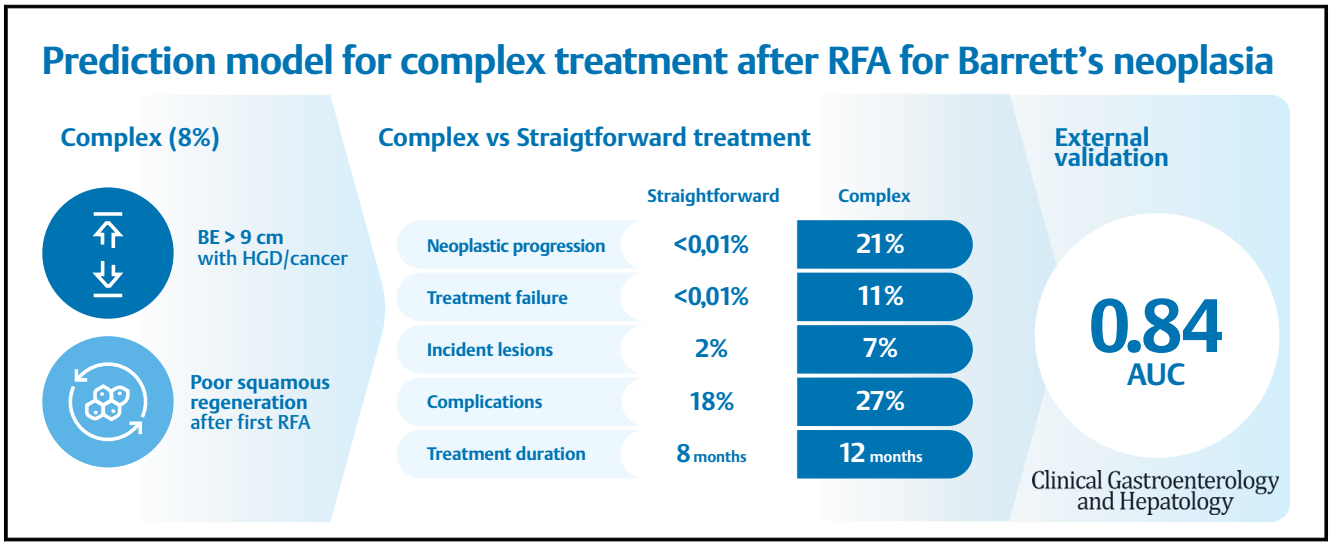
Clinical Gastroenterology and Hepatology 2022;20:2495–2504

ENDOSCOPY

Development and External Validation of a Model to Predict Complex Treatment After Radiofrequency Ablation for Barrett's Esophagus With Early Neoplasia

Sanne N. van Munster,[*,‡] Esther Nieuwenhuis,[‡] 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,[*] and Roos E. Pouw[*]

[*]Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology and Metabolism, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [‡]Department of Gastroenterology and Hepatology, Sint Antonius Hospital, Nieuwegein, The Netherlands; [§]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Koninklijke Universiteit Leuven, Belgium; [||]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [¶]Department of Gastroenterology and Hepatology, Isala Clinics, Zwolle, The Netherlands; [#]Department of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands; [**]GROW School for Oncology and Developmental Biology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; [‡‡]Department of Gastroenterology and Hepatology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands; [§§]Department of Gastroenterology and Hepatology, IJsselland Hospital, Cappelle aan den Ijssel, The Netherlands; [||||]Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen University, Groningen, The Netherlands; [¶¶]Department of Gastroenterology and Hepatology, Haga Teaching Hospital, Den Haag, The Netherlands



Abbreviations used in this paper: AUC, area under the curve; BE, Barrett's esophagus; BEC, Barrett Expert Center; CE-BE, complete eradication of Barrett's esophagus; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapy; ER, endoscopic resection; HGD, high-grade dysplasia; IQR, interquartile range; LASSO, least absolute shrinkage and selection operator; LGD, low-grade dysplasia; RFA, radiofrequency ablation; RR, relative risk.

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2022.02.057

BACKGROUND & 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).**

Keywords: Barrett's Esophagus; Endoscopic Therapy; Esophageal Adenocarcinoma.

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

What You Need to Know

Background

Although endoscopic therapy for Barrett's esophagus with early neoplasia is safe and leads to complete eradication in the majority of patients, a subgroup of patients experiences a complex treatment course.

Findings

Barrett's length greater than 9 cm with a lesion with high-grade dysplasia or cancer, and poor squamous regeneration after radiofrequency ablation are risk factors for complex treatment. The prediction model performed well in external validation with an area under the curve of 0.84.

Implications for patient care

The proposed model may improve patient counseling. Upon a predicted complex treatment, extra attention should be paid to pre–radiofrequency ablation imaging, and peer-review consultation and/or alternative treatment options may be considered.

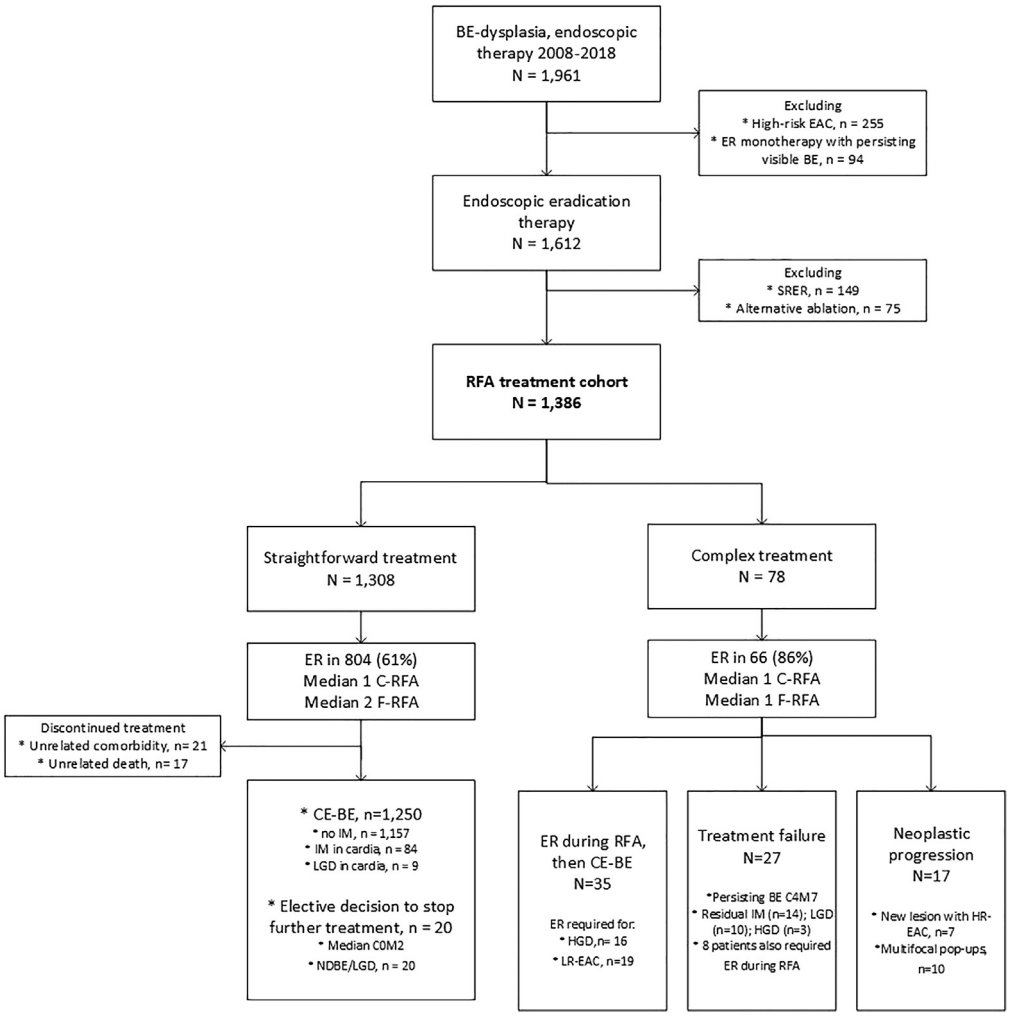


Figure 1. Patient flow. BE, Barrett's esophagus; CE-BE, complete eradication of Barrett's esophagus; C-RFA, circumferential RFA; EAC, esophageal adenocarcinoma; ER, endoscopic resection; F-RFA, focal RFA; HGD, high-grade dysplasia; HR, high risk; IM, intestinal metaplasia; LGD, low-grade dysplasia; LR, low risk; NDBE, nondysplastic Barrett's esophagus; RFA, radiofrequency ablation; SRER, stepwise radical endoscopic resection.

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).

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.

Tabel 1. Baseline Characteristics

	RFA treatment cohort (N = 1386)	Straightforward treatment (N = 1308)	Complex treatment (N = 78)	Leuven registry (N = 282)
Demographics				
Male sex, n (%)	1122 (81)	1063 (81)	58 (74)	243 (87)
Age, *y*, means (±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)	846 (70)	46 (67)	–
y, median (IQR)	4 (2–8)	3 (2–8)	3 (2–7)	
Imaging				
Hiatal hernia, n (%)	1321 (95)	1,246 (95)	75 (96)	265 (94)
cm, mean (±SD)	3 (2–4)			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 (first 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 (%)[a]	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.

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).

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

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

Neoplastic progression, N	17
High-risk EAC,[a] N	7
Multifocal EAC, N	10
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
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 adenocarcinoma; 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, nondysplastic 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+).

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 $\geq$ 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.

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.

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.

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).

Table 4. Model Building

	Univariable	Multivariable
Coefficients, odds ratio (95% CI)		
Age	1.01 (0.99–1.04)	–
Sex	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 specimens	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 to 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.

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

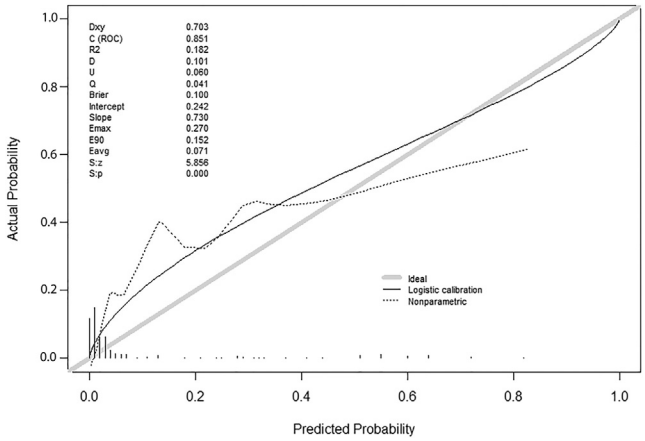


Figure 2. Calibration in external validation. Calibration plot of external validation of the prediction model in an independent data set from Leuven. The x-axis shows the predicted probability according to our model, and the y-axis shows the actual observed probability in the external data set.

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.

Supplementary Material

Note: To access the supplementary material accompanying 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.

References

1. 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;65:555–562.
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 outcomes of multimodal endoscopic eradication therapy in Barrett'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 management of Barrett's esophagus: European Society of Gastrointestinal 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 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.
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 radiofrequency 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 radiofrequency 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 ablation for Barrett's esophagus: a retrospective cohort study. BMC Gastroenterol 2018;18:67.
15. Akiyama J, Marcus SN, Triadafilopoulos G, et al. Effective intraesophageal acid control is associated with improved radiofrequency ablation outcomes in Barrett's esophagus. Dig Dis Sci 2012;57:2625–2632.

Reprint requests
Address requests for reprints to: Jacques J. G. H. M. Bergman, MD, PhD, Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology and Metabolism, Amsterdam University Medical Centers, VU Medical Center, Boeleaan 1105, 1081 HV Amsterdam, The Netherlands. e-mail: j.bergman@amsterdamumc.nl; fax: (31) 20-691-7033.

CRediT Authorship Contributions

Sanne van Munster (Conceptualization: Equal; Data curation: Equal; Formal analysis: Lead; Investigation: Equal; Methodology: Equal; Project administration: Equal; Validation: Equal; Writing – original draft: Lead)

Esther Nieuwenhuis (Data curation: Equal; Formal analysis: Equal; Project administration: Lead; Writing – review & editing: Equal)

R. Bisschops (Data curation: Equal; Methodology: Equal; Supervision: Equal; Writing – review & editing: Equal)

H. Willekens (Data curation: Equal; Writing – review & editing: Equal)

Bas L. A. M. Weusten (Conceptualization: Equal; Data curation: Equal; Methodology: Equal; Supervision: Equal; Writing – review & editing: Equal)

Lorenza Alvarez Herrero (Data curation: Equal; Writing – review & editing: Equal)

Auke Bogte (Data curation: Equal; Writing – review & editing: Equal)

Alaa Alkhalaf (Data curation: Equal; Writing – review & editing: Equal)

B. E. Schenk (Data curation: Equal; Writing – review & editing: Equal)

Erik J. Schoon (Data curation: Equal; Writing – review & editing: Equal)

Wouter Curvers (Data curation: Equal; Writing – review & editing: Equal)

Arjun D. Koch (Data curation: Equal; Writing – review & editing: Equal)

Pieter Jan F. de Jonge (Data curation: Equal; Writing – review & editing: Equal)

Tjon J. Tang (Data curation: Equal; Writing – review & editing: Equal)

Wouter B. Nagengast (Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Equal)

Jessie Westerhof (Data curation: Equal; Writing – review & editing: Equal)

Martin H. M. G. Houben (Data curation: Equal; Writing – review & editing: Equal)

Jacques J. G. H. M. Bergman, MD, PhD (Conceptualization: Lead; Data curation: Equal; Formal analysis: Equal; Methodology: Lead; Validation: Equal; Writing – review & editing: Lead)

Roos E. Pouw (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Supervision: Lead; Writing – review & editing: Lead)

Conflicts of interest

These authors disclose the following: Bas L. A. M. Weusten has received financial support for Institutional Review Board–approved research from C2Therapeutics/Pentax Medical and Aqua Medical; Jacques J. G. H. M. Bergman has received financial support for Institutional Review Board–approved research from C2Therapeutics/Pentax Medical, Medtronic, and Aqua Medical; and R. Bisschops has received research support, speaker's fees, and consultancy fees from Medtronic, Pentax, and Fujifilm. The remaining authors disclose no conflicts.

Supplementary Methods

Treatment Protocol for Barrett Expert Center Registry

Patients were referred to a BEC with LGD, HGD, or EAC after confirmation by at least 1 BE expert pathologist. During an upper gastrointestinal endoscopy, the esophagus was inspected carefully with documentation of the Prague C&M criteria and presence of visible lesions or other abnormalities such as esophagitis or esophageal stenosis. Visible lesions were removed with ER, followed by RFA of the remaining BE, all in 3-month intervals.

Data Collection and Data Management

Information regarding baseline characteristics, the treatment phase, and long-term follow-up evaluation was documented in a joint database. Endoscopy and pathology data were documented on standardized forms by medical students in the final year of their degree. All patients with end points and 50% of the remaining patients were additionally double-checked by dedicated research fellows (all MDs). All fields were examined for missing data, nonlogical values, or outliers, with data being completed or corrected where possible.

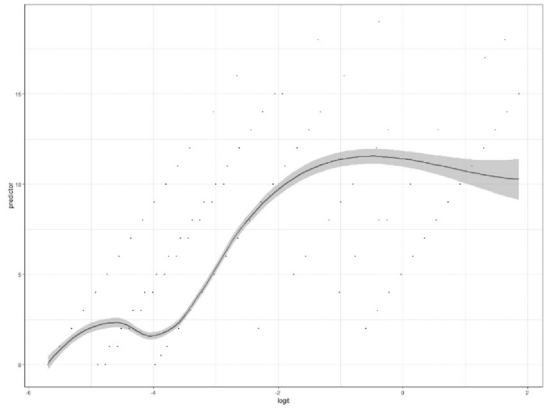
Ethics

For the BEC registry, 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 or patient-informed consent. Patients were approached through an opt-out card with the opportunity to object to participation in the registry.

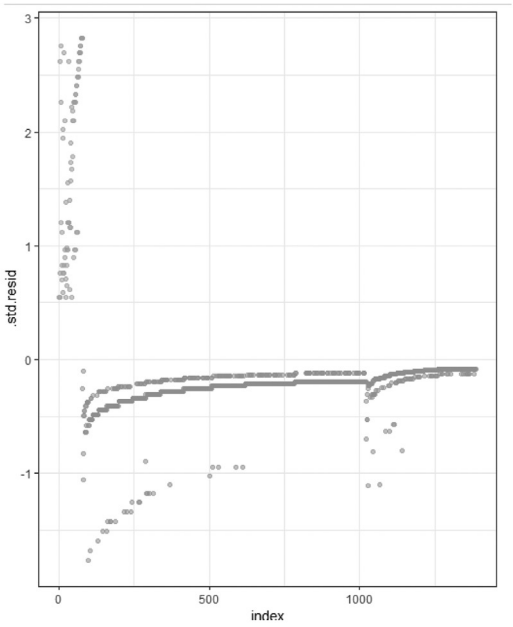
For the Leuven registry, written informed consent was obtained from all patients. The prospective registry has been approved by the Ethical Committee of the University Hospitals Leuven.

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

A. Linearity



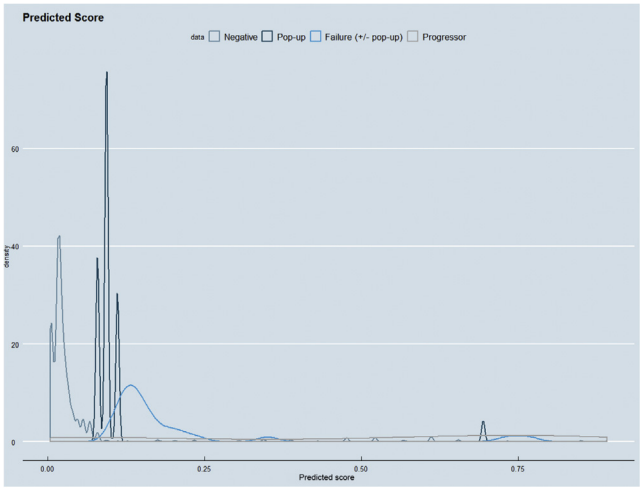
B. Outlyers



C. Multi collinearity

BE length	1.08
Poor squamous regeneration	1.08
Baseline histology	1.26
Baseline visible lesion	1.24

Supplementary Figure 1. Model assumptions: (*A*) linearity and (*B*) outliers. Std. Resid., standardized residuals.

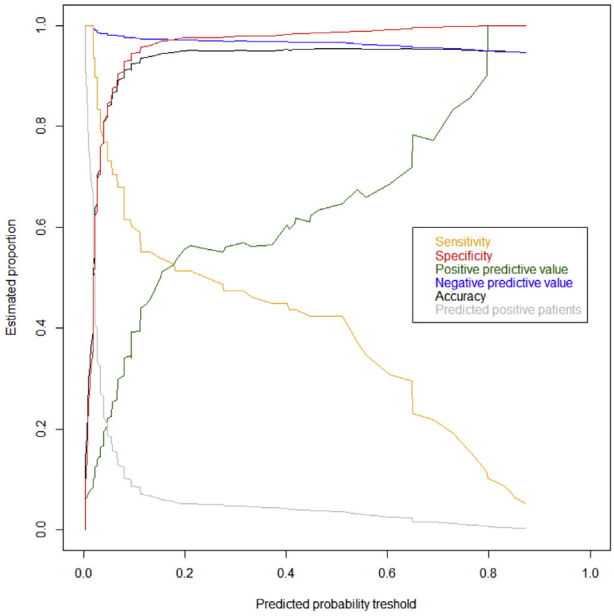


Supplementary Figure 2. This plot shows the different components of our composite endpoint, indicated with different colors in the graph. The predicted score according to our model is indicated on the x-axis, and the frequency (or density) is shown on the y-axis.

Supplementary Table 1. Model Assumptions: Multicollinearity

BE length	1.08
Poor squamous regeneration	1.08
Baseline histology	1.26
Baseline visible lesion	1.24

ER, endoscopic resection; RFA, radiofrequency ablation.
BE, Barrett's esophagus.



Supplementary Figure 3. This graph shows the sensitivity, specificity, positive and negative predictive values, accuracy, and number of predicted positive patients for varying cut-off values (on the x-axis).

Supplementary Table 2. Cut-Offs and Clinical Implications

Cut-off value	Sensitivity, %	Stratified per outcome, n (%)			Specificity, %	Negative predictive value, %	Positive predictive value, %	Patients positive, n (%)
		Progressor	Failures	ER during RFA				
0.5	42 [31–54]	11 (65)	17 (63)	5 (15)	99 [98–99]	97 [96–98]	65 [50–78]	51 (4)
0.4	45 [34–57]	11 (65)	19 (70)	5 (15)	98 [97–99]	97 [96–98]	60 [47–73]	58 (4)
0.3	47 [36–59]	11 (65)	21 (78)	5 (15)	98 [97–99]	97 [96–98]	57 [44–69]	65 (5)
0.2	51 [40–63]	11 (65)	23 (85)	6 (18)	98 [97–99]	97 [96–98]	56 [44–68]	71 (5)
0.15	54 [42–65]	12 (71)	24 (89)	6 (18)	97 [96–98]	97 [96–98]	50 [39–61]	84 (6)
0.1	59 [47–70]	13 (76)	25 (93)	8 (24)	95 [93–96]	97 [96–98]	39 [30–49]	117 (8)
0.05	73 [65–83]	14 (82)	26 (96)	17 (50)	85 [83–87]	98 [97–99]	22 [13–35]	256 (18)

ER, endoscopic resection; RFA, radiofrequency ablation.
BE, Barrett's esophagus.

Supplementary Table 3. Odds Ratios for the Different Parts of the Combined End Point

	Univariable odds ratio for the combined end point	Univariable odds ratio for separate components of the composite end point		
		Pop-up and CE-BE	Treatment failure (±pop-up)	Progression
Age	1.01 [0.99–1.04]	1.00 [0.96–1.03]	1.01 [0.97–1.06]	1.05 [0.99–1.11]
Sex	1.42 [0.81–2.38]	1.28 [0.54–2.73]	1.36 [0.49–3.27]	1.80 [0.57–4.90]
BMI	0.99 [0.93–1.04]	0.99 [0.90–1.07]	1.05 [0.96–1.14]	0.88 [0.76–1.00]
Smoking	0.99 [0.59–1.57]	1.20 [0.55–3.02]	0.64 [0.28–1.54]	1.41 [0.46–6.13]
Fundoplication	1.64 [0.26–5.72]	1.17 [1.08–1.27]	5.33 [0.82–19.71]	–
Hiatal hernia	1.20 [1.08–1.33]	1.05 [0.87–1.24]	1.32 [1.12–1.55]	1.27 [1.04–1.52]
Barrett length	1.30 [1.23–1.37]	1.17 [1.08–1.27]	1.37 [1.26–1.51]	1.42 [1.28–1.60]
Reflux stenosis	1.54 [0.45–3.92]	0.83 [0.05–3.97]	3.83 [0.88–11.58]	–
Reflux esophagitis	2.49 [0.93–5.63]	–	4.01 [0.93–12.16]	6.31 [1.42–2.02]
Baseline visible lesion	3.77 [2.05–7.60]	21.34 [4.60–380.25]	1.12 [0.50–2.66]	10.05 [2.04–7.60]
Number of ER specimens	1.10 [1.02–1.18]	1.07 [0.94–1.18]	1.09 [0.92–1.22]	1.14 [1.00–1.27]
Histology	2.93 [1.53–6.36]	–	2.43 [1.33–4.32]	–
<50% squamous regression after ER	3.84 [2.63–5.88]	3.78 [2.55–5.93]	2.00 [1.03–3.85]	11.11 [5.00–33.33]
<50% squamous regression after RFA	40.54 [23.25–71.76]	7.76 [2.77–18.81]	431.25 [121.16–2756.60]	68.75 [24.71–210.95]

BMI, body mass index; CE-BE, complete eradication of Barrett's esophagus; ER, endoscopic resection; RFA, radiofrequency ablation.

Supplementary Table 4. Sensitivity Analysis

Type of sensitivity analysis	Different outcome		Change in model used		Variability over time	Variability over centers
Actual change	Only progressors and failures		LASSO penalization	Ordinal logistic regression	Cross-validation based on year of inclusion	Cross-validation based on center
Variable selection and OR estimation (95% CI)	New backward regression	Model with the same 4 variables				
BE length, OR (95% CI)	1.26 (1.33-1.40)	1.25 (1.13–1.40)	1.20	1.21 (1.13–1.29)	1.21 (1.20–1.22)	1.21 (1.20–1.21)
Baseline visible lesion, OR (95% CI)	–	1.07 (0.36–3.33)	2.14	2.54 (1.21–5.80)	2.58 (2.42–2.71)	2.55 (2.45–2.95)
Baseline histology, OR (95% CI)	–	1.30 (0.42–4.22)	1.71	2.34 (1.50–5.92)	2.30 (2.02–2.41)	2.11 (1.91–2.35)
PSR, OR (95% CI)	72.47 (31.94-182.30)	71.36 (31.03–182.41)	17.87	26.27 (14.25–49.17)	21.35 (19.63–22.32)	21.66 (21.04–22.37)
AUC (95% CI)	0.94 (0.90–0.97)	0.95 (0.94–0.96)	0.871 (0.847–0.915)		0.83 (0.80–0.89)	0.87 (0.84–0.90)

AUC, area under the curve; BE, Barrett's esophagus; LASSO, least absolute shrinkage and selection operator; OR, odds ratio; PSR, poor squamous regeneration.