess the robustness of our outcomes, sensitivity analysis was performed, with recurrence of HGD or EAC as outcome and recurrence of LGD considered as sustained eradication.

Definition and Description of Potential Predictors

We included patient and treatment characteristics that would be known to the physician at the time of CE-BE and with clinically or biologically plausible effects on the risk for recurrent disease. These included demographics (age at the time of first treatment and sex); characteristics defining the severity of reflux disease (eg, baseline BE length, poor

healing and/or poor squamous regeneration during treatment, and persisting reflux esophagitis at the end of treatment), characteristics defining histologic abnormalities (worst pathology at baseline, presence of a new visible lesion, ie, "incident lesion" during ablation), and characteristics of the treatment course (eg, number of treat- ment sessions and persisting IM in the cardia after treatment). Poor healing was defined as incomplete healing (active ulcers) at least 3 months after treatment, resulting in postponement of treatment and/or incomplete squamous regeneration (<50%) after treatment. Persisting reflux esophagitis at the end of treatment was defined as endoscopically visible evidence of reflux esophagitis Los Angeles classification grade B or higher [13].

For all patients, information on all of these variables were available except for 35 patients (3%) in the BEC cohort, in whom no cardia biopsies were obtained at the end of treatment. We therefore included this variable in 2 ways in our analysis: first as a categorical variable with 3 levels ("no IM in cardia biopsies," "IM in cardia biopsies," or "no cardia biopsies performed") and by adding a new variable with single imputation for those patients without biopsies. The Leuven and Zurich registry had no missing values.

Statistics

Baseline characteristics were analyzed using standard descriptive statistics. Continuous variables were presented as mean (SD) and as median with interquartile range for normally distributed and skewed data, respectively. Categorical variables were presented as numbers with percentages and 95% confidence intervals (CIs) were obtained using internal bootstrapping.

The prognostic model was developed using a Fine and Gray survival model. The time-to-event analysis was time between last treatment endoscopy and occurrence of the event of interest (recurrent dysplasia), the competing risk (unrelated death), or censoring (the last follow-up endoscopy). Because recurrences are generally asymptomatic and therefore only detected at regularly scheduled surveillance endoscopies, the true timing of recurrent disease is unknown. To correct for this interval censoring, timing of recurrence was defined as the moment in the middle of the interval between the last endoscopy without recurrence, and the first endoscopy with recurrence.

To select potential predictors, we used the least absolute shrinkage and selection operator (LASSO) algorithm and hazard ratios (HRs) were estimated by means of this method [14]. The functional form (linear vs nonlinear relations with the outcome) was checked for all continuous variables. The proportional hazard assumption was checked using the Schoenfeld residuals.

Model building consisted of leave-one-out cross-validation for choosing the LASSO penalty. In addition, we performed leave-one-out cross-validation for internal validation to quantify statistical optimism in performance. The final model was assessed for overall model performance (Brier score), discrimination (Harrell's C-statistic), and calibration in both internal and external validation. Bootstrapping was performed to obtain a 95% CI for the C-statistic. Details about all steps performed in the development and validation of the model can be found in the Supplementary Material.

The Fine and Gray model was considered the best model for our dataset because this model can take competing risks into account and LASSO variable selection was preferred, given the low number of events [15]. For sensitivity analysis, we also fitted a Fine and Gray model with backward selection with variable selection based on Akaike Information Criterion. In addition, 2 Cox proportional hazard models were built: one with variable selection based on LASSO and one based on backward selection using Akaike Information Criterion.

No formal sample size was calculated for our primary analysis using LASSO penalization, and the number of predictors in our model was much smaller than the number of outcomes. Data collection was carried out using R, version 3.6.3 with the following packages: cmprsk, crrp, survival, glmnet, shiny, ROCR, survminer, prodlim, ggplot2.

Ethics

The Institutional Review Board of the Amsterdam University Medical Centers (former AMC) declared that the BEC registry was not subject to the Medical Research Involving Human Subjects Act (wet op medisch-wetenschappelijk onderzoek met mensen in Dutch) and waived the need for formal ethical review and patient-informed consent. Patients were approached through an opt-out card with the possibility to object against participation. For the prospective part of the registry, all patients gave written informed consent. Written informed consent for prospective registration was also obtained in Leuven after approval by the Ethical Committee of the University Hospitals Leuven (S52432). In Zurich, written informed consent was deemed unnecessary for prospective registration by the ethical board. All authors had access to the study data and had reviewed and approved the final manuscript.

RESULTS

Definition and Baseline Characteristics of the Barrett Expert Center Cohort

A total of 1154 patients reached complete endoscopic and histologic remission of BE after RFA ± ER and were included for the current follow-up study (Figure 1). The mean follow-up was 4 (±2) years with 4 (±2) endoscopy per patient. We had a substantial number of patients with long-term follow-up in our cohort: 370 patients had follow-up over 5 years and 112 patients over 8 years. Overall, this contributed to 4690 person-years of follow-up. Only 17 patients (2%) were lost to follow-up. Baseline characteristics are reported in Table 1.

Recurrent Disease

Among the 1154 patients in our study, visible recurrent LGD, HGD, or EAC occurred in 38 patients. The worst histologic grade of recurrence was LGD (n = 14), HGD (n = 7), or EAC (n = 17). The annual recurrence risk was 1.0% (95% CI, 0.8–1.4) for recurrent LGD or worse and 0.7% (95% CI, 0.4–1.0) for recurrent HGD or worse. All recurrences were detected as visible BE and/or nonflat abnormalities during endoscopy. Recurrence occurred at a median of 30 months (interquartile range, 22–40 months) after CE-BE was established. Recurrences have been described in detail previously [10].

Figure 2 shows the regular Kaplan–Meier estimate for recurrent disease (ie, considering unrelated death as uninformative censoring) and the cumulative incidence curve (ie, considering unrelated death as competing event).

Unadjusted Associations Between Potential Predictors and Recurrence

In univariable analysis, patients with longer pretreatment BE segments were more likely to develop recurrence during follow-up (Table 2). Also, a higher number of ER treatments, a higher number of RFA treatments, and development of an incident lesion during the treatment phase were associated with a higher risk for recurrence. Although not statistically significant, patients with HGD or EAC at baseline had a 2.5 times higher chance of developing recurrence compared with patients with LGD at baseline.

Effect estimates for the Fine and Gray analysis were comparable with those resulting from regular Cox analysis.

Table 1. Baseline characteristics for 1154 patients included in our cohort, stratified for the primary outcome

	All patients BEC registry N=1,154	No recurrence BEC registry N=1,116	Recurrence BEC registry N=38	Leuven validation registry N=204	Zurich validation registry N=117
Demographics					
Male gender, n (%)	947 (82)	914 (82)	33 (87)	173 (85)	100 (86)
Age, years, mean/SD	64±9	64±9	62±9	63±11	64±10
Barrett					
BE length, cm, mean/SD					
Circumferential	3 ± 3	3 ± 3	5 ± 4	3±3	4±3
Maximum	5 ± 3	5 ± 3	7 ± 3	5±3	6±4
Reflux esophagitis, n (%)	34 (3)	34 (3)	0 (0)		
Visible lesion, n (%)	717 (62)	691 (62)	26 (68)	117 (57)	98 (84)
Worst pathology					
LGD, n (%)	306 (26)	302 (27)	4 (11)	16 (8)	32 (27)
HGD, n (%)	363 (32)	350 (31)	13 (34)	123 (60)	48 (41)
EAC, n (%)	485 (42)	464 (42)	21 (55)	65 (32)	37 (32)
m-EAC	455 (39)	434 (39)	21 (55)	60 (29)	34 (29)
sm-EAC	30 (3)	30 (3)	0 (0)	5 (3)	3 (3)
Treatment					
ER, n (%)	719 (62)	691 (62)	28 (74)	122 (60)	95 (81)
Poor regression after ER	34 (3)	32 (3)	2 (5)		4 (3)
N RFA sessions, median/ IQR	2 (1-3)	2 (1-3)	3 (3-4)	2 (1-3)	1 (1-2)
Poor healing, n (%)	80 (7)	76 (7)	4 (11)	13 (7)	2 (2)
Incident lesion, n (%)	72 (6)	62 (6)	9 (24)	15 (7)	4 (3)
Esophagitis after treatment, n (%)	109 (9)	103 (9)	6 (16)		
Cardia biopsies, at the end of treatment n (%)					
No IM	1045 (91)	1010 (91)	35 (92)		102 (87)
IM	74 (6)	72 (6)	2 (5)		15 (13)
No biopsies	35 (3)	34 (3)	1 (3)		0 (0)
Duration of treatment, median/IQR					
Months	9 (5-13)	5 (8-13)	11 (9-16)	6 (3-11)	11 (8-15)
Endoscopies	3 (2-4)	3 (2-4)	4 (3-5)	3 (2-4)	2 (2-3)

Figure 1. Patient flow and definition of our study cohort

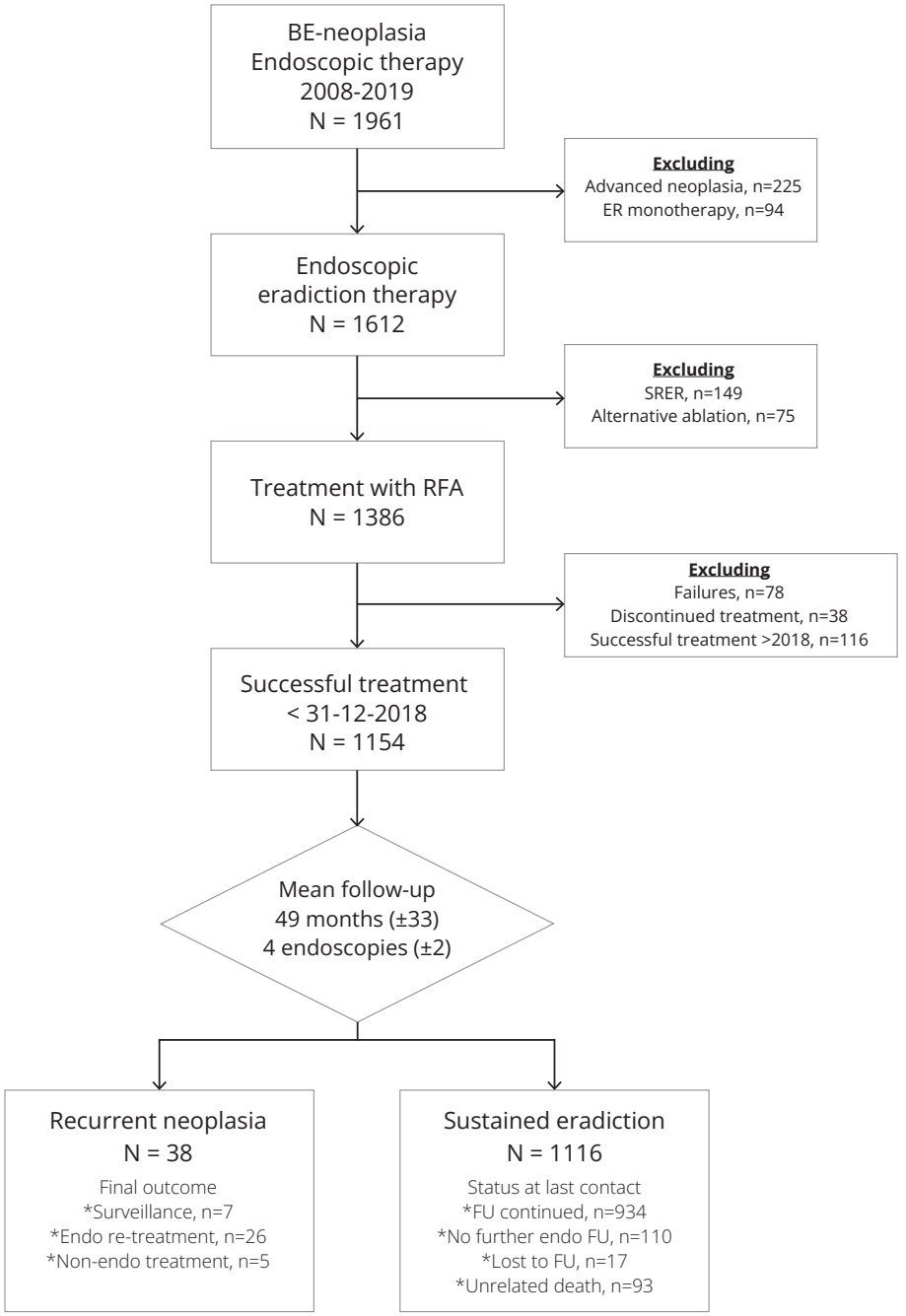
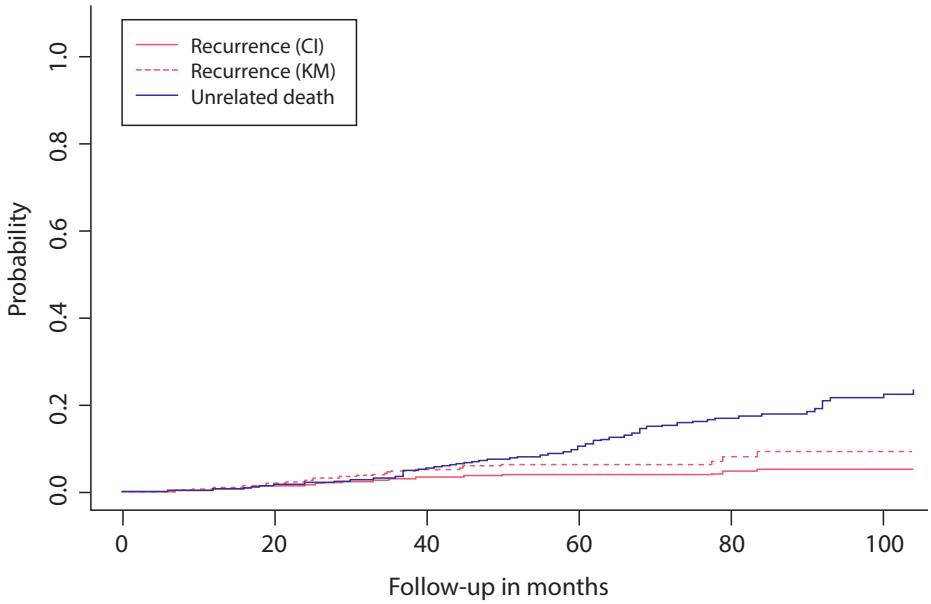


Figure 2. Kaplan–Meier (KM) and cumulative incidence curve



KM (dashed red line) and cumulative incidence curve (CI) (red line) for the risk of recurrent dysplasia, plotted against the risk of unrelated death (blue line).

Table 2. Univariable and Multivariable Fine and Gray Model

Covariate	Univariable analysis, HR (95% CI)	Multivariable LASSO model, HR
Age	0.99 (0.95; 1.01)	0.99
Sex, *male*	0.66 (0.26; 1.68)	0.88
Worst pathology	2.52 (0.89; 7.09)	1.02
BE length	1.18 (1.12; 1.26)	1.16
Incident lesion	4.34 (2.05; 9.31)	2.88
Poor healing	1.46 (0.52; 4.10)	—
Persisting esophagitis	1.57 (0.67; 3.70)	—
No. of ERs	1.63 (1.17; 2.26)	1.18
No. of RFAs	1.33 (1.04; 1.70)	—
Persisting IM in cardia	1.34 (0.48; 3.87)	—
Baseline hazard for 2 y	NA	0.985
Baseline hazard for 5 y	NA	0.962

NOTE. Age was modeled in years. Sex was coded as 1 for female. Worst pathology was coded as 1 for HGD or worse. BE length was the maximum extent of BE at baseline in cm. Incident lesion was defined as a dysplastic visible lesion requiring resection that was noted during the ablation phase. Poor healing was defined as incomplete healing (active ulcers) or incomplete squamous regeneration (<50%) resulting in postponement of treatment. Persisting esophagitis was defined as active reflux esophagitis grade B or higher at the moment of complete eradication. The number of endoscopic resections, radiofrequency ablation, and total treatment endoscopies were modeled continuously. The model is available at: https://barrett-recurrence.shinyapps.io/Barrett/
NA, not applicable

Multivariate Model Building and Predictive Performance

Selected variables for the multivariable LASSO model were age, sex, baseline pathology, BE length, number of ER treatments, and incident lesions (Table 2). Younger age was associated with a higher risk for recurrence (HR, 1.01); as was male sex (HR, 1.37); HGD or EAC at baseline compared with LGD (HR, 1.02); increasing length of BE (HR, 1.16); higher number of ER treatments (HR, 1.18); and an incident lesion (HR, 2.88). Model assumptions were met (Supplementary Figure 1).

For example, a 50-year-old man with a 10-cm-long BE with EAC and 2 ER sessions, including 1 for an incident lesion, had a predicted risk for recurrence of 16% during the first 2 years, which increased to 48% during 7 years. This is an extreme example and we only had 3 such patients (3 of 1154 [0.3%]) in our cohort.

In contrast, a 65-year-old man with C2M5 BE who underwent a single ER for HGD followed by RFA had a 2% risk of developing recurrence during the first 2 years, and this increased to a cumulative 8% risk during 7 years. This is a much more representative case for our population and approximately 50% of our cohort had a comparable or lower risk.

The optimism-corrected concordance index for the prediction model was 0.76 (95% CI, 0.73–0.79). The lambda plot, coefficient plot, and calibration plots can be found in Supplementary Figures 2, 3, and 4.

Sensitivity Analysis

To test the robustness of our findings, sensitivity analyses were performed using different statistical models and a different definition of the outcome (Supplementary Table 2). Using backward regression techniques, fewer variables were included in the models. The most important variables that were selected in all 4 models were BE length and incident lesion during the treatment phase.

External Validation

Our model was externally validated on the Leuven and Zurich RFA registries, including 204 and 117 patients with successful RFA ± prior ER, respectively. Baseline characteristics for the 3 cohorts were comparable, with the exception of 2 variables (Table 1). The proportion of patients with a visible lesion at baseline appeared higher in Zurich (81%) compared with BEC (62%) and Leuven (60%). Furthermore, the proportion of baseline LGD diagnosis was lower in Leuven (8%) compared with the BEC (26%) and Zurich (27%) registry.

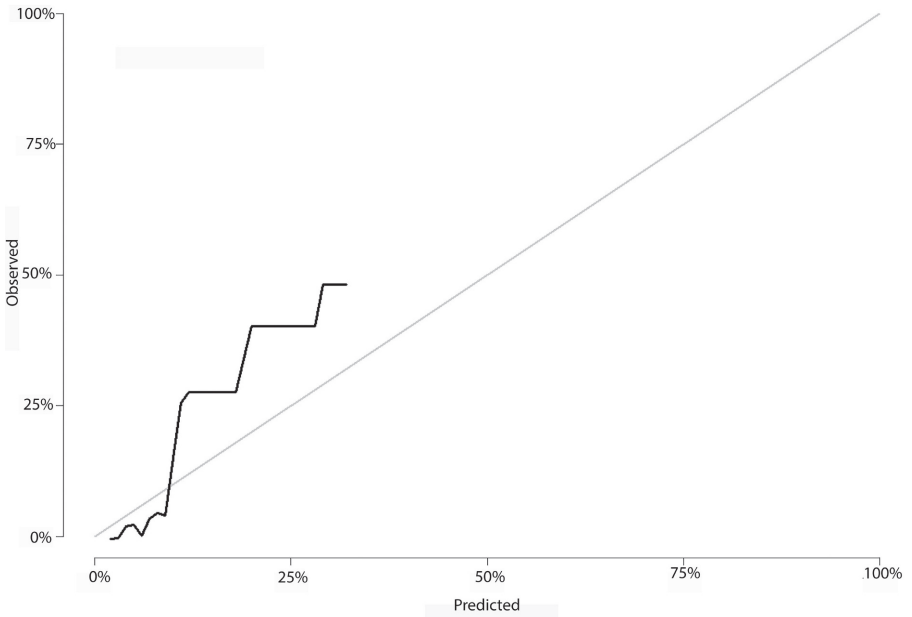
In Leuven, 14 of 204 patients (7%) developed recurrence during a median of 40 months (interquartile range, 19–78 months); worst histology was LGD (n = 2 [14%]), HGD/low-risk EAC (n = 11 [79%]), or advanced EAC (n = 1 [7%]). The annual risk was 1.6 (95% CI, 0.9–3.0) for recurrence of LGD and 1.3 (95% CI, 0.8–2.5) for HGD. The risk for unrelated death was 21 of 204 (10%).

In Zurich, 5 of 117 patients (4%) developed recurrence during median 42 months (18–70 months), consisting of LGD (n = 2), HGD/low-risk EAC (n = 2), or advanced EAC (n = 1). The annual risk was 1.0 (95% CI, 0.4–2.0) for LGD, HGD, or EAC combined and 0.6 (95% CI, 0.2–1.8) for HGD or EAC combined. The risk for unrelated death was 4 of 117 (4%).

We combined the Leuven and Zurich datasets and assessed overall performance, discrimination, and validation of the created model on this external dataset. The

Brier score was 0.38 (95% CI, 0.10–0.74), with lower scores indicating better overall performance (range, 0–1). The C- index was 0.92 (95% CI, 0.86–0.94), with higher scores indicating better discrimination (range, 0–1). The calibration plot at 5 years is shown in Figure 3 and indicates that for a predicted risk for recurrence within 5 years of <10%, the predicted and observed risks were comparable, but for predicted risks >10%, the model tended to underestimate the actual risk. Model performance for the 2 external datasets separately is shown in Supplementary Table 3 and Supplementary Figure 5.

Figure 3. Calibration plot at 5 years for external validation in the Zurich (n 117) and Leuven (n 204) RFA registries.



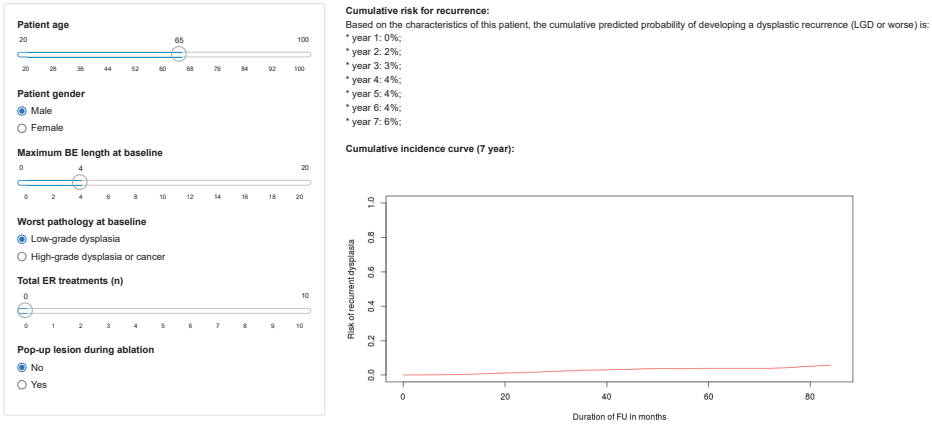
The *horizontal axis* represents the predicted recurrence risk and the *vertical axis* the observed recurrence risk. The *gray line* represents perfect calibration, with the predicted risk equal to the observed risk. The *plot* indicates that for a predicted risk for recurrence within 5 years, the predictions are accurate. For higher predicted risks, the model tends to underestimate the risk for recurrence.

DISCUSSION

This is the first study to develop and externally validate a prediction model for visible dysplastic recurrence after successful endoscopic treatment of early Barrett's neoplasia on a large dataset with significant long-term follow-up data, and is an important step toward personalized post-treatment surveillance. We included 1154 Dutch patients with a mean follow-up of 4 years per patient for model building, and validated the model on

data from 321 patients with a comparable length of follow-up treated in Belgium and Switzerland. We fitted a model for the incidence of recurrent LGD, HGD, or EAC, taking into account the risk for unrelated death, and we found 6 factors that independently predicted recurrence. The created model could discriminate well between patients with and without recurrence in an external dataset with excellent discrimination (C-statistic of 0.92) and good calibration, especially for low predicted risks, as in the majority of patients. Our model is easy to use (https://barrett-recurrence.shinyapps.io/Barrett/) (Figure 4) and may guide individualized post-treatment surveillance for patients with BE.

Figure 4. Easy-to-use online prediction model.



The online risk prediction tool is available at https://barrett-recurrence. shinyapps.io/Barrett. This example shows recurrence risk for a 65-year-old man with a flat Barrett segment at baseline of C2M4 with LGD and underwent successful eradication therapy with RFA.

Recurrence rates after treatment vary widely between different studies. This can be partially explained by heterogeneous definitions for successful treatment, as well as for recurrence; by different indications of treatment; differences in follow-up duration; differences in treatment protocols; varying expertise; and, potentially, due to actual differences in recurrence risks. We included only patients with dysplastic BE at baseline as indication for treatment, in line with current guidelines [1]. We defined recurrence as recurrent visible LGD, HGD, or EAC, but not nondysplastic BE [2,11]. Most studies have reported the incidence of recurrent nondysplastic BE, but have not generally reported the rate of recurrence with dysplasia [6,8,16]. Recurrent LGD or worse appears to be a more suitable end point because recurrence of nondysplastic BE is usually limited to a small surface area; can be treated easily and has minimal risk for progression. The clinical relevance of this end point appears low.

For our prediction model, we hypothesized that the following 3 overarching themes are associated with recurrence: the severity of reflux disease; the severity of histologic abnormalities; and abnormalities during the treatment course. We defined these overarching themes in several baseline and treatment characteristics. Other studies have not assessed the full range of potential predictors [6-9].

In line with prior studies, we found an increasing risk for recurrence along with increasing BE length and higher baseline histologic grades. We also found additional predictive variables, with occurrence of incident lesions during the treatment phase as most important predictor. The occurrence of an incident lesion during the treatment phase (ie, "a pop-up lesion") might indicate multifocal dysplasia, which should have required endoscopic resection at base- line, and/or disease progression during treatment.

Most follow-up studies after RFA have used Cox regression for presentation of results. We used a Fine and Gray analysis, which takes into account competing risks. A significant drawback of Cox regression is that it censors patients who die from unrelated causes, which is, in fact, a violation of the prerequisite of Cox regression that censoring is uninformative. A patient with continued endoscopic surveillance who is censored after the last contact (because the next endoscopy is scheduled in the future, that is, after the moment of data collection), is considered the same type of censoring as a patient who died of an unrelated cause. The first patient may indeed develop recurrence during continued follow-up with a risk comparable with that of the other patients in the dataset (uninformative censoring), whereas a deceased patient has zero risk of developing recurrent disease in the future (no uninformative censoring). A Fine and Gray approach considers this difference and models the risk for the outcome, taking into account patients who died of an unrelated cause. This might explain the inverse association between age and recurrence in the model. With increasing age, the risk of dying (from unrelated causes) will also increase and, as a result, the risk for developing recurrence will go down.

We selected predictive variables based on LASSO penalization, whereas other studies used backward or forward selection in their multivariable analyses. In short, LASSO penalization is a regression analysis that performs both variable selection and regularization to prevent overfitting. This technique is especially beneficial for model building with a large number of parameters in relation to the number of events, as in the current study. Our prediction model was externally validated on 2 separate datasets from expert centers in Leuven and Zurich. Baseline characteristics were comparable, with the exception of a higher proportion of patients with a visible lesion in Zurich; and

a lower proportion of patients with LGD at baseline in Leuven. Recurrence risks were comparable among the datasets.

Our final model included 6 predictors and had good discrimination in internal and external validation (Harrell's C-statistic 0.76 and 0.92, respectively). We performed several sensitivity analyses, varying the model (ie, Cox regression vs Fine and Gray), the method for variable selection (ie, LASSO vs backward regression), and the outcome (ie, combining LGD, HGD, and EAC vs excluding LGD as an end point). Overall, our findings appeared robust in sensitivity analysis, but some differences are worth further elaboration. Consistently through all models, increasing BE length and an incident lesion during the treatment phase significantly predicted recurrence. In the Fine and Gray models, but not the Cox models, younger age was associated with recurrence. This difference might be explained by the fact that the Fine and Gray model take into account competing risks (ie, unrelated death). A younger patient is less likely to die from other causes but instead will enter a long follow-up period with a higher risk for recurrence compared with an older patient with a significant risk of unrelated death but not recurrent disease. Using LASSO penalization instead of backward regression, baseline histologic grade and number of ER sessions were also included in the model. The other way around, all variables selected with backward regression were also selected using LASSO. It is known that backward regression is uncertain for a model with a limited number of outcomes, such as our model. Based on Akaike Information Criterion and C-statistics, LASSO outperformed stepwise backward regression and the Fine and Gray model had improved performance compared with the Cox model.

This work has some limitations. We found 38 recurrences in a dataset of 1154 patients and this low number might limit the performance of our model with a risk for overfitting. This is reflected in the difference in the area under the curve for the 2 external validation datasets. Still, overall external validation showed good model performance. Other limitations include treatment of patients who developed nondysplastic BE during follow-up, which might underestimate the true dysplastic recurrence risk in our dataset. However, this occurred in only 6% of patients, either with short segment BE (0.4%) or tiny BE islands (5.6%) [10]. The model did not correct for interval censoring, but this was corrected by defining recurrence in the middle of the interval between the last follow-up endoscopy and the endoscopy with recurrence. Our model used data from expert centers only, and this may limit the generalizability, although guidelines recommend treatment in expert centers only. Follow-up protocols changed over time, resulting in fewer endoscopies and less sampling, this may potentially affect the moment recurrences were found, but this appears unlikely to influence the incidence for recurrent dysplasia, the end point of our study. We had no data on p53 staining, which

makes it impossible to distinguish true recurrent disease from potential treatment failure that was initially missed. We built an easy-to-use prediction model with readily available parameters, but this may have led to impaired predictive value compared with a model with more detailed parameters that are not routinely performed in our country, such as extent of neoplasia and p53 staining. Although pathologists were highly experienced and extensively trained, the Dutch pathologists were jointly trained but the pathologists from Leuven and Zurich participated in other programs, which may have decreased interobserver agreement. Finally, concrete clinical recommendations for personalized follow-up cannot yet be provided on the basis of this study only.

This study also has important strengths. We built our model using a nationwide cohort that included all patients with BE with endoscopic treatment in the Netherlands. BE care in the Netherlands is centralized and performed in BECs only, with specifically trained endoscopists and pathologists, a common treatment and follow-up protocol, and a required annual case load. This resulted in homogeneous care and collection of high-quality data, with no missing data and only 2% of patients lost to follow-up. Our model was the first model to take into account competing risks in model development, and we systematically assessed a wide range of predictors. Finally, our model showed excellent discrimination in external validation in 2 high-quality, independent datasets of 322 patients treated in BECs in Europe. The centralized setting of our study reflects current guidelines in the Netherlands [17] and Europe [1], which recommend restricting treatment of BE neoplasia to expert centers.

Pending the following steps, the current model can already be used by the endoscopist to assess a patient's individualized risk and to discuss surveillance intervals for patient-centered care (https://barrett-recurrence. shinyapps.io/Barrett).

In conclusion, we developed and externally validated a model to predict visible dysplastic recurrence after initial successful endoscopic treatment of BE-related neoplasia in a setting of centralized care. Based on 6 clinical features, our model showed excellent model performance in external validation. This model may help to determine personalized surveillance intervals.

REFERENCES

1. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position State- ment. Endoscopy 2017;49:191–198.
2. Phoa KN, Pouw RE, Bisschops R, et al. Multimodality endoscopic eradication for neoplastic Barrett oesoph- agus: results of an European multicentre study (EURO-II). Gut 2016;65:555–562.
3. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radio- frequency ablation vs endoscopic surveillance for pa- tients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA 2014;311:1209–1217.
4. Shaheen NJ, Sharma P, Overholt BF, et al. Radio- frequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277–2288.
5. Wani S, Puli SR, Shaheen NJ, et al. Esophageal adeno- carcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. Am J Gastroenterol 2009;104:502–513.
6. Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and predictors of successful radiof- requency ablation for Barrett's esophagus. Clin Gastroenterol Hepatol 2014; 12:1840–1847. e1.
7. Cotton CC, Haidry R, Thrift AP, et al. Development of evidence-based surveillance intervals after radio- frequency ablation of Barrett's esophagus. Gastroenter- ology 2018;155:316–326.e6.
8. Sami SS, Ravindran A, Kahn A, et al. Timeline and location of recurrence following successful ablation in Barrett's oesophagus: an international multicentre study. Gut 2019;68:1379–1385.
9. Tan MC, Kanthasamy KA, Yeh AG, et al. Factors asso- ciated with recurrence of Barrett's esophagus after radiofrequency ablation. Clin Gastroenterol Hepatol 2019;17:65–72.e5.
10. van Munster S, Nieuwenhuis E, Weusten B, et al. Long- term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation /- endoscopic resection: results from the national Dutch database in a 10-year period. Gut 2022;71:265–276.
11. Vliebergh JH, Deprez PH, de Looze D, et al. Efficacy and safety of radiofrequency ablation of Barrett's esophagus in the absence of reimbursement: a multi- center prospective Belgian registry. Endoscopy 2019; 51:317–325.
12. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastro- enterology 2006;131:1392–1399.
13. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional cor- relates and further validation of the Los Angeles classi- fication. Gut 1999;45:172–180.
14. Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Series B Stat Methodol 1996; 58:267–288.

15. Fu Z, Parikh CR, Zhou B. Penalized variable selection in competing risks regression. Lifetime Data Anal 2017; 23:353–376.

16. Phoa KN, Pouw RE, van Vilsteren FG, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. Gastroenterology 2013; 145:96–104.

17. Barrett-Oesofagus Richtlijn. 2017. Nederlandse Ver- eniging van Maag-Darm-Leverartse. Available at: https:// www.mdl.nl/sites/www.mdl.nl/files/richlijnen/Richtlijnen%20Barrett%20oesofagus%20-%20jan%202018%20-%20tbv%20website.pdf. Accessed March 28, 2022.

SUPPLEMENTARY MATERIAL

To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2022.03.020.

CHAPTER 7

Incidence and outcomes of poor healing and poor squamous regeneration after radiofrequency ablation therapy for early Barrett's neoplasia

Sanne N. van Munster*, Charlotte N. Frederiks*, Esther A. Nieuwenhuis, Lorenza Alvarez Herrero, Auke Bogte, Alaa Alkhalaf, Boudewijn E. Schenk, Erik J. Schoon, Wouter L. Curvers, Arjun D. Koch, Steffi E. M. van de Ven, Pieter J. F. de Jonge, Thjon J. Tang, Wouter B. Nagengast, Frans T. M. Peters, Jessie Westerhof, Martin H. M. G. Houben, Jacques J. G. H. M. Bergman, Roos E. Pouw, Bas L. A. M. Weusten

***Authors contributed equally**

Endoscopy. 2021 Jun 1. doi: 10.1055/a-1521-6318

ABSTRACT

Background

Endoscopic eradication therapy with radiofrequency ablation (RFA) is effective in most patients with Barrett's esophagus (BE). However, some patients experience poor healing and/or poor squamous regeneration. We evaluated incidence and treatment outcomes of poor healing and poor squamous regeneration.

Methods

We included all patients treated with RFA for early BE neoplasia from a nationwide Dutch registry based on a joint treatment protocol. Poor healing (active inflammatory changes or visible ulcerations ≥ 3 months post-RFA), poor squamous regeneration (< 50 % squamous regeneration), and treatment success (complete eradication of BE [CE- BE]) were evaluated.

Results

1386 patients (median BE C2M5) underwent RFA with baseline low grade dysplasia (27 %), high grade dysplasia (30 %), or early cancer (43 %). In 134 patients with poor healing (10 %), additional time and acid suppression resulted in complete esophageal healing, and 67/134 (50 %) had normal squamous regeneration with 97 % CE-BE. Overall, 74 patients had poor squamous regeneration (5 %). Compared with patients with normal regeneration, patients with poor squamous regeneration had a higher risk for treatment failure (64 % vs. 2 %, relative risk [RR] 27 [95 % confidence interval [CI] 18–40]) and progression to advanced disease (15 % vs. < 1 %, RR 30 [95 %CI 12–81]). Higher body mass index, longer BE segment, reflux esophagitis, and < 50 % squamous regeneration after baseline endoscopic resection were independently associated with poor squamous regeneration in multivariable logistic regression.

Conclusion

In half of the patients with poor healing, additional time and acid suppression led to normal squamous regeneration and excellent treatment outcomes. In patients with poor squamous regeneration, however, the risk for treatment failure and progression to advanced disease was significantly increased.

INTRODUCTION

Radiofrequency ablation (RFA) is the established ablation modality for treatment of flat Barrett's esophagus (BE) [1, 2]. Typically, 2–3 RFA sessions are required to achieve complete eradication of BE (CE-BE) [3, 4]. Multiple large, high quality, multicenter studies have shown that RFA with or without endoscopic resection is safe and efficient, reporting CE-BE in 77 %– 93 % [3–6].

In a subgroup of patients, however, RFA is unable to convert Barrett's epithelium into squamous epithelium. Some patients experience delayed healing, with mucosal swelling, exudates, and/or ulcerations observed at the first post-RFA endoscopy ("poor healing"), while others (also) experience regeneration with Barrett's mucosa instead of squamous epithelium ("poor squamous regeneration"). Logically, these patients have a higher risk of treatment failure after RFA [7].

Few data are currently available on poor healing and poor squamous regeneration, and current guidelines lack recommendations [1, 2, 8]. Evidence-based recommendations on how to manage poor healing and poor squamous regeneration may improve patient outcomes.

We aimed to assess the incidence of poor healing and poor squamous regeneration, as well as the relative risk (RR) for treatment failure after poor healing or poor squamous regeneration, in a nationwide cohort of all patients with BE who underwent RFA treatment in the Netherlands between 2008 and 2018.

METHODS

This study used data from the Barrett Expert Center (BEC) registry (Netherlands Trial Register, NL7039), which includes outcomes of all patients with BE neoplasia who have undergone endoscopic treatment in the Netherlands since 2008. In the Netherlands, treatment for Barrett's neoplasia has been centralized in nine BECs since 2007, with the implication that every patient in the Netherlands is treated in one of these centers. BE care in these centers is provided solely by specially trained endoscopists and pathologists. Treatments are performed according to a joint treatment and follow-up protocol.

The BEC registry has been described in detail previously [9]. For the current study, we included all patients with BE containing early neoplasia who underwent endoscopic eradication therapy with at least one RFA treatment between 1 January 2008 and 31

December 2018. The treatment and follow-up outcomes for this cohort of patients have been published previously [9], but the current study analyzed and reported different endpoints.

Treatment protocol

Patients with early BE neoplasia (low grade dysplasia [LGD] or high grade dysplasia [HGD] or low risk esophageal adenocarcinoma [EAC; i. e. ≤ sm1 EAC, good–moderate differentiation, no lymphovascular invasion, and negative vertical resection margin]) were referred to a BEC for work-up and staging.

Visible lesions were removed with endoscopic resection. RFA was used to treat flat BE using the Barrx system (Medtronic Inc., Minneapolis, Minnesota, USA). The Barrx-360 balloon catheter was used for circumferential RFA (C-RFA) where the BE length was ≥ 2 cm or in cases of multiple and/or large BE islands over a length of > 3 cm. Otherwise, the Barrx-90 catheter was used for focal RFA (F-RFA). RFA was repeated every 3 months and was eventually followed by touch-up treatment using argon plasma coagulation or endoscopic resection for persisting BE islands of < 10 mm and > 10 mm, respectively. If a new nonflat neoplastic lesion was detected during one of the RFA treatments ("incident lesion"), additional endoscopic resection was performed.

End of treatment

Upon complete endoscopic eradication of BE, random four-quadrant biopsies were obtained < 5 mm below the neosquamocolumnar junction for histological correlation. Patients with complete endoscopic eradication of BE and no dysplasia in the cardia biopsies were considered as CE-BE. Persisting intestinal metaplasia in cardia biopsies was also considered as CE-BE [4].

Patients with persisting visible BE after RFA were classified as treatment failure. RFA was stopped if we anticipated that we would be unable to achieve CE-BE or if expected benefits of continued RFA were considered smaller than the risks. Patients who progressed to high risk EAC (i. e. deep submucosal invasion [sm2–3], lymphovascular invasion, and/or poor differentiation), or who had persisting HGD or EAC that could not be eradicated endoscopically, were referred for nonendoscopic therapy. Other patients with treatment failure underwent annual surveillance in years 1–5 and every 2–3 years thereafter, consisting of careful inspection and histological sampling.

Acid-reducing medication

Double-dose proton pump inhibitors (PPI; 40 mg twice daily, per default esomeprazole) was prescribed during the treatment phase. In addition, patients were administered

ranitidine 300 mg at bedtime and sucralfate suspension 5 mL four times daily during 14 days after every treatment.

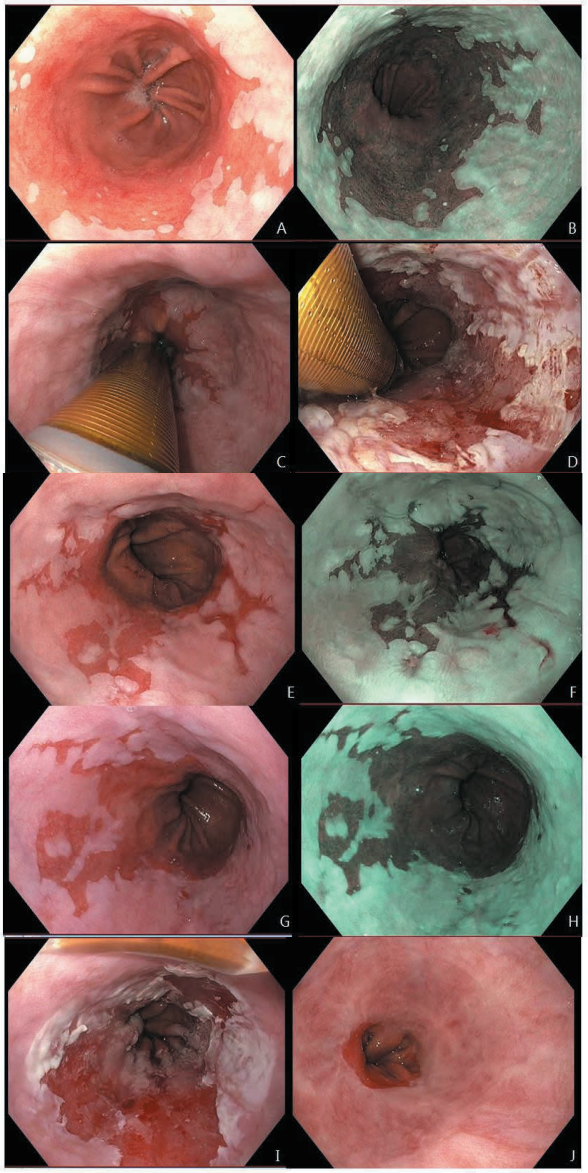
Poor healing

Poor healing was defined as active inflammatory changes with mucosal swelling and exudates and/or ulcerations ≥ 3 months post-RFA (Fig. 1, see also Fig. 1 s in the online-only supplementary material). If poor healing was present, no (ablation) therapy was performed and a repeat endoscopy was scheduled after ≥ 6 weeks. PPI compliance was verified. PPI dose was increased and/or additional acid-reducing medication was prescribed at the physician's discretion. Investigation of 24-hour pH-metry was considered for evaluation of the effects of PPI.

Poor squamous regeneration

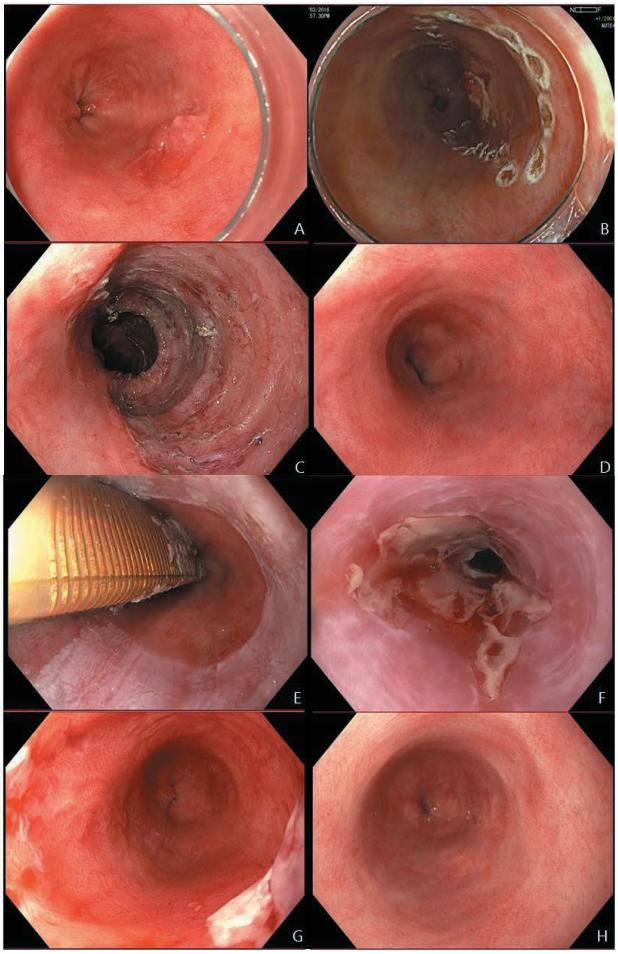
Poor squamous regeneration was defined as < 50 % BE regression 3 months after RFA, provided that the esophagus was completely healed (Fig. 2, Fig. 2 s). Poor squamous regeneration was assessed by the treating endoscopist based on endoscopic appearance. If the outcome was not mentioned in the endoscopy report, endoscopic images and/or videos were reviewed. The management of poor squamous regeneration was determined at the physician's discretion, based on patient age, co- morbidity, and response after prior RFA treatment(s).

Figure 1. Poor healing



C2M5 flat Barrett's esophagus with LGD in random biopsies during baseline endoscopy (A+B). Circumferential RFA was performed first (C+D). Three months post-RFA, active inflammatory changes were found along with mucosal swelling (E+F). We emphasized the importance of PPI compliance and waited for another 10 weeks, when complete healing of the esophagus was found and 80% squamous regeneration (G+H). Upon 2 additional Focal RFA treatments performed at 20 week intervals (I), a complete eradication of Barrett's esophagus was achieved (J).

Figure 2. Poor squamous regeneration preceded by poor healing



C9M10 Barrett's esophagus containing a visible lesion (A). Due to expected deep invasion endoscopic submucosal dissection was performed for a well-differentiated mucosal cancer (B+C). Three months later, the resection scar (between 12 and 7 o'clock) was completely regenerated with Barrett's mucosa (D). Circumferential RFA was performed (E) and resulted in poor healing with visible ulcerations (F) and active inflammatory changes with mucosal swelling (G) after 12 weeks; another 8 weeks later and after verification of PPI compliance, the esophagus was completely healed but regenerated with Barrett's mucosa (H). Random 4Q biopsies showed low-grade dysplasia, after which the decision was made to stop further RFA treatment and switch to endoscopic surveillance.

Study endpoints

The primary end points were 1) the incidence of poor healing and poor squamous regeneration after RFA, and 2) the RR for treatment failure in patients with poor healing and poor squamous regeneration compared with patients without poor healing and with normal squamous regeneration.

Secondary end points included the RR for progression to advanced disease in patients with poor healing and poor squamous regeneration compared with those without poor healing and with normal squamous regeneration. We assessed the long-term risk for recurrent neoplasia among patients with treatment failure who had persisting BE and underwent endoscopic surveillance. Finally, we built a multivariable logistic regression model to identify a set of independent predictors for the development of poor squamous regeneration. Definitions of endpoints are provided in Table 1 s.

Data collection and data management

Data were collected by reviewing endoscopy and pathology reports, endoscopy images, and further clinical information where necessary, as described in detail previously [9]. Dedicated research fellows (all MDs) reviewed the data against source documents for all patients with poor healing, poor squamous regeneration, and/or treatment failure, and additionally for a 50 % random selection of the remaining patients.

Ethics

The Institutional Review Board of the Amsterdam University Medical Centers declared that this study was not subject to the Medical Research Involving Human Subjects Act ("Wet op Medisch-wetenschappelijk Onderzoek met Mensen" in Dutch). The need for formal ethical review and patient-informed consent was waived accordingly. All eligible patients received an opt-out notification, which gave them the possibility to oppose participation in the registry.

Statistics

For descriptive statistics, mean with standard deviation (SD) was used for variables with parametric distribution, and median with interquartile range (IQR) was used for nonparametric distribution. Student's t test, Mann–Whitney U test, two-way analysis of variance, or chi-squared and Fisher's exact tests were used where appropriate to compare groups. The Bonferroni correction was applied to correct for multiple testing to detect differences among subgroups if the overall P value was < 0.05. The RR was defined as the risk for the outcome in the exposed group divided by the risk for the outcome in the unexposed group.

We tested several baseline variables that were known to the physician prior to RFA and with biologically or clinically plausible effects on the risk for poor squamous regeneration. Using backward selection based on the chi-squared test, odds ratios (ORs) with 95 % confidence intervals (CIs) were used to quantify the predictive associations.

Statistical analysis was performed using the Statistical Soft- ware Package IBM SPSS Statistics version 26 for Windows (IBM Corp., Armonk, New York, USA) and R version 3.6.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between 2008 and 2018, 1386 patients underwent at least one RFA treatment for early BE neoplasia and were included in the current study (Fig. 3 s). The overall treatment and follow-up outcomes for this cohort have been published previously [9]. In summary, the majority of patients were male (81 %) and the mean patient age was 66 years (Table 1). The median BE length (circumferential [C] and maximum extent [M]) at baseline was C2M5, with LGD (27 %), HGD (30 %), or EAC (43 %).

Table 1. Baseline characteristics before the first radiofrequency ablation treatment. The cohort of 1386 patients has been published for treatment and follow-up outcomes [9].

	All patients (n = 1386)	**No poor healing or poor squamous regeneration (n = 1245)**	**Poor healing, normal squamous regeneration (n = 67)**	**Poor squamous regeneration[1] (n = 74)**
Male sex, n (%)	1121 (81)	1009 (81)	56 (84)	56 (76)
Age, mean (SD), years	65.5 (6)	66.0 (6)	63.5 (4)	66.0 (4)
BMI, mean (SD), kg/m2	27.6 (2)	27.2 (2)	27.1 (2)	28.1 (2)
Smoking, n (%)				
Never	321 (23)	285 (23)	18 (27)	18 (24)
Former	805 (58)	725 (58)	34 (51)	46 (62)
Current	260 (19)	235 (19)	15 (22)	10 (14)
Surveillance history, n (%)	892 (64)	808 (65)	39 (58)	45 (61)
Duration, median (IQR), years	3 (0–8)	3 (0–8)	3 (0–6)	3 (0–7)
Prior fundoplication, n (%)	23 (2)	15 (1)	5 (7)	3 (4)
PPI 40 mg twice daily or higher, n (%)	1241 (90)	1121 (90)	58 (87)	61 (82)
Reflux esophagitis, n (%)	49 (4)	33 (3)	5 (7)	11 (15)
Reflux stenosis, n (%)	49 (4)	40 (3)	4 (6)	5 (7)
Hiatal hernia, n (%)	1321 (95)	1184 (95)	64 (96)	74 (100)
Size, median (IQR), cm	3.0 (2)	2.9 (2)	3.5 (2)	4.0 (2)
Circumferential BE length, median (IQR), cm	2 (0–5)	2 (0–5)	6 (3–8)	8 (5–10)
Maximum BE length, median (IQR), cm	5 (3–8)	4 (2–7)	7 (4–9)	9 (7–11)

Table 1. (Continued)

	All patients (n = 1386)	No poor healing or poor squamous regeneration (n = 1245)	Poor healing, normal squamous regeneration (n = 67)	Poor squamous regeneration[1] (n = 74)
Visible lesion, n (%)	870 (63)	775 (62)	37 (55)	58 (78)
≥ 1 visible lesion, n (%)	125 (9)	101 (8)	9 (13)	15 (20)
Worst histology, n (%)				
LGD	375 (27)	337 (27)	21 (31)	17 (23)
HGD	422 (30)	380 (31)	25 (38)	17 (23)
EAC	589 (43)	528 (42)	21 (31)	40 (54)
Baseline endoscopic resection, n (%)	870 (63)	775 (62)	37 (55)	58 (78)
Squamous regeneration after endoscopic resection, n (%)[2]				
No endoscopic resection performed	520 (38)	473 (38)	30 (45)	17 (23)
> 50 % squamous regeneration	808 (58)	748 (60)	32 (48)	28 (38)
< 50 % squamous regeneration	58 (4)	24 (2)	5 (7)	29 (39)

BE, Barrett's esophagus; BMI, body mass index; EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; IQR, interquartile range; LGD, low grade dysplasia; PPI, proton pump inhibitor; SD, standard deviation.

1 Poor squamous regeneration was preceded by poor healing in 67 of these patients.

2 Overall, in 4 patients (no poor healing or poor squamous regeneration n = 3; poor squamous regenaration n = 1) squamous regeneration after baseline endoscopic resection was missing.

Poor healing

Poor healing occurred in 134 patients (134/1386; 10 % [95 %CI 8–11]) after RFA. Treatment was postponed for 6–12 weeks and PPI compliance was verified. PPI dose was increased to 80 mg twice daily in 26/134 patients (19 %). A total of 20 patients underwent 24-hour pH-metry (Table 2 s). Nine patients (9/ 134; 7 %) had severe reflux symptoms and/or severe reflux esophagitis and underwent (re-)fundoplication. After additional time and additional acid suppression, complete esophageal healing was confirmed endoscopically in all 134 patients.

Treatment outcomes after poor healing

Upon complete healing, 67/134 patients (50 %) had normal squamous regeneration (i. e. > 50 %) and 65/67 (97 % [95 %CI 90–99]) achieved CE-BE (Fig. 3 s). The CE-BE rate was similar to that in patients with normal healing (1178/1207; 98 % [95 %CI 97 %–98 %]) (Table 2), with an RR of 1.0 (95 %CI 1.0–1.0).

Two patients with poor healing (2/67; 3 %) did not achieve CE- BE and had remaining Barrett's mucosa (C1M3/4) with nondysplastic Barrett's esophagus (NDBE) or LGD (Table 3). Both patients developed severe esophageal stenosis during treatment and an elective decision was made to withhold further treatment in order to prevent recurrent stenosis with continued RFA. No patient progressed to advanced neoplasia.

Treatment characteristics of patients with poor healing

In the 67 patients with normal squamous regeneration after poor healing, poor healing occurred again after RFA in 38/67 patients (57 %) and RFA was continued with prolonged intervals (range 16–20 weeks) between ablation sessions. The treatment duration for patients with poor healing was significantly longer compared with patients with normal healing (15 and 8 months, respectively; $P < 0.01$) (Table 2).

Esophageal stenosis occurred in 34 % (23/67) of patients with poor healing compared with 14 % (168/1245) of patients with normal healing (RR 2.5 [95 %CI 1.8–3.6]). Accordingly, the risk for a severe stenosis that required at least five endoscopic dilations was 9 % (6/67) for patients with poor healing compared with 2 % (30/1245) for patients with normal healing (RR 3.7 [95 %CI 1.6–8.6]).

Poor squamous regeneration

In total, 74/1386 patients (5 % [95 %CI 4–7]) had poor squamous regeneration. The majority of patients (67/74; 91 %) also experienced poor healing, but 7/74 (9 %) had poor squamous regeneration with normal esophageal healing (Fig.3 s). Median BE at baseline for patients with poor squamous regeneration was C8M9 (minimum C3M5).

Table 2. Treatment characteristics for patients with no poor healing or poor squamous regeneration, patients with poor healing and normal squamous regeneration, and patients with poor squamous regeneration after radiofrequency ablation.

	No poor healing or poor squamous regeneration (n = 1245)	Poor healing, normal squamous regeneration (n = 67)	Poor squamous regeneration (n = 74)	*P* value[1]
Treatment characteristics				
Treatment duration, median (IQR), months	8 (4–13)	15 (10–20)[2]	14 (7–23)[2]	<0.01
C-RFA, mean (SD), n	0.6 (0.6)	0.8 (0.8)	1.4 (0.7)[2]	<0.01
F-RFA, mean (SD), n	1.6 (1)	1.9 (1)	1.4 (1)	0.3
Endoscopic resection, mean (SD), n	0.7 (0.7)	0.8 (0.9)	1.1 (1)[2]	<0.01
Incident lesion, n (%)	61 (5)	7 (10)	16 (22)[2]	<0.01
Esophageal stenosis, n (%)	168 (14)	23 (34)[2]	19 (26)[2]	<0.01
Post-procedural bleeding, n (%)	46 (4)	1 (2)	5 (7)	0.25
Treatment outcomes[3]				
CE-BE, n (%)	1178 (98)	65 (97)	27 (36)[2]	<0.01
Treatment failure, n (%)	29 (2)	2 (3)	47 (64)[2]	<0.01
Advanced EAC, n (%)	6(< 1)	0 (0)	11 (15)[2]	<0.01

CE-BE, complete endoscopic eradication of Barret's esophagus; C-RFA, circumferential radiofrequency ablation with BARRX-360 device; EAC, esophageal adenocarcinoma; F-RFA, focal radiofrequency ablation with the Barrx-90 device; IQR, interquartile range; SD, standard deviation.
1 Overall P value for analysis of variance (continuous outcomes) or chi-squared test (categorical outcomes).
2 Is statistically different from no poor healing or poor squamous regeneration group after Bonferroni correction.
3 Overall, in 38 patients, treatment was prematurely ended due to unrelated severe new comorbidity (n = 21) or unrelated death (n = 17).

In all 74 patients, poor squamous regeneration was noted after the first RFA treatment, which was C-RFA in 73/74 patients (99 %). A single patient developed poor squamous regeneration after the first F-RFA for a C3M5 BE segment. This patient had a history of severe reflux symptoms and had undergone Nissen fundoplication and re-fundoplication with moderate relief of symptoms.

Treatment outcomes after poor squamous regeneration

In total, 47/74 patients with poor squamous regeneration (64 % [95 %CI 52–74]) did not achieve CE-BE, with remaining Barrett's mucosa of median C4M7 (Table 3). The risk for treatment failure was significantly higher for patients with poor squamous regeneration compared with patients with normal squamous regeneration (29/1245; 2 % [95 %CI 2–3]; P < 0.01) (Table 2). Patients with poor squamous regeneration also had a higher risk for progression to advanced neoplasia during treatment (15 % [95 %CI 9–25] vs. < 1 % [95 %CI 0–1]; P < 0.01). The RR for treatment failure and for developing advanced neoplasia for patients with poor squamous regeneration compared with patients with normal regeneration was 27 (95 %CI 18–40) and 30 (95 %CI 12–81), respectively.

A total of 14 failure cases had persisting neoplasia (Table 3). Of these, 11 (15 % of all patients with poor squamous regeneration) had advanced neoplasia that exceeded the boundaries for curative endoscopic treatment owing to development of an incident lesion containing high risk EAC (n = 4) or multifocal incident lesions (n = 7). Surgery was performed in five patients for T1N0 (n = 4) or T2N1 (n = 1). The remaining six patients were unfit for surgery, three of whom developed metastasized EAC during follow-up and died.

The remaining three failure cases with persisting neoplasia (3/74, 4 %) had persisting HGD or low risk EAC and underwent stepwise radical endoscopic resection (SRER) after RFA. Complete eradication of neoplasia was achieved in all three patients and CE-BE was achieved in two.

The other 33 failure cases had persisting NDBE (n = 23) or LGD (n = 10) after RFA (Table 3). Three patients achieved CE- BE after SRER and 30 patients with remaining Barrett's mucosa (C4M7) were kept under endoscopic surveillance. During a mean surveillance period of 42 months and 4 endoscopies, 7 patients (23 % [95 %CI 12–41]) developed HGD (n = 5) or low risk EAC (n = 2), all of which were identified at early stages and were curatively treated endoscopically.

Overall, six patients underwent SRER as alternative treatment after failed RFA. Complete endoscopic eradication of dysplasia was achieved in all patients and CE-BE was achieved in 5/6 (Table 3 s).

Table 3. All treatment failures. A total of 29/1245 patients with no poor healing or poor squamous regeneration, 2/67 patients with poor healing and normal squamous regeneration, and 47/74 patients with poor squamous regeneration were recorded as treatment failure after radiofrequency ablation.

	No poor healing or poor squamous regeneration (n=29)	Poor healing, normal squamous regeneration (n = 2)	Poor squamous regeneration (n = 47)
Age, mean (SD), years	71 (4)	71 (1)	68 (4)
Initial BE length, median (IQR), cm	C4M5 (2–7; 4–9)	C8M9 (7–9; 9–10)	C9M11 (6–12; 7–13)
Initial pathology, n (%)			
LGD	7 (24)	0	9 (19)
HGD	6 (21)	0	10 (21)
EAC	16 (55)	2 (100)	28 (60)
Endoscopic resection, median (IQR), n	1 (1–1)	1 (1–2)	1 (1–2)
C-RFA, median (IQR), n	1 (0–1)	1 (1–1)	1 (1–2)
F-RFA, median (IQR), n	1 (1–1)	1 (1–1)	0 (0–2)
Treatment duration, median (IQR), months	14 (12–16)	26 (18–32)	15 (3–17)
Extent of residual BE, median (IQR), cm	C0M2 (0–0; 1–2)	C1M3 (0–2; 2–3)	C4M7 (1–7; 4–10)
Proportion of initial BE, %	C8, M30	C15, M50	C60, M75
Residual pathology, n (%)			
NDBE/LGD[1]	23 (79)	2 (100)	33 (70)
HGD/EAC (in incident lesion)[2]	6 (21)		14 (30)
Final outcome, n (%)			
Nonendoscopic therapy	6 (21)		11 (23)[3]
CE-D after extensive endoscopic resection			6 (13)
Endoscopic surveillance	23 (79)	2 (100)	30 (64)
Endoscopic surveillance			
Duration, mean (SD), months	47 (21)	33 (4)	42 (29)
Endoscopies, mean (SD), n	5 (3)	4 (3)	4 (3)
HGD/EAC, n (%)	4 (14)	0	7 (23)

BE, Barrett's esophagus; C-RFA, circumferential radiofrequency ablation with BARRX-360 device; CE-D, complete endoscopic eradication of dysplasia; EAC, esopha- geal adenocarcinoma; F-RFA, focal radiofrequency ablation with the Barrx-90 device; HGD, high grade dysplasia; IQR, interquartile range; LGD, low grade dysplasia; NDBE, nondysplastic Barrett's esophagus; SD, standard deviation.
1 Patients were referred for endoscopic surveillance.
2 Patients were referred for nonendoscopic therapy.
3 Indication for nonendoscopic therapy; 5 underwent surgery for T1N0 (n = 4) or T2N1 (n = 1).

Treatment characteristics of patients with poor squamous regeneration

Patients with poor squamous regeneration had a higher risk for a visible abnormality ("incident lesion") developing during RFA treatment. An incident lesion occurred in 16/74 patients (22 %) with poor squamous regeneration compared with 61/1245 patients (5 %) with normal squamous regeneration (RR 4.4 [95 %CI 2.7–7.3]) (Table 2). For patients with poor squamous regeneration, 11/16 (69 %) incident lesions were noted to have progressed to advanced neoplasia, compared with 6/61 incident lesions (10 %) among patients with normal squamous regeneration (RR 7.0 [95 %CI 3–16]).

In 17/74 patients (23 %) with poor squamous regeneration, treatment was stopped after the first RFA treatment (Fig. 4 s). The remaining 57 patients all underwent a second RFA treatment, which resulted in normal squamous regeneration in 27/ 57 patients (47 %) and poor squamous regeneration in 30/57 patients (53 %). All patients with normal squamous regeneration after the second RFA treatment (n = 27) achieved CE-BE after additional F-RFA. In contrast, all patients with poor squamous regeneration after the second RFA treatment (n = 30) ultimately failed to achieve CE-BE, regardless of additional C-RFA and/or F-RFA.

Characteristics associated with poor squamous regeneration

Higher body mass index, longer BE length, presence of reflux esophagitis at baseline, and < 50 % squamous regeneration after baseline endoscopic resection were independently associated with poor squamous regeneration after RFA in multivariable logistic regression (Table 4). Poor regression after endoscopic resection was the strongest predictor for occurrence of poor squamous regeneration: patients with < 50 % squamous regeneration after endoscopic resection had a 13-times higher odds of poor squamous regeneration after RFA compared with patients with normal squamous regeneration after endoscopic resection (OR 13.08 [95 %CI 6.82–25.92]). If the endoscopic resection scar regenerated with < 50 % squamous epithelium, 50 % of patients (29/58) also had poor squamous regeneration after subsequent RFA.

Table 4. Univariable and multivariable analysis of potential risk factors for poor squamous regeneration. Assessment of the predictive value of several predefined patient and treatment characteristics known to the physician prior to initiation of radiofrequency ablation (RFA) for poor squamous regeneration, defined as < 50 % squamous regression after RFA.

	Univariable OR (95 %CI)	Multivariable OR (95 %CI)
Age, years	1.00 [0.98; 1.02]	
Male sex	1.36 [0.77; 2.31]	
BMI[2], kg/m^2	1.04 [0.98; 1.09]	1.09 [1.02; 1.16]
Smoking	0.86 [0.53; 1.55]	
Prior fundoplication	2.69 [0.62; 8.08]	
Length of hernia diafragmatica[1], cm	1.24 [1.11; 1.37]	
Length BE (circumferential)[2], cm	1.34 [1.26; 1.42]	1.33 [1.24; 1.43]
Reflux stenosis	2.06 [0.67; 4.9]	
Reflux esophagitis[2]	5.76 [2.70; 11.46]	7.10 [2.89; 16.60]
Baseline HGD or EAC	1.28 [0.75; 2.29]	
≥1 visible lesion at baseline[1]	2.78 [1.48; 4.94]	
<50% squamous regeneration after ER[2]	22.55 [12.44; 42.34]	13.08 [6.82; 25.92]

BE, Barrett's esophagus; BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; OR, odds ratio.
1 Statistically significant in univariable analysis using backward selection based on chi-squared test
2 Statistically significant in multivariable analysis using backward selection based on chi-squared test

Poor regression after endoscopic resection without RFA

A total of 12 patients had poor squamous regeneration after endoscopic resection and no RFA was performed owing to expected poor regression in combination with older age and/or comorbidity (Fig. 3 s, Fig. 5 s). Although no RFA was performed and these patients were not formally included in the study cohort, we describe the follow-up for these patients. During a mean endoscopic follow-up of 25 (SD 18) months and 4 endoscopies (SD 3), no patient developed HGD or EAC.

DISCUSSION

In this nationwide cohort of 1386 patients with early BE neoplasia who were treated with RFA, we found that poor healing and poor squamous regeneration occurred in 10 % and 5 % of patients, respectively. Poor healing resolved after additional time and acid suppression. Half of the patients with poor healing showed normal squamous

regeneration and 97 % of these reached CE-BE, which was comparable to the success rate in patients with normal healing and regeneration. The other 50% of patients with poor healing also showed poor squamous regeneration and only 36 % of these patients were treated successfully. Furthermore, patients with poor squamous regeneration had a significantly higher risk for progression to advanced disease during treatment compared with patients with normal squamous regeneration. None of the patients who also demonstrated poor squamous regeneration after their second RFA treatment achieved CE-BE. Risk factors for poor squamous regeneration included higher body mass index, longer BE segments, presence of reflux esophagitis, and < 50 % squamous regeneration of the initial endoscopic resection wound.

The underlying mechanisms of poor healing and poor squamous regeneration are unknown. Hypothetically, three main factors may play a role in regeneration with BE: patient/genetic factors, the severity of acid exposure, and the thickness of the BE segment [10–12]. The severity of acid exposure is a well- known risk factor in the pathogenesis of BE [13] and presumably also influences wound healing after RFA. If the esophagus is exposed to severe acid reflux, the mucosa is likely to heal with Barrett's mucosa [14–16], whereas eliminating acid exposure may lead to regeneration of squamous epithelium. Adequate acid suppression is therefore essential during endoscopic treatment for BE [1, 2, 8]. The thickness of the BE may also play a role in response to ablation [17, 18]. Hypothetically, this may explain why some cases of BE regeneration after RFA do respond after endoscopic resection.

Based on our observations, we present practical advice on a number of clinical scenarios for the management of poor healing or poor squamous regeneration following RFA (Table 5). Our data suggest that it is important to differentiate poor healing from poor squamous regeneration. Poor healing was defined as active inflammatory changes with mucosal swelling and exudates and/or visible ulcerations ≥ 3 months after RFA treatment. If this is the case, RFA treatment should be postponed because the edematous mucosa has a thickness greater than the depth of RFA penetration, and because incident lesions may be masked and missed. The focus must be on optimizing the circumstances for the next endoscopy: provide at least 6 weeks' extra time, verify PPI compliance, and consider increasing the PPI dose. We demonstrated that with sufficient time and sufficient acid suppression, the esophagus will heal completely.

The effects of RFA (i. e. conversion of the BE into squamous epithelium and the presence/absence of incident lesions) can only be evaluated when the esophagus is completely healed. Half of the patients with poor healing were found to have normal squamous regeneration and, although treatment was of longer duration and with a

higher risk for esophageal stenosis, these patients had a > 95 % chance of CE-BE, which was similar to that observed in patients with normal healing.

However, the other 50 % of patients with poor healing also showed poor squamous regeneration when complete healing of the BE was awaited, and in these cases, CE-BE was achieved in only 36 %. Poor squamous regeneration was defined as < 50 % regression with squamous epithelium of a BE area after treatment with RFA and after complete healing. Poor squamous regeneration occurred predominantly in longer BE segments and after circumferential RFA. Logically, patients with long BE segments represent more severe reflux disease.

What should we do in cases of poor squamous regeneration? We suggest to reconsider the indication for RFA and to carefully balance the anticipated success of continuing RFA against its associated risks (Table 5). Although initially the RFA may have been justified based on an anticipated success rate of >95 % and a treatment duration of 9 months, the chance of achieving CE-BE in cases of poor squamous regeneration was only 36 % and included a prolonged treatment time and a significantly higher risk for stenosis (26 %). Moreover, poor squamous regeneration is also an important warning sign, with a risk for progression to advanced neoplasia that exceeds the boundaries for curative endoscopic treatment of 15 %, which is 30 times greater than the baseline value of < 1 %. In our opinion, therefore, in younger and fit patients with poor squamous regeneration and persisting long-segment BE containing persisting neoplasia, esophagectomy should be strongly considered. Another alternative option could be radical endoscopic resection, although we believe this is only a valid strategy in patients with poor squamous regeneration and > 50 % squamous regeneration after baseline endoscopic resection.

On the other hand, if the residual BE is completely flat and free of neoplasia, endoscopic surveillance is an acceptable alternative, especially in older patients with comorbidities. In our study, only 23 % of such patients developed a visible lesion during 42 months of follow-up and all were curatively treated with a single endoscopic resection. These data are in line with other studies, which reported rates of metachronous neoplasia after endoscopic resection ranging from 15 % in 5 years to 30 % in 3 years [19–22], all detected at early stages. Remaining Barrett's mucosa without neoplasia is therefore, in our opinion, not a valid indication for fundoplication if performed to increase the chance for successful RFA.

Considering such alternative strategies may also be appropriate prior to the initial RFA if this is preceded by endoscopic resection healing with < 50 % squamous regeneration.

If this was observed, 50 % of patients were noted to have poor squamous regeneration after RFA (adjusted OR 13). Our study confirmed the results of other studies showing that poor regression after endoscopic resection is a strong predictor for poor squamous regeneration after RFA [7].

Alternatively, if the remaining BE is completely flat and RFA appears to have had some effects, a second RFA may be justified. With repeat RFA therapy, the endoscopist should be aware of incident lesions, which may be associated with disease progression: incident lesions occurred in 22 % of patients with poor squamous regeneration and careful endoscopic imaging is therefore essential. However, if this second RFA session is again associated with poor squamous regeneration, continuing RFA treatment is strongly discouraged: none of the 30 patients in our study with two consecutive RFAs with poor squamous regeneration achieved CE-BE.

This is the first study to report the incidence, treatment characteristics, and outcomes for patients with poor healing and/or poor squamous regeneration after RFA. Our findings are relevant as definitions and recommendations are lacking in current guidelines [1, 2, 8] and physicians often struggle to decide what to do with this challenging group of RFA patients. Our study used a nationwide cohort that included all patients who underwent endoscopic treatment for BE neoplasia in the Netherlands. Patients were treated according to a homogeneous treatment protocol and in expert centers only. We retrieved complete data on outcomes for all patients and only a small proportion of baseline data was missing.

Some limitations need to be addressed. A formal joint treatment protocol was used in all BECs and although this included a section about poor healing and poor squamous regeneration, this content served only as a guide, with no strict guidelines, and was based on expert opinion. Therefore, the strategy for patients with poor healing and/or poor squamous regeneration with regard to decision making on PPI increase, fundoplication, additional tests, and when to stop further RFA, may have differed between BECs. A total of 17 patients were already defined as treatment failure after the first RFA treatment, which may raise debate about the definition of failure; however, 10/17 also had <50% regeneration after endoscopic resection, and in 2/17 treatment was stopped due to progression to advanced neoplasia. Furthermore, the decision to stop was made by expert endoscopists in the field and complicated patients were discussed during multidisciplinary meetings. Outcomes of 24- hour pH-metry are hard to interpret, as these were performed in a minority of patients and for varying indications (Table 2 s). As fundoplication was performed rarely and not for uniform

in- dications, we were unable to detect its effects with regard to reflux disease and response to RFA.

The decision to stop further RFA treatment partially depends on patient characteristics, and treatment failure therefore is a relative concept. Proposed conclusions and recommendations should therefore be interpreted as guidance, rather than as exact rules.

Other limitations include the risk for misclassification bias. If the endoscopy reports were incomplete for poor squamous regeneration, endoscopic images and videos were reviewed to obtain complete data without blinding of the assessor to the outcome. We used a cutoff of 50 % for the definition of poor squamous regeneration, which is arbitrary, and a more continuous score might have provided more information. However, we preferred a simple cutoff that could easily be used in clinical practice.

In conclusion, poor healing should be managed with additional time and acid suppression instead of applying RFA. Half of these patients showed normal squamous regeneration with excellent treatment outcomes. However, if upon healing, poor squamous regeneration is observed (5 % of patients treated with RFA), two-thirds of patients may experience treatment failure, which carries a significant risk for progression to advanced disease.

Table 5. Clinical advice. Based on our data, we present practical advice on a number of clinical scenarios for the management of poor healing and/or poor squamous regeneration.

Clinical problem	Advice	Rationale
Less than 50 % squamous regeneration after baseline endoscopic resection (Fig. 4 s)	Consider surveillance of the remaining BE instead of proceeding with ablation therapy, as this is a valid alternative in patients with flat BE without neoplasia after endoscopic resection.	Of the 58 patients with < 50 % squamous regeneration after endo- scopic resection, 59 % developed poor healing and/or poor squa- mous regeneration after subsequent RFA. The risk increased fur- ther for patients with a higher BMI, a longer BE segment, and/or reflux esophagitis. In 12 patients with older age and/or comorbidity and endoscopic resection with < 50 % squamous regeneration, a remaining flat BE with NDBE or LGD persisted and RFA was not initiated; during mean 25 months of follow-up, no patient progressed to HGD or EAC.
Poor healing (active inflamma- tory changes with mucosal swelling and exudates, and/or visible ulcerations ≥ 3 months post-RFA; ▶ Fig. 1, ▶ Fig. 2)	Postpone treatment.	The edematous mucosa is too thick for effective ablation and visible lesions may be masked.
	Optimize circumstances for healing:	In all 134 patients with poor healing after RFA, complete healing was accomplished after these steps were followed.
	1. Provide sufficient time: schedule a new endoscopy in ≥ 6 weeks.	
	2. Provide sufficient acid suppression: ver- ify PPI compliance and consider dose in- crease.	
	3. Only perform 24-hour pH-metry if a finding of pathological reflux would result in referring the patient for fundoplication, or in other clinical consequences.	
	Upon complete healing, assess conversion to squamous epithelium.	Upon complete healing, 50 % (67/134) of patients with initial poor healing had normal squamous regeneration.

Table 5. (Continued)

Clinical problem	Advice	Rationale
Initial poor healing, with now complete healing and > 50 % squamous conversion (▶ Fig. 1)	Continue RFA on 4–6-month intervals.	97 % (65/67) achieved CE-BE (similar to 94 % of patients with initial normal healing).
	Counsel your patient:	
	1. Continuing treatment carries a higher risk for esophageal stenosis.	30 % of patients (40/134) developed esophageal stenosis and 8 % (10/134) had a severe stenosis that required > 5 endoscopic dila- tions. These risks were significantly higher compared with patients with normal healing (14 % and 2 %, respectively; *P* <0.01).
	2. The treatment phase will take more compared time.	Median treatment duration was 15 months (IQR 10–20) with 8 months (IQR 4–13) for patients with normal healing (*P* <0.01).
Poor squamous regeneration as (< 50 % squamous regression after the first RFA upon complete healing; ▶ Fig. 2)	Consider poor squamous regeneration a warning sign. Careful inspection is crucial as patients have a significant risk for new visible lesions that pop-up during RFA and for progression to advanced neoplasia.	22 % of patients with poor squamous regeneration (16/74) devel- oped an incident lesion compared with (5 %, *P* < 0.01) for patients with normal regeneration. Moreover, 69 % of incident lesions in patients with poor squamous regeneration (11/16) had advanced neoplasia compared with 10 % of the incident lesions in patients with normal regeneration (6/61; *P* < 0.01).
	Reconsider continuation of ablative therapy.	Outcomes of RFA are worse if poor squamous regeneration occurs after the first RFA: only 36 % of patients (27/74) achieved CE-BE after continued RFA compared with 98 % of patients with normal squamous regeneration (1178/1207).
	Decision making after the first RFA with poor squamous regeneration:	
	A second RFA may be justified, based on the following considerations: *(continued on next page)*	

Table 5. (Continued)

Clinical problem	Advice	Rationale
	1. Arguments in favor of a second RFA: • < 50 % squamous regeneration, but some areas with normal regeneration • Completely flat BE.	Overall, 47% (27/57) of patients had normal squamous regeneration after the second RFA. For patients with remaining circumferential BE of <2cm and an indication for focal RFA, 67% (20/30) had normal squamous regeneration.
	2. Arguments in favor of no further RFA: • Patients of older age and/or with comorbidity. • Slightest suspicion for the presence of a visible lesion.	In older patients, the decision to continue with surveillance instead of RFA may be justified: 23 % of patient developed a visible lesion during long-term surveillance, all effectively treated endo- scopically and none progressed to advanced EAC (see below). A cautious approach is called for with regard to inspection for visible lesions, as a second RFA may potentially again lead to a period of ±4–6 months with poor healing, during which no adequate inspection can be accomplished. Incident lesions in patients with poor squamous regeneration harbored advanced neoplasia in 69 % (11/16) compared with 10 % (6/61) of incident lesions in patients with normal squamous regeneration.
	Decision making after the second RFA:	
	1. If a second RFA results in > 50 % squa- mous regeneration, RFA may be contin- ued.	All 27 patients with normal squamous regeneration after the second RFA achieved CE-BE.
	2. If a second RFA again results in < 50 % squamous regeneration, additional RFA should be restrained.	None of the 30 patients with poor squamous regeneration after the second RFA achieved CE-BE, despite additional RFA treatment in 16/30 patients.

Table 5. (Continued)

Clinical problem	Advice	Rationale
A decision was made to stop further RFA owing to poor squamous regeneration	The remaining BE should be accurately staged with inspection, targeted biopsies, and/or endoscopic resection in cases with visible lesions, and four-quadrant random biopsies.	
	1. Radical endoscopic resection may be considered if baseline endoscopic resec- tion had > 50 % squamous regeneration.	5/6 patients achieved CE-BE after radical endoscopic resection. The single patient who did not achieve CE-BE was the only one who had < 50 % squamous regeneration after baseline endoscopic resection.
	2. Persisting HGD, EAC, and/or visible le- sions: radical endoscopic resection may be an option, but esophagectomy should be considered in early stages, especially in younger patients.	Overall, patients with poor squamous regeneration had a high risk for progression to advanced EAC during treatment (15 % vs. < 1 % of patients with normal regeneration; $P < 0.01$). Five patients with persisting visible lesions were referred for surgery, four of whom had ≤ T1N0, and one had T2N1 (20 %).
	3. Persisting flat BE with intestinal meta- plasia or LGD: endoscopic surveillance is a valid policy.	During a mean follow-up of 3.5 years, 23 % developed HGD or early EAC, all of which were successfully treated with curative endoscopic resection.

REFERENCES

1 Shaheen NJ, Falk GW, Iyer PG et al. ACG Clinical Guideline: Diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016; 111: 30–50

2 Weusten B, Bisschops R, Coron E et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2017; 49: 191–198

3 Phoa KN, van Vilsteren FGI, Weusten BLAM et al. Radiofrequency ab- lation vs endoscopic surveillance for patients with Barrett esophagus and low grade dysplasia. JAMA 2014; 311: 1209

4 Phoa KN, Pouw RE, Bisschops R et al. Multimodality endoscopic era- dication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut 2016; 65: 555–562

5 Shaheen NJ, Sharma P, Overholt BF et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009; 360: 2277– 2288

6 Pouw RE, Wirths K, Eisendrath P et al. Efficacy of radiofrequency ab- lation combined with endoscopic resection for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol 2010; 8: 23–29

7 van Vilsteren FGI, Alvarez Herrero L, Pouw RE et al. Predictive factors for initial treatment response after circumferential radiofrequency ablation for Barrett's esophagus with early neoplasia: a prospective multicenter study. Endoscopy 2013; 45: 516–525

8 Nederlandse Vereniging van Maag-darm-leverartsen. Richtlijn Bar- rett-Oesofagus. 2018: http://www.mdl.nl/richtlijnen2?no-Cache=214;1484584659

9 van Munster S, Nieuwenhuis E, Weusten BLAM et al. Long-term out- comes after endoscopic treatment for Barrett's neoplasia with radio- frequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period. Gut 2021: doi:10.1136/gutjnl-2020-322615

10 Sengupta N, Ketwaroo GA, Bak DM et al. Salvage cryotherapy after failed radiofrequency ablation for Barrett's esophagus-related dys- plasia is safe and effective. Gastrointest Endosc 2015; 82: 443–448

11 Weusten BLAM, Bergman JJGHM. Cryoablation for managing Barrett's esophagus refractory to radiofrequency ablation? Don't embrace the cold too soon! Gastrointest Endosc 2015; 82: 449–451

12 Timmer MR, Brankley SM, Gorospe EC et al. Prediction of response to endoscopic therapy of Barrett's dysplasia by using genetic biomar- kers. Gastrointest Endosc 2014; 80: 984–991

13 Shaheen NJ, Richter JE. Barrett's oesophagus. Lancet 2009; 373: 850– 861

14 Akiyama J, Marcus SN, Triadafilopoulos G. Effective intra-esophageal acid control is associated with improved radiofrequency ablation outcomes in Barrett's esophagus. Dig Dis Sci 2012; 57: 2625–2632

15 Krishnan K, Pandolfino JE, Kahrilas PJ et al. Increased risk for persistent intestinal metaplasia in patients with Barrett's esophagus and un- controlled reflux exposure before radiofrequency ablation. Gastroen- terology 2012; 143: 576–581

16 Kruger L, Gonzalez LM, Pridgen TA et al. Ductular and proliferative response of esophageal submucosal glands in a porcine model of esophageal injury and repair. Am J Physiol Gastrointest Liver Physiol 2017; 313: G180–G191

17 Becq A, Camus M, Rahmi G et al. Emerging indications of endoscopic radiofrequency ablation. United Eur Gastroenterol J 2015; 3: 313–324

18 Trunzo JA, McGee MF, Poulose BK et al. A feasibility and dosimetric evaluation of endoscopic radiofrequency ablation for human colonic and rectal epithelium in a treat and resect trial. Surg Endosc 2011; 25: 491–496

19 May A, Gossner L, Pech O et al. Local endoscopic therapy for intraepi- thelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treat- ment approach. Eur J Gastroenterol Hepatol 2002; 14: 1085–1091

20 Ell C, May A, Pech O et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007; 65: 3–10

21 Pech O, Behrens A, May A et al. Long-term results and risk factor a- nalysis for recurrence after curative endoscopic therapy in 349 pa- tients with high-grade intraepithelial neoplasia and mucosal adeno- carcinoma in Barrett's oesophagus. Gut 2008; 57: 1200–1206

22 van Munster SN, Nieuwenhuis EA, Weusten BLAM et al. Endoscopic resection without subsequent ablation therapy for early Barrett's neoplasia: endoscopic findings and long-term mortality. J Gastrointest Surg 2021; 25: 67–76

SUPPLEMENTARY MATERIAL

To access the supplementary material accompanying this article, visit the online version of Endoscopy at https://doi.org/10.1055/a-1521-6318.

CHAPTER 8

Development and external validation of a model to predict complex treatment after RFA for Barrett's esophagus with early neoplasia

Esther Nieuwenhuis*, Sanne N van Munster*, Raf Bisschops, Hilde Willekens, Bas L A M Weusten, Lorenza Alvarez Herrero, Auke Bogte, Alaa Alkhalaf, Ed B E Schenk, Erik J Schoon, Wouter Curvers, Arjun D Koch, Pieter Jan F de Jonge, Tjon J Tang, Wouter B Nagengast, Jessie Westerhof, Martin H M G Houben, Jacques J G H M Bergman, Roos E Pouw

***authors contributed equally**

Clin Gastroenterol Hepatol. 2022 Mar 12;S1542-3565(22)00246-4.
doi: 10.1016/j.cgh.2022.02.057

ABSTRACT

Background and Aims

Endoscopic eradication therapy for Barrett's esophagus (BE)-related neoplasia is safe and leads to complete eradication in the majority of patients. However, a subgroup will experience a more complex treatment course with a risk for failure or disease progression. Early identification of these patients may improve patient counseling and treatment outcomes. We aimed to develop a prognostic model for a complex treatment course.

Methods

We collected data from a nationwide registry that captures outcomes for all patients undergoing endoscopic eradication therapy for early BE neoplasia. A complex treatment course was defined as neoplastic progression, treatment failure, or the need for endoscopic resection during the radiofrequency ablation treatment phase. We developed a prognostic model using logistic regression. We externally validated our model in an independent registry.

Results

A total of 1386 patients were included, of whom 78 (6%) had a complex treatment course. Our model identified patients with a BE length of 9 cm or longer with a visible lesion containing high-grade dysplasia/cancer, and patients with less than 50% squamous conversion after radiofrequency ablation were identified as high risk for a complex treatment. This applied to 8% of the study population and included 93% of all treatment failures and 76% of all patients with advanced neoplastic progression. The model appeared robust in multiple sensitivity analyses and performed well in external validation (area under the curve, 0.84).

Conclusions

We developed a prognostic model that identified patients with a BE length of 9 cm or longer and high-grade dysplasia/esophageal adenocarcinoma and those with poor squamous regeneration as high risk for a complex treatment course. The good performance in external validation suggests that it may be used in clinical management (Netherlands Trial Register: NL7039).

INTRODUCTION

Endoscopic eradication therapy (EET) is well established for Barrett's esophagus (BE) with early neoplasia. EET typically consists of endoscopic resection (ER) of visible abnormalities, followed by radiofrequency ablation (RFA) of the remaining flat BE, or RFA monotherapy if no visible lesions are present. This dual-modality treatment has been proven safe and results in complete eradication of BE (CE-BE) in 74% to 98% of patients [1–4].

For most BE patients with early neoplasia, EET is relatively straightforward. Patients generally achieve CE- BE after a baseline ER and 2 to 3 RFA sessions. However, a subgroup of patients will experience a more complex treatment course. In these patients, the esophagus may regenerate with columnar epithelium instead of squamous epithelium, or new visible abnormalities may appear during the course of RFA, requiring repeat ER and carrying a risk of neoplastic progression to advanced esophageal adenocarcinoma (EAC) when left undetected. Early identification of these patients may improve patient counseling on what to expect in their treatment course and also may function as a warning sign for the endoscopist.

Furthermore, the European and Dutch guidelines recommend that EET for BE-related neoplasia is centralized in expert centers [5,6]. In such expert centers, endoscopists and pathologists have followed specific EET training, have an annual case load of 10 or more new BE neoplasia, have regular multidisciplinary meetings, and access to experienced esophageal surgery. Prior studies have provided circumstantial evidence that treatment outcomes may be better in expert centers [7–9]. Centralization of EET may not be feasible in all countries, however, referral of the small subset of patients with a predicted, more complex, treatment course may be considered.

We therefore aimed to develop a prognostic model to predict a more complex treatment course during EET for BE-associated neoplasia.

METHODS

This study used data from the Barrett Expert Center (BEC) registry (Netherlands Trial Register: NL7039), which has been described in detail elsewhere [7]. In summary, this registry captures outcomes for all patients with BE neoplasia in The Netherlands undergoing EET since 2008. EET in The Netherlands is centralized in 9 BECs, with the implication that every patient is treated in one of these BECs. This infrastructure was established in 2007 after a joint training program for endoscopists and pathologists. All

BE treatments since then have been provided by these specifically trained endoscopists and pathologists. BECs adhered to a joint treatment and follow-up protocol and multidisciplinary meetings were organized twice a year to expand on training and to guarantee homogeneity of protocol adherence.

External validation was performed in a prospective RFA registry from the University Hospital Leuven (Leuven, Belgium) [10]. This center has a tertiary referral function for treatment of BE-related neoplasia. A single expert endoscopist (R.B.) provided care in this hospital, after joint training with endoscopists from the Dutch centers.

Additional information can be found in the Supplementary Methods section.

Study population

For the current study, we included all patients from the BEC registry and the Leuven registry who underwent at least 1 RFA treatment for BE initially containing low- grade dysplasia (LGD), high-grade dysplasia (HGD), or low-risk-EAC (ie, radical resection of mucosal or superficial submucosal [sm1] EAC with good to moderate differentiation and without lymphovascular invasion). Prior ER was allowed.

Study end point

The primary end point was a complex treatment course, an end point comprising neoplastic progression, treatment failure, and/or the need for resection during the RFA treatment phase.

Neoplastic progression was defined as EAC diagnosed during RFA treatments exceeding the boundaries for curative EET, owing to one of the following characteristics: deep submucosal invasion (ie, sm2/3), poor differentiation, lymphovascular invasion, or extensive and multifocal EAC ineligible for ER.

Treatment failure was defined as failure to achieve complete eradication of BE owing to post-RFA regeneration with Barrett's epithelium, despite optimal acid control (ie, absence of reflux esophagitis on endoscopy), and sufficient time for healing. RFA was stopped if we anticipated that we would be unable to achieve CE-BE. This included patients in whom more than 20% of the initial BE persisted and/or in whom neoplasia persisted. In contrast, patients with more than 80% of the initial BE removed and with complete eradication of neoplasia, in whom an elective decision was made to withhold further treatment, were not included in this end point [7,11].

Need for resection during the RFA treatment phase was defined as a new, visible abnormality, defined as a nonflat lesion and/or a lesion with an irregular mucosal pattern, that was encountered during the RFA treatment sessions and contained HGD or EAC.

Definition and Description of Potential Predictors

We included patient and treatment characteristics that would be known to the physician after the first RFA treatment and with clinically or biologically plausible effects on the treatment course. We included 4 subgroups of predictors. First, demographics were defined as age, sex, body mass index, and smoking. Second, the severity of reflux was assessed by prior fundoplication, length of the BE, length of the hiatal hernia, presence of a reflux stenosis at baseline, or presence of reflux esophagitis at baseline. Third, the severity of histologic changes was defined by the presence of a visible lesion at baseline, worst histology at baseline, and the number of ER specimens at baseline. Finally, parameters related to the initial treatment response were assessed as poor squamous regeneration (ie, <50% squamous regeneration) after ER (ie, of the ER scar) and after RFA (ie, of the entire BE area treated with RFA).

Information on all variables was available, resulting in no missing data.

Statistics

Baseline characteristics were analyzed using standard descriptive statistics. Continuous variables were presented as means with SD and as the median with interquartile range (IQR) for normally distributed and skewed data, respectively. The 95% CIs were obtained using internal bootstrapping. Relative risk (RR) was defined as the risk in the exposed patients divided by the risk in the unexposed patients. The odds ratio was defined as odds in the exposed patients divided by the odds in the unexposed patients.

The prognostic model was developed on the Dutch data set using logistic regression with backward selection based on Aikake's Information Criterion. The functional form (linear vs nonlinear relations with the outcome) was checked for all continuous variables. Internal validation was assessed by the area under the curve (AUC) and calibration plots, corrected for optimism based on leave-one-out cross-validation. Additional cross-validation was performed based on year of inclusion and center, to detect potential differences over time and/or per center.

For sensitivity analysis, we performed model building using the least absolute shrinkage and selection operator (LASSO) algorithm. Leave-one-out cross-validation was used for

choosing the LASSO penalty. The model was externally validated in the Leuven registry using the AUC and calibration plots.

Data analysis was performed using R version 3.6.3 (R foundation for Statistical Computing, Vienna, Austria: http://www.R-project.org) with the following packages: Hmisc, ggplot2, ROCR, caret, rms, pROC, epi, tidyverse, broom, dplyr, car, and glmnet.

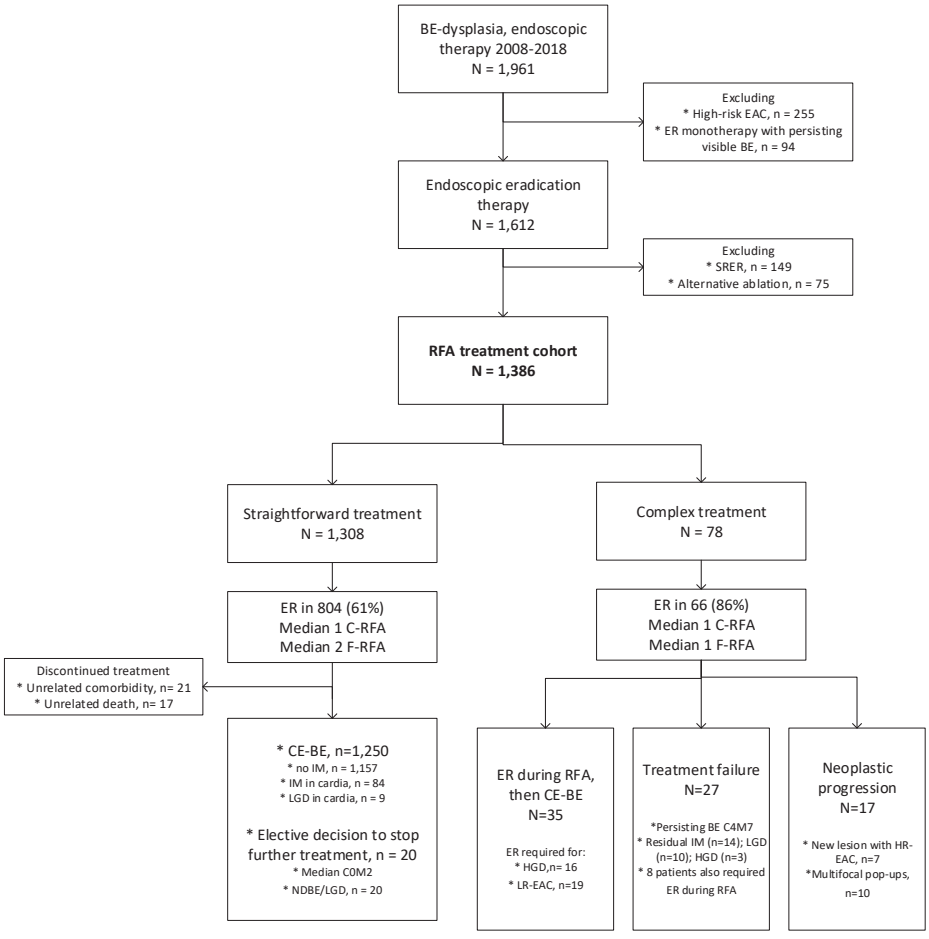
All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

A total of 1386 patients enrolled in the BEC registry met the inclusion criteria for the current study for model building (Figure 1, Table 1). This cohort of patients has been described in detail previously [7].

The vast majority of patients (1308 of 1386; 94%) had a straightforward treatment course. For these patients, treatment had a median duration of 8 months (p25-p75 5-13) and consisted of a baseline ER in 61% and a median of 1 circumferential RFA and 2 focal RFA sessions. This resulted in CE-BE in 98% of patients (1250 of 1270). For the remaining 2% (20 of 1270), an elective decision was made to withhold further treatment owing to older age and/or comorbidity, and only minimal residual BE remaining (median C0M2).

Figure 1. Patient flow



BE, Barrett's esophagus; CE- BE, complete eradication of Barrett's esophagus; C- RFA, circumferential RFA; EAC, esophageal adeno- carcinoma; ER, endo- scopic resection; F-RFA, focal RFA; HGD, high- grade dysplasia; HR, high risk; IM, intestinal meta- plasia; LGD, low-grade dysplasia; LR, low risk; NDBE, nondysplastic Barrett's esophagus; RFA, radiofrequency ablation; SRER, stepwise radical endoscopic resection.

Table 1. Baseline characteristics

		RFA treatment cohort N=1,386	Straightforward treatment N=1,308	Complex treatment N=78	Leuven registry N=282
Demographics	Male gender, n (%)	1,122 (81)	1,063 (81)	58 (74)	243 (87)
	Age, years, mean (±SD)	65 (10)	65 (10)	66 (10)	64 (11) 64 (11)
	BMI, kg/m^2, mean (±SD)	28 (4)	28 (4)	27 (4)	-
	Smoking, n (%)				-
	Never	321 (23)	303 (23)	18 (23)	
	Former	805 (58)	757 (58)	48 (62)	
	Current	260 (19)	248 (19)	12 (15)	
BE history	Prior fundoplication, n (%)	23 (2)	21 (2)	2 (3)	-
	Surveillance history, n (%)	892 (64)4 (2-8)	846 (70)	46 (67)	-
	In years, median (IQR)		3 (2-8)	3 (2-7)	
Imaging	Hiatal hernia, n (%)	1321 (95)	1,246 (95)	75 (96)	265 (94)3 (2-4)
	In cm, mean (±SD)	3 (2-4)			
	Esophagitis, n (%)	49 (4)	43 (3)	6 (8)	-
	Reflux stenosis, n (%)	49 (4)	45 (3)	4 (5)	-
	Circumferential BE, median (IQR)	2 (1-6)	2 (0-5)	8 (5-10)	3 (0-6)
	Maximum BE, median (IQR)	5 (3-8)	5 (3-7)	9 (6-12)	5 (2-7)
	Visible lesion, n (%)	860 (62)	803 (61)	67 (86)	164 (58)
Pathology	Worst pathology, n (%)				
	LGD	375 (27)	366 (28)	9 (12)	18 (7)
	HGD	422 (30)	404 (31)	18 (23)	154 (60)
	EAC	589 (43)	538 (41)	51 (65)	84 (33)
Initial treatment (1st RFA +/- ER)	Baseline endoscopic resection, n (%)	860 (62)	803 (61)	67 (86)	164 (58)
	Specimen, n, median (IQR)	2 (1-4)	2 (1-4)	3 (2-5)	2 (0-3)
	<50% regression after ER, n (%*)	107 (12)	80 (10)	27 (41)	-
	<50% regression after RFA, n (%)	74 (5)	33 (3)	41 (53)	26 (9)

BE, Barrett's ssophagus; BMI, Body Mass Index; EAC, esophageal adenocarcinom; ER, endoscopic resection; HGD, high-grade dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; RFA, radiofrequency ablation; SD, standard deviation.

[a]The percentage of patients with ER, regression percentage of area of ER.

Complex treatment course

Overall, 78 patients (78 of 1386; 6%) had a complex treatment course (Tables 1 and 2).

Seventeen of 78 patients progressed to neoplastic stages that exceeded the boundaries for curative EET, all were detected through new visible lesions that were encountered during RFA (for a more detailed case description of the 17 patients with progression to advanced neoplasia, see van Munster et al [7] and http://best-academia.eu).

Twenty-seven of 78 patients failed to achieve CE-BE after RFA, but did not progress to advanced cancer.

The remaining 34 of 78 patients required ER for a new visible lesion that was encountered during RFA.

Table 2. Seventy-Eight Patients with a Complex Treatment Course

1. Neoplastic progression, N	**17**
High-risk EAC,[a] N	7
Multifocal EAC, N	17
2. Failure to achieve CE-BE, N	**27**
Remaining BE segment (median, IQR)	C4M7 (2–7; 5–11)
Worst histology	
NDBE, N	14
LGD, N	10
HGD, N	3
Prior ER for a new visible lesion during RFA, N	8
3. ER for a new visible lesion during RFA, N	**34**
Histology ER specimen	
HGD, N	16
LR-EAC, N	18

BE, Barrett's esophagus; CE, complete eradication; EAC, esophageal adeno- carcinoma; ER, endoscopic resection; HGD, high-grade dysplasia; HR, high- risk; IQR, interquartile range; LGD, low-grade dysplasia; LR, low-risk; LVI , with lymphovascular invasions; m2/3, deep submucosal; NDBE, nondys- plastic Barrett's esophagus; sm1, superficial submucosal; RFA, radiofrequency ablation.

[a]Three patients had sm1 LVI+ EAC, and 4 patients had sm2/3 EAC (of whom 2 had poor differentiation and 1 had LVI+).

Treatment characteristics

Treatment characteristics showed significant differences between patients with a straightforward and a complex treatment course (Table 3). The median treatment duration was 8 months (IQR, 5–13 mo) and 12 months (IQR, 7–20 mo), respectively (P < .01). The risk that more than 4 RFA treatments were required was increased significantly (RR, 2.7; 95% CI, 1.3–5.6).

Patients with a complex treatment course had a significantly increased risk for esophageal stenosis (RR, 2.3; 95% CI, 1.6–3.1) and for bleeding (RR, 2.6; 95% CI, 1.2–5.6).

Table 3. Treatment Characteristics

	RFA treatment cohort (N = 1386)	**Straightforward treatment (N = 1308)**	**Complex treatment (N = 78)**	***P* value**
Treatment				
Treatment duration, *mo*, median (IQR)	8 (5–13)	8 (5–13)	12 (7–20)	<.01
ER				
Number of ER treatments, median (IQR)	1 (0–1)	1 (0–1)	1 (1–2)	<.01
Patients with >1 ER, n (%)	136 (10)	98 (7)	38 (49)	<.01
RFA				
C-RFA, median (IQR)	1 (0–1)	1 (0–1)	1 (1–2)	<.01
F-RFA, median (IQR)	2 (1–2)	2 (1–2)	1 (0–2)	<.01
Total RFA, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	<.01
Patients with >2 C-RFA, n (%)	9 (1)	6 (0)	3 (4)	<.01
Patients with >4 total RFA, n (%)	57 (4)	49 (4)	8 (10)	<.01
Complications				
Any esophageal stenosis, n (%)	210 (15)	185 (14)	25 (32)	<.01
Severe esophageal stenosis, n (%)	40 (3)	32 (2)	8 (11)	.02
Postprocedural bleeding, n (%)	52 (4)	45 (3)	7 (9)	.03

C-RFA, circumferential RFA; ER, endoscopic resection; F-RFA, focal RFA; IQR, interquartile range; RFA, radiofrequency ablation.

Derivation of the Prediction Model

In univariable analysis we found that the following characteristics were associated with a higher risk for a complex treatment course: increasing length of hiatal hernia, increasing

BE length, visible lesion at baseline, a higher number of baseline ER specimens, HGD/EAC at baseline compared with LGD, less than 50% squamous regeneration after ER, and less than 50% squamous regeneration after RFA (Table 4).

We included all 14 candidate predictors (Table 4) in our initial multivariate model. Four predictors were associated independently with a complex treatment course: BE length, visible lesion at baseline, HGD/EAC at baseline, and less than 50% squamous conversion after first RFA. A finding of less than 50% squamous regeneration after RFA had the highest predictive value with an adjusted odds ratio of 21.2 (95% CI, 11.5–40.5). Interaction terms did not significantly improve the model. Model assumptions were met (Supplementary Figure 1 and Supplementary Table 1).

Internal Validation

Using the 4 independent predictors, discrimination of patients with a straightforward treatment course from patients with a complex treatment course was good (cross-validated AUC, 0.88; 95% CI, 0.85–0.92) (Table 4).

Prediction Model and Clinical Decision Making

The created model provides a predicted probability for each patient, ranging from 0 to 1. However, for optimal use of the model in clinical practice, a cut-off value is required to label patients either as straightforward (ie, predicted probability < cut-off value) or as complex (ie, predicted probability cut-off value). In multiple meetings with the research team, a cut-off value of 0.1 was determined to have optimal diagnostic accuracy.

The 0.1 cut-off value indicates that patients with poor squamous regeneration after RFA as well as patients with BE greater than 9 cm containing a visible lesion with HGD/EAC are predicted to have a complex treatment course. This includes 8% (n 117) of our study population.

Using the 0.1 cut-off value, the model would correctly identify 59% (46 of 78) of all patients with a complex treatment course (sensitivity) and 95% (1207 of 1278) of all straightforward patients (specificity). Based on our study population, the positive predictive value for this cut-off value was 39% (46 of 117) and the negative predictive value was 97% (1207 of 1239).

Stratified for different aspects of the composite endpoint, we found that the majority of patients with neoplastic progression (13 of 17; 76%) and treatment failure (25 of 27; 93%) were identified correctly by the prediction model as a complex patient (true

positives). For patients who required ER during the RFA course, 8 of 34 (24%) patients were identified correctly as having a high risk.

Table 4. Model Building

		Univariable	Multivariable
Coefficients, Odds ratio [95% CI]	Age	1.01 [0.99-1.04]	-
	Gender	1.42 [0.81-2.38]	-
	BMI	0.99 [0.93-1.04]	-
	Smoking	0.99 [0.59-1.57]	-
	Fundoplication	1.64 [0.26-5.72]	-
	Hiatal hernia	1.20 [1.08-1.33]	-
	Barrett length	1.30 [1.23-1.37]	1.21 [1.13-1.29]
	Reflux stenosis	1.54 [0.45-3.92]	-
	Reflux esophagitis	2.49 [0.93-5.63]	-
	Baseline visible lesion	3.77 [2.05-7.60]	2.55 [1.17-6.06]
	Number of ER specimen	1.10 [1.02-1.18]	-
	Histology	2.93 [1.53-6.36]	2.28 [1.25-5.05]
	<50% squamous regression after ER	3.84 [2.63-5.88]	-
	<50% squamous regression after RFA	40.54 [23.25-71.76]	21.24 [11.53-40.49]
Internal validation			
Discrimination	Original AUC		0.881
	Optimism-corrected AUC [95% CI]		0.877 [0.854-0.918]
Calibration	Slope		1.00 [0.85-1.16]
	Intercept		0.00 [-0.42-0.44]
External validation			
Discrimination	AUC		0.84
Calibration	Slope		0.73
	Intercept		0.24

AUC, area under the curve; BMI, body mass index; ER, endoscopic resection; CI, confidence interval; RFA, radiofrequency ablation.

The prediction model incorrectly labeled 32 of 78 complex patients as patients with a straightforward treatment course. Most of these false-negative patients (26 of the total 34 patients that required ER during RFA) required ER during the RFA treatment phase, yet achieved CE-BE afterward. The model incorrectly labeled 5 of 17 (29%) patients with neoplastic progression and 2 of 27 (7%) patients as having a low risk.

Additional data for varying cut-off values are presented in Supplementary Figure 3 and Supplementary Table 2.

Sensitivity analysis

Our primary outcome is a composite endpoint of neoplastic progression, treatment failure, and need for ER during RFA. Univariable odds ratios for the 3 end points separately showed no major differences (Supplementary Figure 2 and Supplementary Table 3). We compared predicted scores for each of the 3 end points separately. The mean predicted score was 0.04 for patients with a straightforward treatment, 0.15 for patients with ER during RFA, 0.50 for treatment failure, and 0.51 for patients with neoplastic progression (Supplementary Figure 2 and Supplementary Table 3).

Several sensitivity analyses were performed to estimate the robustness or our findings varying the outcome, model, year of inclusion, and center of inclusion (Supplementary Table 4). Overall, our model appeared robust in these sensitivity analyses.

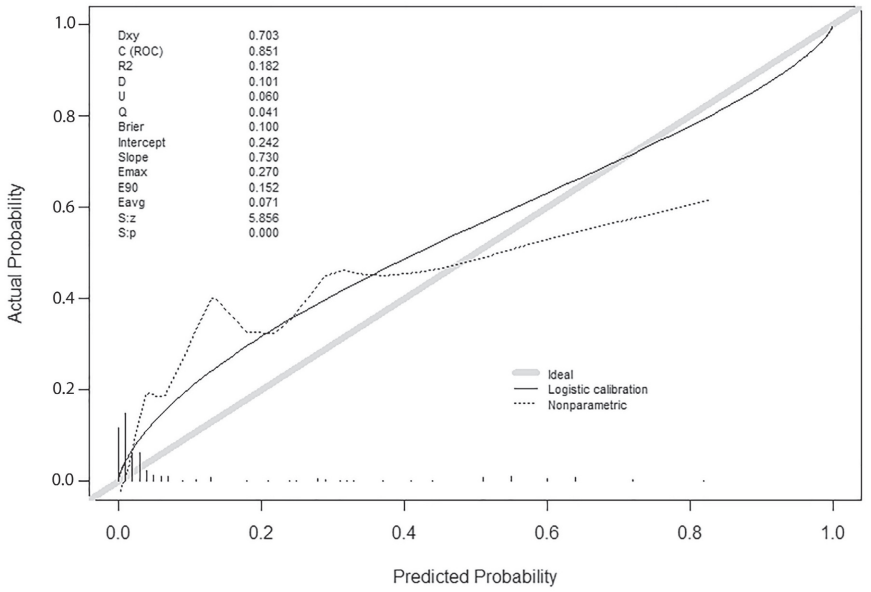
External Validation

In a final step, we validated our prediction model in 282 patients from the Leuven RFA registry (Table 4). Baseline characteristics were comparable with the exception of baseline histology: 7% of the Leuven registry patients had LGD compared with 27% of the Dutch patients.

Overall, 38 of 282 patients (12%) were identified as having a complex treatment course. This was subdivided further into 3 of 282 (1%) patients who progressed to a disease stage that exceeded boundaries for endoscopic treatment, 12 of 282 (4%) were treatment failures with a median C0M3 BE remaining, and 23 of 282 (8%) had ER during the RFA treatment phase and achieved CE-BE afterward.

In the validation set, an AUC of 0.84 (95% CI, 0.78–0.90) was achieved. The calibration plots showed good calibration (Figure 2).

Figure 2. Calibration in external validation



Calibration plot of external validation of the prediction model in an independent data set from Leuven. The x-axis shows the predicted probability according to our model, and the y-axis shows the actual observed probability in the external data set.

DISCUSSION

EET for BE-associated early neoplasia usually entails the combination of endoscopic resection and endoscopic ablation, typically RFA. When treatment is performed in expert centers, the majority of patients will achieve CE- BE after a single ER and 2 to 3 RFAs. However, a subgroup of patients experiences a complex treatment course with a significant risk for multiple treatment endoscopies, failed eradication of BE, or even neoplastic progression to advanced cancer during the treatment course. Identifying these patients at an early stage may improve patient counseling and clinical decision making.

In the current study, we developed a prognostic model to identify patients with a complex treatment course. Our model defined patients with BE of 9 cm or greater containing HGD/EAC and patients with poor squamous regeneration after the first RFA as having a high risk for a complex treatment. This subgroup represents 8% of all patients undergoing RFA, yet included 76% of patients with neoplastic progression

and 93% of treatment failures. These patients also had a significantly longer treatment duration with a higher risk for complications. Our model appeared robust in multiple sensitivity analyses and performed well in an independent data set with an AUC of 0.84.

We defined a complex treatment course as one or more of the following problems that may occur during treatment: neoplastic progression to disease stages that exceed boundaries for curative EET and persisting BE after adequate EET. We also included the need for ER during RFA as a feature of a complex treatment course. Although the predictive value of the model including this third outcome was slightly lower, we think that early identification of these patients is important. Development of a new visible lesion during RFA may indicate multifocal neoplasia and/or rapidly developing neoplasia. Early detection of these lesions is of vital importance to enable curative ER and prevent neoplastic progression to advanced neoplasia.

We tested several easily available characteristics that would be known to the endoscopists after the first RFA. Four factors independently increased the risk for a complex treatment course: increasing BE length, presence of a visible lesion, baseline HGD/EAC compared with LGD, and poor squamous regeneration after RFA. Poor squamous regeneration was the utmost important predictor in our model. Patients with poor squamous regeneration had a 21 times higher odds of experiencing a complex treatment course compared with patients with normal squamous regeneration. Logically, our model therefore is applicable after the first RFA. In prior work, we showed that poor squamous regeneration always occurred after the first RFA treatment [11].

A number of studies has reported that ongoing reflux disease is associated with failure to achieve CE-BE [12–15]. Hiatal hernia size and a small-diameter esophageal lumen also are associated with failed RFA treatment [12–14]. In our model, these reflux-related parameters were excluded in favor of poor squamous regeneration, the most prominent predictive factor in univariable and multivariable analysis. Poor squamous regeneration is a phenomenon that appears to occur in patients with severe and/or ongoing reflux disease. For clinical use, a prediction model that includes poor squamous regeneration, a single characteristic that is easy to recognize and with a strong predictive value, may be preferred over a model that includes multiple other, difficult-to-measure, reflux-related parameters.

Baseline BE length often is reported as a risk factor for failure as is confirmed in the current study [3,12–14]. Longer pretreatment BE lengths may reflect more injury and more severe reflux disease. From a procedural standpoint, it also may be related to having more tissue to convert to squamous epithelium.

A visible lesion with HGD/EAC at baseline was associated with a complex treatment course in the current study. Although this may seem intuitive, prior studies failed to identify baseline histology as a risk factor [3,12–14]. Potentially, the choice for a composite end point that also included the need for ER during RFA and neoplastic progression may have played a role in selecting baseline histology as a predictor. Furthermore, most studies that reported predictors for failure included a limited number of patients, with a risk for underpowered analysis.

The good overall performance in external validation with an AUC of 0.84 strengthens the generalizability of our model. For use in daily practice, however, a cut-off value is required that classifies an individual patient as being either at low or high risk for a complex treatment. In multiple discussions with the research team, we defined an arbitrary cut-off value of 0.1 based on optimum balance between sensitivity and specificity.

Upon a predicted low risk (ie, <0.1), 97% of patients truly had straightforward treatment. Overall, 8% of patients had a predicted high risk and 39% of these patients actually had a complex treatment course. This 8% of patients with a predicted high risk included 76% of the patients with neoplastic progression and 93% of the treatment failures.

The definition of this cut-off value translates into 2 high-risk patient profiles: all patients with poor squamous regeneration after RFA, and all patients with baseline BE length greater than 9 cm containing a visible lesion with HGD/EAC. All other patients have a predicted low risk.

We believe that our model may help to improve clinical care for BE patients. First and most importantly, it may improve patient counseling. Early identification of patients with a complex treatment course may help to manage patient expectations. These patients may be informed that the risks for treatment failure and for complications are increased and that treatment might take longer.

If a complex treatment course occurs, early discontinuation with RFA may be considered. The chance for a successful outcome is low, while the risk for complications increases significantly. This consideration holds especially for prophylactic RFA, that is, treatment of remaining nondysplastic BE after ER, or when RFA is used for flat BE with LGD. But even in the case of remaining HGD in flat BE, strict endoscopic follow-up evaluation may be considered an alternative to RFA in such high-risk patients.

Furthermore, labeling of patients as high risk for a complex treatment may serve as a warning sign to the endoscopist to create extra awareness. We suggest that endoscopists pay special attention to these patients, with extra careful imaging during each treatment endoscopy. Early consultation with colleagues in the field and/or in a multidisciplinary meeting is supported. Especially in a setting where treatment is not restricted to expert centers, less-experienced endoscopists could consider early referral to a more experienced colleague for high-risk cases. This study had important strengths. It is a prognostic model to identify early neoplastic Barrett's patients with a complex treatment course and may have direct implications for clinical care. Our data were homogeneous: all endoscopists and pathologists participated in joint training programs, followed uniform protocols, and participated in quarterly meetings for discussion of difficult cases. We provide high-quality data that were collected by dedicated researchers. We performed several sensitivity analyses, varying the outcome (ie, only failure and neoplastic progression) and the model (ie, LASSO penalization and ordinal logistic regression), and we performed cross-validation based on the year of inclusion and treatment center. In these analyses, our model appeared robust. Finally, our model performed well in external validation in an independent data set.

We have to address some limitations as well. We defined a composite end point that consists of 3 negative outcomes. Although single components of the composite end point may have different clinical implications, a single model to identify these patients early, used for patient counseling and as a warning sign to the endoscopist, is, in our opinion, preferred over 3 separate models. Generalizability may be limited owing to data collected in expert centers only. To minimize this problem, we chose a wide definition for "a complex treatment course" including the 3 earlier-mentioned features. It should be noted that our model is applicable only to patients undergoing RFA. A key requirement for RFA is removal of all visible lesions before RFA, to render the mucosa completely flat. Of note, a subgroup of patients may require extensive and/or repetitive ER at baseline. In some of these patients, subsequent ablation treatment may no longer be indicated and stepwise radical endoscopic resection may be the treatment of choice. Although the baseline features of such patients (ie, visible lesion[s] at baseline and HGD/EAC at baseline) match 2 of the risk factors in our model and thus might indicate a higher risk for a complex treatment course, these patients were not included in our study, and therefore not identified by the model.

For some predictors, the distinction between patient characteristics and endoscopist characteristics is difficult. This may hold especially for the presence of a new visible lesion during RFA treatment. Although this may be a true patient characteristic, indicating multifocal and/or rapidly growing neoplasia, it also may be a lesion that

already was present at baseline but was missed by the endoscopist (endoscopist characteristic). One could argue that poor squamous regeneration is an intermediate step toward treatment failure and using poor squamous regeneration as a predictor is a self-fulfilling prophecy. However, from a clinical perspective, our aim was simply to make the best prediction for a complex treatment course. Using this strong predictor that is identified early in the treatment phase therefore makes sense.

We have developed a new risk prediction model to risk-stratify patients after the first RFA treatment. The scoring system uses clinical variables that are easily available including BE length, baseline histology, baseline visible abnormality, and squamous regeneration after RFA. Our model identified 2 patient profiles with a high risk for complex treatment, patients with BE length more than 9 cm containing HGD/EAC, and patients with poor squamous regeneration after RFA. Our model performed well in external validation. This model has the potential to impact treatment of BE patients in terms of patient counseling and rational application of ablation therapy.

REFERENCES

1. Phoa KN, Pouw RE, Bisschops R, et al. Multimodality endo- scopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut 2016;65:555–562.
2. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA 2014;311:1209–1217.
3. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277–2288.
4. Desai M, Saligram S, Gupta N, et al. Efficacy and safety out- comes of multimodal endoscopic eradication therapy in Bar- rett's esophagus-related neoplasia: a systematic review and pooled analysis. Gastrointest Endosc 2017;85:482–495 e4.
5. Weusten B, Bisschops R, Coron E, et al. Endoscopic manage- ment of Barrett's esophagus: European Society of Gastroin- testinal Endoscopy (ESGE) position statement. Endoscopy 2017;49:191–198.
6. Dutch Society for Gastroenterology and hepatology. Richtlijn Barrett Oesofagus. Available at: https://www.mdl.nl/sites/www. mdl.nl/files/richlijnen/Richtlijnen%20Barrett%20oesofagus%20-%20jan%202018%20-%20tbv%20website.pdf. Accessed April 13, 2022.
7. van Munster S, Nieuwenhuis E, Weusten B, et al. Long-term out- comes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation þ/- endoscopic resection: results from the national Dutch database in a 10-year period. Gut 2022;71:265–276.
8. Barret M, Pioche M, Terris B, et al. Endoscopic radiofrequency ablation or surveillance in patients with Barrett's oesophagus with confirmed low-grade dysplasia: a multicentre randomised trial. Gut 2021;70:1014–1022.
9. Scholvinck DW, van der Meulen K, Bergman J, et al. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy 2017;49:113–120.
10. Vliebergh JH, Deprez PH, de Looze D, et al. Efficacy and safety of radiofrequency ablation of Barrett's esophagus in the absence of reimbursement: a multicenter prospective Belgian registry. Endoscopy 2019;51:317–325.
11. van Munster S, Frederiks C, Nieuwenhuis E, et al. Incidence and outcomes of poor healing and poor squamous regeneration after radiofrequency ablation therapy for early Barrett's neoplasia. Endoscopy 2022;54:229–240.
12. Krishnan K, Pandolfino JE, Kahrilas PJ, et al. Increased risk for persistent intestinal metaplasia in patients with Barrett's esophagus and uncontrolled reflux exposure before radio- frequency ablation. Gastroenterology 2012;143:576–581.
13. van Vilsteren FG, Alvarez Herrero L, Pouw RE, et al. Predictive factors for initial treatment response after circumferential radio- frequency ablation for Barrett's esophagus with early neoplasia: a prospective multicenter study. Endoscopy 2013;45:516–525.
14. Luckett T, Allamneni C, Cowley K, et al. Length of Barrett's segment predicts failure of eradication in radiofrequency abla- tion for Barrett's esophagus: a retrospective cohort study. BMC Gastroenterol 2018;18:67.
15. Akiyama J, Marcus SN, Triadafilopoulos G, et al. Effective intra- esophageal acid control is associated with improved radio- frequency ablation outcomes in Barrett's esophagus. Dig Dis Sci 2012;57:2625–2632.

SUPPLEMENTARY MATERIAL

To access the supplementary material accom- panying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal. org, and at https://doi.org/10.1016/j.cgh.2022.02.057.

PART III

Pushing boundaries in endoscopic management

CHAPTER 9

Reassessing histological risk factors in surgical specimens of T1b esophageal adenocarcinoma – A proof of concept study

Esther A. Nieuwenhuis, Sybren L. Meijer,
Mark I. van Berge Henegouwen, Roos E. Pouw

Submitted to 'Diseases of the Esophagus'

ABSTRACT

Background

Endoscopic resection is an accepted treatment for patients with low-risk mucosal esophageal adenocarcinoma, since the risk of lymph node metastasis associated with these tumors is very low. However, for more advanced stages of early esophageal adenocarcinoma, guidelines still advise esophagectomy due to a higher metastasis risk. Nevertheless, reported lymph node metastases rates in these tumors could have been overestimated in surgical series when compared to endoscopic series, due to differences in specimen preparation for histological assessment.

Methods

This was a cross-sectional study based on a search in the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA foundation). Inclusion criteria were submucosal invasion and lymph node metastasis who were surgically treated in Amsterdam UMC location AMC (1994-2005), without prior ER and/or neo-adjuvant chemoradiotherapy. An expert gastrointestinal pathologist reassessed the slides for: a) deepest infiltration depth; b) differentiation grade; c) presence of lymphovascular invasion. Endpoints were i) tumor invasion into the muscularis propria instead of invasion limited to the submucosa; ii) presence of poor differentiation or lymphovascular invasion after reassessment.

Results

After reassessment, 9/12 (75%) patients had an additional histological risk factor for lymph node metastasis next to submucosal invasion, as compared to 5/12 (42%) patients based on the original pathology report.

Conclusions

This study implies that data on lymph node metastasis risk from surgical series are not applicable to endoscopically treated patients due to differences in specimen preparation for histological assessment.

INTRODUCTION

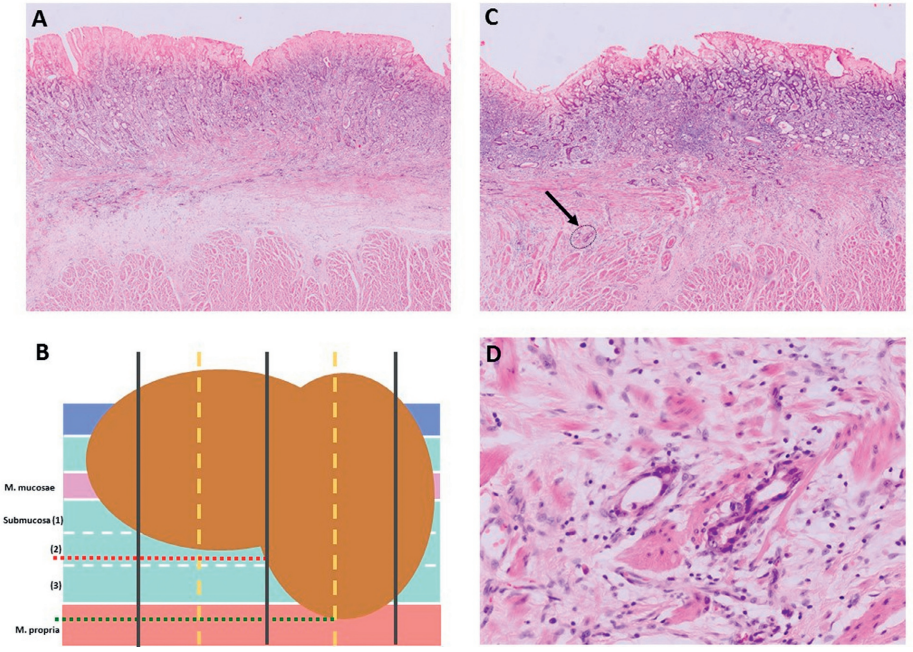
Endoscopic resection (ER) is an accepted treatment for patients with low-risk mucosal esophageal adenocarcinoma (EAC), defined as tumors limited to the mucosa or superficial submucosa (<500µm), with well to moderate differentiation grade and without lymphovascular invasion (LVI). Since the risk of lymph node metastasis (LNM) associated with these tumors is very low (<2%) [1–3], esophagectomy for this indication, has been replaced by ER [4]. However, for more advanced stages of EAC invading the submucosa ≥500um, guidelines still advise esophagectomy. This advice is based on older surgical series reporting a risk of LNM up to 45% for submucosal EAC [5,6], which is considered too high to justify ER. However, more recent endoscopic studies suggest a lower LNM risk of 0-30% [3,7,8]. This implies that in the majority of patients with deeper submucosal EAC, radical ER, after adequate baseline staging and stringent follow-up, can be curative, and invasive esophagectomy may be unnecessary.

We hypothesized that reported LNM rates in surgical series on submucosal EAC could have been overestimated when compared to endoscopic series, due to differences in specimen preparation for histological assessment. Surgical specimens are cut in 4-5mm slices, whereas ER specimens are cut in 2-3 mm slices with additional serial cuts (5µm) of the deepest point of invasion in case of submucosal extension.

This different approach could lead to underestimation of tumor invasion depth in surgical resection specimens if the deepest part of infiltration was not included directly in cut slides. Furthermore, this could results in less accurate assessment of LVI as less tissue is analyzed. This underestimation of infiltration depth and presence of other histological risk factors for LNM in surgical specimens may have resulted in overestimation of associated LNM rates associated with a certain tumor depth (Figure 1c).

We aimed to test this hypothesis by reassessing histopathological risk factors in surgical specimens from metastasized submucosal EAC patients.

Figure 1. Histopathology images of an EAC previously staged as submucosal cancer (T1b), with invasion into the muscularis propria (T2) after cutting additional slides and reassessment.



A. Hematoxylin and Eosin (HE) stained surgical slide (5mm) of an esophageal adenocarcinoma, showing invasion in the submucosal layer.
B. Schematic figure of a malignant tumor (brownish colour) growing into the m. Propria of the esophageal wall. The vertical lines in black represent histopathological assessment cuts of a surgical specimen. The vertical striped lines in yellow represent the extra cuts that would have been made in an ER specimen. When looking to the horizontal green dotted line, one can see that the thinner slices will reveal M. propria (T2) invasion of the tumor, while the horizontal red dotted line of the surgical histopathological assessment will only reveal submucosal (i.e. sm2) invasion.
C, D: M. propria invasion in deeper cut (5µm) slide from the same patient.

METHODS

We performed a cross-sectional study based on a search in the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA foundation). Inclusion period was 1994-2005, before ER was embedded in clinical practice. We included patients with submucosal EAC (T1b) and LNM who were surgically treated in Amsterdam UMC location AMC, without prior ER and/or neo-adjuvant chemoradiotherapy.

After reassessment of the pre-existing 5mm slides, additional 5µm cuts for H&E staining were made from the part with deepest submucosal invasion. Thereafter, one expert

gastrointestinal pathologist (SM) reassessed the slides for: a) deepest infiltration depth; b) differentiation grade; c) presence of LVI.

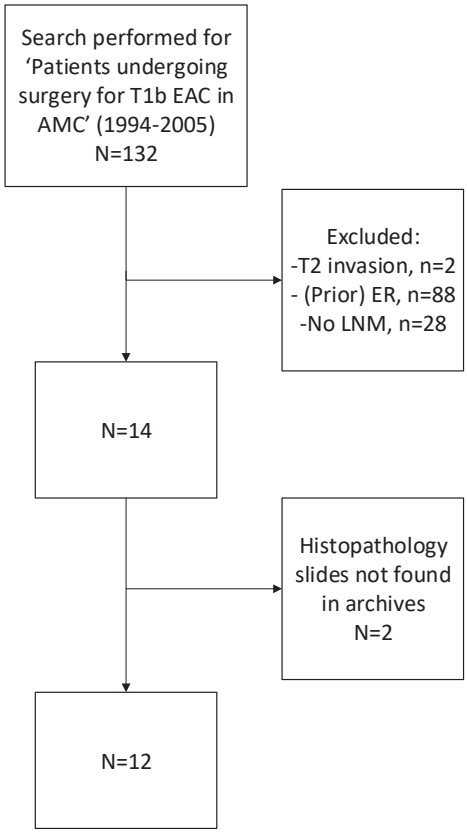
Study endpoints:

1. Tumor invasion into the muscularis propria (T2) instead of invasion limited to the submucosa
2. Presence of poor differentiation or LVI after reassessment

RESULTS

Twelve cases with T1bN1/2 EAC were included (Figure 2). The original pathology reports specified depth of submucosal invasion in only 1 case (sm2). Differentiation was moderate in 3 and poor in 9 cases. LVI was present in 4 cases and not reported in 8 cases (Table 1).

Figure 2. Patient selection process



At reassessment, one patient (8% [95% CI 0,2-38]) registered as T1b EAC, was found to have tumor infiltration into the m. propria (T2) (Figure 1 C,D). Another 4 patients had deep submucosal invasion, classified as borderline T2. More extensive areas of poor differentiation were found and tumor grade was scored as (partially) poor instead of moderate in 5 patients. Suspicion on LVI was found in 4 additional patients. After revision, 9/12 (75%) patients had an additional histological risk factor for LNM next to submucosal invasion, as compared to 5/12 (42%) patients based on the original pathology report.

Table 1. Overview of revision outcomes of included patients

Reported pTNM stage	Revision: infiltration depth	Reported differentiation grade	Revision: differentiation grade	Reported LVI presence	Revision: LVI presence
T1sm N2 M0	T1sm3 (borderline T2)	Moderate	Poor*	LVI+	LVI+
T1sm N1 M0	T1sm1	Poor	Poor	LVI+	LVI+
T1sm N1 M0	T1sm2	Moderate	Moderate-poor*	Not reported	LVI+*
T1sm N2 M0	T1sm3 (borderline T2)	Moderate	Good-moderate	Not reported	LVI suspicious*
T1sm N1 M0	T1sm3 (borderline T2)	Moderate	Moderate	Not reported	No
T1sm N1 M0	T1sm1	Moderate	Poor*	Not reported	LVI suspicious*
T1sm N1 M0	T1sm3 (borderline T2)	Moderate	Poor*	LVI+	LVI suspicious
T1sm N3 M0	T1sm2	Poor	Poor	LVI+	LVI+
T1sm N1 M0	T2*	Poor	Moderate	Not reported	No
T1sm2 N1 M0	T1sm2	Moderate	Poor*	Not reported	LVI+*
T1sm N2 M0	T1sm1	Moderate	Moderate	Not reported	No
T1sm N1 M0	T1sm2	Moderate	Moderate	Not reported	No

*Upstaged histopathology diagnosis

DISCUSSION

We reassessed histopathological risk factors in surgical specimens from T1b EAC and LNM, by dedicated histological revision. We found one patient (8%) with T2 cancer instead of T1b cancer and 4 patients with borderline T2 invasion. Histopathology diagnosis was upstaged in 7 patients after reassessment.

Due to the retrospective nature and limited patient numbers, there might be selection bias. During revision, infiltration depth was difficult to assess in some cases due to retraction artefacts, and there might be interobserver variation regarding differentiation grade and LVI.

Nevertheless, this study implies that data on LNM risk from surgical series are not applicable to endoscopically treated patients. Ideally, a larger revision study could confirm these findings. However, this may be a disproportionate amount of work with limited relevance, since multiple studies in endoscopically treated patients have already demonstrated a lower risk of LNM than previously reported. Large prospective studies have to point out whether endoscopic management is safe in patients with deeper T1b EAC (PREFER trial; NCT03222635).

REFERENCES

1. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology*. 2014;146(3):652-660.e1. doi:10.1053/j.gastro.2013.11.006
2. Alvarez Herrero L, Pouw RE, van Vilsteren FG, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. *Endoscopy*. 2010;42(12):1030-1036. doi:10.1055/s-0030-1255858
3. Schölvinck D, Künzli H, Meijer S, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. *Surg Endosc*. 2016;30(9):4102-4113. doi:10.1007/s00464-016-5071-y
4. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy*. 2017;49(02):191-198. doi:10.1055/s-0042-122140
5. Buskens CJ, Westerterp M, Lagarde SM, Bergman JJGHM, ten Kate FJW, van Lanschot JJB. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. *Gastrointest Endosc*. 2004;60(5):703-710. doi:10.1016/s0016-5107(04)02017-6
6. Westerterp M, Koppert LB, Buskens CJ, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. *Virchows Arch*. 2005;446(5):497-504. doi:10.1007/s00428-005-1243-1
7. Manner H, Pech O, Heldmann Y, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. *Surg Endosc*. 2015;29(7):1888-1896. doi:10.1007/s00464-014-3881-3
8. Künzli HT, Belghazi K, Pouw RE, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. *United Eur Gastroenterol J*. 2018;6(5):669-677. doi:10.1177/2050640617753808

CHAPTER 10

Analysis of metastases rates during follow-up after endoscopic resection of early “high-risk” esophageal adenocarcinoma

Esther A. Nieuwenhuis, Sanne N. van Munster, Sybren L. Meijer, Lodewijk A. A. Brosens, Marnix Jansen, Bas L. A. M. Weusten, Lorenza Alvarez Herrero, Alaa Alkhalaf, Ed Schenk, MD, Erik J. Schoon, Wouter L. Curvers, Arjun D. Koch, Steffi E. M. van de Ven, Eva P. D. Verheij, Wouter B. Nagengast, Jessie Westerhof, Martin H. M. G. Houben, Thjon Tang, Jacques J. G. H. M. Bergman, Roos E. Pouw

Gastrointestinal Endoscopy 2022 Mar (online first)
doi; 10.1016/j.gie.2022.03.005

ABSTRACT

Background and aims

After endoscopic resection (ER) of early esophageal adenocarcinoma (EAC), the optimal management of patients with high-risk histologic features for lymph node metastases (ie, submucosal invasion, poor differentiation grade, or lymphovascular invasion) remains unclear. We aimed to evaluate outcomes of endoscopic follow-up after ER for high-risk EAC.

Methods

For this retrospective cohort study, data were collected from all Dutch patients managed with endoscopic follow-up (endoscopy, EUS) after ER for high-risk EAC between 2008 and 2019. We distinguished 3 groups: intramucosal cancers with high-risk features, submucosal cancers with low-risk features, and submucosal cancers with high-risk features. The primary outcome was the annual risk for metastases during follow-up, stratified for baseline histology.

Results

One hundred twenty patients met the selection criteria. Median follow-up was 29 months (interquar- tile range, 15-48). Metastases were observed in 5 of 25 (annual risk, 6.9%; 95% confidence interval [CI], 3.0-15) high-risk intramucosal cancers, 1 of 55 (annual risk, .7%; 95% CI, 0-4.0) low-risk submucosal cancers, and 3 of 40 (annual risk, 3.0%; 95% CI, 0-7.0) high-risk submucosal cancers.

Conclusions

Whereas the annual metastasis rate for high-risk submucosal EAC (3.0%) was somewhat lower than expected in comparison with previous reported percentages, the annual metastasis rate of 6.9% for high-risk intramucosal EAC is new and worrisome. This calls for further prospective studies and suggests that strict follow-up of this small subgroup is warranted until prospective data are available.

INTRODUCTION

Endoscopic resection (ER) is established as the first choice treatment for early esophageal adenocarcinoma (EAC) without histopathologic risk factors of lymph node metastases (LNM). Multiple studies and long-term analyses have demonstrated excellent efficacy and safety of ER as an alternative to surgery for these lesions [1-3]. Nevertheless, after radical ER of a tumor with histopathologic risk factors for LNM, optimal management is still unclear. These risk factors include submucosal invasion (T1b), poor tumor differentiation grade (grade 3), and lymphovascular invasion (LVI).

Today, the indication for endoscopic therapy has extended to tumors invading into the superficial submucosa (<500 µm; sm1) with a good to moderate differentiation grade that do not display LVI. For these sm1 tumors without high-risk features, the risk of LNM is <2% [4,5], and strict endoscopic follow-up is an accepted alternative to esophagectomy [6,7]. A small number of mainly surgical studies have assessed the LNM rates in patients with deep submucosal invasion (ie, ≥500 µm; sm2/3), and/or poor differentiation grade, and/or LVI, reporting a wide range of LNM rates between 16% and 46% [5,8,9]. Therefore, ER is considered insufficient treatment for these patients, and surgery is still advised.

However, these LNM rates are mainly based on historical surgical studies, in which the invasion depth and other risk features of tumors in the surgical specimen may have been less accurately reported compared with ER specimens. Because histologic assessment of surgical specimens is based on relatively large cuts of 5 mm, invasion depth may have been underestimated if the deepest part of infiltration was not included in slides cut for histologic assessment. Accurate assessment of histologic risk factors was also less relevant, because the esophagectomy had already been performed and the presence or absence of these risk factors would not influence further management. A number of more recent endoscopy-based studies show an LNM risk for submucosal EAC with high-risk features of 0% to 37% during a median follow-up of 23 to 63 months, which is lower than that reported in the surgical series, rendering an invasive esophagectomy possibly unnecessary in a subset of patients [5,10-12].

Comparatively less is known about the risk of LNM for intramucosal EAC with high-risk features. This disparity drives heterogeneous clinical decision-making and patient management. An alternative to immediate adjuvant surgery may be to survey patients after ER of an EAC with high-risk features and limit further treatment such as chemoradiotherapy and/or surgery to those patients with proven LNM during follow-up. This would require additional evidence about the long-term safety of this conservative strategy from prospective cohort studies. The aim of this study was to assess the

outcomes of patients who underwent radical ER for an EAC with high-risk histologic features without metastases at baseline and who were followed endoscopically.

METHODS

The study included patients from the Barrett Expert Center (BEC) registry (Netherlands Trial Register, NL7039), which has been described in detail [13]. In summary, this registry represents outcomes for all patients who underwent endoscopic treatment for Barrett's neoplasia in the Netherlands from 2008 onward. Dutch Barrett's neoplasia care is uniquely organized in 9 BECs with treatment provided by jointly trained endoscopists and pathologists. The BECs comply with a common endoscopic management protocol and gather several times a year to safeguard homogeneity. Furthermore, because every patient in the Netherlands receives treatment in 1 of the BECs, data on treatment and outcomes of all patients treated for Barrett's neoplasia are registered in this uniform, nationwide database.

Patients diagnosed with EAC and histologic risk factors after ER with negative deep resection margins were counseled for endoscopic management or surgery depending on age, comorbidity, and preference following national guidelines [14,15]. None of the included patients participated in the prospective PREFER study (NCT03222635). Our study partly overlaps with 2 earlier reports from our group (n = 52) [5,11].

Study population

For this study, we included all patients who underwent ER of an EAC with high-risk histologic features, with tumor-negative deep resection margins, between January 2008 and October 2019. We distinguished 3 histological subgroups:

- T1a EAC with high-risk features (HR-T1a) was defined as intramucosal adenocarcinoma, with poor differentiation grade (grade), and/or LVI.
- T1b EAC with low-risk features (LR-T1b) was defined as submucosal cancer with superficial invasion in the sub- mucosa (<500 μm; sm1), well to moderately differentiated (grades 1 to 2), without LVI.
- T1b EAC with high-risk features (HR-T1b) was defined as submucosal cancer with deep invasion in the submucosa (≥500 μm; sm2/3), and/or poor differentiation grade (grade 3), and/or LVI presence.

Exclusion criteria were tumor-positive deep resection margin, residual lesion not amendable to re-ER at the first endoscopy after initial ER, metastases (LNM or distant metastases) diagnosed at baseline, and referral for surgery or chemoradiotherapy directly after ER.

Histopathologic evaluation

Histologic evaluation of all ER specimens was performed by pathologists experienced in Barrett's esophagus. After tissue fixation, specimens were cut into 2- to 3-mm strips, processed to paraffin blocks, cut into 4-µm slides, and stained with hematoxylin and eosin and for p53 expression. Hereafter, 4 histologic features were assessed: (1) tumor infiltration depth, with submucosal invasion measured in microns (ie, <500 µm was subclassified as sm1; ≥500 µm as sm2/3. In most, immunohistochemistry using desmin and/or pankeratin staining was performed on a blank hematoxylin and eosin slide with the deepest submucosal tumor invasion.); (2) tumor differentiation grade16; (3) presence of LVI (including D2-40 staining in most cases); and (4) status of vertical resection margins and lateral resection margins in cases of en-bloc resection. Three pathologists discovered that Barrett's esophagus independently revised the histopathology of all included T1a cases to ensure no submucosal invasion.

Baseline staging

The joint treatment protocol did not prescribe a standard procedure for baseline staging after ER. Generally, patients underwent endoscopy and EUS 6 weeks after ER to assess for the presence of residual intraluminal neoplasia and locoregional lymph nodes. Lymph nodes that appeared suspicious as assessed by the treating physician were sampled using EUS-FNA. In addition, a CT of the thorax and abdomen, or a positron emission tomography (PET)-CT was often performed, to evaluate for the presence of distant metastases.

Follow-up and retreatment

Endoscopic follow-up was performed in the BECs, and intervals were determined by the treating physician because no strict protocol was available. Follow-up consisted of endoscopy ± EUS every 3 to 6 months and FNA in case of suspicious lymph nodes. To guarantee endoscopic imaging quality, most patients were sedated, and high-quality, high-definition endoscopes were used with virtual chromoendoscopy next to normal white-light endoscopy. The Barrett's segment was described using the Prague C & M classification [17]. Targeted biopsy sampling or direct ER was performed if any mucosal irregularity was detected. These irregularities were described using the Paris classification [18]. In addition, random biopsy samples following the Seattle protocol were taken from the (remaining) flat Barrett's segment. PET-CTs were performed in some cases during follow-up at the discretion of the treating physician. Residual Barrett's epithelium was generally kept under surveillance for at least 1 year after ER because of the relatively higher LNM risk in the first 1 to 2 years after resection of a high-risk lesion. Thereafter, eradication treatment of the residual Barrett's neoplasia was initiated in most patients per the physician's discretion.

Endpoints

The primary endpoint was the annual risk for metastases during endoscopic follow-up, stratified for the baseline histopathologic risk group. The secondary endpoint was tumor-related mortality and overall mortality during follow-up. Tumor-related mortality was defined as death directly or indirectly caused by EAC (eg, because of EAC treatment adverse events).

Data collection and management

Medical interns in the final year of their degree collected endoscopy, pathology, and imaging data using the standardized form in all BECs. All patients with endpoints and an additional 70% to 80% were double-checked by dedicated research fellows (all MDs). Missing data and illogical values were completed and corrected where possible. All authors had access to the study data and re- viewed and approved the final manuscript. The BEC registry [13] was merged with the nonpublic microdata from Statistics Netherlands to record date and cause of death.

Statistics

Data analysis was performed using the SPSS statistical software package (version 25; SPSS Inc, Chicago, Ill, USA) and R studio for windows (version 3.6.1, Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean with standard deviation or median with interquartile range (IQR) for normally distributed or skewed data, respectively. Categorical variables are presented as counts with percentages and 95% confidence intervals (CIs).

Length of follow-up was calculated from the date of baseline ER to the most recent endoscopy, EUS, or scan. Annual risk for metastases was calculated as the number of patients with metastases divided by the total follow-up duration in years. Because competing risks were significant in this cohort, we created cumulative incidence curves performing Fine and Gray survival analysis. The time-to-event analysis was the time between baseline ER and occurrence of the event of interest (progression to LNM/ distant metastases or EAC-related death), the competing risk (unrelated death), or censoring (the last follow-up endoscopy).

Patient and public involvement

Patients and public were not involved in the research.

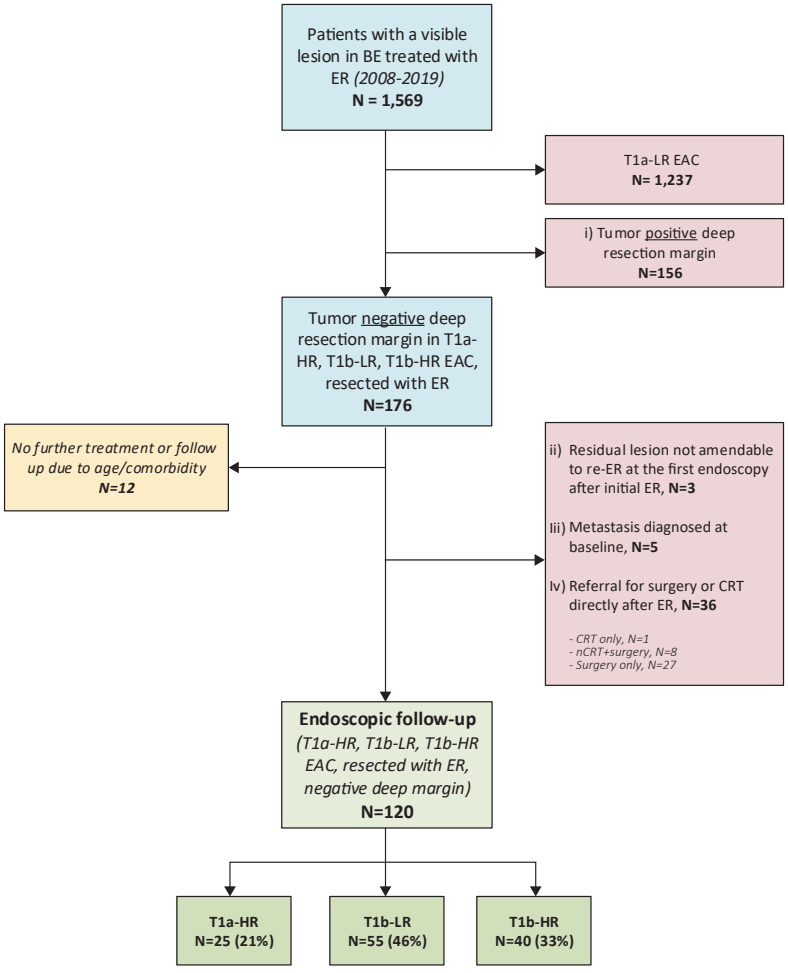
Ethics

The Institutional Review Board of the Amsterdam University Medical Centers declared that the registry was not subject to the Medical Research Involving Human Subjects Act

and waived the need for formal ethical review and patient-informed consent. Patients were approached through an opt-out card with the possibility to object to participation in the registry.

RESULTS

Figure 1.



Flow of patients representing the selection of the study cohort. Numbers i to iv state our exclusion criteria as mentioned in Methods. BE, Barrett esophagus; (n)CRT, (neoadjuvant) chemoradiation therapy; EAC, esophageal adenocarcinoma; ER, endoscopic resection; T1a-LR, mucosal tumor with low-risk histopathologic features such as no lymphovascular invasion and good or moderate differentiation grade; T1a-HR, intramucosal tumor with high-risk histopathologic features such as lymphovascular invasion or poor differentiation; T1b-LR, submucosal tumor with superficial invasion in the submucosa (<500 µm; sm1), well to moderately differentiated, without lymphovascular invasion; T1b-HR, submucosal tumor with either deep invasion in the submucosa (≥500 µm; sm2/3), and/or poor differentiation grade, and/or lymphovascular invasion presence.

Table 1. Baseline characteristics of 120 patients included in follow-up analysis

Characteristics	All	High-risk intramucosal tumor	Low-risk submucosal tumor	High-risk submucosal tumor
Total patients	**120**	**25 (21)**	**55 (46)**	**40 (33)**
Age, y	74 (66-81)	74 (66-82)	76 (69-80)	73 (65-82)
Male sex	99 (83)	21 (84)	43 (78)	35 (88)
Esophageal characteristics				
Barrett's length, cm				
Circumferential	2 (0-5)	2 (1-5)	2 (0-5)	2 (0-5)
Maximal	4 (2-7)	4 (3-8)	5 (2-7)	4 (2-6)
Paris classification (primary component)*				
0-Ip	6 (5)	1 (4)	0	4 (10)
0-Is	32 (27)	2 (8)	8 (15)	15 (38)
0-IIa	65 (55)	12 (48)	29 (53)	11 (28)
0-IIb	7 (6)	3 (12)	3 (6)	1 (3)
0-IIc	8 (7)	1 (4)	4 (7)	2 (5)
Lesion size,y mm	20 (15-30)	20 (20-30)	20 (15-40)	20 (15-30)
Endoscopic resection				
Endoscopic resection technique				
Multiband mucosectomy	83 (70)	20 (80)	41 (75)	22 (55)
Endoscopic cap resection	10 (9)	2 (8)	5 (9)	3 (7)
Endoscopic submucosal dissection	24 (21)	3 (12)	9 (16)	12 (38)

Table 1. (Continued)

Characteristics	All	High-risk intramucosal tumor	Low-risk submucosal tumor	High-risk submucosal tumor
Total patients	**120**	**25 (21)**	**55 (46)**	**40 (33)**
Histopathologic examination of endoscopic resection specimen				
Infiltration depth				
T1m3	25 (21)	25 (100)	-	-
T1sm1 (<500 μm)	70 (58)	-	55 (100)	15 (38)
T1sm2/3 (≥500 μm)	25 (21)	-	-	25 (62)
Differentiation grade				
Good (grade 1)	24 (20)	-	19 (35)	5 (12)
Moderate (grade 2)	54 (45)	1 (4)	36 (65)	17 (43)
Poor (grades 3-4)	42 (35)	24 (96)	-	18 (45)
Lymphovascular invasion				
Absent	97 (81)	16 (64)	55 (100)	26 (65)
Present	23 (19)	9 (36)	-	14 (35)

Values are n (%) or median (25th-75th percentiles). d, No patients with these specific histopathologic characteristics.
*Missing, n Z 2 (1.7%).
Y Missing, n Z 17 (14%).

Patient cohort

Between January 2008 and June 2019, 1569 patients underwent ER for a neoplastic lesion in a Barrett's segment (Fig. 1 and Supplementary Fig. 1, available online at www.giejournal.org). One hundred twenty patients met our inclusion criteria, and their baseline characteristics are presented in Table 1. Included patients were subdivided into HR-T1a (25/120; 21%), LR-T1b (55/120; 46%), and HR-T1b (40/120; 33%).

Baseline staging and investigations during follow-up

Most patients underwent baseline staging examinations before initiation of endoscopic follow-up (78% EUS and/or CT) (Table 2). The median duration of follow-up in all 120 patients was 29 months (IQR, 15-48) after baseline ER. Stratified for risk group, the median follow-up duration was 35 months (IQR, 22-53) for HR-T1a, 30 months (IQR, 18-48) for LR-T1b, and 23 months (IQR, 12-50) for HR- T1b (Table 2). Overall, the median number of endoscopies was 5 (IQR, 3-7) with 2 EUSs (IQR, 0-5) per patient. Analyzing results over time, the number of follow-up EUSs appeared to increase over time, especially for HR-T1a EAC (median of 1 EUS per patient in 2008- 2011 vs 3 in 2017-2019). An additional PET-CT was performed in 28 patients (23%) during follow-up (median, 1 [IQR, 1-1]). Per histologic subgroup, PET-CT was per- formed in 4 of 28 (14%) HR-T1a patients, 7 of 28 (25%) LR-T1b patients, and 17 of 28 (61%) HR-T1b patients. Twenty-one patients (18% [95% CI, 12-25]) were diagnosed with a visible intraluminal recurrence during regular endoscopic follow-up. The median time to intraluminal recurrence was 10 months (IQR, 9-20).

LNM and distant metastases detected during follow-up

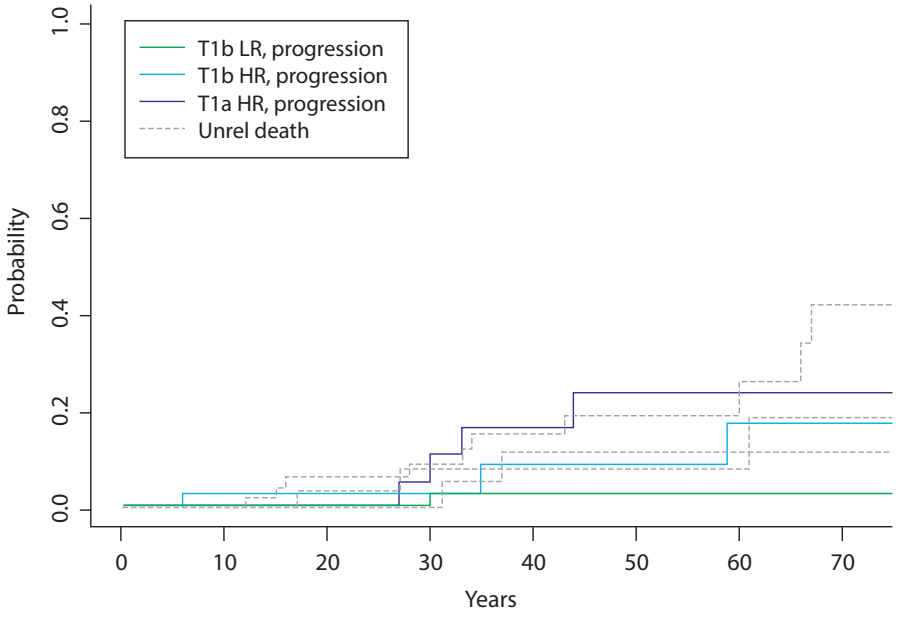
Nine patients (7.5% [95% CI, 3.5-14]) were diagnosed with metastatic disease (LNM, n = 4 [3.3%]) and/or distant metastases (n = 5 [4.2%]) during a median follow-up of 29 months, corresponding to an annual risk of 2.7% (95% CI, .5-7.1). Metastases were detected after a median of 27 months (IQR, 23-38). In 5 patients, metastases were detected as part of routinely performed follow-up examinations; 4 of these patients had regional LNM and 1 patient was found to have liver metastases. In the remaining 4 patients in whom metastases were detected, additional examinations were carried out because of symptoms. These detected 1 patient with regional LNM and 3 patients with distant metastases. For the latter group, EUS had been performed a median of 9 months (IQR, 7-11) before the onset of symptoms. All 9 patients with metastases had undergone baseline EUS and/or CT without evidence of metastases. Three of 9 patients (33%) also had intraluminal recurrence at the time of metastatic disease detection. The first patient underwent re-ER for an LR-T1b EAC (same as the initial tumor), whereas the second (initial histopathology showed HR-T1b) and third (initial histopathology HR-T1a) patients underwent re-ER for a visible lesion with high-grade dysplasia. Figure 2 shows the cumulative incidence curves for progression to LNM or distant metastases during follow-up stratified for baseline histology group.

Table 2. Summary of patients during follow-up divided per risk group (n = 120)

N=120	Follow-up, months (IQR)	Number of endoscopies (IQR)	Number of EUS (IQR)	LNM/DM during follow-up N (%)	Annual metastasis risk during follow-up (95% CI)	Time to metastasis, months (IQR)	Tumor related death N (%)
High-risk intramucosal tumor (n=25)	35 (22-53)	6 (3-9)	1 (0-4)	5 (20%)	6,9% (3-15)	31 (25-64)	4 (16%)
Low-risk submucosal tumor (n=55)	30 (18-48)	4 (2-7)	1 (0-3)	1 (2%)	0,7% (0-4)	22 (NA)	1 (2%)
High-risk submucosal tumor (n=40)	23 (12-50)	5 (3-8)	5 (2-8)	3 (8%)	3,0% (0-7)	24 (NA)	2 (5%)

Values are median (interquartile range) unless otherwise defined. NA, Not applicable.

Figure 2.



Nr of patients	120	101	74	48	33	21	12
Months FU	0	12	24	36	48	60	72

Cumulative incidence curves for progression to metastases versus unrelated deaths per histopathological risk group. T1b LR, Submucosal tumor with superficial invasion in the submucosa (<500 µm; sm1), well to moderately differentiated, without lymphovascular invasion; T1b HR, submucosal tumor with either deep invasion in the submucosa (≥500 µm; sm2/3), and/or poor differentiation grade, and/or lymphovascular invasion presence; T1a HR, intramucosal tumor with high-risk histopathologic features such as lymphovascular invasion or poor differentiation; FU, follow-up.

After resection of HR-T1a, 5 of 25 patients (20%) developed metastases during a median of 35 months (IQR, 22-53) of follow-up (annual risk, 6.9%; 95% CI, 3.0-15). The median time to metastases in this group was 31 months (IQR, 25-64). For patients with LR-T1b, 1 of 55 patients (2%) developed metastases during a median of 30 months (IQR, 18- 48) of follow-up (annual risk, .7%; 95% CI, 0-4.0). Time to metastases in this group was 22 months.

Among the HR-T1b patients, 3 of 40 patients (8%) developed metastases during a median of 23 months (IQR, 12-50) of follow-up. The annual risk was 3.0% (95% CI, 0-7.0). The median time to metastases was 24 months. Table 3 displays histopathologic features of these patients per risk group.

Table 3. Histopathologic features of patients with metastasis detected during follow-up disaggregated per risk group (n = 120)

Histopathologic risk factors	High-risk intramucosal tumor (n = 25)			Low-risk submucosal tumor (n = 55)	High-risk submucosal tumor (n = 40)			Total
	Grades 3/4 and LVI+	Grades 3/4	LVI+	Sm1	Sm1 and LVI+	Sm2/3 and grades 3/4	Sm2/3 and grades 3/4 and LVI+	
No. of patients with LNM+	1	1	0	1	1	0	0	4
No. of patients with LNM+ and DM+	1	1	1	0	0	1	1	5
Total no. of patients with metastases	2	2	1	1	1	1	1	9
		5/25 (20%)		1/55 (2%)		3/40 (8%)		9/120 (7.5%)
Total no. of patients with these high-risk factors	8/25	16/25	1/25	55/55	6/40	6/40	3/40	

LNM, Lymph node metastasis; LVI, lymphovascular invasion; DM, distant metastases.

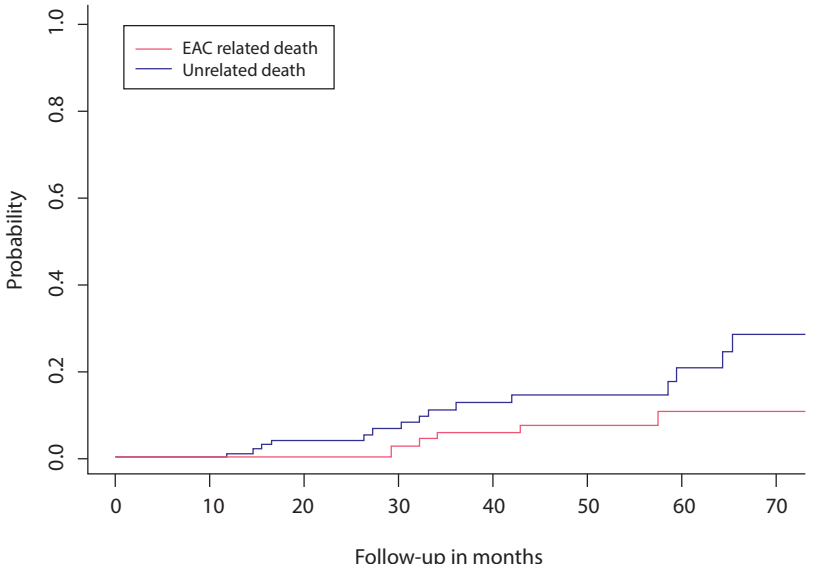
EAC-related and -unrelated mortality during follow-up

Of the 9 patients with metastases, 5 developed distant metastases and died. Overall, the risk for EAC-related death was 5.8% (95% CI, 2.4-12) during a median of 70 months (IQR, 55-126).

The remaining 4 patients with metastases had LNM and were additionally treated with curative intent, of which 2 patients were treated successfully (ie, 1 patient with neoadjuvant chemoradiotherapy and esophagectomy and 1 patient with definite chemoradiotherapy). The 2 other patients died because of treatment adverse events: 1 of adverse events after esophagectomy and 1 of severe radiation pneumonitis. Supplementary Table 1 (available online at www.giejournal.org) shows an extensive overview of all patients with metastases including outcomes.

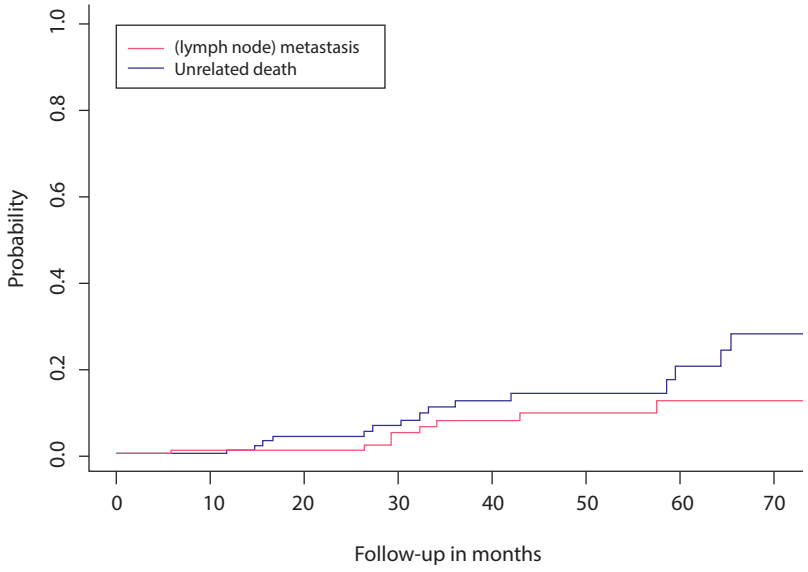
Mortality not related to EAC was 13% (95% CI, 8.0-21) during a median of 33 months, and patients died a median of 34 months (IQR, 20-61) after baseline. Figure 3 shows the cumulative incidence curves for EAC-related versus EAC-nonrelated mortality, and Figure 4 shows the cumulative incidence of progression to LNM or distant metastases compared with unrelated death during follow- up, which indicates that the probability to die from unrelated causes was higher than the probability to develop metastases during follow-up. Finally, Table 2 provides a summary of all patients, including outcomes.

Figure 3.



Cumulative incidence curves for EAC-related versus -unrelated death. EAC, Esophageal adenocarcinoma.

Figure 4.



Cumulative incidence curves for lymph node metastases versus unrelated death.

DISCUSSION

This study includes outcomes of all 120 patients who underwent endoscopic follow-up after radical ER of an EAC with histopathologic risk features for LNM in the Netherlands. Of 120 patients, 9 (7.5%) developed metastases during a median follow-up of 29 months (IQR, 15-48). The cohort was subdivided in T1a with high-risk features, T1b with low-risk features, and T1b with high-risk features in the initial ER specimen. The annual risks for metastases for the histologic subgroups during follow-up were 6.9% (95% CI, 3.0-15), .7% (95% CI, 0-4.0), and 3.0% (95% CI, 0-7.0), respectively. EAC-specific related mortality and -nonrelated mortality were 5.8% and 13% during a median of 70 months (IQR, 55-126).

Our results regarding metastases rates in the LR-T1b group are in line with previously published endoscopy-orientated studies. A study that analyzed long-term outcomes showed a metastasis rate of 2% in patients with LR-T1b EAC during 60 ± 30 months of follow-up [10]. Our analysis, which also showed a metastasis rate of 2% during a median follow-up of 30 months, confirms the data supporting endoscopic management for patients with LR- T1b EAC. Metastases rates in patients with HR-T1b EAC (3/40 [8%] during 23 months of follow-up) were at the lower side of the spectrum compared

with existing endoscopic literature (ie, rates differ between 0% and 37% during 23-63 months of follow-up) [5,10-12]. In comparison with our study, the previous reported studies focused on submucosal EACs only, whereas the current study also included intramucosal EAC with high-risk features. Furthermore, some studies included patients with a positive deep resection margin in their cohort, whereas this study only included tumor-negative deep resection margins. In addition, in most previous reported studies, metastases rates were analyzed for patients who underwent ER with or without subsequent surgery, whereas our study focused on the metastasis rate after ER during endoscopic follow-up. Our study partly overlaps with 2 previous reports from our group [5,11].

An explanation for the observed low metastases rates of HR-T1b EACs in this study is that in contrast to previous surgical series, all T1b cancers had to be amendable to ER in the first place, ER had to result in negative deep resection margins, and staging after ER could not show (locoregional) metastases. In this regard, 5 patients who were found to have metastatic disease at baseline staging on EUS-FNA and/or PET-CT were excluded, resulting in a subgroup with a lower metastasis risk compared with surgical retrospective studies without a preselection excluding these high-risk cases. There was 1 HR-T1b patient with LNM found during subsequent surgery after radical ER for a baseline staged N0M0 EAC in this study.

Although we cannot compare the metastasis rate of HR- T1a patients with other studies, we found the annual metastasis rate of 6.9% (5/25 [20%]) to be surprisingly high, especially when compared with T1b cases in this cohort. Because this was unexpected, the T1a cases were reviewed by expert pathologists to confirm the diagnosis. There is scarce knowledge regarding the individual histologic risk factors for metastases (ie, deep submucosal invasion, poor differentiation grade, LVI). One study assessed LNM rates in surgical specimens shortly after ER for HR-T1a EAC (of 5 patients, none had LNM) [19]. The same study also analyzed patients with T1b EAC and poor differentiation grade or LVI, showing that, although not significant, the highest odds ratio for nodal involvement was for LVI (5.2) followed by poor differentiation grade (3.0), independent of invasion depth. A second study assessed clinical and histologic variables associated with survival of T1a and T1b EAC patients after endoscopic treatment with or without subsequent esophagectomy [20]. Patients with metastasis at baseline and positive resection margin were not excluded. Older age, deep margin involvement, and presence of LVI were associated with decreased (tumor-free) survival (hazard ratio, 1.67; 95% CI, 1-3; P Z .009) [20]. To assess independent predictors of survival of endoscopic versus surgically treated T1b EAC patients, Otaki et al [21] built a Cox proportional hazards model and concluded that having 1 more high-risk histologic feature (ie, deep margin

positivity, LVI, poor differentiation) was associated with decreased survival compared with the group without any high-risk features. The 5-year survival rate was higher in patients treated surgically. However, as illustrated by the differences in age and comorbidity score between both groups, patients with poorer life expectancy were followed endoscopically and were not treated with esophagectomy, leading to a biased comparison of overall survival in favor of surgery [21]. Another recently published study developed a prediction tool that estimated the risk of metastases in patients with T1b EAC, also combined with other histopathologic risk factors. The highest risk was found in EAC with LVI (subdistribution hazard ratio of 2.95) [22]. In our study, 23 patients had LVI of which 5 (22%) were diagnosed with metastases. On the other hand, 4 of 97 patients (4%) without LVI developed metastases. These data seem to suggest that LVI and poor differentiation grade strongly affect the risk of metastasis. However, the number of events in our study was too low to further analyze the risk of LNM for individual histologic risk factors. In addition, comparing our study results with other studies is difficult because of the discrepancy in inclusion and exclusion criteria and study aims.

Several limitations of this study must be addressed. First, the retrospective setting of this study could have resulted in selection and information bias. In addition, this was a preselected cohort, in which frail and/or elderly patients with a higher likelihood of dying of causes not related to EAC were more likely to have been offered endoscopic follow-up instead of surgery. This may play a role in our higher EAC-nonrelated mortality rate (13%) versus EAC-related mortality (5.8%). Furthermore, different ER techniques were used during the years, such as endoscopic submucosal dissection, which has become more frequent from 2018 and onward. This may make the cohort less homogeneous.

Second, the baseline and follow-up strategy was heterogeneous because of a lack of strict guidelines and policy changes over time, and the median number of EUSs per patient was low (Supplementary Table 2, available online at www. giejournal.org). This may have led to an unjustified inclusion of patients who actually already had metastases at baseline. In addition, metastases that developed during follow-up may have been missed, because the median time to detection of metastases (27 months) was comparable with the overall median follow-up duration (29 months). Eventually, 9 patients were diagnosed with metastases during follow-up in our study. Because of heterogeneous follow-up, the moment of detection and therefore the stage and the possibility to initiate curative treatment may be less reliable. Nonetheless, we still found 4 of 9 patients who developed LNM only that were detected at curable stages. Two of these 4 patients died of treatment adverse events, which indicates the complex trade-off between these competing strategies. Despite a few patients in this

cohort having distant metastases at detection, we believe the stringent follow-up after radical resection of early high-risk EAC, performed by dedicated endoscopists only and following strict guidelines when to conduct EUS-FNA, remains a valid strategy in a subset of patients.

Third, this cohort was preselected and contained small numbers per LNM risk group. Therefore, it is not suitable to perform comparative or predictive analysis on LNM regarding specific (histopathologic) features or types of (subsequent) endoscopic treatment in this study.

Fourth, histopathology review was only performed for HR-T1a cases. Finally, the median follow-up of 29 months (IQR, 15-48) is relatively short. Although studies have shown that most metastases are found during the first 2 years of follow-up, only 4 of 9 metastases in this study were detected within 24 months of follow-up.9 [23], As previously mentioned, this might be a consequence of heterogeneous follow-up.

Strong points of this study are the uniquely harmonized setting of the BECs with care provided by jointly trained endoscopists and pathologists, and registration in a uniform database. This study reflects current clinical practice because some patients with high-risk EAC are deemed unfit for surgery or prefer endoscopic management. These patients are offered endoscopic management after extensive informed consent by both the gastroenterologist and surgeon. This study adds value to the available literature because it describes the largest cohort of endoscopic management outcomes in early high-risk EAC, including HR-T1a patients. It reflects a clean cohort of patients who underwent radical ER with subsequent endoscopic follow-up, with a rather long median follow-up duration after treatment. In comparison with other studies assessing metastases in high-risk EAC, the number of included patients is reasonably large.

Our study provides additional data regarding metastasis risk during endoscopic follow-up of patients with early EAC with histologic risk factors. Whereas the observed annual metastasis rate for HR-T1b EAC (3.0%) is somewhat lower than expected in comparison with previous reported percentages, the observed annual metastasis risk of 6.9% for HR-T1a EAC is new and worrisome. Our findings and optimal management strategies for these patients warrant further prospective evaluation (PREFER study, NCT03222635).

REFERENCES

1. Pech O, Behrens A, May A, et al. Long-term results and risk factor anal- ysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarci- noma in Barrett's oesophagus. Gut 2008;57:1200-6.
2. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenter- ology 2000;118:670-7.
3. Vieth M, Ell C, Gossner L, et al. Histological analysis of endoscopic resection specimens from 326 patients with Barrett's esophagus and early neoplasia. Endoscopy 2004;36:776-81.
4. Manner H, May A, Pech O, et al. Early Barrett's carcinoma with "low- risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008;103:2589-97.
5. Schölvinck D, Künzli H, Meijer S, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on pa- tient management and risk of metastatic disease. Surg Endosc 2016;30: 4102-13.
6. Markar SR, Karthikesalingam A, Thrumurthy S, et al. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg 2012;16:1055-63.
7. Fuchs HF, Harnsberger CR, Broderick RC, et al. Mortality after esopha- gectomy is heavily impacted by center volume: retrospective analysis of the Nationwide Inpatient Sample. Surg Endosc 2017;31:2491-7.
8. Buskens CJ, Westerterp M, Lagarde SM, et al. Prediction of appropriate- ness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest En- dosc 2004;60:703-10.
9. Westerterp M, Koppert LB, Buskens CJ, et al. Outcome of surgical treat- ment for early adenocarcinoma of the esophagus or gastro- esophageal junction. Virchows Arch 2005;446:497-504.
10. Manner H, Pech O, Heldmann Y, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incip- ient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc 2015;29:1888-96.
11. Künzli HT, Belghazi K, Pouw RE, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United Eur Gastroenterol J 2018;6:669-77.
12. Manner H, Wetzka J, May A, et al. Early-stage adenocarcinoma of the esophagus with mid to deep submucosal invasion (pT1b sm2-3): the frequency of lymph-node metastasis depends on macroscopic and his- tological risk patterns. Dis Esophagus 2017;30:1-11.
13. van Munster S, Nieuwenhuis E, Weusten BLAM, et al. Long-term out- comes after endoscopic treatment for Barrett's neoplasia with radiofre- quency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period. Gut 2021.
14. Nederlandse Vereniging van Maag-Darm-Leverartsen. Richtlijn Barrett- oesofagus [in Dutch]. IKNL;2018:1-71. Available at: https://www.mdl.nl/sites/www.mdl.nl/files/richlijnen/Richtlijnen%20Barrett%20oesofagus%20-%20jan%202018%20-%20tbv%20website.pdf. Accessed April 25, 2022.

15. Nederlandse Vereniging van Maag-Darm-Leverartsen. Richtlijn Oesofaguscarcinoom [In Dutch]. 2014:1-173. Available at: https:// richtlijnendatabase.nl/richtlijn/oesofaguscarcinoom/oesofaguscarci noom_-_startpagina.html. Accessed April 25, 2022.
16. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-8.
17. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology 2006;131:1392-9.
18. Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58(6 Suppl):S3-43.
19. Boys JA, Worrell SG, Chandrasoma P, et al. Can the risk of lymph node metastases be gauged in endoscopically resected submucosal esoph- ageal adenocarcinomas? A multi-center study. J Gastrointest Surg 2016;20:6-12; discussion 12.
20. Leggett CL, Lewis JT, Wu TT, et al. Clinical and histologic determinants of mortality for patients with Barrett's esophagus-related T1 esopha- geal adenocarcinoma. Clin Gastroenterol Hepatol 2015;13: 658-64.
21. Otaki F, Ma GK, Krigel A, et al. Outcomes of patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study. Gastro- intest Endosc 2020;92:31-9.
22. Gotink AW, van de Ven SEM, Ten Kate FJ, et al. Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study. Endoscopy 2022;54:109-17.
23. Dresner SM, Lamb PJ, Bennett MK, et al. The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogas- tric junction. Surgery 2001;129:103-9.

SUPPLEMENTARY MATERIAL

To access the supplementary material accom- panying this article, visit www. giejournal. org; *Gastrointestinal Endoscopy 2022 Mar (online first) doi; 10.1016/j.gie.2022.03.005*

PART IV

General discussion and
future prospects

The aim of this thesis was to optimize patient-tailored treatment in patients with Barrett's neoplasia. We evaluated the entire spectrum: from low-grade dysplasia to early cancer, and assessed long-term efficacy and safety of endoscopic therapy. We zoomed in on patients with confirmed low-grade dysplasia, patients with recurrences after successful endoscopic eradication treatment, and patients with high-risk early cancer. Moreover, we questioned the value of endoscopic eradication treatment in patients with a limited life expectancy. In the following paragraphs, we will discuss the implications of this thesis for clinical care and provide directions for future research.

ENDOSCOPIC SURVEILLANCE OF BARRETT'S ESOPHAGUS

Endoscopic detection and characterization of Barrett's neoplasia

The goal of Barrett-surveillance is to prevent advanced esophageal adenocarcinoma (EAC) by detecting neoplasia at a stage in which curative treatment can be offered, preferably by minimally invasive, endoscopic treatment. Also, surveillance may detect pre-cursor lesions of EAC, i.e. high-grade or low-grade dysplasia, which may also be treated to prevent progression to cancer. In general, endoscopic surveillance of non-dysplastic Barrett's esophagus (NDBE) is performed every three to five years with careful endoscopic inspection of the whole Barrett's segment (1). Despite of this, early neoplastic lesions in BE may be missed during surveillance since they are often subtle and flat. Next to the subtle appearance of these lesions during endoscopy, recognition remains poor due to low incidence of early BE neoplasia (2–4), making most endoscopists unfamiliar with its appearance. Therefore, - in absence of detected visible lesions - random four-quadrant biopsies are obtained every 2 cm with the intention to detect "invisible" dysplasia. However, this provides samples from only 4-6% of the entire Barrett's segment, and since neoplasia is often focally distributed, this random biopsy protocol is associated with a significant sampling error (5). In addition, the protocol is also time-consuming, especially in long Barrett segments.

Since the majority of Barrett patients will never develop dysplasia or cancer (6), it is unclear whether surveillance is beneficial in the way it is currently performed. To improve the current surveillance strategy, optimization was carried out in two key themes the past years. First, endoscopic detection and characterization of neoplasia in Barrett's esophagus have been improved by development of several techniques, including optical chromoscopy techniques such as narrow-band imaging (NBI), blue light imaging (BLI) and linked color imaging (LCI) and optical enhancement techniques. These visualization techniques, however, still suffer from subjective interpretation by endoscopists (7). Therefore, novel artificial intelligence tools analyzing endoscopic images automatically have gained popularity in endoscopic research. Especially computer-aided detection

(CAD) systems using deep neural networks to identify early neoplasia in a Barrett's esophagus have shown promising results (8–11). Primarily because these systems are not subject to interpretation by the endoscopist. Therefore, CAD systems are very promising, not only regarding to the field of Barrett's surveillance alone, but to the entire endoscopic spectrum. Nevertheless, CAD is not able to compensate for a poorly executed endoscopy. That is why our research group invested in setting up training programs together with other international experts in this field, such as the BORN *(Barrett's Oesophagus Related Neoplasia)* module (BORN start page (mediamotor.academy)) and BEST *(Barrett's endoscopic training)*-academia (best-academia.eu). The BORN training platform is aimed at teaching endoscopists to recognize early Barrett neoplasia, and the BEST-academia website aims to teach endoscopists how and in which Barrett's esophagus patients to perform safe and justified endoscopic treatment.

Second, to overcome the problem of sampling error associated with the current random forceps biopsy protocol (4 quadrants every 2cm along the Barrett segment), a wide field sampling technique "*wide-area transepithelial sampling with computer-assisted 3D analysis (WATS-3D)"* has been gaining ground (12). Where dysplasia and early cancer may be focal and can be missed by the endoscopist and random forceps biopsies, WATS-3D allows sampling of an extensive area of the Barrett segment by using a brush with long and abrasive bristles to obtain deep, trans-epithelial tissue specimens. The tissue undergoes computer-assisted analysis that helps to identify neoplasia, which are then presented to a pathologist for further evaluation and diagnosis. A recent prospective randomized study assessed the value of WATS-3D compared to random forceps biopsies for detection of high-grade dysplasia/EAC in Barrett patients without visible abnormalities (13). The study showed no significant difference in detection of dysplasia or early cancer between the WATS-3D brush and normal forceps biopsies. These results prompt the question of whether a brush will bring the advantage we are looking for (i.e. less sampling error and better detection of neoplasia). On the other hand, for the latest American Barrett's surveillance guideline a systematic search regarding benefits of WATS-3D in known Barrett patients was performed, showing that the performance of WATS-3D resulted in identification of 137 additional cases missed with random biopsy sampling alone (absolute increase in dysplasia detection using WATS was 10.6% (95% CI, 1.5%-19.8%)(14). As a result, the latest ASGE guideline recommends the use of WATS-3D in addition to white light endoscopy with the Seattle biopsy protocol during surveillance of patients with known Barrett's esophagus. Although WATS-3D may be more endoscopist-friendly and less time consuming, the brush technique has been raising other questions as well. For example, what should we do with biopsy-negative yet WATS-3D positive patients? Do such patients eventually develop biopsy-positive diagnosis during further endoscopic surveillance? If yes, this may be clinically relevant

early detection of neoplasia. On the other hand, these cases could also be a reflection of a population with a lower risk of progression never developing any clinically relevant disease. To learn more about the natural history of WATS-positive-biopsy-negative cases, a multicenter, prospective, tandem arm trial is currently being performed. In this study, the rate of developing a biopsy-based diagnosis of high-grade dysplasia/EAC in Barrett patients at high risk of progression as well as in patients in a standard Barrett surveillance program is being assessed. Patients at high risk for progression include: i) patients with residual Barrett's mucosa after ER of high-grade dysplasia/EAC; and ii) patients with Barrett's mucosa without visible lesions, but with confirmed low-grade dysplasia (NTR, NL8216).

Risk stratification

Above-mentioned developments in Barrett's surveillance are mainly focusing on optimizing techniques that have already gained ground and fit in the current surveillance strategy. However, to optimize surveillance even more, it would benefit from predicting progression to dysplasia or cancer at an early as possible stage. This way, patients with a very low risk of progression could be surveyed at wider intervals or surveillance can be stopped, whereas patients with increased risk of progression could be offered stricter surveillance or even prophylactic ablation of their Barrett's esophagus. One of the technologies that may play a future role in the respect is called TissueCypher® (Cernostics, Inc). TissueCypher® enables both detection and prediction of prevalent incident neoplasia. The technique is immunohistochemistry assay-based and automatically assesses morphological aspects and the protein expression of nine different biomarkers in biopsy specimens derived from the Barrett's segment. In previous studies, TissueCypher® has already shown that it accurately risk stratifies NDBE patients into low, intermediate, or high-risk of progression to high-grade dysplasia (HGD) or EAC within 5 years (15,16). And also in patients with low-grade dysplasia diagnosed in a community cohort, TissueCypher® provided significant risk stratification and identified progressors that expert pathologists downstaged to non-dysplastic Barrett's(17). This means that the technology could be used to detect present dysplasia that was missed during surveillance endoscopy, but also to predict progression to higher grades of dysplasia, which may be used to personalize surveillance intervals or even consider prophylactic eradication treatment.

ENDOSCOPIC TREATMENT OF BARRETT'S RELATED NEOPLASIA

Paradigm shift in the treatment spectrum

Endoscopic eradication therapy for Barrett's related neoplasia in the Netherlands is uniquely organized in Barrett Expert Centers (BECs). After a finding of dysplasia or early cancer in a community hospital, patients are referred to a BEC where care is provided by experienced endoscopists and pathologists, adhering to homogeneous treatment and follow-up protocols based on Dutch and European guidelines (1,18). All expert endoscopists and pathologists participated in shared training programs and difficult cases are discussed in regular meetings. Pathologists were specifically trained using pre-set benchmark scores for quality criteria, and a digital national review panel was developed to facilitate review requests (19,20). Patients undergo a dedicated imaging endoscopy in the expert center, searching for potential early neoplastic visible lesions that can be removed by endoscopic resection (ER). Findings of high-grade dysplasia and early cancer without histopathological high-risk factors (i.e. deep submucosal invasion ≥500µm, poor differentiation, lymphovascular invasion, tumor free resection margins (R0)) are clear indications for endoscopic treatment. After removal of any visible lesions, the (remaining) flat Barrett's mucosa is treated with radiofrequency ablation (RFA) until complete eradication of all Barrett's mucosa (CE-BE) is achieved. Since 2017, patients with a repeat diagnosis of histopathological confirmed low-grade dysplasia are considered for endoscopic eradication therapy as well, because the risk to progress to high-grade dysplasia or cancer is significantly reduced after RFA when compared to surveillance alone (21–23).

In Chapter 3 (24), we describe efficacy outcomes including the long-term follow-up results of all patients treated for Barrett's related neoplasia (low- and high-grade dysplasia and low-risk EAC) in the Netherlands between 2008 and 2018. In 94% (1.270/1.348) of patients, complete eradication of Barrett's was achieved at the end of endoscopic treatment phase (i.e., RFA with or without prior ER for a visible lesion). Only 3% (38/1.154 included in long-term analysis) developed dysplastic recurrence during median 43 months of follow-up. The annual recurrence rate was 1% and all recurrences were detected as endoscopically visible abnormalities. Frequent FU visits in the first year of FU were not associated with recurrence risk. Thus, in a setting of centralized care, RFA +/- ER is effective for eradication of Barrett's related neoplasia and has remarkably low rates of dysplastic recurrence. Therefore, more lenient FU intervals – with emphasis on careful endoscopic inspection – could be considered.

Another ablation technique that has been studied is cryoballoon ablation (CbAS). This may have better patient tolerability than RFA (i.e., shorter duration of post-procedural pain, lower peak-pain score during the procedure, and less dysphagia) (25). Another advantage of CbAS is preservation of the extracellular matrix and therefore this technique may allow for deeper ablation with lower stricture rates (26,27). Focal devices already have shown to be safe, effective and feasible(28). In a recent first-in-human study, assessing the outcomes of a large-area device, the median BE regression in 23 treated patients was 80%. Only 1 patient developed a severe stricture requiring 2 endoscopic dilatations, and patients reported only limited retrosternal pain. However, the optimal dose has not yet been set(29).

A more simple endoscopic technique, such as steam (i.e., radiofrequency vapor ablation (RFVA)), might also be promising. RFVA is a novel endoscopic through-the-scope treatment technique, which has shown to be safe in a first proof-of-principle study including in vitro, animal, and human testing. In 12 treated patients, the majority of Barrett areas treated with RFVA transformed into squamous epithelium (30).

Nevertheless, it is questionable whether an alternative ablation technique could replace RFA, since RFA already is proven safe and effective in multiple high quality studies (24,31,32). It is not likely that a newly developed technique holds that much benefit and is worth the effort of a large (non-inferiority) randomized trial to replace RFA if possible. Other than that, we should focus on exploring these new devices to use them complementary to RFA; e.g. in patients with poor response to RFA or patients with altered anatomy and a strictures esophagus.

Patient-tailored endoscopic management

A couple of important questions have risen after analyzing above-mentioned results representing the success of centralized endoscopic treatment for Barrett's neoplasia. The overarching theme of these questions was *"working towards more patient-tailored endoscopic management of Barrett's related neoplasia"*. Due to the quick development of endoscopy, the treatment spectrum has broadened further and further whilst we have lost sight of the main goal of endoscopic treatment: to prevent progression to advanced 'non-endoscopically-curable' disease. For example, one may question if treatment with RFA after successful ER of an early cancerous lesion in an old and frail patient, with limited life expectancy, is always clinically relevant and necessary. Simply because RFA can be considered as prophylactic therapy (i.e., to prevent intestinal metaplasia or low-grade dysplasia to develop into high-grade dysplasia or (early) cancer). We believe that endoscopists should ask themselves which patients will truly benefit from such

additional prophylactic eradication treatment, aimed at preventing a second, clinically relevant cancer, and which patients may not require such additional treatment.

In Chapter 4 (33), we demonstrated that Barrett's esophagus with confirmed low-grade dysplasia often harbors more severe dysplasia. Confirmation of low-grade dysplasia by an expert pathologist is important, because this is the strongest predictor of malignant progression. The histological diagnosis of low-grade dysplasia is challenging since the distinction between dysplastic changes and reactive atypia of reflux-induced inflammation is challenging. Two studies demonstrated that low-grade dysplasia diagnosed by a community pathologist was downgraded to 'no dysplasia' in 73-85% after review by an expert pathologist. After downstaging, the risk of neoplastic progression was <1% per patient-year. On the contrary, the risk of neoplastic progression was increased to 9-13% per patient-year in patients with confirmed low-grade dysplasia (6,34). Of the 248 patients with histopathological confirmed low-grade dysplasia our this study (33), re-staging endoscopy in a BEC revealed high-grade dysplasia or cancer in 23% of patients, mostly in a newly detected visible lesion that was not detected in the referring hospital. In 68%, low-grade dysplasia was confirmed a second time. Previous studies showed that the risk of malignant progression is 9-13% per patient-year in confirmed low-grade dysplasia without prophylactic RFA treatment(34,35). The findings of this study are therefore of great importance and a reason to refer patients without visible lesions, but a confirmed diagnosis of low-grade dysplasia, to a BEC for dedicated endoscopy.

In chapter 5 (36), we have shown that none of the patients treated with ER without subsequent RFA (i.e. ER monotherapy) – mostly because of limited life expectancy – developed advanced cancer during median 21 months follow-up. 18% (17/94) of patients developed high-grade dysplasia/EAC during follow-up, but all were curatively treated endoscopically. Moreover, 40% (29/73) of patients with *predicted* limited life expectancy died due to unrelated causes during follow-up (i.e. none of EAC).

Currently, surveillance intervals after successful endoscopic eradication therapy are chosen based on baseline histopathology diagnosis. However, as we have shown in our cohort study, the annual dysplastic recurrence rate is only 1% and all recurrences were detected as visible lesions during follow-up endoscopy. We therefore think that surveillance intervals could be extended in the majority of successfully treated patients. In some patients, one could consider to not even initiate follow-up or to stop follow-up after a certain number of endoscopies or a certain age. One should realize that surveillance is only valuable if treatment will be initiated in case neoplasia is found during surveillance. However, there is no consensus yet in which patients this may be

worth considering. Both recurrence prediction models and biomarker technologies could contribute to avoiding clinically irrelevant follow-up after successful treatment and personalize the follow-up strategy. Therefore, we developed an externally validated model to predict the recurrence of dysplasia and early cancer after successful treatment of Barrett neoplasia as described in Chapter 6 (37). The model can help clinicians and patients to manage expectations and determine a patient-tailored surveillance strategy. At present, our research group is working on more data and models to improve patient-tailored endoscopic treatment and follow-up. One of the relevant issues to consider in this respect, is that patients have a risk of dying from other causes than EAC. Data regarding EAC-**unrelated** death after successful endoscopic treatment for low-risk EAC in the Dutch Barrett cohort (24) were analyzed and showed that the risk of dying from causes other than EAC is 40 times higher than dying from **recurrent** EAC, and that the beneficial effect of intensive follow-up is likely overrated(38). Hopefully, future studies will help us individualize surveillance options in patients after successful endoscopic eradication therapy, taking into account risk of recurrence and risk of dying from unrelated causes.

Early cancer with high-risk features

An exciting and rapidly developing aspect of Barrett's management is endoscopic management of patients with early EAC with *high-risk* histopathological features. These features include deep submucosal invasion (≥500 µm), poor differentiation, and lympho-vascular invasion (LVI). The choice of treatment for patients with high-risk EAC is based on the risk for the development of lymph node metastasis (LNM). Current guidelines still advise surgery for high-risk EAC, since the risk of LNM, mainly based on old surgical studies, is reported to be as high as 46% (39–41). However, there are several reasons to believe that the tumor invasion depth in these old surgical studies may have underestimated, resulting in overestimation of the risk of LNM associated with a certain tumor invasion depth. We tested this hypothesis in our proof of concept study (Chapter 9), in which we analyzed histopathological slides of patients with submucosal EAC and metastases who were surgically treated (without prior ER and/or neo-adjuvant chemoradiation treatment). The results were affirmative, since we found that 1/12 patients (8%) registered as submucosal EAC was found to have tumor infiltration into the m. propria. After revision, 9/12 (75%) patients had an additional histological risk factor for LNM next to submucosal invasion (i.e. LVI or poor differentiation), as compared to 5/12 (42%) patients based on the original pathology report. High-quality prospective studies assessing the LNM risk in endoscopically managed high-risk EAC are lacking. As of now, the real LNM risk is unknown. Several studies reported retrospective data, presenting LNM risk percentages between 0-37% during 23-63 months of follow-up, which is already lower than the reported 16-46% in

surgical series (39,42–44). Endoscopic management may therefore be acceptable for selected patients with early high-risk EAC.

In addition, one should realize that not all patients with early high-risk EAC directly benefit from surgery since radical ER already ensures local disease control. Several studies have shown that endoscopic management for this indication does not result in significant difference in survival compared to surgical treatment (39,45,46).

To estimate whether the presence of one or multiple high-risk features contributes to LNM development in patients with submucosal EAC, the authors of the Sublyme study developed a prediction tool (47). The highest risk is found in EAC with LVI (subdistribution hazard ratio of 2.95). However, since the cohort is very heterogeneous (i.e. included patients 1989-2017), includes mainly surgically treated patients, and external validation is lacking, one should interpret the results of this study with caution. The same cautiousness has to be applied to the results of our own retrospective study assessing LNM rates in three patient groups with high-risk histopathological features (Chapter 10, i.e. high-risk mucosal EAC (n=25), low-risk submucosal EAC (n=55), and high-risk submucosal EAC (n=40)) (48). The annual risks to develop LNM were 7%, 1%, and 3%, respectively. Especially the high annual risk in high-risk *mucosal* EAC was a new and worrisome finding suggesting that strict follow-up of this small subgroup is warranted. Based on these results, we have concluded that the classical distinction of mucosal versus submucosal may not be the optimal way of risk stratifying patients after ER. Stratifying by presence of poor differentiation and LVI might be of greater importance.

However, we need more data to define the risk for LNM in patients with early high-risk EAC accurately and to determine which patients could be managed endoscopically, without the need of invasive surgery. Therefore, our group is currently conducting the PREFER study (NCT 03222635). This is an international, prospective cohort study evaluating the safety of endoscopic treatment followed by watchful waiting instead of surgery in patients with a *high-risk mucosal or submucosal* Barrett's carcinoma, radically removed by ER without LNM or distant metastasis at baseline (N0M0). Before inclusion and six weeks after ER, patients undergo baseline-staging examinations consisting of gastroscopy, endoscopic ultrasound, and (PET)-CT-scan to ensure N0M0 status. Follow-up consists of frequent gastroscopy and endoscopic ultrasound, every 3 months during year 1 and 2, every 6 months during year 3 and 4 and annually thereafter, to inspect the esophagus for residual or recurrent neoplasia, and to detect metastatic lymph nodes at a still curable stage. Endpoints of the study are disease-specific 5-year survival, 5-year mortality, and quality of life. Furthermore, the study may help to identify certain

histopathological risk factors, which may influence risk of lymph node metastases. A panel of expert pathologists will review all ER specimen. The non-inferiority sample size is calculated on 141 patients with *submucosal* EAC. Nevertheless, the results of our retrospective study considering the high LNM rates in high-risk *mucosal* EAC patients have led to including this subgroup as a separate prospective sub cohort in the study as well, following the same protocol as with the *submucosal* EAC patients.

Another alternative approach for the treatment of patients with early high-risk EAC is currently being evaluated. This approach entails a combined endoscopic and surgical approach consisting of radical ER of the tumor, followed by sentinel node navigation surgery (SNNS), using lymphoscintigraphy with radioactive tracer and near-infrared technology with indocyanine green (49). The feasibility, safety, and accuracy of this new treatment algorithm is currently assessed in both the SNAP-III and -IV study (NL8100 and NL8558, www.trialregister.nl). This may be an option in patients who are predicted to have a high risk of lymph node metastases, based on the histopathological risk factors in the ER/ESD specimen, as a bridge to assess if additional surgery is truly necessary or not.

REFERENCES

1. Nederlandse Vereniging van Maag-Darm-Leverartsen. Richtlijn Barrett-oesofagus. 2018;
2. Sikkema M, de Jonge PJF, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2010 Mar;8(3):235–44; quiz e32.
3. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011 Oct;365(15):1375–83.
4. Schölvinck DW, van der Meulen K, Bergman JJGHM, Weusten BLAM. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy. 2017 Feb;49(2):113–20.
5. Abela J-E, Going JJ, Mackenzie JF, McKernan M, O'Mahoney S, Stuart RC. Systematic four-quadrant biopsy detects Barrett's dysplasia in more patients than nonsystematic biopsy. Am J Gastroenterol. 2008 Apr;103(4):850–5.
6. Klaver, E., Mallant R. PR. Prospective Barrett's esophagus surveillance in a Dutch multi-centre community-based cohort of 985 patients demonstrates low risk of neoplastic progression. United Eur Gastroenterol J. 2021;Forthcomin.
7. de Groof AJ, Fockens KN, Struyvenberg MR, Pouw RE, Weusten BLAM, Schoon EJ, et al. Blue-light imaging and linked-color imaging improve visualization of Barrett's neoplasia by nonexpert endoscopists. Gastrointest Endosc. 2020;91(5):1050–7.
8. de Groof J, van der Sommen F, van der Putten J, Struyvenberg MR, Zinger S, Curvers WL, et al. The Argos project: The development of a computer-aided detection system to improve detection of Barrett's neoplasia on white light endoscopy. United Eur Gastroenterol J. 2019;7(4):538–47.
9. de Groof AJ, Struyvenberg MR, van der Putten J, van der Sommen F, Fockens KN, Curvers WL, et al. Deep-Learning System Detects Neoplasia in Patients With Barrett's Esophagus With Higher Accuracy Than Endoscopists in a Multistep Training and Validation Study With Benchmarking. Gastroenterology. 2020;158(4):915-929.e4.
10. de Groof AJ, Struyvenberg MR, Fockens KN, van der Putten J, van der Sommen F, Boers TG, et al. Deep learning algorithm detection of Barrett's neoplasia with high accuracy during live endoscopic procedures: a pilot study (with video). Gastrointest Endosc. 2020;91(6):1242–50.
11. Struyvenberg MR, de Groof AJ, van der Putten J, van der Sommen F, Baldaque-Silva F, Omae M, et al. A computer-assisted algorithm for narrow-band imaging-based tissue characterization in Barrett's esophagus. Gastrointest Endosc. 2021;93(1):89–98.
12. Johanson JF, Frakes J, Eisen D, EndoCDx Collaborative Group. Computer-assisted analysis of abrasive transepithelial brush biopsies increases the effectiveness of esophageal screening: a multicenter prospective clinical trial by the EndoCDx Collaborative Group. Dig Dis Sci. 2011 Mar;56(3):767–72.

13. S.N. Van Munster*1, 2, Ph. Leclercq*3, R. Haidry4, H. Messmann5, A Probst5, K Ragunath6, P. Bhandari7, A. Repici8, M. Munoz-Navas9, S. Seewald10, A. Lemmers11, G. Fernández-Esparrach12, O. Pech13, E.J. Schoon14, 15, R. Kariv16, H. Neuhaus17, B. Weusten2, RB. Wide Area Transepithelial Sample Esophageal Biopsy Combined with Computer Assisted 3-Dimensional Tissue Analysis (WATS3D) for the Detection of High Grade Dysplasia and Adenocarcinoma in Barrett: A Multi-Center, Prospective, Randomized, Tandem Study. Submitt to Gastrointest Endosc.

14. ASGE STANDARDS OF PRACTICE COMMITTEE, Qumseya B, Sultan S, Bain P, Jamil L, Jacobson B, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointest Endosc. 2019;90(3):335-359.e2.

15. Prichard JW, Davison JM, Campbell BB, Repa KA, Reese LM, Nguyen XM, et al. TissueCypher(™): A systems biology approach to anatomic pathology. J Pathol Inform. 2015;6:48.

16. Frei NF, Konte K, Bossart EA, Stebbins K, Zhang Y, Pouw RE, et al. Independent Validation of a Tissue Systems Pathology Assay to Predict Future Progression in Nondysplastic Barrett's Esophagus: A Spatial-Temporal Analysis. Clin Transl Gastroenterol. 2020;11(10):e00244.

17. Frei NF, Khoshiwal AM, Konte K, Bossart EA, Stebbins K, Zhang Y, et al. Tissue Systems Pathology Test Objectively Risk Stratifies Barrett's Esophagus Patients With Low-Grade Dysplasia. Am J Gastroenterol. 2021;116(4):675–82.

18. Weusten B, Bisschops R, Coron E, Dinis-Ribeiro M, Dumonceau J-M, Esteban J-M, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy [Internet]. 2017;49(02):191–8. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0042-122140

19. van der Wel MJ, Klaver E, Duits LC, Pouw RE, Seldenrijk CA, Offerhaus G, et al. Adherence to pre-set benchmark quality criteria to qualify as expert assessor of dysplasia in Barrett's esophagus biopsies - towards digital review of Barrett's esophagus. United Eur Gastroenterol J. 2019;7(7):889–96.

20. Klaver E, van der Wel M, Duits L, Pouw R, Seldenrijk K, Offerhaus J, et al. Performance of gastrointestinal pathologists within a national digital review panel for Barrett's oesophagus in the Netherlands: results of 80 prospective biopsy reviews. J Clin Pathol. 2021 Jan;74(1):48–52.

21. Phoa KN, van Vilsteren FGI, Weusten BLAM, Bisschops R, Schoon EJ, Ragunath K, et al. Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia. Jama [Internet]. 2014;311(12):1209. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.2511

22. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med [Internet]. 2009 May 28;360(22):2277–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19474425

23. Small AJ, Araujo JL, Leggett CL, Mendelson AH, Agarwalla A, Abrams JA, et al. Radiofrequency Ablation Is Associated With Decreased Neoplastic Progression in Patients With Barrett's Esophagus and Confirmed Low-Grade Dysplasia. Gastroenterology. 2015 Sep;149(3):567-76.e3; quiz e13-4.

24. van Munster S, Nieuwenhuis E, Weusten BLAM, Alvarez Herrero L, Bogte A, Alkhalaf A, et al. Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period. Gut. 2021 Mar;
25. van Munster SN, Overwater A, Haidry R, Bisschops R, Bergman JJGHM, Weusten BLAM. Focal cryoballoon versus radiofrequency ablation of dysplastic Barrett's esophagus: impact on treatment response and postprocedural pain. Gastrointest Endosc. 2018;88(5):795-803.e2.
26. Baust JG, Gage AA. The molecular basis of cryosurgery. BJU Int. 2005 Jun;95(9):1187–91.
27. Künzli HT, Schölvinck DW, Meijer SL, Seldenrijk KA, Bergman JGHM, Weusten BLAM. Efficacy of the CryoBalloon Focal Ablation System for the eradication of dysplastic Barrett's esophagus islands. Endoscopy. 2017 Feb;49(2):169–75.
28. Canto MI, Shaheen NJ, Almario JA, Voltaggio L, Montgomery E, Lightdale CJ. Multifocal nitrous oxide cryoballoon ablation with or without EMR for treatment of neoplastic Barrett's esophagus (with video). Gastrointest Endosc. 2018 Sep;88(3):438-446.e2.
29. Overwater A, van Munster SN, Nagengast WB, Pouw RE, Bergman JJGHM, Schoon EJ, et al. Novel cryoballoon 180° ablation system for treatment of Barrett's esophagus-related neoplasia: a first-in-human study. Endoscopy. 2022;54(1):64–70.
30. van Munster SN, Pouw RE, Sharma VK, Meijer SL, Weusten BLAM, Bergman JJGHM. Radiofrequency vapor ablation for Barrett's esophagus: feasibility, safety and proof of concept in a stepwise study with in vitro, animal, and the first in-human application. Endoscopy. 2021;53(11):1162–8.
31. Wolfson P, Ho KMA, Wilson A, McBain H, Hogan A, Lipman G, et al. Endoscopic eradication therapy for Barrett's esophagus-related neoplasia: a final 10-year report from the UK National HALO Radiofrequency Ablation Registry. Gastrointest Endosc. 2022 Feb 18;
32. Gupta M, Iyer PG, Lutzke L, Gorospe EC, Abrams JA, Falk GW, et al. Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US Multicenter Consortium. Gastroenterology. 2013 Jul;145(1):79-86.e1.
33. Nieuwenhuis EA, van Munster SN, Curvers WL, Weusten BLAM, Alvarez Herrero L, Bogte A, et al. Impact of expert center endoscopic assessment of confirmed low grade dysplasia diagnosed in community hospitals. Endoscopy. 2022 Jan 28;
34. Duits LC, Phoa KN, Curvers WL, Ten Kate FJW, Meijer GA, Seldenrijk CA, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut. 2015 May;64(5):700–6.
35. Curvers WL, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. 2010 Jul;105(7):1523–30.
36. van Munster SN, Nieuwenhuis EA, Weusten BLAM, Herrero LA, Bogte A, Alkhalaf A, et al. Endoscopic Resection Without Subsequent Ablation Therapy for Early Barrett's Neoplasia: Endoscopic Findings and Long-Term Mortality. J Gastrointest Surg. 2021;25(1):67–76.
37. van Munster SN, Nieuwenhuis E, Bisschops R, Willekens H, Weusten BLAM, Herrero LA, et al. Dysplastic Recurrence After Successful Treatment for Early Barrett's Neoplasia: Development and Validation of a Prediction Model. Gastroenterology. 2022 Jul;163(1):285–94.

38. E.P.D. Verweij SN van M et al. All-cause mortality after successful endoscopic eradication therapy for Barrett's related neoplasia in a nationwide cohort of 1.154 patients. Endoscopy 2022; 54(S 01): S93. DOI: 10.1055/s-0042-1744783.

39. Schölvinck D, Künzli H, Meijer S, Seldenrijk K, van Berge Henegouwen M, Bergman J, et al. Management of patients with T1b esophageal adenocarcinoma: a retrospective cohort study on patient management and risk of metastatic disease. Surg Endosc. 2016;30(9):4102–13.

40. Buskens CJ, Westerterp M, Lagarde SM, Bergman JJGHM, ten Kate FJW, van Lanschot JJB. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc. 2004 Nov;60(5):703–10.

41. Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJW, Bergman JJHGM, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch. 2005 May;446(5):497–504.

42. Manner H, Pech O, Heldmann Y, May A, Pauthner M, Lorenz D, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc. 2015 Jul;29(7):1888–96.

43. Künzli HT, Belghazi K, Pouw RE, Meijer SL, Seldenrijk CA, Weusten B, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United Eur Gastroenterol J. 2018 Jun;6(5):669–77.

44. Manner H, Wetzka J, May A, Pauthner M, Pech O, Fisseler-Eckhoff A, et al. Early-stage adenocarcinoma of the esophagus with mid to deep submucosal invasion (pT1b sm2-3): the frequency of lymph-node metastasis depends on macroscopic and histological risk patterns. Dis esophagus Off J Int Soc Dis Esophagus. 2017 Feb;30(3):1–11.

45. Ngamruengphong S, Wolfsen HC, Wallace MB. Survival of patients with superficial esophageal adenocarcinoma after endoscopic treatment vs surgery. Clin Gastroenterol Hepatol. 2013 Nov;11(11):1424-1429.e2; quiz e81.

46. Berry MF, Zeyer-Brunner J, Castleberry AW, Martin JT, Gloor B, Pietrobon R, et al. Treatment modalities for T1N0 esophageal cancers: a comparative analysis of local therapy versus surgical resection. J Thorac Oncol. 2013 Jun;8(6):796–802.

47. Gotink AW, van de Ven SEM, Ten Kate FJC, Nieboer D, Suzuki L, Weusten BLAM, et al. Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a multicenter cohort study. Endoscopy. 2021 Feb;

48. Nieuwenhuis EA, van Munster SN, Meijer SL, Brosens LAA, Jansen M, Weusten BLAM, et al. Analysis of metastases rates during follow-up after endoscopic resection of early "high-risk" esophageal adenocarcinoma. Gastrointest Endosc. 2022 Mar 12;

49. Overwater A, Weusten BLAM, Ruurda JP, van Hillegersberg R, Bennink RJ, de Keizer B, et al. Feasibility of sentinel node navigated surgery in high-risk T1b esophageal adenocarcinoma patients using a hybrid tracer of technetium-99 m and indocyanine green. Surg Endosc. 2022;36(4):2671–9.

APPENDICES

English summary
Nederlandse samenvatting
List of publications
Contributing authors
PhD portfolio
Dankwoord
About the author

ENGLISH SUMMARY

The combined endoscopic treatment approach with endoscopic resection (ER) and radiofrequency ablation (RFA) for Barrett's related early neoplasia (i.e. low-grade dysplasia (LGD), high-grade dysplasia (HGD), early adenocarcinoma (EAC) without histopathological risk factors for lymph node metastasis) has proven its safety and efficacy. The consecutive step is to work towards patient-tailored management. In this thesis we, therefore, aimed to evaluate optimization of endoscopic treatment and surveillance for early neoplasia arising from Barrett's esophagus and explored whether an endoscopic approach could be a valid treatment option in more advanced stages of early EAC.

Part I: The cornerstone of successful endoscopic treatment of early Barrett's neoplasia

The first part of this thesis focuses on ER and RFA. **Chapter 1 and 2** are reviews that elaborate on the background, technical aspects and indications of treatment with ER and RFA, and discuss why this combined endoscopic treatment approach is successful. The combination of ER with RFA have shown to achieve complete eradication rates between 74%-98% in earlier studies. However, robust long-term durability remains poorly characterized. Therefore, **in chapter 3,** we describe outcomes of all patients who underwent endoscopic treatment for early neoplasia with RFA (+/- ER) in a cohort of 1.386 patients treated in one of the eight Dutch Barrett Expert Centers in the Netherlands between 2008 and 2018. Complete eradication of Barrett was achieved in 94% (1.270/1.348) of patients who completed treatment. 78 patients (6%) had remaining Barrett mucosa and/or dysplasia, and were defined as treatment failures. Most failures had achieved a complete eradication of HGD/EAC, yet 1% of patients progressed to disease stages that exceeded the boundaries for curative endoscopic treatment. A total of 1.154 patients were analyzed for long-term outcomes. The median duration of endoscopic follow-up (FU) was 43 months (22-69, minimum 8) with median 4 FU endoscopies (1-5) per patient. During FU, recurrent LGD, HGD or EAC occurred in 38/1.154 (3%) patients, after a median of 31 months after complete eradication was achieved (annual risk of only 1% (95% CI 0.8-1.4)). Only 0.4% of patients with recurrence progressed to advanced EAC. In this cohort, frequent FU visits in the first year did not contribute to detection of recurrences, nor did random biopsies from the neosquamous epithelium (NSE) or cardia. Therefore, our data suggest that in expert centers, after achievement of complete eradication, FU intervals could be extended, that 3-monthly endoscopies in the first FU year may be omitted, and random biopsies from NSE and cardia may be abandoned. We concluded that dedicated endoscopic inspection, and if needed, target biopsies are the most relevant method to detect post-RFA recurrences.

Part II: Improving patient-tailored endoscopic management for Barrett's neoplasia

Part two of this thesis focuses on improving personalization of early Barrett's neoplasia management by elaborating on different topics within this spectrum. Since international guidelines provide conflicting advice whether to initiate RFA treatment upon a new LGD diagnosis, in **chapter 4**, we evaluated whether LGD – confirmed by an expert histopathologist – is an indicator for detection of higher grades of synchronous dysplasia or visible lesions in the Barrett segment, and thus, should be referred to an expert care setting for treatment. We assessed the proportion of patients with HGD/cancer during re-evaluation in expert setting for confirmed LGD. In total, 248 patients were referred for this indication, of whom 57/248 (23%; [95% CI 18-29]) were found to have HGD (n=23) or EAC (n=25) during re-evaluation endoscopy in the expert center. In 168 patients (68%; [95% CI 62-74]), re-evaluation confirmed the diagnosis of LGD. Overall, 92% of patients had an indication for subsequent (prophylactic) treatment within 1 year of referral. Based on our results, we plead for confirmation of LGD diagnosis by an expert histopathologist, and the referral of patients upon confirmation to an expert center for re-evaluation endoscopy.

Optimization of patient tailored endoscopic management also means knowing when to cease treatment. Especially in patients with limited life expectancy, subsequent RFA after successful ER may not be the most optimal treatment approach. To assess this hypothesis, we analyzed in **chapter 5** whether endoscopic surveillance instead of RFA, after ER for early neoplasia, would be a valid alternative. 94 patients were retrospectively included in this cohort. Mean age was 74 years (± 10). No additional ablation was performed for several reasons, but the main argument was limited life expectancy (73 patients (78%)). None of the patients progressed to advanced cancer during endoscopic FU (median 21 months (11-51) and 4 endoscopies). In total, 29/73 patients (40%) with limited life expectancy died during FU, all due to EAC-unrelated causes. We concluded that, in selected patients, ER without subsequent ablation but with endoscopic surveillance of the residual Barrett is a valid alternative to the standard combination therapy.

Some patients are more prone to develop dysplastic recurrences after achievement of complete eradication of Barrett than others. Therefore, optimization of endoscopic management should also include the prediction of developing recurrences during FU, and thereby optimizing surveillance intervals in order to prevent development to advanced cancer. Therefore, in **chapter 6,** a prediction model for dysplastic recurrence after initial successful endoscopic treatment was created and externally validated. Predictors related to demographics, severity of reflux, baseline histology, and treatment

characteristics were included. A total of 1.154 patients (i.e. the earlier mentioned Dutch Expert Center durability cohort in which only 38 patients (1%/person year) developed dysplastic recurrence) were included. Several characteristics were independently associated with recurrence (strongest to weakest): "incident" lesion during treatment phase, higher number of ER treatments, male gender, longer BE length, HGD or more advanced pathology at baseline, and younger age. External validation showed a C-statistic of 0.91 [95% CI 0.86-0.94] with good calibration. The model might be helpful for clinicians and patients to manage expectations and determine a personalized surveillance strategy.

Chapter 7 describes the incidence and outcomes of poor healing (PH) and poor squamous regeneration (PSR) after RFA in the Dutch nationwide Expert Center cohort of 1.386 patients. We analyzed 134 patients (10%) with PH and 74 patients (5%) with PSR. In half of all patients with PH, additional time and acid suppression resulted in complete esophageal healing with a complete eradication of Barrett rate of 97%. Therefore, our advice is to manage these patients with time and optimal acid suppression. However, if patients experience PSR upon healing, a higher risk for treatment failure in comparison with patients with normal squamous regeneration exists (64% versus 2%; RR 27 [95% CI 18-40]). The risk of progression to advanced disease was also higher (15% versus 1%; RR 30 [95% CI 12-81]).

Patients with PH and/or PSR may develop a complex treatment course, including progression of disease, failure of treatment and/or "incident" lesions showing up during treatment phase. We hypothesized that it may be helpful to have the possibility to predict such a complex treatment course. Therefore, in **chapter 8**, we developed and externally validated a prognostic model, again using our Dutch Expert Center treatment cohort of 1.356 patients. 77 patients (6%) had a complex treatment course. Baseline BE length; visible lesions; HGD or EAC; and <50% squamous conversion after RFA were independently associated with a complex treatment. Our model identified 8% of patients after RFA as having a high-risk for a complex treatment, including 76% of all patients with progression to disease stages that exceed boundaries for endoscopic treatment and 93% of patients with persisting BE despite adequate RFA. Apart from these adverse outcomes, these patients also had a significantly longer treatment duration with a higher risk for complications. The model appeared robust in multiple sensitivity analysis and performed well in external validation with an area under the curve (AUC) of 0.84

Part III: Pushing boundaries in endoscopic management

Part three of this thesis discusses exploring the boundaries of endoscopic management as a treatment for patients with EAC with histopathological risk factors for lymph node metastasis (LNM) (i.e. submucosal invasion, poor differentiation, lymphovascular invasion (LVI)) and started with a proof of concept study (**chapter 9**). We aimed to assess whether previous reported LNM rates on surgically treated submucosal EAC could have been overestimated, due to differences in specimen preparation in comparison with endoscopic resection specimens. We analyzed 12 patients with a surgically treated lymph node metastasized submucosal EAC (1994-2005, before endoscopic resection was embedded) and revised tumor invasion depth, differentiation grade, and lymphovascular invasion after additional cuts have been made on the pre-existing surgical slides. We found 1 patient (8%) with cancer invading the m. propria instead of the submucosa and 4 patients with borderline m. propria invasion. After revision, 9/12 (75%) patients had an additional histologic risk factor for LNM next to submucosal invasion, as compared to 5/12 (42%) based on the original histopathology report. Therefore, we concluded that data on LNM risk regarding early submucosal EAC from surgical series might not be applicable to endoscopically treated patients.

Because it remains unclear what the optimal management is of patients with EAC with histological risk features after ER (i.e. endoscopic management or additional surgery), in **chapter 10**, we assessed the annual risk for metastasis during endoscopic follow-up in these patients from our own Dutch Expert Center cohort. We distinguished 3 groups of patients with high-risk features: intramucosal cancers with high-risk features, submucosal cancers with low-risk features, and submucosal cancers with high-risk features. A total of 120 patients met the selection criteria. Median FU was 29 months (IQR 15-48). Metastases were observed in 5/25 (annual risk 6.9%; 95%CI 3.0-15), 1/55 (annual risk 0.7%; 95%CI 0-4.0) and 3/40 (annual risk 3.0%; 95%CI 0-7.0) in high-risk intramucosal, low-risk submucosal, and high-risk submucosal cancers, respectively. Especially the annual metastasis risk of 6.9% in high-risk intramucosal EAC was a new and worrisome finding that warrants further prospective studies and suggests that strict follow-up of this small subgroup should be taken into consideration until further prospective data is available.

NEDERLANDSE SAMENVATTING

Gecombineerde endoscopische behandeling met endoscopische resectie (ER) en radiofrequente ablatie (RFA) voor vroege Barrett neoplasie (d.w.z. laaggradige dysplasie (LGD), hooggradige dysplasie (HGD) of vroegcarcinoom zonder histopathologische risicofactoren voor lymfekliermetastasen) is een bewezen veilige en effectieve behandelmethode. Het doel is nu om richting een methode te werken die gepersonaliseerde zorg op maat biedt aan patiënten. In dit proefschrift hebben we daarom geëvalueerd of de huidige vorm van endoscopische behandeling en surveillance voor vroege Barrett neoplasie geoptimaliseerd kan worden. Daarnaast hebben we gekeken of endoscopisch management ook geschikt kan zijn voor vroegcarcinomen met histopathologische risicofactoren voor lymfekliermetastasen.

Deel I: De hoeksteen van succesvolle endoscopische behandeling van vroege Barrett neoplasie

In het eerste deel van dit proefschrift focussen we ons op ER en RFA. In **Hoofdstuk 1 en 2** worden de achtergrond, technische aspecten en indicaties van de behandeling met ER en RFA besproken. Ook wordt uitgelegd waarom gecombineerde endoscopische behandeling zo succesvol is gebleken: uit eerder onderzoek blijkt dat in 74%-98% van de patiënten complete eradicatie van Barrett weefsel wordt bereikt na ER in combinatie met RFA. Echter, solide lange termijn data over het behouden van dit effect ontbrak. In **hoofdstuk 3** beschrijven we de resultaten van een cohort van 1.386 patiënten, die behandeld zijn in één van de acht Nederlandse Barrett Expert Centra van 2008 tot en met 2018. Complete eradicatie van het Barrett segment werd in 94% van de patiënten met endoscopische combinatiebehandeling bereikt (1.270/1.348). Bij 78 patiënten (6%) bleek sprake van resterend Barrett weefsel en/of resterende dysplasie na behandeling. Deze groep werd gedefinieerd als patiënten waarbij de behandeling was mislukt. Bij de meerderheid van deze patiënten was er echter wel sprake van complete eradicatie van HGD/EAC. Slechts 1% ontwikkelde een verder gevorderd stadium oesofaguscarcinoom dat niet meer curatief endoscopisch behandeld kon worden. In totaal werden de lange termijn uitkomsten van 1.154 patiënten geanalyseerd. De mediane endoscopische follow-up (FU) duur bedroeg 43 maanden (22-69, minimaal 8) na baseline, met mediaan 4 FU-endoscopieën (1-5) per patiënt. Gedurende FU, bleek bij 38/1.154 (3%) patiënten sprake van recidieven met LGD, HGD of EAC. De recidieven werden mediaan 31 maanden na het bereiken van complete eradicatie ontdekt (jaarlijks risico van 1% (95% CI 0.8-1.4)). Van de patiënten met een recidief ontwikkelde slechts 0.4% kanker in een vergevorderd stadium. Frequente FU onderzoeken in het eerste jaar na behandeling en random biopten van het neosquameuze epitheel (NSE) of de cardia bleken niet bij te dragen aan de detectie van recidieven. Uit onze data kan worden afgeleid dat de FU

intervallen na het bereiken van complete eradicatie in expert centra verlengd kunnen worden. Daarnaast laat onze data ook zien dat driemaandelijkse endoscopieën in het eerste jaar na de behandeling niet nodig zijn en hetzelfde geldt voor random biopten van het NSE en de cardia. We concludeerden dat zorgvuldige endoscopische inspectie – met zo nodig gerichte biopten – het belangrijkst is om recidieven na behandeling met RFA te ontdekken.

Deel II: Het verbeteren en personaliseren van endoscopisch management voor Barrett neoplasie

Het tweede deel van dit proefschrift gaat over het verbeteren en personaliseren van het endoscopische management van patiënten met vroege Barrett neoplasie. Dit wordt gedaan door verschillende onderdelen van het Barrett neoplasie spectrum te onderzoeken en verder uit te lichten. Omdat internationale richtlijnen conflicterende adviezen geven over het wel of niet starten met RFA bij een patiënt met een nieuwe LGD diagnose, hebben we in **hoofdstuk 4** geëvalueerd of LGD – bevestigd door een expert patholoog – een aanwijzing kan zijn voor het tegelijk aanwezig zijn van slechtere dysplasie of zichtbare afwijkingen in het Barrett segment en of patiënten daarom verwezen zouden moeten worden naar een expert centrum voor behandeling. We onderzochten de proportie patiënten met HGD/kanker gedurende herbeoordeling na verwijzing voor een bevestigde LGD diagnose in een expert centrum. In totaal werden 248 patiënten verwezen met bevestigde LGD, waarvan 57/248 (23%; [95% CI 18-29]) uiteindelijk toch HGD (n=23) of kanker (n=25) bleken te hebben. LGD werd opnieuw bevestigd bij 168 patiënten (68%; [95% CI 62-74]). Dit houdt in dat 92% van de patiënten in dit cohort een indicatie had voor (profylactische) endoscopische behandeling binnen 1 jaar na verwijzing naar het expert centrum. Gebaseerd op deze data pleiten we voor histopathologische herbeoordeling van elke nieuwe LGD diagnose ter bevestiging, en voor verwijzing van patiënten met bevestigde LGD naar een expert centrum voor endoscopische herbeoordeling.

Verbeteren en personaliseren van endoscopisch management betekent ook dat we kennis moeten hebben over wanneer we behandeling zouden moeten staken. Vooral bij oudere patiënten met een beperkte levensverwachting is vervolgbehandeling met RFA na geslaagde ER soms niet nodig en/of gewenst. Om deze hypothese verder te analyseren hebben we in **hoofdstuk 5** onderzocht of endoscopische surveillance, in plaats van RFA na ER voor vroege neoplasie, een goed alternatief is. 94 patiënten werden retrospectief geïncludeerd in dit cohort. De gemiddelde leeftijd was 74 jaar (± 10). Er waren verschillende redenen om geen RFA te verrichten in deze groep, maar de voornaamste reden was een beperkte levensverwachting (73 patiënten (78%)). Geen van de patiënten vertoonde progressie naar vergevorderde kanker tijdens endoscopische

FU (mediaan 21 maanden (11-51) en 4 endoscopieën). In totaal overleden er 29 patiënten (40%) met beperkte levensverwachting gedurende endoscopische FU. Geen van hen overleed aan een oesofaguscarcinoom. We concludeerden dat – bij een specifieke groep patiënten – ER met endoscopische surveillance in plaats van vervolgbehandeling met RFA voor het resterend Barrett segment een goed alternatief is.

Daarnaast zijn sommige patiënten gevoeliger voor het ontwikkelen van dysplastische recidieven na het behalen van complete eradicatie van Barrett dan anderen. Het verbeteren van endoscopisch management betreft daarom ook de poging tot het voorspellen van het ontstaan van recidieven tijdens FU. Daarmee kunnen we de surveillance intervallen optimaliseren en wellicht ook de ontwikkeling van vergevorderde kanker voorkomen. In **hoofdstuk 6** beschrijven we een extern gevalideerd predictiemodel om deze dysplastische recidieven na initiële succesvolle endoscopische behandeling te voorspellen. Verschillende voorspellers gerelateerd aan demografische karakteristieken, ernst van reflux, baseline pathologie en behandelkarakteristieken werden geïncludeerd in het model. Het eerder beschreven cohort van 1.154 patiënten (met 38 dysplastische recidieven (1%/persoonsjaar)) werd hiervoor gebruikt. Verschillende variabelen bleken onafhankelijk geassocieerd met de ontwikkeling van een recidief. Van sterkst naar zwakst voorspellend waren dit: "incident" laesie tijdens behandelfase, hoger aantal ER behandelingen, mannelijk geslacht, langere Barrett, HGD of kanker op baseline en lagere leeftijd. Externe validatie liet een C-statistiek van 0.91 zien [95% CI 0.86-0.94] met goede kalibratie. Het model zou patiënten en behandelaars kunnen helpen bij het managen van verwachtingen van endoscopische behandeling en bij het kiezen van een gepersonaliseerde surveillance strategie.

Hoofdstuk 7 beschrijft de incidentie en uitkomsten van slechte genezing en slechte regeneratie met plaveiselcelepitheel na RFA in het gehele Nederlandse expert centra cohort van 1.386 patiënten. We hebben 134 patiënten (10%) met slechte genezing en 74 patiënten (5%) met slechte regeneratie geanalyseerd. Extra tijd tussen de behandelingen en voldoende zuurremming bleek bij de helft van de patiënten met slechte genezing voldoende om volledige genezing en 97% eradicatie van het Barrett segment te bewerkstelligen. Echter, als patiënten slechte regeneratie laten zien, bestaat er een groter risico op het niet slagen van de behandeling in vergelijking met patiënten met normale regeneratie naar squameus epitheel (64% versus 2%; RR 27 [95% CI 18-40]). Het risico op het ontwikkelen van vergevorderde kanker blijkt dan ook hoger in deze groep (15% versus 1%; RR 30 [95% CI 12-81]).

Patiënten met slechte genezing en/of slechte regeneratie lijken een grotere kans te hebben op een complex behandelbeloop. Dat houdt in dat progressie naar

vergevorderde kanker, het mislukken van behandeling of het tevoorschijn komen van een "incident" laesie tijdens behandelfase vaker kunnen voorkomen. De mogelijkheid om een complex behandelbeloop bij patiënten te kunnen voorspellen leek ons waardevol voor in de kliniek. Daarom hebben we in **hoofdstuk 8** een prognostisch model ontwikkeld en extern gevalideerd, waarbij opnieuw de data vanuit het Nederlandse expert centra cohort (1356 patiënten) is gebruikt. Van hen hadden 77 patiënten (6%) een complex behandelbeloop. Baseline Barrett lengte, zichtbare afwijkingen, HGD of kanker en <50% squameuze regeneratie na RFA waren onafhankelijk geassocieerd met een complex behandelbeloop. Ons model identificeerde 8% van de patiënten na RFA die een hoog risico hadden op een complex behandelbeloop. Deze 8% omvatte 76% van alle patiënten die uiteindelijk vergevorderde kanker hadden ontwikkeld en 93% van de patiënten met persisterende Barrett ondanks adequate behandeling met RFA. Naast deze ongunstige behandeluitkomsten hadden deze patiënten ook een significant langer behandeltraject en een groter risico op complicaties tijdens de behandeling. Het model bleek robuust in multipele sensitiviteitsanalyses en deed het goed bij externe validatie (AUC 0.84).

Deel III: De grenzen van endoscopisch management verleggen

In deel drie van dit proefschrift onderzoeken we de grenzen van endoscopisch management voor de behandeling van patiënten met een vroegcarcinoom met histopathologische risicofactoren voor lymfekliermetastasen (d.w.z. submucosale invasie, slechte differentiatie of lymfovasculaire invasie). Dit deel begon met een "proof-of-concept" studie (**hoofdstuk 9**), waarin het doel was te onderzoeken of het eerder gerapporteerde lymfkliermetastase risico bij patiënten met een chirurgisch behandeld submucosaal vroegcarcinoom overschat zou kunnen zijn. Onze hypothese berustte op het feit dat chirurgische en endoscopische resectiepreparaten verschillend geprepareerd worden alvorens de beoordeling. We analyseerden de gegevens van 12 patiënten met een chirurgisch behandeld submucosaal vroegcarcinoom met lymfekliermetastasen (1994-2005, voordat endoscopische resectie werd opgenomen in de richtlijnen). We reviseerden tumor invasiediepte, differentiatiegraad en de aanwezigheid van lymfovasculaire invasie in de bestaande chirurgische coupes met extra diepere doorsnedes. Bij 1 patiënt (8%) vonden we tumorinvasie in de m. propria in plaats van in de submucosa. Bij 4 patiënten werd diepe submucosale invasie – op de grens van invasie in de m. propria – gevonden. Na revisie bleek uiteindelijk dat 9/12 patiënten (75%) een extra histopathologische risicofactor hadden voor lymfekliermetastasen naast submucosale invasie. In het initiële pathologie verslag was dit slechts in 5/12 (42%) . We concludeerden dat het eerder gerapporteerde risico op lymfekliermetastasen voor submucosale vroegcarcinomen mogelijk niet toepasbaar is op endoscopisch behandelde patiënten.

Omdat het onduidelijk blijft wat nu de optimale behandelstrategie is voor patiënten met een vroegcarcinoom met histopathologische risicofactoren voor (lymfeklier) metastasen – endoscopisch management of chirurgie – hebben we in **hoofdstuk 10** het jaarlijks risico op metastasen onderzocht in een groep patiënten die endoscopische follow-up onderging binnen ons Nederlandse expert centra cohort (2008-2019). We onderscheidden 3 groepen patiënten: intramucosale vroegcarcinomen met histopathologische risicofactoren (T1a-HR), submucosale vroegcarcinomen zonder andere histopathologische risicofactoren (T1b-LR) en submucosale vroegcarcinomen met andere histopathologische risicofactoren (T1b-HR). Er werden 120 patiënten geïncludeerd, waarvan de mediane endoscopische FU duur 29 maanden bedroeg (IQR 15-48). Metastasen werden gevonden bij 5/25 patiënten (jaarlijks risico 6.9%; 95% CI 3.0-15), 1/55 patiënten (jaarlijks risico 0.7%; 95% CI 0-4.0) en 3/40 patiënten (jaarlijks risico 3.0%; 95% CI 0-7.0) met respectievelijk T1a-HR, T1b-LR en T1b-HR. Vooral het jaarlijks risico van 6.9% in de T1a-HR groep was een nieuw verontrustend resultaat dat verder prospectief onderzoek behoeft en suggereert dat strikte endoscopische FU bij deze kleine subgroep overwogen moet worden totdat prospectieve data beschikbaar is.

LIST OF PUBLICATIONS

Publications in this thesis

Nieuwenhuis E*, van Munster S*, Bisschops R, et al. Dysplastic recurrence after successful treatment for early Barrett's neoplasia: development and validation of a prediction model. Gastroenterology. Open Access Published: March 16, 2022 DOI https://doi.org/10.1053/j.gastro.2022.03.020

Nieuwenhuis E*, van Munster S*, Bisschops R, et al. Development and external validation of a model to predict complex treatment after RFA for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol. 2022 Mar 12:S1542-3565(22)00246-4. doi: 10.1016/j.cgh.2022.02.057. Epub ahead of print. PMID: 35292379.

Nieuwenhuis E, van Munster S, Weusten B, et al. Analysis of metastases rates during follow-up after endoscopic resection of early "high-risk" esophageal adenocarcinoma. Gastrointest Endosc. 2022 Mar 11:S0016-5107(22)00195-X. doi: 10.1016/j.gie.2022.03.005. Epub ahead of print. PMID: 35288149.

Nieuwenhuis E*, van Munster S*, Curvers W, et al. Impact of Expert Center endoscopic assessment of confirmed LGD diagnosed in community hospitals. Endoscopy. 2022 Jan 28. doi: 10.1055/a-1754-7309. Epub ahead of print. PMID: 35098524.

Frederiks C*, van Munster S*, **Nieuwenhuis E**, et al. Incidence and outcomes of poor healing and poor squamous regeneration after radiofrequency ablation therapy for early Barrett's neoplasia. Endoscopy. 2022 Mar;54(3):229-240. doi: 10.1055/a-1521-6318. Epub 2021 Jun 1. PMID: 34062597.

van Munster S, **Nieuwenhuis E**, Weusten BLAM, et al. Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation ± endoscopic resection: results from the national Dutch database in a 10-year period. Gut Published Online First: 22 March 2021. doi: 10.1136/gutjnl-2020-322615

Nieuwenhuis E, Pech O, Bergman J, Pouw R. Role of Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection in the Management of Barrett's Related Neoplasia. Gastrointestinal Endoscopy Clinics of North America, Volume 31, Issue 1, 2021

van Munster, S., **Nieuwenhuis, E.A.**, Weusten, B.L.A.M. et al Endoscopic Resection Without Subsequent Ablation Therapy for Early Barrett's Neoplasia: Endoscopic Findings and Long-Term Mortality. J Gastrointest Surg 25, 67–76 (2021).

Nieuwenhuis E.A., Bergman J.J.G.H.M., Pouw R.E. In: Testoni P.A., Inoue H., Wallace M.B. (eds). Radiofrequency Ablation of Barrett's Epithelium. Gastrointestinal and Pancreatico-Biliary Diseases: Advanced Diagnostic and Therapeutic Endoscopy. Springer, Cham (2020).

Publications not in this thesis

Man Wai Chan, **Esther A Nieuwenhuis**, Roos E Pouw. Today's Mistakes and Tomorrow's Wisdom… in the Management of T1b Barrett's Adenocarcinoma. Visc Med. 2022 Jun;38(3). Epub 2022 Apr 25.

Sanne N van Munster, Eva P D Verheij, **Esther A Nieuwenhuis** et al. Extending treatment criteria for Barrett's neoplasia: results of a nationwide cohort of 138 endoscopic submucosal dissection procedures. Endoscopy. 2022 Jun;54(6):531-541. Epub 2021 Sep 30.

Esther A. Nieuwenhuis, Jacques J. Bergman, Roos E. Pouw. Letter to the Editor: What to do with our T1b esophageal adenocarcinoma patients? Gastrointestinal Endoscopy, Volume 92, Issue 1, P226, JULY 01, 2020.

Weijer, R., Broekgaarden, M., van Golen, R.F., **Nieuwenhuis, E.A.** et al. Low-power photodynamic therapy induces survival signaling in perihilar cholangiocarcinoma cells. BMC Cancer 15, 1014 (2015).

CONTRIBUTING AUTHORS

Alaa Alkhalaf
Department of Gastroenterology and Hepatology
Isala Clinics
Zwolle, the Netherlands

Lorenza Alvarez Herrero
Department of Gastroenterology and Hepatology
Sint Antonius Hospital
Nieuwegein, the Netherlands

Jacques JGHM Bergman
Department of Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, the Netherlands

Raf Bisschops
Department of Gastroenterology and Hepatology
University Hospital Leuven
Leuven, Belgium

Auke Bogte
Department of Gastroenterology and Hepatology
University Medical Center Utrecht
Utrecht, the Netherlands

Lodewijk AA Brosens
Department of pathology
University Medical Center Utrecht
Utrecht, the Netherlands

Man Wai Chan
Department of Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, the Netherlands

Wouter Curvers
Department of Gastroenterology and Hepatology
Catharina Hospital
Eindhoven, the Netherlands

Sanford M Dawsey
Department of Cancer Epidemiology & Genetics
National Cancer Institute
Bethesda, Maryland, United States of America

David E Fleischer
Department of Gastroenterology & Hepatology
Mayo Clinic
Scottsdale, Arizona, United States of America

Charlotte Frederiks
Department of Gastroenterology and Hepatology
University Medical Center Utrecht
Utrecht, the Netherlands

Rehan Haidry
Department of Gastroenterology and Hepatology
University College Hospital London
London, United Kingdom

Martin H M G Houben
Department of Gastroenterology and Hepatology
Haga hospital
Den Haag, the Netherlands

Martina Invernizzi
Department of Gastroenterology and Hepatology
Hirslanden Private Clinic Group
Zurich, Swiss

Marnix Jansen
Department of pathology
University College Hospital London
London, United Kingdom

Pieter Jan F de Jonge
Department of Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, the Netherlands

Arjun D Koch
Department of Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, the Netherlands

Sybren L Meijer
Department of Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, the Netherlands

Helmut Messmann
Department of gastroenterology
Universtiy Clinics Augsburg
Augsburg, Germany

Wouter B Nagengast
Department of Gastroenterology and Hepatology
University Medical Center Groningen
Groningen, the Netherlands

Horst Neuhaus
Department of Gastroenterology and Hepatology
Evangelisches Krankenhaus
Düsseldorf

Dusseldorf, Germany
Johan GJA Offerhaus
Department of pathology
University Medical Center Utrecht
Utrecht, the Netherlands

Anouk Overwater
Department of Gastroenterology and Hepatology
University Medical Center Utrecht
Utrecht, the Netherlands

Oliver Pech
Department of Gastroenterology and Hepatology
Krankenhaus Barmherzige Brüder
Regensburg, Germany

Frans T M Peters
Department of Gastroenterology and Hepatology
University Medical Center Groningen
Groningen, the Netherlands

Roos E Pouw
Department of Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, the Netherlands

Andreas Probst
Department of gastroenterology
Universtiy Clinics Augsburg
Augsburg, Germany

Mihaela G M Raicu
Department of Pathology, Pathology DNA
Sint Antonius Hospital
Nieuwegein, the Netherlands

Philip Rieder
Department of Gastroenterology and Hepatology
Hirslanden Private Clinic Group
Zurich, Swiss

B E Schenk
Department of Gastroenterology and Hepatology
Isala Clinics
Zwolle, the Netherlands

Erik J Schoon
Department of Gastroenterology and Hepatology
Catharina Hospital
Eindhoven, the Netherlands

Stefan Seewald
Department of Gastroenterology and Hepatology
Hirslanden Private Clinic Group
Zurich, Swiss

Kees CA Seldenrijk
Department of Pathology, Pathology DNA
Sint Antonius Hospital
Nieuwegein, the Netherlands

Peter Siersema
Department of Gastroenterology and Hepatology
Radboud Medical Center
Nijmegen, the Netherlands

Virender K Sharma
Department of Gastroenterology and Hepatology
Arizona Centers for Digestive Health
Scottsdale, Arizona, United States of America

Manon Spaander
Department of Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, the Netherlands

Tjon J Tang
Department of Gastroenterology and Hepatology
Ijsselland hospital
Capelle aan den Ijssel, the Netherlands

Laurelle van Tilburg
Department of Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, the Netherlands

Steffi EM van de Ven
Department of Gastroenterology and Hepatology
Erasmus Medical Center
Rotterdam, the Netherlands

Eva Verheij
Department of Gastroenterology and Hepatology
Amsterdam University Medical Centers
Amsterdam, the Netherlands

Jessie Westerhof
Department of Gastroenterology and Hepatology
University Medical Center Groningen
Groningen, the Netherlands

Bas L A M Weusten
Department of Gastroenterology and Hepatology
Sint Antonius Hospital
Nieuwegein, the Netherlands

Hilde Willekens
Department of Gastroenterology and Hepatology
University Hospital Leuven
Leuven, Belgium

PHD PORTFOLIO

Name PhD student:	**Esther Nieuwenhuis**
PhD period:	**November 2018 – June 2021**
Name supervisor:	**Prof. dr. J.J.G.H.M. Bergman**
Name co-supervisor:	**Dr. R.E. Pouw**

	Year	Workload (ECTS*)
PhD training		
General courses		
• The AMC World of Science	2019	0.7
• Practical Biostatistics	2019	1.4
• eBROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2019	1.5
• Project Management	2019	0.6
• Advanced biostatistics NKI-AvL	2019	1.5
• Scientific writing in English	2020	1.5
• Clinical epidemiology (observational)	2020	0.9
• Talents in PhD	2020	0.2
Specific courses		
• Nutrition courses Wageningen University (3)	2020-2021	6.0
Seminars, workshops and master classes		
• Weekly department seminars	2018-2021	6.0
• Bi-weekly esophageal research meetings	2018-2021	6.0
• Gut club	2018-2021	1.5
Oral presentations		
• Dutch Barrett Expert Center Cohort Study, Upper GI Research Meeting	2019	0.5
• Several presentations at (inter)national Barrett Expert Center meetings	2019-2021	1.5
• Digestive Disease Days (DDD), voorjaarscongres Veldhoven**	2020	0.5
• European Society of Gastrointestinal Endoscopy Days (ESGE) Dublin**	2020	0.5
• Digestive Disease Days (DDD), voorjaarscongres Online (2x)	2021	1.0
• European Society of Gastrointestinal Endoscopy Days (ESGE), Online (2x)	2021	1.0
• Digestive Disease Week (DDW), Online (2x)	2021	1.0
Poster presentations		
• Digestive Disease Week (DDW) Chicago**	2020	0.5
(Inter)national conferences		
• Digestive Disease Days (DDD)	2019,2020,2021	2.5
• European Society of Gastrointestinal Endoscopy Days (ESGE)	2020**, 2021	2.0
• Digestive Disease Week (DDW)	2020**, 2021	2.0
Other		
• Peer reviewing manuscripts	2019-2021	3.5

	Year	Workload (ECTS*)
Teaching		
Lecturing		
• Endoscopic interventions (for sedation practice specialists)	2021	1.0
Supervising (All master thesis medical students) • Sophia van der Graaff • Man Wai Chan • Sadaf Nedjat • Milou van Riswijk • Eva Verheij • Aydan Kumcu • Chessety Kroeze • Michael Siim	2018-2020	10
Parameters of Esteem		
Grants		
• KWF Grant PREFER study	2019	
• Travel grant ESGE days 2020 (cancelled, covid-19)	2020	
• ESGE registration grant	2021	

*ECTS: European Credit Transfer System
** Cancelled due to Covid-19

DANKWOORD

Het is klaar, er zit een kaft omheen! Wat ben ik blij dat ik de kans heb gekregen dit traject te doorlopen, want wat heb ik ongelofelijk veel geleerd de afgelopen jaren. Dat een PhD veel meer is dan alleen wetenschappelijk onderzoek doen kan ik alleen maar beamen. Van meetings organiseren, studenten begeleiden en schrijven, tot statistiek en leren fotoshoppen, het hoorde er allemaal bij. Wat een geluk had ik dat dit avontuur mocht beginnen binnen de voor mij zo bekende muren van het "betonnen kolos", het AMC. Ik heb geen seconde getwijfeld toen ik de kans kreeg te starten als arts-onderzoeker en voort te borduren op het werk waar ik al aan begonnen was als wetenschappelijke stage student. De werkwijze van het Slokdarmteam onder leiding van Jacques en Roos wordt wel vaker vergeleken met de spoorwegen ("een rijdende trein") of met de industrie ("een geoliede machine"). Ook ik heb dat zo ervaren, maar wat misschien nog wel belangrijker is, is dat er mensen werken met drive en passie voor het vak, want dat is de reden dat die trein blijft rijden. Wat was dit een top plek om me verder te ontwikkelen van student naar onderzoeker, dokter en mens die ik nu ben. Ik kijk terug op prachtige jaren.

Dit proefschrift had zonder hulp van heel veel mensen niet tot stand kunnen komen. Daarom wil ik een aantal mensen in het bijzonder bedanken.

Aan alle patiënten die deelnamen aan een van onze studies, hartelijk bedankt. Door jullie tillen we de zorg naar een hoger niveau.

*

Roos, je nuchterheid en relativerend vermogen gaven mij altijd het vertrouwen dat alles uiteindelijk wel goed komt, een mindset waar ik veel van geleerd heb en ook nu nog steeds iets aan heb. Naast vertrouwen gaf je me ook veel vrijheid om alles te doen op mijn manier, met wat subtiele sturing waar nodig. Dat heb ik echt enorm gewaardeerd. Je combineert hoogstaand klinisch werk met wetenschap op topniveau en wordt als spreker gevraagd op grote internationale congressen, maar daarnaast ben je ook enorm betrokken bij iedereen met wie je samenwerkt. Dat vind ik buitengewoon krachtig. De top van de medische wereld is nu nog een mannenbolwerk, maar door mensen zoals jij gaat het binnen nu en niet al te lange tijd wèl lukken om een promotiecommissie samen te stellen waarin in elk geval de helft vrouw is. Je bent en blijft een groot voorbeeld, bedankt!

Jacques, ik heb zoveel van je geleerd door vaak alleen maar heel goed te luisteren. Je manier van leidinggeven aan onze groep is zo bewonderenswaardig. Wat me misschien

nog wel de grootste glimlach op mijn gezicht zal blijven geven als ik terugdenk aan mijn tijd bij jou in de groep is je fantastische skill hele belangrijke dingen om te vormen in (soms hilarische) beeldspraak. Niet alleen tovert dat een lach op ieders gezicht tijdens een serieuze onderzoeksmeeting, het zorgt er ook voor dat de kern direct voor iedereen duidelijk is. Je legt op wonderbaarlijke wijze binnen enkele minuten alle pijnpunten van een studieopzet of presentatie bloot. Je enthousiasme en passie werken enorm aanstekelijk en motiverend. Dagelijks denk ik nog aan "the monkey of my back" krijgen, juist ook nu in de kliniek. Ik wil je enorm bedanken voor de leerzame jaren.

Ik wil graag de leden van de *promotiecommissie* – prof. van Laarhoven, prof. van Hooft, prof. Seewald, prof. Bredenoord, dr. Meijer en dr. Eshuis – hartelijk bedanken voor de bereidheid zitting te nemen in mijn promotiecommissie en voor de kritische beoordeling van mijn proefschrift.

All PhD fellows, nurse practitioners, gastroenterologists and pathologists from national and international Barrett Expert Centers - This thesis would not have been there without you. Many thanks for the wonderful collaboration in all different projects we have done together. Special thanks to *Stefan and Martina* for the amazing time Kiki and I had in Zürich (2020)!

Alle studenten die na mij kwamen, Chessety, Michael, Sophia, Sadaf, Milou, Aydan, Eva, Man Wai, Richard en Emmeline, heel veel dank voor jullie onmisbare inzet. Zonder jullie was het BEC cohort nu nog steeds niet compleet geweest.

Slokdarmteamcollega's, wat zijn we toch een topteam met z'n allen. Heel veel dank voor alle hulp, brainstormsessies, maar met name ook voor de gezelligheid en alle koffie. Wilda, Nancy, Marjon, Patricia en in de eerdere jaren ook Chantal – de steunpilaren van het Slokdarmteam. Niet te vergeten ook keiharde werkers en voor onze patiënten fantastisch. In het bijzonder wil ik *Eva en Man Wai* bedanken – Ook allebei begonnen als student op het BEC cohort en vervolgens doorgestoomd als PhD'er. Ik ben blij dat alle projecten bij jullie in goede handen zijn. Jullie zijn toppers!

Lieve Sanne, het begon allemaal toen ik als streberige co-assistent onderzoek deed bij je C2 kamergenootje Maxime en m'n wetenschappelijke stage in Australië niet van de grond kwam. Jij was voor het BEC cohort op zoek naar een student, kwam dat even mooi uit! Blijer kon je me niet maken toen ik dankzij jou mocht blijven voor een PhD. Wat hebben we samen ontzettend veel gedaan en voor elkaar gekregen. Ik heb zo veel geleerd van je eindeloze doorzettingsvermogen en intense drive om het onderste uit de kan te halen. Niemand werkt zo hard als jij en soms snap ik niet hoe je ook nog tijd

overhoud om familie en vrienden te zien en zo veel klaar te staan voor anderen. Maar daaraan ook al geen gebrek! Tijdens onze rondjes op de racefiets ging het veel over de gezamenlijke projecten, maar we konden vooral ook even lekker stoom afblazen. Langzaam verschoven die gesprekken op de fiets naar ook persoonlijke dingen uit ons dagelijks leven en ontstond een dierbare vriendschap. Op nog vele rondjes op de racefiets, doppio's in het Antonius en biertjes in de kroeg.

Lieve Kiki, niet alleen slokdarmmaatjes, maar ook vriendinnen! Wat was het fijn om jou als partner in crime te hebben in het Slokdarmteam en alle feestelijke (en minder feestelijke) activiteiten mee te organiseren (Kiki en Esther, aka "De Feestcommissie"!). Het meest memorabel vind ik misschien nog wel de online Bingo in corona-tijd. Zelfs via het scherm weten we er een feestje van te maken! Ik ben er trots op dat je je eigen beslissingen maakt in het leven en doet waar je gelukkig van wordt en ben blij dat we nu praktisch buren zijn in Utrecht. Op nog vele pre-kerst diners met Indonesische rijsttafels van Blauw met "de vriendinnen".

Lieve Liselotte, het voelt alweer eeuwen geleden dat we onze semiarts stage in het – inmiddels niet meer bestaande – MC Slotervaart liepen. Wat een fantastische en intense maanden waren dat. Ik herinner me eigenlijk vooral hoeveel we daar samen gelachen hebben (en oké, ook wel de avonden die we samen doorwerkten om vervolgens scheel kijkend naar huis te fietsen). Niet te geloven dat daar de basis van onze vriendschap ligt! Wat was het fijn om samen met jou te kunnen sparren over onze bizar gelijkende PhD trajecten en lief en leed te delen over van alles en nog wat de afgelopen jaren. Ik ben blij dat we zulke goede vriendinnen zijn geworden, jij maakt me altijd aan het lachen en ik ben ook ontzettend trots op je!

Mede arts-onderzoekers, bedankt voor de geweldige tijd in beide huizen. Van het corona jaar thuiswerken heb ik vooral geleerd hoe erg je vrijmibo's en koffiepauzes met collega's kunt missen. *Lieve Floor en Bente*, alweer een tijdje arts-onderzoeker af, maar ook jullie wil ik bedanken voor de gezelligheid!

Antonianen van de interne geneeskunde en MDL, bedankt voor de humor, de koffie en de uitjes. Maar bovenal bedankt voor het enorm leerzame afgelopen jaar. Ik had me geen betere plek kunnen wensen om mijn eerste jaar als klinische dokter te mogen doorbrengen dan bij jullie.

*

Lieve G weekend vriendinnen* – Wie had ooit gedacht dat een random AMC-UvA introductieweekgroepje in 2011 zou escaleren tot inmiddels meer dan 10 jaar hechte vriendschap! We delen zo intens veel mooie herinneringen. Van de vele reizen, verjaardagsdiners thuis op sterrenniveau, de jaarlijkse kerstdiners met aanhang (die af en toe in april zijn vanwege de vele diensten en drukke schema's), tot al die eindeloze vrijdagavonden in de kroeg. Ik vind het zo mooi om te zien hoe ieder van ons keihard werkt om te bereiken wat we willen bereiken, zonder onze vriendschap uit het oog te verliezen.

Fiek, zoals een echte Brabander altijd in voor gezelligheid. Ik waardeer je nuchterheid en je doorzettingsvermogen enorm. We hebben samen veel van de wereld gezien en stiekem hoop ik dat we ooit nog eens een mooie reis maken. Ik zie ons als pensionado's wel chillen in een tropisch oord na een mooie bergwandeling. Dan wel zonder pasta met ketchup, beloofd.

El, goudeerlijk, een schaterlach en met klaverjassen bloedfanatiek. Altijd een luisterend oor en een fantastische raadgever. Je wordt 100% zeker een geweldige moeder. Ik weet hoe jammer je het vindt dat ik Amsterdam verlaten heb, maar onze vriendschap overbrugt elke afstand, zelfs als het buiten de ring is.

Juud, Amsterdamse Bourgondiër en levensgenieter. Gelukkig vind je het altijd goed dat ik met een wijntje tegen de muur aan sta geleund in de keuken als jij weer eens bezig bent de allerlekkerste dingen te bereiden. Van die momenten geniet ik altijd intens. Je bent een fantastische moeder voor de eerste mini-Ajacied van de groep. Alleen jij krijgt het voor elkaar dat een kind van 10 maanden zelfgemaakte viscurry eet, petje af.

Bul, de alleskunner en de allesweter van de groep, maar nog veel belangrijker altijd in voor koffie op het terras of een biertje in de kroeg. Natuurlijk wel pas nadat je op je vrije zondagochtend nog even in het lab geweest bent. Als je daarover vertelt krijg ik altijd flashbacks naar onze 'kippetjes-tijd' in het lab tijdens de bachelor. Uren op 10cm afstand van elkaar minuscule bloedvaatjes proberen te raken. Als dat geen echte vriendschap is.

Ies, zo ontzettend lief, zorgzaam en ook nog eens een keiharde werker. De hilarische momenten die we samen in de Epsteinbar in het AMC meemaakten staan voor altijd op m'n netvlies gebrand. Gelukkig staat een groot deel van die avonturen ook zwart op wit. Dat boekje lezen we binnenkort samen met een monsterlijk groot bierglas weer eens door, waarna jij dat glas stuk laat vallen onderweg naar de wc, deal?

Jo, gangmaker, feminist en allemansvriendin. Als jij weer eens een leuk verhaal vertelt, hangen we allemaal aan je lippen. Jou lukt het om enorm veel ballen in de lucht te houden, maar je bent er altijd als het nodig is. Ik vind het enorm bewonderenswaardig hoe je dat allemaal voor elkaar krijgt.

Lieve vriendinnen, we kennen elkaar door en door en zijn echt samen volwassen geworden. Ik hoop dat we tot het einde der tijden naar ons zo geliefde Guilty Pleasure festival zullen blijven gaan, inclusief tuinfeest vooraf! Ik ben intens blij met jullie!

*

Lieve Marijn en Sophie, deel van de Ijsland crew – Marijn, jij bent het grote voorbeeld van "doe alsjeblieft wat je leuk vindt, als je maar hard genoeg werkt (en oké, daarnaast een flinke dosis talent hebt) dan komt het allemaal goed". Ik ben heel trots op je, je wordt een fantastische chirurg en moeder. *Soof*, wat een heerlijk mens ben je. Ook jij volgt je hart en hebt alles lekker voor elkaar met je gezin in Breda. Je bent een enorme levensgenieter en altijd in voor een feestje, dank voor alle gezelligheid.

Lieve Celine, Hester en Tessa "ECHT" – Mijn Gerrit maatjes. We kennen elkaar door en door en hebben ontzettend veel meegemaakt de afgelopen jaren. Hoe verschillend onze levens er nu ook uit zien, goede wijn drinken, herinneringen ophalen en nieuwe dingen met elkaar delen zal altijd blijven.

Lieve vrienden en familie van Jaap, wat kwam ik in een warm bad terecht, die zomer van 2020. De fietsweekenden, feestjes en etentjes zijn altijd ontzettend genieten. *Bart en Geertje*, bij jullie voel ik me altijd welkom, zelfs bezweet na een lange tocht op de racefiets als we aan het uitpuffen zijn bij jullie in de prachtige tuin in Olland. Daarvoor wil ik jullie enorm bedanken!

*

Lieve Iris, van onze eindeloze beach tennis sessies als kinderen, naar eindeloze shopsessies als pubers en nu eindeloze etentjes met goede wijn. Mijn "kleine" zusje ben je allang niet meer. We hoeven maar een blik uit te wisselen en weten precies van elkaar hoe we ergens over denken. Wat ben ik ongelofelijk trots op jou! Enorm veel doorzettingsvermogen met een gezonde dosis pit. Welke (bij)baan jij ook had en hebt, de eerste week kom je al thuis met verhalen over hoe dingen beter, efficiënter en mooier kunnen. Binnen een mum van tijd ben je onmisbaar op de werkvloer, net zoals je onmisbaar bent voor je vrienden en familie. Al voelt het nog steeds gek dat je nu in

Barcelona woont, ik vind het zo stoer dat je je dromen najaagt en er gewoon voor gaat samen met Niels! Blijf zo van het leven genieten als je nu doet. En blijf vooral ook m'n personal shopping assistant, wordt gewaardeerd! *Niels*, bedankt dat je er altijd bent voor Ier en ook dat je haar hebt omgetoverd tot Bourgondiër.

Lieve pap & mam, jullie hebben Iris en mij de beste thuisbasis gegeven die je je kunt bedenken. We zijn altijd gestimuleerd om onze dromen na te jagen, alles mocht en kon altijd. Of we nu op atletiek, turnen, hockey, basketbal, tennis, tekenen, piano en/of roeien wilden, niets was te veel en we hebben het ook (letterlijk) allemaal gedaan. Of we nu voor de zoveelste keer gaan verhuizen of feedback nodig hebben op sollicitatiebrieven, jullie staan altijd voor ons klaar. Door jullie zijn wij de zelfstandige, sterke vrouwen die we zijn. *Mam,* ik kan me geen lievere en meer betrokken moeder voorstellen. Bedankt voor je 100% procent vertrouwen in mijn kunnen. De dag dat de decentrale selectie brief van de UvA binnen kwam vergeet ik nooit meer, jij juichte nog harder dan ik. *Pap,* in mijn jongere jaren ook wel "taxi Bartje", ook jij doet altijd alles om ons te helpen waar nodig en bent er altijd, nooit is iets te veel gevraagd. In onze WhatsApp – ergens beginnend in 2014 – staan tal van vragen over de meest uiteenlopende dingen. Bizar genoeg heb je altijd overal een antwoord op! Ik hoop nog heel lang gebruik te kunnen maken van jouw advies.

Op nog vele etentjes, boswandelingen en – niet te vergeten – de fantastische jaarlijkse wintersporten.

Allerliefste Jaap – mijn vrolijke krullenbol die de eerste maanden verfrissend weinig wist van promoveren en geneeskunde. 'Maak je dan dus echt een boekje-boekje?' Nou hier is ie dan schat, m'n boekje! Hoe afgezaagd het ook klinkt, jij bent mijn allerbeste vriend en lover in één. Altijd in voor avontuur en ik ken niemand anders die zo succesvol van dag tot dag (of zelfs uur tot uur) leeft als jij. Van jou leer ik nog meer te genieten van het hier en nu. Wat voor mij het leven van alledag is, maakt jou apetrots en andersom ben ik net zo trots op jou. We kunnen keihard lachen, lekker samen fietsen en er dan bergop stiekem toch een wedstrijdje van maken en ook gewoon samen niks doen (al blijft dat laatste voor mij een leerpuntje). Ik hoop dat ik tot in het einde der tijden mag horen dat je Hello Fresh bent vergeten af te zeggen als we het weekend niet thuis zijn, wat voor belangrijke dingen je geliefde "voetbalappje" die dag weer te melden heeft - of ik dat nou wil of niet -, dat er helaas weer een cactus verzopen is en dat je zelfgebouwde racefiets - nu echt - helemaal soepel loopt. Ik weet zeker dat ik er geen genoeg van krijg. Het leven met jou is een feestje, ik verheug me op alles dat we samen nog gaan meemaken.

Don't worry about being cool. Never worry what the cool people think. Life is warmth. You'll be cool when you're dead. Head for the warm people. Head for life.

Matt Haig, Notes on a Nervous Planet

ABOUT THE AUTHOR

Esther Nieuwenhuis was born on the 30th of June 1993 in Amsterdam, the Netherlands. In 2011 she graduated from pre-university college at the Gerrit van der Veen College in Amsterdam. That same year she started Medical School at the University of Amsterdam. She obtained her medical degree in 2018 after writing her master's thesis about endoscopic therapy for Barrett's related neoplasia at the department of Gastroenterology and Hepatology at the Amsterdam University Medical Centers. Upon graduating as a Medical Doctor, she continued working in the same research group as a PhD fellow under the supervision of Professor Jacques Bergman and Dr. Roos Pouw. The focus of this PhD thesis is the optimization of endoscopic management for patients with early Barrett's neoplasia. In September 2021, Esther moved to Utrecht and started working as a resident-not-in-training at the department of Internal Medicine and Gastroenterology & Hepatology at the St. Antonius Hospital in Nieuwegein. In 2023, she will start her training in Gastroenterology and Hepatology as a resident at the University Medical Center Utrecht and affiliated hospitals.