

Predictive factors for initial treatment response after circumferential radiofrequency ablation for Barrett's esophagus with early neoplasia: a prospective multi-center study

Authors

F. G. I. van Vilsteren¹, L. Alvarez Herrero^{1,2}, R. E. Pouw¹, D. Schrijnders¹, C. M. T. Sondermeijer¹, R. Bisschops³, J. M. Esteban⁴, A. Meining⁵, H. Neuhaus⁶, A. Parra-Blanco^{1,15}, O. Pech⁸, K. Ragunath⁹, B. Rembacken¹⁰, B. E. Schenk¹¹, M. Visser¹², F. J. W. ten Kate¹², S. L. Meijer¹², J. B. Reitsma¹³, B. L. A. M. Weusten^{1,2}, E. J. Schoon¹⁴, J. J. G. H. M. Bergman¹

Institutions

Institutions are listed at the end of article.

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Corresponding author

J. Bergman, MD PhD
Department of
Gastroenterology and
Hepatology
Academic Medical Center
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands
Fax: +31-20-6917033
j.j.bergman@amc.uva.nl

Background and study aims: Radiofrequency ablation (RFA) is safe and effective for the eradication of neoplastic Barrett's esophagus; however, occasionally there is minimal regression after initial circumferential balloon-based RFA (c-RFA). This study aimed to identify predictive factors for a poor response 3 months after c-RFA, and to relate the percentage regression at 3 months to the final treatment outcome.

Methods: We included consecutive patients from 14 centers who underwent c-RFA for high grade dysplasia at worst. Patient and treatment characteristics were registered prospectively. "Poor initial response" was defined as <50% regression of the Barrett's esophagus 3 months after c-RFA, graded by two expert endoscopists using endoscopic images. Predictors of initial response were identified through logistic regression analysis.

Results: There were 278 patients included (median Barrett's segment C4M6). In poor initial responders (n=36; 13%), complete response for neoplasia (CR-neoplasia) was ultimately achieved in 86% (vs. 98% in good responders; $P < 0.01$) and

complete response for intestinal metaplasia (CR-IM) in 66% (vs. 95%; $P < 0.01$). Poor responders required 13 months treatment (vs. 7 months; $P < 0.01$) for a median of four RFA sessions (vs. three; $P < 0.01$). We identified four independent baseline predictors of poor response: active reflux esophagitis (odds ratio [OR] 37.4; 95% confidence interval [CI] 3.2–433.2); endoscopic resection scar regeneration with Barrett's epithelium (OR 4.7; 95%CI 1.1–20.0); esophageal narrowing pre-RFA (OR 3.9; 95%CI 1.0–15.1); and years of neoplasia pre-RFA (OR 1.2; 95%CI 1.0–1.4).

Conclusions: Patients with a poor initial response to c-RFA have a lower ultimate success rate for CR-neoplasia/CR-IM, require more treatment sessions, and a longer treatment period. A poor initial response to c-RFA occurs more frequently in patients who regenerate their endoscopic resection scar with Barrett's epithelium, and those with ongoing reflux esophagitis, neoplasia in Barrett's esophagus for a longer time, or a narrow esophagus.

Introduction

Radiofrequency ablation (RFA) is an endoscopic ablation technique for safe and effective eradication of Barrett's esophagus containing early neoplasia. In patients with visible lesions, RFA can be safely and effectively preceded by endoscopic resection of these focal lesions, yielding a specimen for histological staging and rendering the mucosa flat prior to RFA. Multicenter studies have reported complete eradication of all intestinal metaplasia and neoplasia in 77%–100% of patients after RFA with or without endoscopic resection [1–6]. RFA treatment usually starts with a circumferential ablation (c-RFA) with the balloon-based HALO³⁶⁰ device (BARRX Medical, Sunnyvale, California, USA), followed by focal ablation sessions with the smaller HALO⁹⁰ device to treat residual

Barrett's esophagus. Generally, three endoscopic RFA sessions are sufficient to achieve complete conversion of the Barrett's esophagus into squamous mucosa. Despite the good results of RFA treatment, sporadically, patients demonstrate a poor response to RFA.

In our first five prospective RFA studies, there were six patients (4%) in whom the RFA treatment protocol failed to achieve complete removal of all intestinal metaplasia and/or early neoplasia [2–4,6,7]. In these patients, the median percentage regression of the Barrett's epithelium 3 months after the initial c-RFA was 35% compared with 90% for other patients. We therefore hypothesized that there is a small subgroup of patients that demonstrates minimal regression of the Barrett's epithelium 3 months after the initial c-RFA, and that in some of these patients complete era-

dication of Barrett's esophagus will not be achieved despite repeated RFA sessions.

The early identification of patients with a high chance of failing RFA may influence the choice between RFA and other endoscopic treatment modalities such as complete stepwise endoscopic resection, a conservative approach with regular endoscopic follow-up, or surgery.

In this multicenter study, we prospectively collected baseline factors relating to patient characteristics, features of the Barrett's segment, and technical aspects of the c-RFA procedure. These factors were subsequently related to the regression of the Barrett's esophagus surface area 3 months after c-RFA to identify potential predictive factors for initial treatment response after c-RFA.

Patients and methods

Patients were eligible for c-RFA treatment if they met the following inclusion criteria: no worse than high grade dysplasia (HGD) in flat-type Barrett's esophagus prior to RFA. Exclusion criteria included: visible lesions (meaning nodularity) on high resolution endoscopy (HRE) prior to RFA; signs of metastasis on endoscopic ultrasound (EUS) or computed tomography (CT) scanning of thorax and abdomen (in case of cancer); symptomatic dysphagia; or an esophageal inner diameter (EID) <18 mm prior to RFA. In patients who had undergone prior endoscopic resection, exclusion criteria included: endoscopic resection specimens that demonstrated >T1sm1; positive deep-resection margins; G3–G4 tumor differentiation; and presence of lymphatic/vascular invasion [2–4, 6, 7].

Radiofrequency ablation

RFA was performed using the HALO system, which consists of the HALO³⁶⁰ balloon catheter for c-RFA and the smaller HALO⁹⁰ electrode for focal ablation [4, 8].

Prior to RFA, the esophagus was evaluated using HRE and narrow band imaging (NBI), Fuji Intelligent Chromo Endoscopy (FICE), or iScan (Pentax). The extent of the Barrett's esophagus was recorded according to the Prague C & M classification [9]. The number of Barrett's islands and squamous islands in the Barrett's esophagus were noted. The presence and location of visible abnormalities and (relative) narrowing of the esophagus were documented. Still images with HRE and NBI were obtained for every 1–2 cm of the Barrett's esophagus while pulling the endoscope back from the top of the gastric folds.

Initial c-RFA was performed using the HALO³⁶⁰ balloon catheter, using two ablation passes (12 J/cm², 40 Watt/cm²) and cleaning of the ablation zone and balloon catheter after the first pass. During the study period, patients were administered esomeprazole 40 mg orally twice daily, with addition of ranitidine 300 mg at bedtime and sucralfate suspension 5 mL four times daily for 14 days after every treatment session [4, 8].

After 3 months, the treatment effect was assessed with HRE and NBI. Still images were again obtained of every 1–2 cm of the Barrett's esophagus, and the percentage regression of the Barrett's esophagus was scored by the endoscopist. RFA was repeated every 2–3 months until complete eradication of the endoscopic Barrett's esophagus was achieved [4, 8]. For persisting Barrett's epithelium after a maximum of five RFA sessions (≤ 2 HALO³⁶⁰ procedures), escape endoscopic resection was performed.

Once complete eradication of the endoscopic Barrett's esophagus had been achieved, four quadrant biopsies were obtained for ev-

ery 2-cm section of esophagus throughout the entire area of the original Barrett's esophagus and immediately distal (<5 mm) to the neosquamocolumnar junction to document complete response (histological eradication) for early neoplasia (CR-neoplasia) and for intestinal metaplasia (CR-IM). Patients were then scheduled for a follow-up endoscopy at 6 months and annually thereafter.

Outcome assessment

The primary outcome measure was the percentage regression of the visible Barrett's esophagus surface area 3 months after the initial c-RFA session. We hypothesized that regression of the Barrett's esophagus surface area at 3 months (response after the first c-RFA session) is predictive of the final response at the end of the treatment period, defined by CR-neoplasia and CR-IM. "Poor initial response" was defined as <50% regression of the Barrett's esophagus surface area 3 months after c-RFA.

Secondary treatment outcomes measures were: CR-neoplasia; CR-IM; number of RFA sessions; duration of the RFA treatment period; and escape treatment required to achieve complete response.

Blinded scoring of the percentage regression of the Barrett's surface area

The endoscopist who scored the regression of the Barrett's surface area in "real time" during the procedure at 3 months was not blinded to the patient history and features of the Barrett's esophagus. Two endoscopists therefore performed an independent review to guarantee an unbiased assessment.

The still images obtained at the initial c-RFA session (prior to c-RFA) and at the 3-month follow-up endoscopy (post c-RFA) were placed in a PowerPoint presentation. Two experienced endoscopists (B.W. and E.S.) independently reviewed the PowerPoint presentation to estimate the regression of the Barrett's surface area at 3 months. They were advised of the baseline Barrett's esophagus length, but were blinded to the patient history, clinical features, images of previous endoscopies, and information on the technical features of the initial c-RFA treatment.

The reviewing endoscopists indicated if the endoscopic images allowed them to reliably estimate the surface area regression (scored as good, moderate, or poor). For cases scored as poor by either one of the endoscopists, the real-time assessment of the surface area regression from the 3-month follow-up endoscopy was used in the analysis. Cases in which the surface area regression scores of the two endoscopists differed by $\geq 30\%$ were reviewed during a consensus meeting to establish a single consensus score. For all other cases, the mean of the two independent assessment scores for the percentage surface area regression was used in the analysis.

Potential predictors of poor initial response

Baseline variables were categorized as patient characteristics, Barrett's esophagus characteristics, and treatment characteristics of c-RFA. Variables were selected based on the existing literature or on their hypothetical contribution to poor initial regression based on our clinical observations [5, 10–20]. Data were extracted from clinical charts and a self-administered patient questionnaire and were recorded on standardized case record forms (CRFs). Variables were dichotomous (yes/no) unless otherwise specified.

Recorded patient characteristics included: age (years), gender, body mass index (weight/[height²]). The questionnaire provided

data on: history of gastroesophageal reflux disease (GERD); GERD duration (time from GERD diagnosis until first RFA, years); duration of antacid use (years); current smoking habit and previous smoking habit; and alcohol abuse (male >3 U/day; female >2 U/day). The clinical charts provided data on: diabetes mellitus (diabetes or antidiabetic medication mentioned in the clinical record); use of immunosuppressant drugs (inhaled corticosteroids, oral corticosteroids, or other immunosuppressant drugs); use of nonsteroidal anti-inflammatory drugs (NSAIDs including acetylsalicylic acid); and use of any medication besides antacids. Barrett's esophagus characteristics included: duration of Barrett's esophagus (years since the first histological Barrett's esophagus diagnosis); and duration of neoplasia (years between first histological diagnosis of low grade dysplasia (LGD), HGD, or carcinoma and first RFA). Endoscopic features recorded included: Barrett's esophagus M length (distance between the upper end of the gastric folds and the proximal margin of the Barrett's esophagus tongues, cm); Barrett's esophagus C length (distance between the gastric folds and the upper end of the proximal margin of the circumferential Barrett's esophagus, cm); C & M difference (M length minus C length, cm); hiatal hernia length (cm); endoscopic signs of active reflux esophagitis (grade A, or grade $\geq$ B if RFA was postponed); endoscopic resection scar regeneration with Barrett's epithelium (as opposed to regeneration with squamous epithelium).

Other features of the pre-RFA Barrett's esophagus that were noted included: the presence of Barrett's esophagus islands; the presence of squamous islands; and a "bell-shaped" esophagus (endoscopically visible relative narrowing of the proximal esophagus with relative widening distally) if reported in the endoscopy report or CRF. Relative narrowing pre-RFA (presence of a visible mild, asymptomatic stenosis or relative narrowing) was recorded if it was reported in the endoscopy report or CRF and was graded as follows: mild stricture, non-circumferential scarring; moderate stricture, circumferential scarring or stenosis that can be passed by an endoscope; severe stricture, stenosis that cannot be passed by an endoscope). The most advanced histology prior to the RFA (nondysplastic Barrett's esophagus + LGD versus HGD in biopsies) and the most advanced histology prior to any endoscopic treatment (nondysplastic Barrett's esophagus + LGD versus HGD + carcinoma) were also noted.

Treatment characteristics were: endoscopic resection prior to RFA; size of the RFA balloon; smallest EID (as measured during sizing prior to RFA); smallest EID minus RFA-balloon size.

Ethics, data collection, and statistics

This prospective multicenter cohort study was superimposed on several European multicenter projects and institutional review board-approved prospective RFA study protocols [2–4,6,7]. All patients signed informed consent. A cut-off value of <50% regression of the Barrett's esophagus 3 months after c-RFA was used to define poor initial responders.

Mean $\pm$ standard deviation (SD) was used for data with a parametric distribution and median (interquartile range, IQR) for that with a non-parametric distribution. Mann-Whitney *U* test, Chi-square test and Fisher exact test were used to compare groups where appropriate.

Baseline variables associated with poor initial response in the univariate analysis with $P < 0.10$ were subsequently entered in a multivariate regression model to detect potential predictive factors for a poor initial response to c-RFA. Odds ratios (OR) and 95% confidence intervals (95%CI) were used to quantify the pre-

dictive associations. Pearson and Spearman's test were used to detect multicollinearity between predictors and in the case of a strong association ($\rho \geq 0.9$), only one of the predictors was entered in the multivariate model.

A simplified and robust version of the final multivariate model was created by counting the number of risk factors present and providing the observed risk for the different categories (e.g. no risk factor present, one risk factor, two risk factors, etc.) Two-sided *P* values were considered statistically significant if *P* was ≤ 0.05 . The SPSS statistical software package (SPSS Inc.16.0.2, Chicago, Illinois, USA) was used for data analysis.

Results

▼ Patients

Between July 2005 to March 2010, 278 consecutive patients (219 men [79%]; mean age 63 ± 13) were included in 14 European centers [2–4,6,7]. The median length of Barrett's esophagus was C4M6 (IQR C2–8, M4–10). A prior endoscopic resection had been performed in 177 patients (64%). The most advanced overall histological diagnoses on biopsies and endoscopic resection specimens were carcinoma in 116 patients, HGD in 116, LGD in 44, and intestinal metaplasia without dysplasia in two patients (● Table 1).

Regression of the Barrett's esophagus surface area at 3-month follow-up

The median regression of the Barrett's esophagus surface area 3 months after the initial c-RFA of the whole cohort of 278 patients was 85% (IQR 60%–95%). Regression scores for the Barrett's esophagus surface area were based on the review scores of the two expert endoscopists in 219 patients (79%), including 28 patients (10%) in whom the surface area regression score was established in a consensus meeting. The median difference in the percentage regression of the Barrett's esophagus was 0% (IQR –5.0% to 7.0%) when comparing the two endoscopists. In 59 patients (21%) the surface area regression score was based on the real-time estimation of the endoscopist performing the 3-month endoscopy because endoscopic images were either not representative or unavailable. The median difference in the percentage regression of the Barrett's esophagus between the real-time score and the mean score of the two endoscopists was 2.5% (IQR –5.0% to 10.0%).

Relevance of a poor initial response in predicting overall treatment results

Poor initial response, categorized by <50% regression in the surface area of the Barrett's esophagus 3 months after the c-RFA, was identified in 36 patients (13%), whilst 242 patients (87%) had >50% regression of the Barrett's esophagus surface area and were categorized as good initial responders. Six of the 278 patients (2%) did not finish the treatment protocol for unrelated reasons (see next section for further details; ● Table 2; ● Fig. 1 and ● Fig. 2).

Of the poor initial responders, 14% (5/36) ultimately failed to achieve CR-neoplasia (vs. 3% [6/236] in the good initial responders; $P < 0.01$) and 33% (12/36) ultimately failed to achieve CR-IM (vs. 5% [12/236] in the good initial responders; $P < 0.01$). Of patients who ultimately failed to achieve CR-IM and CR-neoplasia, 50% and 46% respectively had a poor initial response to c-RFA.

Table 1 a Baseline characteristics for the 278 patients who were treated with radiofrequency ablation (RFA) +/- endoscopic resection for Barrett's esophagus containing early neoplasia, divided according to initial response: **a** patient characteristics; **b** Barrett's esophagus characteristics; **c** treatment characteristics. Poor initial response was defined as <50% regression of the Barrett's esophagus 3 months after initial circumferential balloon-based RFA.

Variable	Number of evaluable patients ¹ overall (good / poor responders)	Results			Odds ratio ² (95% confidence interval)	P value
		All evaluable patients	Good initial responders	Poor initial responders		
Age, mean (SD), years	278 (242/36)	63 (13)	65 (13)	64 (11)	1.01 (0.98 – 1.04)	0.52
Male, n (%)	278 (242/36)	219 (79%)	192 (79%)	27 (75%)	0.78 (0.35 – 1.77)	0.55
Body mass index, mean (SD)	214 (219/29)	27 (4)	27 (4)	27 (4)	0.99 (0.89 – 1.09)	0.82
History of GERD, n (%)	225 (197/28)	203 (90%)	176 (89%)	27 (96%)	3.22 (0.42 – 24.94)	0.26
Duration of GERD, mean (SD), years	67 (57/10)	18.4 (17.0)	18.7 (17.4)	16.7 (14.8)	0.99 (0.95 – 1.04)	0.73
Duration of antacid use, mean (SD), years	212 (187/25)	8.2 (9.3)	8.2 (9.4)	8.0 (8.6)	1.00 (0.95 – 1.04)	0.90
Current smoker, n (%)	135 (114/21)	34 (25%)	27 (24%)	7 (33%)	1.61 (0.59 – 4.40)	0.35
Ever smoked, n (%)	134 (113/21)	105 (78%)	88 (78%)	17 (81%)	1.21 (0.37 – 3.92)	0.75
Alcohol abuse, n (%)	129 (109/20)	26 (20%)	25 (23%)	1 (5%)	0.18 (0.02 – 1.39)	0.10
Diabetes mellitus, n (%)	237 (209/30)	29 (12%)	25 (12%)	4 (13%)	1.12 (0.36 – 3.48)	0.85
Immunosuppressant drugs, n (%)	236 (206/30)	24 (10%)	21 (10%)	3 (10%)	0.98 (0.27 – 3.50)	0.97
No NSAID use, n (%)	230 (200/30)	180 (78%)	152 (76%)	28 (93%)	4.42 (1.02 – 19.24)	0.05
Any other medication, n (%)	232 (202/30)	169 (73%)	147 (73%)	22 (73%)	1.03 (0.43 – 2.45)	0.95

SD, standard deviation; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; LGD/IM, low grade dysplasia or intestinal metaplasia; HGD, high grade dysplasia; EID, esophageal inner diameter.

¹ In patients where data was not available, this was registered as missing data.

² Univariate logistic regression analysis with odds ratios was used to assess the predictive value of each clinical variable.

Poor initial responders were more likely to discontinue treatment after c-RFA (10/36 poor initial responders [28%] vs. 2/236 good initial responders [1%]; $P < 0.01$) or required more RFA sessions and a longer treatment period as compared with the good initial responders: poor initial responders required a median treatment period of 13 months (IQR 9–18) vs. 7 months (IQR 4–10) for good initial responders ($P < 0.01$), and a median of four RFA sessions (IQR 4–5) vs. three RFA sessions (IQR 2–4) for good initial responders ($P < 0.01$).

Complete response for early neoplasia and intestinal metaplasia

Of the 278 patients included in this study, 272 finished the treatment protocol. Six patients did not finish the treatment protocol for unrelated reasons: cardiac death, lung cancer death, renal failure, colon cancer, cardiac disease, and psychiatric disease. Overall, 261 of the 272 available patients (96%) achieved CR-neoplasia and 248 (91%) achieved CR-IM, after a median of three RFA sessions (IQR 2–4).

There were 11 patients who eventually failed to achieve CR-neoplasia. One patient died from inoperable esophageal adenocarcinoma 13 months after endoscopic resection of a visible lesion demonstrating a T1sm1 carcinoma during the RFA treatment phase. Three patients underwent successful esophagectomy for persistent early neoplasia. Three patients required multiple additional endoscopic resections after RFA and had residual areas of visible

Barrett's esophagus containing LGD. Two patients showed poor regression of the Barrett's esophagus surface area and poor healing after c-RFA, but once the Barrett's esophagus had healed, only LGD was found and no further RFA was performed. Two other patients with HGD at baseline refused to be followed up with biopsies after endoscopic eradication of the Barrett's esophagus with RFA, so CR-neoplasia or CR-IM could not be confirmed.

An additional 13 patients failed to achieve CR-IM during the treatment period. Eight patients demonstrated poor regression and/or slow healing. Three patients had complete endoscopic regression of their Barrett's esophagus, but showed focal intestinal metaplasia of the cardia. In one patient, buried Barrett's glands were observed in a single biopsy during the first follow-up endoscopy. Finally, one patient refused further RFA treatment once biopsies of the residual Barrett's esophagus showed no dysplasia.

In 22 patients who achieved CR-neoplasia and CR-IM, additional endoscopic resection (escape endoscopic resection) was performed to remove persisting Barrett's esophagus after five RFA sessions (no intestinal metaplasia, $n = 7$; intestinal metaplasia, $n = 6$; LGD, $n = 3$) or to remove a focal lesion during the RFA treatment phase (LGD, $n = 4$; HGD, $n = 1$; T1sm1, $n = 1$).

Table 1 b

Variable	Number of evaluable patients in total ¹ (good / poor responders)	Results			Odds ratio ² (95% confidence interval)	P value
		All evaluable patients	Good initial responders	Poor initial responders		
Barrett's esophagus duration, mean (SD), years	227 (198/29)	5.8 (6.4)	5.9 (6.4)	6.0 (6.4)	1.01 (0.95 – 1.07)	0.88
Neoplasia duration, mean (SD), years	235 (204/31)	2.5 (2.9)	2.3 (2.4)	3.9 (4.8)	1.15 (1.03 – 1.28)	0.01
Maximal (M) Barrett length, mean (SD), cm	278 (242/36)	6.8 (3.5)	6.7 (3.5)	7.2 (3.9)	1.04 (0.94 – 1.15)	0.45
Circumferential (C) Barrett length, mean (SD), cm	278 (242/36)	4.8 (3.9)	4.7 (3.8)	4.9 (4.2)	1.01 (0.90 – 1.11)	0.78
C & M difference, mean (SD), cm	278 (242/36)	2.0 (1.5)	2.0 (1.5)	2.3 (1.4)	1.13 (0.90 – 1.40)	0.29
Hiatal hernia length, mean (SD), cm	267 (234/33)	3.3 (1.8)	3.3 (1.8)	3.6 (1.9)	1.11 (0.91 – 1.35)	0.32
Signs of active reflux esophagitis, n (%)	274 (240/34)	15 (6%)	10 (4%)	5 (15%)	3.97 (1.27 – 12.41)	0.02
Scar regeneration with Barrett's esophagus, n (%)	153 (132/21)	16 (11%)	11 (8%)	5 (24%)	3.44 (1.06 – 11.17)	0.04
Barrett's islands pre-RFA, n (%)	256 (225/31)	119 (47%)	106 (47%)	13 (42%)	1.36 (0.63 – 2.96)	0.44
Absence of squamous islands pre-RFA, n (%)	253 (222/31)	57 (23%)	44 (20%)	13 (42%)	2.92 (1.33 – 6.41)	<0.01
Bell-shaped esophagus, n (%)	233 (203/30)	44 (19%)	35 (17%)	9 (30%)	2.06 (0.87 – 4.87)	0.10
Relative esophageal narrowing (asymptomatic) pre-RFA, n (%)	278 (242/36)	40 (14%)	29 (12%)	11 (31%)	3.23 (1.44 – 7.25)	<0.01
Most advanced histology						
LGD/IM pre-RFA, n (%)	278 (242/36)	164 (59%)	139 (57%)	25 (70%)	1.68 (0.79 – 3.58)	0.18
HGD/carcinoma prior to any endoscopic treatment, n (%)	278 (242/36)	232 (81%)	203 (84%)	29 (81%)	0.80 (0.33 – 1.95)	0.62

SD, standard deviation; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; LGD/IM, low grade dysplasia or intestinal metaplasia; HGD, high grade dysplasia; EID, esophageal inner diameter.

¹ In patients where data was not available, this was registered as missing data.

² Univariate logistic regression analysis with odds ratios was used to assess the predictive value of each clinical variable.

Table 1 c

Variable	Number of evaluable patients ¹ in total (good / poor responders)	Results			Odds ratio ² (95% confidence interval)	P value
		All evaluable patients	Good initial responders	Poor initial responders		
Endoscopic resection prior to RFA, n (%)	278 (242/36)	177 (64%)	151 (62%)	26 (72%)	1.57 (0.72 – 3.40)	0.26
Balloon size: number using 18/22 mm, n (%)	267 (232/35)	90 (34%)	75 (32%)	15 (43%)	1.57 (0.76 – 3.24)	0.22
Smallest EID, mean (SD), mm	261 (227/34)	26.7 (3.8)	26.7 (3.8)	26.4 (4.0)	0.98 (0.89 – 1.07)	0.61
Smallest EID minus balloon size, mean (SD), mm	254 (221/33)	1.2 (2.4)	1.2 (2.4)	1.2 (2.8)	1.01 (0.87 – 1.17)	0.92

SD, standard deviation; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; LGD/IM, low grade dysplasia or intestinal metaplasia; HGD, high grade dysplasia; EID, esophageal inner diameter.

¹ In patients where data was not available, this was registered as missing data.

² Univariate logistic regression analysis with odds ratios was used to assess the predictive value of each clinical variable.

Table 2 Comparison of treatment results for poor and good initial responders after radiofrequency ablation (RFA) +/- endoscopic resection for Barrett's esophagus containing early neoplasia. Poor initial response was defined as <50% regression of the Barrett's surface area 3 months after the initial circumferential balloon-based RFA.

Number of patients achieving	All patients n=272	Good initial responders n=236	Poor initial responders n=36	P value
CR-neoplasia, %	96 %	98 %	86 %	<0.01
CR-IM, %	91 %	95 %	66 %	<0.01
Median time for RFA treatment ¹ (IQR), months	7 (4–11)	7 (4–10)	13 (9–18)	<0.01
Median number of RFA sessions ¹ (IQR)	3 (2–4)	3 (2–4)	4 (4–5)	<0.01
Escape endoscopic resection required to achieve CR-IM, %	12 %	10 %	22 %	0.05

CR-IM, complete response for intestinal metaplasia; IQR, interquartile range.

¹ Conditional on finishing the treatment protocol.

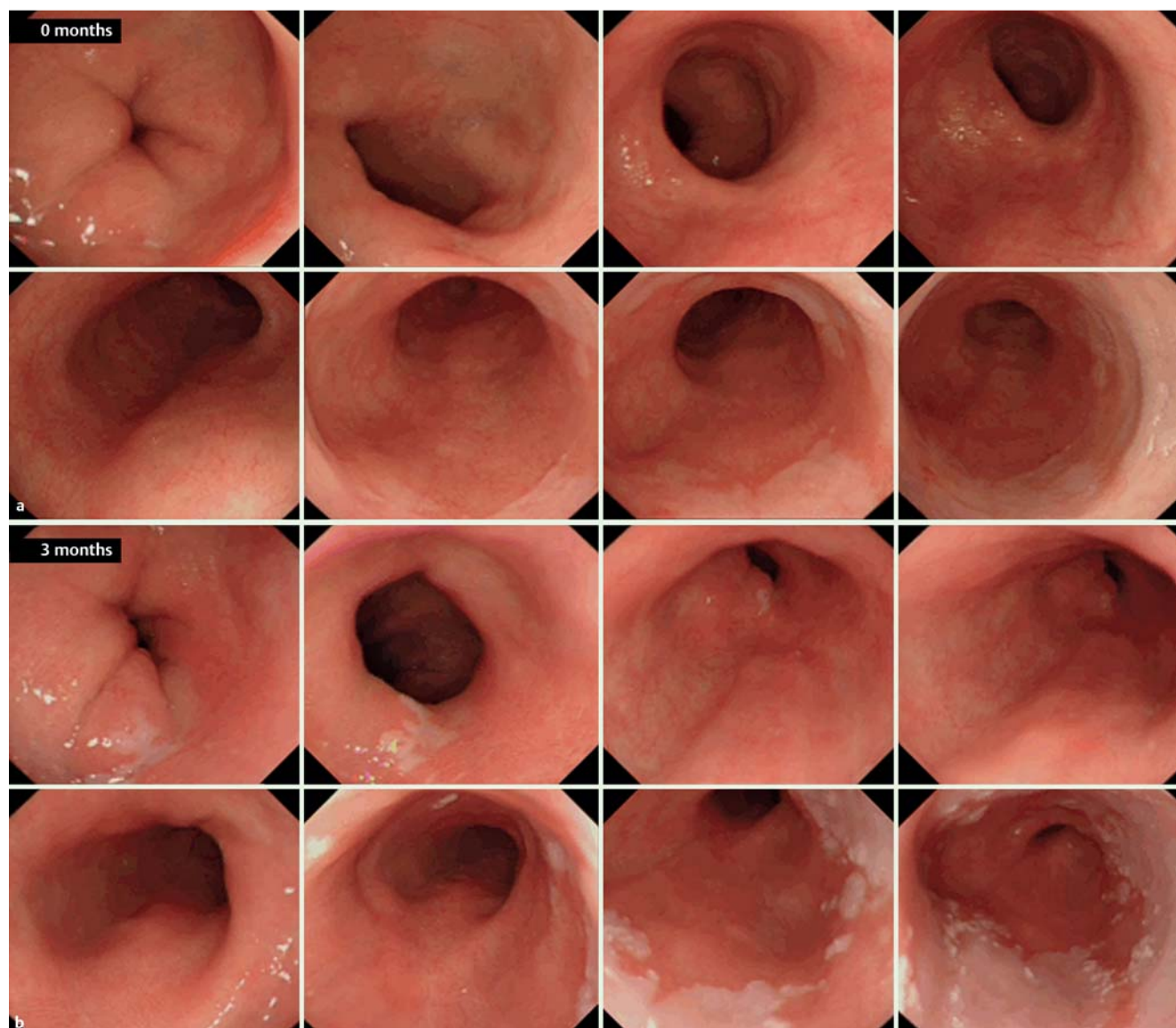


Fig. 1 Endoscopic images of a patient treated with circumferential balloon-based radiofrequency ablation (c-RFA) for a C7M9 Barrett's esophagus with prior endoscopic resection for a T1m2 carcinoma: **a** before treatment; **b** 3 months after treatment showing a poor initial response with an estimated regression of the Barrett's esophagus surface area of 0%. In this patient RFA treatment was discontinued because of the poor response.

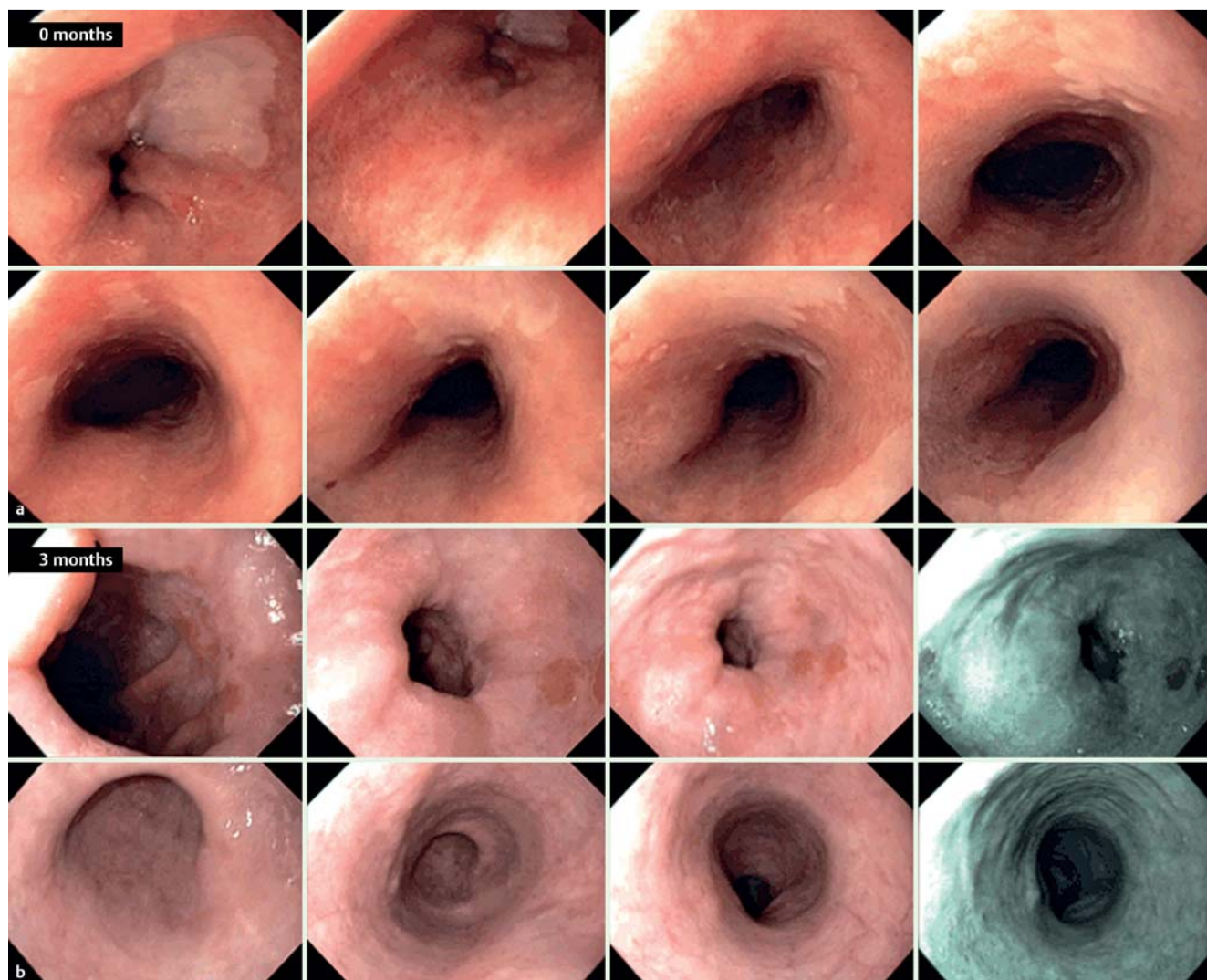


Fig. 2 Endoscopic images of a patient treated with circumferential balloon-based radiofrequency ablation (c-RFA) for C11M12 Barrett's esophagus containing low grade dysplasia: **a** before treatment; **b** 3 months after treatment showing a good initial response with an estimated regression of the Barrett's esophagus surface area of 99%. After two additional focal RFA sessions, complete response in terms of both intestinal metaplasia and neoplasia was achieved.

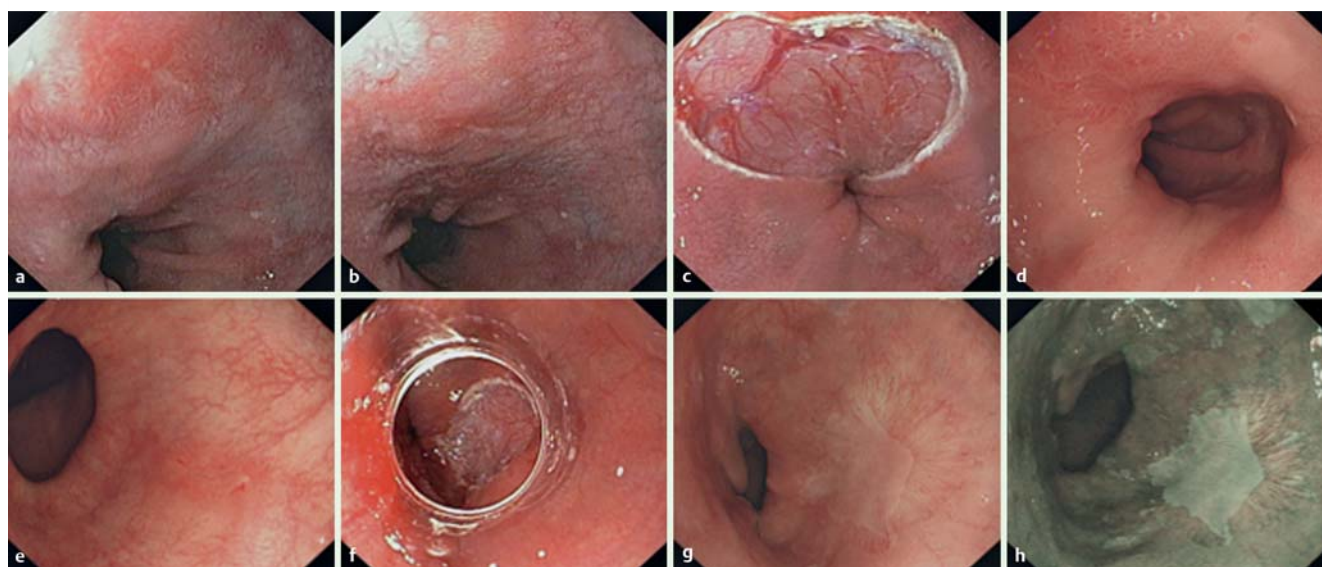


Fig. 3 Images of typical scar appearances following endoscopic resection. **a, b** A C5M7 Barrett's esophagus with a lesion containing high grade dysplasia; **c** the endoscopic resection wound; **d** the endoscopic resection scar showing regeneration with Barrett's epithelium. **e** A C9M10 Barrett's esophagus with a subtle lesion containing a T1m3 carcinoma; **f** the endoscopic resection wound; **g** the endoscopic resection scar showing regeneration with squamous epithelium, using white light; and **h** narrow band imaging.

Variable	Good initial response	Poor initial response	Odds ratio (95%CI)	P value
Sign of active reflux esophagitis, n (%)	10 (4%)	5 (14%)	37.4 (3.2 – 433.2)	<0.01
Scar regeneration with Barrett's esophagus, n (%)	11 (8%)	5 (24%)	4.7 (1.1 – 20.0)	0.03
Relative esophageal narrowing (asymptomatic) pre-RFA, n (%)	29 (12%)	11 (31%)	3.9 (1.0 – 15.1)	0.05
Neoplasia duration, mean (SD), years	2.3 (2.4)	3.9 (4.8)	1.2 (1.0 – 1.4)	0.03
No NSAID use, n (%)	152 (76%)	28 (93%)	3.0 (0.4 – 22.0)	0.27
Absence of squamous islands pre-RFA, n (%)	44 (20%)	13 (42%)	1.8 (0.4 – 7.3)	0.43

CI, confidence interval; SD, standard deviation; NSAID, nonsteroidal anti-inflammatory drug.

¹ Variables with $P < 0.10$ on univariate logistic regression analysis were entered into the multivariate model.

Table 3 Potential predictive factors 3 months after initial circumferential balloon-based radiofrequency ablation (c-RFA) identified by multivariate logistic regression.¹ Poor initial response was defined as <50% regression of the Barrett's epithelium.

Predictors for poor regression of the Barrett's esophagus 3 months after c-RFA

Univariate analysis detected six significant predictive factors for a poor initial response at 3 months after c-RFA: no NSAID use (OR 4.4; $P = 0.05$); presence of active reflux esophagitis (OR 4.0; $P = 0.02$); regeneration of the endoscopic resection scar with Barrett's epithelium (OR 3.4; $P = 0.04$); relative esophageal narrowing (asymptomatic) pre-RFA (OR 3.2; $P < 0.01$); absence of squamous islands pre-RFA (OR 2.9; $P < 0.01$); and the number of years with neoplasia before RFA (OR 1.2; $P = 0.01$; [Table 1](#)). There was no multicollinearity among variables.

Multivariate analysis (model-fit significance <0.01; Hosmer and Lemeshow test significance 0.09, Nagelkerke R^2 0.31) demonstrated that the presence of active reflux esophagitis (OR 37.4; $P < 0.01$), regeneration of the endoscopic resection scar with Barrett's epithelium (OR 4.7; $P = 0.03$; [Fig. 3](#)), relative esophageal narrowing (asymptomatic) pre-RFA (OR 3.9; $P = 0.05$), and the number of years with neoplasia before RFA (OR 1.2; $P = 0.03$) were independent predictors of poor response 3 months after c-RFA ([Table 3](#)).

In our study, poor initial responders had a median history of 2 years of neoplasia before c-RFA treatment (IQR 2–6) vs. 1 year (IQR 1–3) for good responders. Baseline esophageal narrowing pre-RFA was present in 11/36 poor responders (31%) vs. 29/242 good responders (12%). Regeneration of the endoscopic resection scar with Barrett's epithelium occurred in 5/21 poor responders (24%) vs. 11/132 good responders (8%). Signs of active reflux esophagitis prior to RFA despite proton pump inhibitor (PPI) treatment were observed in 5/35 poor responders (14%) vs. 10/240 good responders (4%).

The predictive capability of the multivariable model can be illustrated by counting the number of risk factors present in each patient ([Table 4](#)). In this analysis, the predictor “years of neoplasia before c-RFA” was categorized as ≤ 2 years or > 2 years of neoplasia. The observed proportion of poor initial responders in the study population was 9% if none of the four independent predictors of poor response were present, whereas it was 13% in the presence of one independent predictor, 38% in the presence of two independent predictors, and 100% in the presence of three independent predictors ($P < 0.00$).

Table 4 Observed proportion of patients with poor response 3 months after initial circumferential balloon-based radiofrequency ablation (c-RFA) in the presence or absence of one or more independent multivariate predictors of poor initial response. Poor initial response was defined as <50% regression of the Barrett's epithelium 3 months after the initial c-RFA.

Number of independent risk factors	Number of patients n = 278	Observed proportion of patients with poor initial response to c-RFA
0	165	9% (14/165)
1	90	13% (12/90)
2	21	38% (8/21)
3 or more	2	100% (2/2)

Discussion

Despite the generally good results of RFA for the ablation of dysplastic Barrett's esophagus, we have shown in this prospective multicenter study that 13% of patients show poor regression of the Barrett's esophagus surface area 3 months after the initial c-RFA session, and that these patients require more RFA sessions or a longer interval between RFA sessions to obtain complete healing of the esophagus [1–6]. Additionally, this study has demonstrated that these patients are more likely to ultimately fail to achieve a complete response in terms of either intestinal metaplasia or neoplasia. CR-neoplasia and CR-IM were achieved in as many as 98% and 95% respectively of good initial responders; in contrast, they were achieved only 86% and 66% respectively of poor initial responders. Furthermore, poor initial responders required a median treatment period of 13 months for a median of four RFA sessions, compared with 7 months for three RFA sessions in good initial responders.

This is the first study to focus on potential early predictors in the RFA treatment phase of a poor ultimate response to RFA treatment, which would allow for an early change in individual patient management. Our results show that a poor initial response after c-RFA may be predicted by the presence of the certain baseline characteristics: active reflux esophagitis despite PPI use prior to RFA, regeneration of the endoscopic resection scar with Barrett's epithelium, esophageal narrowing prior to RFA, or a longer history of Barrett's neoplasia prior to RFA. Remarkably, the characteristics of the Barrett's esophagus were more important in predicting a poor response 3 months after c-RFA than patient characteristics or technical aspects of the RFA treatment.

The presence of active reflux esophagitis at baseline was the strongest predictor of a poor initial response after c-RFA. This is

in agreement with two recent small studies in which patients underwent pH-impedance measurements prior to RFA, which showed that patients who failed to achieve CR-IM had a higher rate of reflux despite PPI treatment [15,21]. These data suggest that ongoing reflux disease despite PPI treatment may compromise the success rate of RFA.

In our study, we did not systematically perform pH studies. However, given our finding that active reflux esophagitis is a potential predictor of poor response, further research is required to study the clinical implications of uncontrolled reflux disease in patients scheduled for RFA. These studies should include pH-impedance measurements to assess the severity of GERD and its influence on the regression of Barrett's esophagus in patients undergoing RFA, including examination of the contents of the refluxate (bile acid, pancreatic juices) [15]. If indeed the response to RFA treatment can be related to the quantification of esophageal reflux under double-dose PPI, it may help to tailor medical and even surgical therapy such as fundoplication prior to RFA in order to increase the success rates of RFA.

At this time, the study protocols used so far have adhered to an aggressive acid-suppression regimen, consisting of esomeprazole 40 mg twice daily as maintenance, with the addition of ranitidine 300 mg at bedtime and sucralfate sachets four times daily for 2 weeks after every RFA session [1–6]. In patients with active reflux, it may be advisable—based on our results—to postpone the RFA procedure whilst optimizing acid suppression and the patient's compliance with medical treatment and lifestyle advice. Furthermore, in patients with a poor initial response to RFA, a low threshold for pH measurements and referral for Nissen fundoplication in those with ongoing reflux or poor healing is advisable during the RFA treatment phase.

We detected two new predictors of response to RFA that are related to the esophageal regeneration capacity: regeneration of the endoscopic resection wound with Barrett's instead of squamous epithelium (multivariate analysis) and the absence of squamous islands in the Barrett's segment (univariate analysis). We hypothesize that squamous regeneration of the endoscopic resection scar and a high number of squamous islands in the Barrett's segment reflect a tendency of the Barrett's segment to re-epithelialize with normal squamous cell mucosa after damage to the Barrett's epithelium [22–25].

Presence of an asymptomatic relative narrowing or mild stenosis of the Barrett's esophagus was an independent predictor of poor response in our study. These mild stenoses may influence the response to RFA by two mechanisms. First, and most likely, these patients may be part of a subgroup of patients with more severe reflux than others, because the narrowing may be caused by reflux-induced scarring. Second, it is conceivable that stenosis caused by scarring due to endoscopic resection or reflux disease may result in suboptimal electrode contact and less effective ablation. Additionally, RFA treatment may be suboptimal because of conservative balloon selection in patients with a prior endoscopic resection, or reflux stenosis or scarring, as in these patients it is advisable to use an ablation balloon with a diameter that is two sizes smaller than the smallest measurement to prevent laceration during RFA [4].

Our finding that a longer history of neoplasia was a predictor of poor regression of the Barrett's esophagus surface area is consistent with the results of others who have demonstrated a relationship between longer history of neoplasia and failure to achieve CR-IM [5]. In contrast, presence of Barrett's esophagus alone for a longer time was not a predictor of poor response. Theoretically,

neoplastic Barrett's epithelium has less optimal regeneration capacity than non-neoplastic Barrett's esophagus.

A limitation of this study is the use of logistic regression analysis on the relatively small number of patients with a poor initial response. Therefore, the relationships detected in our study may appear stronger than they would be in a larger population. However, by selecting potential variables based on our clinical knowledge of existing data and by presenting the predictive capability of a simplified, robust version of the multivariable model, we aimed to reduce the influence of potential overfitting of the regression model. Nevertheless, our findings require external validation in other large study populations.

Another limitation is that we have related potential predictive markers for response to a surrogate end point. We selected regression of the Barrett's esophagus surface area after c-RFA to define efficacy, assuming that this end point is a better measure of the efficacy of c-RFA than the rates of CR-neoplasia and CR-IM after multiple RFA sessions. Furthermore, we evaluated the agreement between the real-time percentage regression of the Barrett's esophagus, as scored during endoscopy, and the surrogate end point of the mean percentage regression of the Barrett's esophagus, as scored by two experienced endoscopists on review of the endoscopic images. The median difference between the endoscopists and the real-time score was found to be small (2.5%). In addition, we used the mean score of both endoscopists as the primary end point, thus partially ruling out interobserver variation.

An important strength of our study is its multicenter design, with centers uniformly trained in RFA, either as a part of participation in several European multicenter studies or as participants of the "European ER & RFA training program" initiated by our center (www.endosurgery.eu) [2–4,6,7]. This ensured that all centers were proficient in RFA treatment for Barrett's esophagus. Furthermore, this study contains a large number of patients, and patients were treated with RFA for a wide range of indications, including HGD, LGD, nondysplastic Barrett's esophagus, Barrett's esophagus ≤ 5 cm, Barrett's esophagus ≥ 10 cm, and Barrett's esophagus after endoscopic resection of HGD or early carcinoma. All patients were prospectively registered using case registration forms that were available online. Another strength of our study is the independent blinded scoring of the percentage regression of the Barrett's esophagus at 3 months by two endoscopists to validate the primary end point.

In conclusion, this prospective multicenter study showed that 13% of patients have less than 50% surface regression of their Barrett's esophagus after initial c-RFA. These poor initial responders have significantly lower success rates, require more RFA sessions, and have a prolonged treatment period. Our results suggest that a poor initial response to c-RFA occurs more often in patients who regenerate their endoscopic resection wound with Barrett's epithelium, have endoscopic signs of active reflux esophagitis despite PPI treatment, have had neoplasia in Barrett's esophagus for a longer time prior to RFA, or have a narrowing of their esophagus prior to RFA.

These findings need to be confirmed in other large studies focusing on the possible role of refractory reflux. Ultimately, this may help to stratify patients and permit alternative management strategies to be used, including endoscopic surveillance, esophagectomy, stepwise radical endoscopic resection, or Nissen fundoplication followed by RFA.

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Institutions

- ¹ Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands
- ² Department of Gastroenterology, St Antonius Hospital, Nieuwegein, The Netherlands
- ³ Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium
- ⁴ Department of Gastroenterology, Hospital Clínico San Carlos, Madrid, Spain
- ⁵ Department of Gastroenterology, Klinikum rechts der Isar, München, Germany
- ⁶ Department of Gastroenterology, Evangelisches Krankenhaus, Düsseldorf, Germany
- ⁷ Department of Gastroenterology, Hospital Universitario Central de Asturias, Oviedo, Spain
- ⁸ Department of Gastroenterology, Dr.-Horst-Schmidt-Kliniken, Wiesbaden, Germany
- ⁹ Department of Gastroenterology, Queens Medical Centre, Nottingham, UK
- ¹⁰ Department of Gastroenterology, St James Hospital, Leeds, UK
- ¹¹ Department of Gastroenterology, Isala Klinieken, Zwolle, The Netherlands
- ¹² Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands
- ¹³ Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
- ¹⁴ Department of Gastroenterology, Catharina Hospital Eindhoven, The Netherlands
- ¹⁵ Department of Gastroenterology, Pontificia Universidad Católica de Chile, Santiago, Chile

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