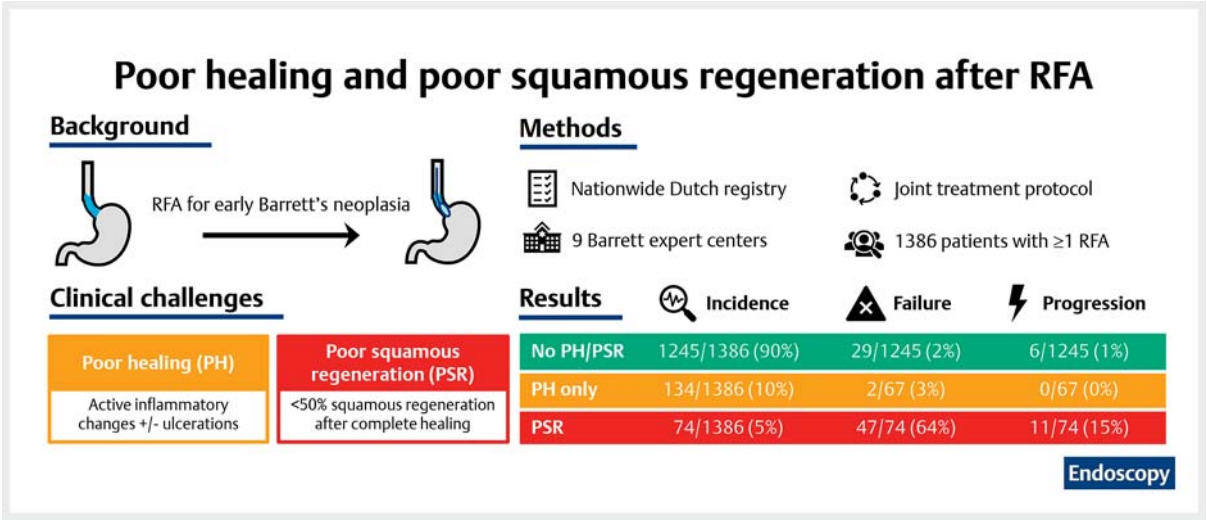
Incidence and outcomes of poor healing and poor squamous regeneration after radiofrequency ablation therapy for early Barrett's neoplasia

GRAPHICAL ABSTRACT



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ABSTRACT

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

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

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

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

Introduction

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

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

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

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

Methods

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

The BEC registry has been described in detail previously [9]. For the current study, we included all patients with BE containing early neoplasia who underwent endoscopic eradication therapy with at least one RFA treatment between 1 January 2008 and 31 December 2018. The treatment and follow-up outcomes for this cohort of patients have been published previously [9], but the current study analyzed and reported different end points.

Treatment protocol

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

Visible lesions were removed with endoscopic resection. RFA was used to treat flat BE using the Barrx system (Medtronic Inc., Minneapolis, Minnesota, USA). The Barrx-360 balloon catheter

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

End of treatment

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

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

Acid-reducing medication

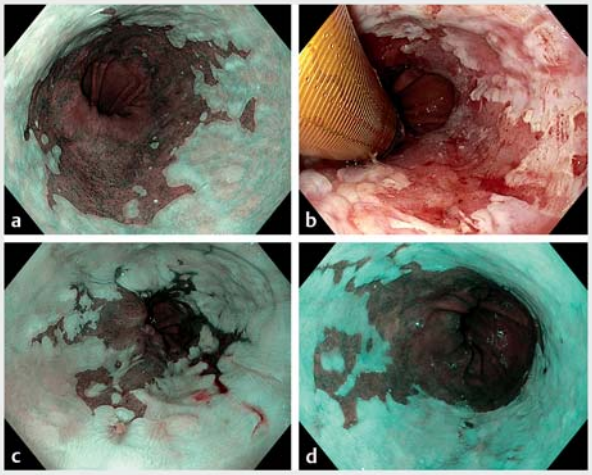
Double-dose proton pump inhibitors (PPI; 40 mg twice daily, per default esomeprazole) was prescribed during the treatment phase. In addition, patients were administered ranitidine 300 mg at bedtime and sucralfate suspension 5 mL four times daily during 14 days after every treatment.

Poor healing

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

Poor squamous regeneration

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



▶ **Fig. 1** Poor healing. **a** C2M5 flat Barrett's esophagus with low grade dysplasia in random biopsies during baseline endoscopy. **b** Circumferential radiofrequency ablation (RFA) was performed first. **c** At 3 months post-RFA, active inflammatory changes were found, along with mucosal swelling. **d** We emphasized to the patient the importance of compliance with proton pump inhibitor therapy and waited for another 10 weeks, at which point complete healing of the esophagus was found with 80 % squamous regeneration. After two additional focal RFA treatments performed at 20-week intervals, complete eradication of Barrett's esophagus was achieved. Please refer to **Fig. 1 s** for additional endoscopic images.

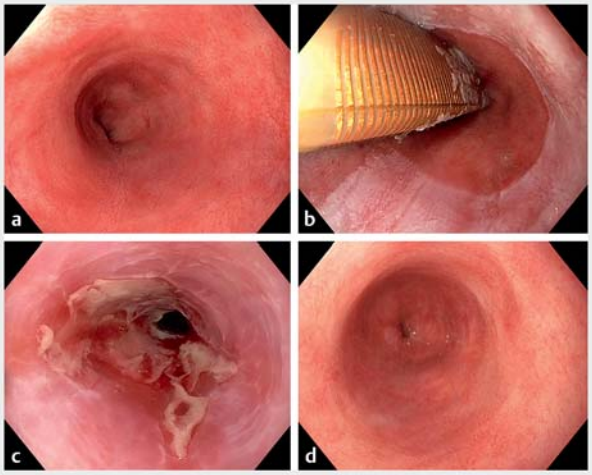
Study end points

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

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

Data collection and data management

Data were collected by reviewing endoscopy and pathology reports, endoscopy images, and further clinical information where necessary, as described in detail previously [9]. Dedicated research fellows (all MDs) reviewed the data against source



▶ **Fig. 2** Poor squamous regeneration preceded by poor healing. C9M10 Barrett's esophagus containing a visible lesion. Owing to expected deep invasion, endoscopic submucosal dissection was performed for a well-differentiated mucosal cancer. **a** After 3 months, the resection scar (between the 12 and 7 o'clock positions) was completely regenerated with Barrett's mucosa. **b** Circumferential radiofrequency ablation (RFA) was performed and resulted in poor healing with visible ulcerations and active inflammatory changes with mucosal swelling after 12 weeks (**c**). **d** After another 8 weeks and verification of proton pump inhibitor compliance, the esophagus was completely healed but had regenerated with Barrett's mucosa. Random four-quadrant biopsies showed low grade dysplasia. The decision was made to stop further RFA treatment and switch to endoscopic surveillance. Please refer to **Fig. 2 s** for additional endoscopic images.

documents for all patients with poor healing, poor squamous regeneration, and/or treatment failure, and additionally for a 50 % random selection of the remaining patients.

Ethics

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

Statistics

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

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

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

Results

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

Poor healing

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

Treatment outcomes after poor healing

Upon complete healing, 67/134 patients (50 %) had normal squamous regeneration (i. e. > 50 %) and 65/67 (97 % [95 %CI 90–99]) achieved CE-BE (**Fig. 3 s**). The CE-BE rate was similar to that in patients with normal healing (1178/1207; 98 % [95 %CI 97 %–98 %]) (▶ **Table 2**), with an RR of 1.0 (95 %CI 1.0–1.0). Two patients with poor healing (2/67; 3 %) did not achieve CE-BE and had remaining Barrett's mucosa (C1M3/4) with nondysplastic Barrett's esophagus (NDBE) or LGD (▶ **Table 3**). Both patients developed severe esophageal stenosis during treatment and an elective decision was made to withhold further treatment in order to prevent recurrent stenosis with continued RFA. No patient progressed to advanced neoplasia.

Treatment characteristics of patients with poor healing

In the 67 patients with normal squamous regeneration after poor healing, poor healing occurred again after RFA in 38/67 patients (57 %) and RFA was continued with prolonged intervals (range 16–20 weeks) between ablation sessions. The treatment duration for patients with poor healing was significantly longer

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

	All patients (n = 1386)	No poor healing or poor squamous regeneration (n = 1245)	Poor healing, normal squamous regeneration (n = 67)	Poor squamous regeneration[1] (n = 74)
Male sex, n (%)	1121 (81)	1009 (81)	56 (84)	56 (76)
Age, mean (SD), years	65.5 (6)	66.0 (6)	63.5 (4)	66.0 (4)
BMI, mean (SD), kg/m2	27.6 (2)	27.2 (2)	27.1 (2)	28.1 (2)
Smoking, n (%)				
▪ Never	321 (23)	285 (23)	18 (27)	18 (24)
▪ Former	805 (58)	725 (58)	34 (51)	46 (62)
▪ Current	260 (19)	235 (19)	15 (22)	10 (14)
Surveillance history, n (%)	892 (64)	808 (65)	39 (58)	45 (61)
▪ Duration, median (IQR), years	3 (0–8)	3 (0–8)	3 (0–6)	3 (0–7)
Prior fundoplication, n (%)	23 (2)	15 (1)	5 (7)	3 (4)
PPI 40 mg twice daily or higher, n (%)	1241 (90)	1121 (90)	58 (87)	61 (82)
Reflux esophagitis, n (%)	49 (4)	33 (3)	5 (7)	11 (15)
Reflux stenosis, n (%)	49 (4)	40 (3)	4 (6)	5 (7)
Hiatal hernia, n (%)	1321 (95)	1184 (95)	64 (96)	74 (100)
▪ Size, median (IQR), cm	3.0 (2)	2.9 (2)	3.5 (2)	4.0 (2)
Circumferential BE length, median (IQR), cm	2 (0–5)	2 (0–5)	6 (3–8)	8 (5–10)
Maximum BE length, median (IQR), cm	5 (3–8)	4 (2–7)	7 (4–9)	9 (7–11)
Visible lesion, n (%)	870 (63)	775 (62)	37 (55)	58 (78)
≥ 1 visible lesion, n (%)	125 (9)	101 (8)	9 (13)	15 (20)
Worst histology, n (%)				
▪ LGD	375 (27)	337 (27)	21 (31)	17 (23)
▪ HGD	422 (30)	380 (31)	25 (38)	17 (23)
▪ EAC	589 (43)	528 (42)	21 (31)	40 (54)
Baseline endoscopic resection, n (%)	870 (63)	775 (62)	37 (55)	58 (78)
Squamous regeneration after endoscopic resection, n (%)[2]				
▪ No endoscopic resection performed	520 (38)	473 (38)	30 (45)	17 (23)
▪ > 50 % squamous regeneration	808 (58)	748 (60)	32 (48)	28 (38)
▪ < 50 % squamous regeneration	58 (4)	24 (2)	5 (7)	29 (39)

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

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

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

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

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

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

compared with patients with normal healing (15 and 8 months, respectively; *P* < 0.01) (▶ **Table 2**).

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

Poor squamous regeneration

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

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

Treatment outcomes after poor squamous regeneration

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

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

The remaining three failure cases with persisting neoplasia (3/74, 4 %) had persisting HGD or low risk EAC and underwent stepwise radical endoscopic resection (SRER) after RFA. Com-

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

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

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

plete eradication of neoplasia was achieved in all three patients and CE-BE was achieved in two.

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

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

Treatment characteristics of patients with poor squamous regeneration

Patients with poor squamous regeneration had a higher risk for a visible abnormality ("incident lesion") developing during RFA treatment. An incident lesion occurred in 16/74 patients (22 %) with poor squamous regeneration compared with 61/1245 pa-

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

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

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

tients (5 %) with normal squamous regeneration (RR 4.4 [95 %CI 2.7–7.3]) (▶ **Table 2**). For patients with poor squamous regeneration, 11/16 (69 %) incident lesions were noted to have progressed to advanced neoplasia, compared with 6/61 incident lesions (10 %) among patients with normal squamous regeneration (RR 7.0 [95 %CI 3–16]).

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

Characteristics associated with poor squamous regeneration

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

Poor regression after endoscopic resection without RFA

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

Discussion

In this nationwide cohort of 1386 patients with early BE neoplasia who were treated with RFA, we found that poor healing and poor squamous regeneration occurred in 10 % and 5 % of patients, respectively. Poor healing resolved after additional time and acid suppression. Half of the patients with poor healing showed normal squamous regeneration and 97 % of these reached CE-BE, which was comparable to the success rate in patients with normal healing and regeneration. The other 50 % of patients with poor healing also showed poor squamous regeneration and only 36 % of these patients were treated successfully. Furthermore, patients with poor squamous regeneration had a significantly higher risk for progression to advanced disease during treatment compared with patients with normal squamous regeneration. None of the patients who also demonstrat-

▶ **Table 5** Clinical advice. Based on our data, we present practical advice on a number of clinical scenarios for the management of poor healing and/or poor squamous regeneration[1].

Clinical problem	Advice	Rationale
Less than 50 % squamous regeneration after baseline endoscopic resection (**Fig. 4 s**)	Consider surveillance of the remaining BE instead of proceeding with ablation therapy, as this is a valid alternative in patients with flat BE without neoplasia after endoscopic resection.	Of the 58 patients with < 50 % squamous regeneration after endoscopic resection, 59 % developed poor healing and/or poor squamous regeneration after subsequent RFA. The risk increased further for patients with a higher BMI, a longer BE segment, and/or reflux esophagitis. In 12 patients with older age and/or comorbidity and endoscopic resection with < 50 % squamous regeneration, a remaining flat BE with NDBE or LGD persisted and RFA was not initiated; during mean 25 months of follow-up, no patient progressed to HGD or EAC.
Poor healing (active inflammatory changes with mucosal swelling and exudates, and/or visible ulcerations ≥ 3 months post-RFA; ▶ **Fig. 1**, ▶ **Fig. 2**)	Postpone treatment.	The edematous mucosa is too thick for effective ablation and visible lesions may be masked.
	Optimize circumstances for healing:	In all 134 patients with poor healing after RFA, complete healing was accomplished after these steps were followed.
	1. Provide sufficient time: schedule a new endoscopy in ≥ 6 weeks.	
	2. Provide sufficient acid suppression: verify PPI compliance and consider dose increase.	
	3. Only perform 24-hour pH-metry if a finding of pathological reflux would result in referring the patient for fundoplication, or in other clinical consequences.	
	Upon complete healing, assess conversion to squamous epithelium.	Upon complete healing, 50 % (67/134) of patients with initial poor healing had normal squamous regeneration.
Initial poor healing, with now complete healing and > 50 % squamous conversion (▶ **Fig. 1**)	Continue RFA on 4–6-month intervals.	97 % (65/67) achieved CE-BE (similar to 94 % of patients with initial normal healing).
	Counsel your patient:	
	1. Continuing treatment carries a higher risk for esophageal stenosis.	30 % of patients (40/134) developed esophageal stenosis and 8 % (10/134) had a severe stenosis that required > 5 endoscopic dilations. These risks were significantly higher compared with patients with normal healing (14 % and 2 %, respectively; $P < 0.01$).
	2. The treatment phase will take more time.	Median treatment duration was 15 months (IQR 10–20) compared with 8 months (IQR 4–13) for patients with normal healing ($P < 0.01$).

ed poor squamous regeneration after their second RFA treatment achieved CE-BE. Risk factors for poor squamous regeneration included higher body mass index, longer BE segments, presence of reflux esophagitis, and < 50 % squamous regeneration of the initial endoscopic resection wound.

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

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

▶ **Table 5** (Continuation)

Clinical problem	Advice	Rationale
Poor squamous regeneration (< 50 % squamous regression after the first RFA upon complete healing; ▶ **Fig. 2**)	Consider poor squamous regeneration as a warning sign. Careful inspection is crucial as patients have a significant risk for new visible lesions that pop-up during RFA and for progression to advanced neoplasia.	22 % of patients with poor squamous regeneration (16/74) developed an incident lesion compared with (5 %, P < 0.01) for patients with normal regeneration. Moreover, 69 % of incident lesions in patients with poor squamous regeneration (11/16) had advanced neoplasia compared with 10 % of the incident lesions in patients with normal regeneration (6/61; P < 0.01).
	Reconsider continuation of ablative therapy.	Outcomes of RFA are worse if poor squamous regeneration occurs after the first RFA: only 36 % of patients (27/74) achieved CE-BE after continued RFA compared with 98 % of patients with normal squamous regeneration (1178/1207).
	Decision making after the first RFA with poor squamous regeneration:	
	A second RFA may be justified, based on the following considerations:	
	1. Arguments in favor of a second RFA: ▪ < 50 % squamous regeneration, but some areas with normal regeneration ▪ completely flat BE	Overall, 47 % (27/57) of patients had normal squamous regeneration after the second RFA. For patients with remnant circumferential BE of < 2 cm and an indication for focal RFA, 67 % (20/30) had normal squamous regeneration.
	2. Arguments in favor of no further RFA: ▪ Patients of older age and/or with comorbidity. ▪ Slightest suspicion for the presence of a visible lesion.	In older patients, the decision to continue with surveillance instead of RFA may be justified: 23 % of patient developed a visible lesion during long-term surveillance, all effectively treated endoscopically and none progressed to advanced EAC (see below). A cautious approach is called for with regard to inspection for visible lesions, as a second RFA may potentially again lead to a period of ±4–6 months with poor healing, during which no adequate inspection can be accomplished. Incident lesions in patients with poor squamous regeneration harbored advanced neoplasia in 69 % (11/16) compared with 10 % (6/61) of incident lesions in patients with normal squamous regeneration.
	Decision making after the second RFA:	
	1. If a second RFA results in > 50 % squamous regeneration, RFA may be continued.	All 27 patients with normal squamous regeneration after the second RFA achieved CE-BE.
	2. If a second RFA again results in < 50 % squamous regeneration, additional RFA should be restrained.	None of the 30 patients with poor squamous regeneration after the second RFA achieved CE-BE, despite additional RFA treatment in 16/30 patients.
A decision was made to stop further RFA owing to poor squamous regeneration	The remaining BE should be accurately staged with inspection, targeted biopsies, and/or endoscopic resection in cases with visible lesions, and four-quadrant random biopsies.	
	1. Radical endoscopic resection may be considered if baseline endoscopic resection had > 50 % squamous regeneration.	5/6 patients achieved CE-BE after radical endoscopic resection. The single patient who did not achieve CE-BE was the only one who had < 50 % squamous regeneration after baseline endoscopic resection.
	2. Persisting HGD, EAC, and/or visible lesions: radical endoscopic resection may be an option, but esophagectomy should be considered in early stages, especially in younger patients.	Overall, patients with poor squamous regeneration had a high risk for progression to advanced EAC during treatment (15 % vs. < 1 % of patients with normal regeneration; P < 0.01). Five patients with persisting visible lesions were referred for surgery, four of whom had ≤ T1N0, and one had T2N1 (20 %).
	3. Persisting flat BE with intestinal metaplasia or LGD: endoscopic surveillance is a valid policy.	During a mean follow-up of 3.5 years, 23 % developed HGD or early EAC, all of which were successfully treated with curative endoscopic resection.

BE, Barrett's esophagus; BMI, body mass index; CE-BE, complete endoscopic eradication of Barret's esophagus; EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; IQR, interquartile range; LGD, low grade dysplasia; NDBE, nondysplastic Barrett's esophagus; PPI, proton pump inhibitor; RFA, radiofrequency ablation.
[1] Poor healing was defined as active inflammatory changes with mucosal swelling and exudates, and/or visible ulcerations ≥ 3 months post-RFA. Poor squamous regeneration was defined as < 50 % regression to squamous epithelium after RFA, assessed after complete healing.

time and sufficient acid suppression, the esophagus will heal completely.

The effects of RFA (i. e. conversion of the BE into squamous epithelium and the presence/absence of incident lesions) can only be evaluated when the esophagus is completely healed. Half of the patients with poor healing were found to have normal squamous regeneration and, although treatment was of longer duration and with a higher risk for esophageal stenosis, these patients had a > 95 % chance of CE-BE, which was similar to that observed in patients with normal healing.

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

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

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

Considering such alternative strategies may also be appropriate prior to the initial RFA if this is preceded by endoscopic resection healing with < 50 % squamous regeneration. If this was observed, 50 % of patients were noted to have poor squamous regeneration after RFA (adjusted OR 13). Our study confirmed the results of other studies showing that poor regression after endoscopic resection is a strong predictor for poor squamous regeneration after RFA [7].

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

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

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

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

Other limitations include the risk for misclassification bias. If the endoscopy reports were incomplete for poor squamous regeneration, endoscopic images and videos were reviewed to obtain complete data without blinding of the assessor to the outcome. We used a cutoff of 50 % for the definition of poor squamous regeneration, which is arbitrary, and a more contin-

uous score might have provided more information. However, we preferred a simple cutoff that could easily be used in clinical practice.

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

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Competing interests

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Clinical trial

Trial Registration: Netherlands National Trial Register (http://www.trialregister.nl) | Registration number (trial ID): NL7039 | Type of study: Retrospective, multicenter study

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