Self-sizing radiofrequency ablation balloon for eradication of Barrett's esophagus: results of an international multicenter randomized trial comparing 3 different treatment regimens

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Background and Aims: Recently, the 360 Express radiofrequency ablation balloon catheter (360 Express, Medtronic, Minneapolis, Minn, USA) has replaced the traditional system for circumferential radiofrequency ablation (RFA) of Barrett's esophagus (BE). The aim was to compare 3 different ablation regimens for the 360 Express.

Methods: An international multicenter noninferiority randomized controlled trial was conducted in which patients with a BE (2-15 cm) with dysplasia or early cancer were randomly assigned to the standard (1 10 J/cm²-clean-1 10 J/cm²), simple-double (2 10 J/cm²-no clean), or simple-single ablation regimen (1 10 J/cm²-no clean). The primary outcome was the percentage endoscopically visual BE regression at 3 months. Secondary outcomes were procedure time, adverse events, and patient discomfort.

Results: Between September 2015 and October 2017, 104 patients were enrolled. The simple-double ablation arm was closed prematurely because of a 21% stenosis rate. The trial continued with the standard (n = 37) and simple-single arm (n = 38). Both arms were comparable at baseline. Noninferiority of the simple-single arm could not be demonstrated: BE regression was 73% in the simple-single arm versus 85% in the standard arm; the median difference was 13% (95% confidence interval, 5%-23%). The procedure time was significantly longer in the standard arm (31 vs 17 minutes, $P < .001$). Both groups were comparable with regard to adverse events and patient discomfort.

Conclusions: This randomized trial shows that circumferential RFA with the 360 Express using the simple-double ablation regimen results in an unacceptable high risk of stenosis. Furthermore, the results suggest that a single ablation at 10 J/cm² results in inferior BE regression at 3 months. We therefore advise using the standard ablation regimen (1 10 J/cm²-clean-1 10 J/cm²) for treatment of BE using the 360 Express. (Clinical trial registration number: NTR5191.) (Gastrointest Endosc 2019;90:415-23.)

INTRODUCTION

Radiofrequency ablation (RFA), with previous endoscopic resection (ER) of visible lesions when present, has been shown to be effective and safe in the treatment of dysplastic Barrett's esophagus (BE).¹⁻⁴ Most patients first undergo circumferential balloon-based RFA, followed by subsequent focal RFA sessions. Traditionally, circumferential RFA of BE was performed using the Barrx360 system (Medtronic, Minneapolis, Minn, USA). The Barrx360 procedure started with sizing the esophageal inner diameter (EID) at multiple levels. Based on these measurements, an appropriately sized ablation catheter, with a 3-cm-long electrode, was selected and used to ablate the Barrett's segment. For the traditional system, 2 ablation regimens could be applied: the standard regimen consisting of 2 ablations at 12 J/cm² with a cleaning phase in between, and a simplified regimen in which the same zone was sequentially ablated twice without a cleaning step. A previous randomized trial showed that both ablation regimens were equally effective and safe; however, the simplified regimen was significantly faster and required fewer introductions of the endoscope and ablation catheter.⁵ Disadvantages of the traditional Barrx360 system were that it required separate introduction of the sizing catheter and subsequently the ablation catheter, and that the entire Barrett's segment was treated with an ablation catheter with a fixed diameter. To

overcome these disadvantages, the traditional system was recently replaced by the 360 Express RFA balloon catheter (360 Express, Medtronic, Minneapolis, Minn, USA). The 360 Express consists of a 4-cm-long electrode that is wrapped around a balloon and has the ability to self-adjust to the esophageal lumen ensuring optimal tissue contact during each ablation. A recent pilot study showed that circumferential RFA with the 360 Express using the standard ablation regimen (12 J/cm^2 -clean- 12 J/cm^2) leads to a decreased procedure time but maintains efficacy when compared with the traditional system.⁶ However, after one 360 Express treatment, pronounced esophageal scarring was observed in 23% of the patients. Although no symptomatic stenosis was seen after a single treatment session, 10% of the patients did develop a stenosis requiring dilation after subsequent focal RFA treatment.

In the current study, we sought to evaluate the optimal ablation regimen for the 360 Express. Because the new 360 Express balloon adjusts to the EID and has a longer electrode, it may be a more effective but also potentially a more aggressive ablation tool, and therefore the energy density settings for the 360 Express were lowered from 12 J/cm^2 to 10 J/cm^2 .⁶ We evaluated the standard regimen at 10 J/cm^2 , a simplified regimen with 2 ablations at 10 J/cm^2 without a cleaning phase, and a third arm in which a single hit at 10 J/cm^2 was performed. The aim of this study was to compare these 3 different regimens for circumferential RFA of BE using the 360 Express.

METHODS

Study design and setting

This study was designed as a multicenter noninferiority randomized controlled trial comparing 3 arms. The trial was conducted in 5 tertiary referral centers for the management of early Barrett's neoplasia in the Netherlands and Belgium: Amsterdam University Medical Center, location AMC, Amsterdam; Catharina Hospital, Eindhoven; Erasmus MC, University Medical Center, Rotterdam; St. Antonius Hospital, Nieuwegein; and UZ Gasthuisberg, Leuven.

An independent data and safety monitoring board (DSMB), consisting of 2 gastroenterologists with experience in using RFA and a statistician, was assigned to monitor the safety of the participants. Safety stopping rules were created to guide the DSMB in decision making.

Patient selection

Patients were eligible if they met all of the following inclusion criteria: age 18 to 85 years; BE between 2 and 15 cm at baseline (before any ER); and biopsy-proven low-grade dysplasia, high-grade dysplasia, or cancer confirmed by an expert pathologist. In the case of previous ER for early cancer or visible lesions, the resection had to be limited to <2 cm in length and <50% of the circumference. Patients were excluded if they had any of the following exclusion criteria: previous ablation treatment; significant esophageal stenosis preventing passage of a diagnostic endoscope or any previous dilatation for esophageal stenosis; presence of esophageal varices; anti-coagulant therapy (apart from aspirin or nonsteroidal anti-inflammatory drugs) that could not be discontinued; uncorrectable hemostatic disorders; an interval of >6 months between the last high-resolution endoscopy with biopsies and RFA treatment; an interval <6 weeks between ER and RFA; residual cancer in biopsy specimens obtained after ER and before RFA; and in the case of previous ER, specimen(s) showing positive vertical resection margins, deep submucosal invasion (>T1sm1), poorly or undifferentiated cancer, or lymphatic/vascular invasion. In addition, patients had to give informed consent.

Randomization

Patients were randomly assigned in a 1:1:1 ratio to treatment with the standard (1 10 J/cm²-clean-1 10 J/cm²), simple-double (2 10 J/cm²-no clean), or simple-single (1 10 J/cm²-no clean) ablation regimen. Randomization of eligible patients was performed on site by the local study coordinator during the study endoscopy after eligibility of the patient was confirmed by the endoscopist. The randomization sequence was computer generated (ALEA randomization software, FormsVision, Abcoude, The Netherlands) and was stratified by previous ER. The allocation sequence was concealed from the study personnel enrolling patients by using random block sizes of 3, 6, and 9.

The 2 primary outcome assessors (R.H., O.P.) were blinded to the allocation. Patients and study personnel were aware of the allocated treatment arm.

Study device

All patients were treated with the 360 Express. The 360 Express consists of a 4-cm-long, 360-degree electrode array that is wrapped around a self-adjusting balloon that can range in diameter from 18 mm to 31 mm (Fig. 1). Further details were described previously.⁶ The Barrx360 express catheters used in this investigator-initiated study were supplied by Medtronic (Minneapolis, Minn, USA).

Interventions

Work-up endoscopy before inclusion. Within 6 months before inclusion (as part of standard clinical care), a high-resolution endoscopy was performed during which the entire Barrett's segment was carefully inspected. If present, visible abnormalities were removed using ER. The (residual) Barrett's segment was sampled by taking random biopsy samples according to the Seattle protocol (4Q/2 cm). Study procedure: 360 Express RFA. All procedures were performed with the patients under monitored anesthesia or conscious sedation. The Barrett's segment was cleaned with water. The procedure started with inspection of the Barrett's segment using high-resolution white-light endoscopy (WLE) and optical chromoendoscopy (eg, narrow-band imaging, blue-light imaging, or Fuji Intelligent Chromo Endoscopy, Fuji, Tokyo, Japan). When no visible abnormalities and no significant stenosis were present, patients were randomized. Still images were taken of every centimeter of the Barrett's segment using WLE and optical chromoendoscopy. After placement of a stiff guidewire, the 360 Express was introduced, followed by reintroduction of the endoscope to position the catheter at the

upper end of the Barrett's segment using visual guidance.

For the standard ablation regimen (1X 10 J/cm² -clean-1 X 10 J/cm²), the entire Barrett's segment was ablated (10 J/cm² at 300 W) working from proximal to distal, repositioning the catheter under visual control. After the first ablation pass, the endoscope and ablation catheter were removed. The catheter was cleaned and the endoscope with a distal attachment cap attached to its tip was reintroduced to wipe off the coagulum from the ablated segment. Then the guidewire was replaced, the endoscope was removed, and the catheter and endoscope were reintroduced to repeat the ablation.

For the simple-double ablation regimen (2 10 J/cm² - no clean), immediately after the first ablation (10 J/cm² at 300 W), a second ablation was performed on the same zone without cleaning. The balloon was advanced distally to ablate subsequent zones under visual control with a double ablation in an identical way.

For the simple-single ablation regimen (1 10 J/cm² -no clean), the entire Barrett's segment was ablated with 1 hit of energy (10 J/cm² at 300 W) under visual control, working from proximal to distal, using visual repositioning without cleaning.

Postablation care. All patients received a maintenance high-dose proton pump inhibitor throughout the treatment period. For most patients, this medication was supplemented with ranitidine 300 mg at bedtime and sucralfate suspension 3 times a day for a period of 2 weeks after the RFA procedure.

Follow-up after treatment. Three months after the 360 Express procedure, post-treatment follow-up endoscopy was performed. Still images with high-resolution WLE and optical chromoendoscopy were again obtained at 1-cm intervals throughout the extent of the original Barrett's segment. Further treatment and follow-up were performed according to standard clinical guidelines. In general, repeat RFA treatment was performed at 3-monthly intervals until complete endoscopic eradication of all Barrett's tissue was achieved.

Outcomes

Definitions of all outcome parameters are summarized in Table 1. The primary outcome was the mean percentage of endoscopically visual surface regression of BE epithelium at 3 months, as scored by 2 independent endoscopists (R.H. and O.P.) blinded to the allocated ablation regimen. The secondary outcomes were adverse events, procedure time, and patient discomfort after RFA treatment. Patient discomfort consisted of 2 parameters: retrosternal pain directly after the procedure and the cumulative daily discomfort score (for 30 days after the procedure).

Sample size

We assumed that there would be no difference in the percentage of BE regression among the 3 ablation protocols.¹

Therefore, a noninferiority design was used comparing the standard protocol with either of the simplified protocols. We assumed that a difference of 15% or more in percentage BE regression would be clinically relevant. Using a significance level of .0125 (Bonferroni correction because of 2 comparisons), a noninferiority margin of 0.15, a standard deviation (SD) of 0.17, and power of 0.9, we calculated that 36 patients would be required per arm when taking a 10% dropout rate into consideration. Therefore, we sought to enroll a total of 108 patients. For the sample size calculation, statistical software R version

3.4.3 SampleSize4ClinicalTrial package was used.

Changes to study design after commencement of the trial

The DSMB recommended early closure of the simple-double arm because of an unacceptable high risk of adverse events. After approval of the Medical Ethical Committee (MEC), the trial continued with the 2 remaining arms and patients were randomized in a 1:1 fashion.

Statistical methods

For descriptive statistics, the mean (SD) was used in cases of normal distribution of variables, and the median (interquartile range [IQR]) was used for variables with a skewed distribution. Categorical variables are presented as frequencies with percentages. For the primary outcome, the median difference between the percentage Barrett's regression of the standard ablation arm and the simple-single arm was calculated together with the corresponding 95% confidence interval (CI). Noninferiority of the simple-single arm could be concluded when the prespecified noninferiority margin was not included in the CI, whereas inferiority could be concluded when the prespecified noninferiority margin was included in

the CI. For the secondary outcomes a Student t test or Wilcoxon rank sum test was used for the comparison of continuous variables with a normal distribution or skewed distribution, respectively.

Categorical variables were compared using the chi-squared or Fisher exact test. For the cumulative discomfort score, the duration of discomfort symptoms was estimated using Kaplan-Meier analysis. The event in the analysis was "free of discomfort symptoms," which was defined as a cumulative discomfort score of 0. The 2 groups were compared with a log rank test. A 2-sided *P* value <.05 was considered significant in the analyses. All analyses were performed on the modified intention-to-treat (m-ITT) population. Data analysis was performed using SPSS statistical software package (version 24; SPSS Inc, Chicago, Ill).

Post hoc analysis. Poor response was defined as 50% endoscopically visible BE regression after one 360 Express treatment, as scored by the 2 blinded endoscopists mentioned previously. In a post hoc analysis, we compared the presence of 4 known baseline independent predictors associated with a poor response between the groups: active reflux esophagitis, ER regeneration with BE, esophageal narrowing pre-RFA, and months of dysplasia pre-RFA.⁷

Ethical considerations

The study protocol was reviewed and approved by the MEC of Amsterdam UMC and the UZ Gasthuisberg Leuven and approved by the local MECs in the remaining 3 participating centers. Written informed consent was obtained from all participants. The trial was registered at www.trialregister.nl (registration number NTR5191). All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Patients

Between September 14, 2015, and October 23, 2017, a total of 104 patients were enrolled (Fig. 2). In February 2017, inclusion in the simple-double ablation arm was stopped prematurely because of an unexpected high risk of stenosis. At that moment, 28 patients (24 men, median C4M5 BE, previous ER in 12 patients) were already included in this arm (Table 2). The interim analysis showed that 6 patients (21%; 95% CI, 10%-39%) developed a stenosis. Of these 6 patients, 4 developed a severe stenosis requiring 12 dilations and 2 incision therapies, 8 dilations, 7 dilations, 4 dilations and 1 incision therapy, respectively. One patient had a moderate stenosis requiring 4 dilations, and one stenosis was graded as mild (1 dilation). Figure 3 shows endoscopic images of the severe stenoses. The DSMB recommended early closure of the simple-double arm because of the frequency and the severity of the stenoses (median, 6 dilations; range, 1-12). Table 3 shows the outcomes of the simple-double regimen arm.

The trial continued with the 2 remaining arms. Thirty-seven patients were allocated to the standard ablation regimen and 39 to the simple-single regimen. One patient received treatment that was not in concordance with randomization and was therefore excluded. The remaining 75 patients were included in the m-ITT population. For 3 patients, no data were available on the primary endpoint, and these patients could therefore not be included in the primary analysis (Fig. 2). Both groups were similar at baseline (Table 2).

Primary outcome: Barrett's regression at 3 months

The median Barrett's regression was 85% (IQR, 75%-94%) in the standard arm versus 73% (IQR, 46%-83%) in the simple-single arm, based on blinded assessor scores. In 79% (57 of 72) of the cases, there was <10% agreement between the 2 assessors. For 2 cases, there was >30% difference in regression score, and a consensus diagnosis was made.

The median difference between both groups was 13% (95% CI, 5%-23%). Because the prespecified noninferiority margin of 15% is included in the 95% CI of the median difference, we concluded that the percentage BE regression was inferior in the simple-single arm.

In a post hoc analysis, the proportion of patients showing a poor response was significantly lower in the standard arm compared with the simple-single arm: 3 of 35 (9%) versus 12 of 36 (33%) (*P* Z .013). The 4 known baseline predictors for a poor response are presented in Table 2. No statistically significant difference was found in these baseline predictors between the standard and the simple-single arm: active reflux esophagitis (*P* Z .32), esophageal narrowing (*P* Z .25), ER scar

regeneration with Barrett's epithelium ($P = .70$), and months of dysplasia before RFA treatment ($P = .34$).

Secondary outcomes

Adverse events. There was no significant difference in the number of adverse events between the groups: 5 (14%) in the standard arm versus 4 (11%) in the simple-single arm ($P = .74$) (Table 3). In the standard arm, 4 patients had a minor laceration during the 360 Express ablation (mild adverse event). In 1 patient the laceration occurred after inflation of the balloon and further 360 Express treatment could not be performed. All 4 lacerations required no treatment. One patient died due to an unrelated cause 10 weeks after the 360 Express treatment. Because this event occurred before the patient had his first follow-up endoscopy and he was thus still in the study, we reported this as a serious adverse event. In the simple-single arm, all 4 adverse events were graded as mild. Three patients had a minor laceration during the 360 Express ablation without the need for treatment. The fourth patient was admitted for 1 night due to retrosternal pain. No stenoses were reported in the standard or simple-single arm.

Procedure time. The median total procedure duration was 31 minutes (IQR, 26-35 minutes) in the standard arm versus 17 minutes (IQR, 13-20 minutes) in the simple-single arm ($P < .001$). The median ablation duration was also significantly longer in the standard arm compared with the simple-single arm: median, 18 minutes (IQR, 15-22 minutes) versus 6 minutes (IQR, 5-8 minutes) ($P < .001$).

Patient discomfort after RFA treatment. The median pain score for retrosternal pain directly after the procedure was 2 in both groups ($P = .4$). In the standard ablation group, 31 patients completed the diary for the cumulative discomfort score 30 days after the procedure versus 30 in the simple-single arm. There was no statistically significant difference in the duration of discomfort symptoms. Patients in both arms were free of symptoms after a median of 10 days ($P = .11$) (Fig. 4).

DISCUSSION

This international multicenter randomized controlled trial aimed to evaluate the optimal ablation regimen for circumferential RFA of BE using the 360 Express. We found

that a simple-single hit (10 J/cm^2) regimen was less effective and did not meet the criteria for noninferiority in comparison with a standard regimen using 2 hits of 10 J/cm^2 with a cleaning step. In addition, a double 10 J/cm^2 hit regimen resulted in an unacceptable high stricture rate and should therefore not be used.

The trial was originally designed to compare 3 different ablation regimens: the standard ablation regimen, the simple-double regimen, and the simple-single regimen. However, during the trial, a stenosis rate of 21% was found in the simple-double ablation arm and, after studying all the stenoses cases, the DSMB advised early closure of this arm. In the literature, the stenosis rate for RFA varies between 0% and 14%,⁸ but this stenosis rate is based on the entire treatment period (so after additional ablation sessions). The 21% stenosis rate found in our study was after 1 simple-double ablation procedure and was therefore much higher than one would expect based on the literature. More importantly, the severity of the stenosis in our study was worse than anticipated based on previous studies and experience. Most patients required more than 4 dilations and/or incision therapy, whereas the stenoses reported in the literature are generally mild and well treatable with a median of 1 to 2 dilations. A previous randomized trial showed that the simple-double regimen did not result in more stenoses compared with the standard regimen when using the traditional Barrx360 system.⁵ So, why does the simple-double regimen result in an increased risk of severe stenosis when the 360 Express is used? First, when using the Barrx360 system, a 3-cm-long ablation catheter was chosen based on the smallest measured EID. Therefore, with the former system, the apposition of the electrode to the esophageal mucosa was less effective and often obtained by additional suctioning. In contrast, the new 360 Express balloon adjusts to the EID, creating a maximal and optimal contact between the electrode and the esophageal wall. In addition, the ablation catheter has a longer electrode of 4 cm and delivers more energy to the esophagus than the traditional system. Second, when using the standard regimen, the esophageal wall has time to "cool down" during the cleaning step. Furthermore, the time until the next ablation allows submucosal edema induced by the first ablation to have its protective effect on the submucosa and deeper wall layers. When the cleaning step is omitted, as is the case in the simple-double regimen, the ablation damage may be deeper, resulting in more fibrosis.

After closure of the simple-double arm, the trial was temporarily put on hold and a safety signal was published to inform readers of the increased stenosis risk that is associated with the simple-double ablation regimen.⁹ Furthermore, the study design was adjusted, and after approval of the MEC, the trial was continued with the 2 remaining arms.

The final results of our trial show that circumferential ablation with the 360 Express using the single hit regimen results in inferior endoscopically visible BE surface regression at 3 months compared with the standard regimen. In addition, the number of patients showing a poor BE regression response at 3 months was significantly higher in the simple-single arm. A previously published prospective study identified 4 independent predictors for a poor initial response 3 months after circumferential RFA.⁷ We performed a post hoc analysis and both groups were comparable with regard to the presence of the above-mentioned predictors. Therefore, it is unlikely that the patients in the simple-single arm were more prone to have a poor regression response.

One may argue that the standard ablation regimen results in a longer procedure time and that a single ablation with a higher energy setting (12 J/cm^2) may be a valid alternative ablation protocol. However, we believe that the difference in BE regression between the 2 groups is most likely to be explained by the number of hits (1 vs 2). A regimen with 2 hits of energy is probably more effective in ablating all Barrett's mucosa because there is another chance to hit areas that were not optimally ablated during the first ablation pass or to ablate skipped zones during the second pass. We therefore believe that increasing the energy setting from 10 to 12 J/cm^2 will not significantly increase the efficacy of a single hit ablation regimen.

When interpreting the endoscopically visible BE regression results, one should keep in mind that additional focal ablation sessions will be performed and that a difference of Barrett's regression at 3 months does not necessarily affect the overall efficacy measured at the end of the treatment period. However, one may argue that less residual BE mucosa during follow-up will require less-extensive additional RFA treatment, thus exposing the patient to a lower risk of adverse events than when more extensive additional ablation is required.

Strengths of this study include the stratified randomized design of the study and the blinded primary outcome assessment, increasing the internal validity. In addition, to improve generalizability, we included patients with a wide range in BE length and performed the study in multiple centers. Furthermore, a DSMB commission was assigned to monitor the safety of the patients. Finally, the perspective of patients was taken into account by adding patient reported measurements to the outcomes.

This study has several limitations that need to be addressed. First, the study was conducted in 5 tertiary referral centers and treatment was performed by Barrett expert endoscopists. Therefore, one should be careful about extrapolating the results to general practice. However, we believe that treatment of early Barrett's neoplasia should be limited to expert centers with dedicated endoscopists who are trained in the detection of early neoplastic lesions and experienced in performing endoscopic treatment. Second, only 61 of the 74 patients completed the 30-day discomfort diary. However, the response rate was comparable in both groups, so it is not likely that the suboptimal response rate has introduced bias because of selective nonresponse. Third, 4 patients could not be included in the primary analysis. One patient was excluded from the study after randomization because he was accidentally treated with the wrong ablation regimen, and this may have introduced bias in favor of the alternative hypothesis. In 3 patients, no data on the primary outcome were available. Two of these patients were assigned to the standard arm; this resulted in 35 analyzable patients in this arm instead of the required 36 patients based on the initial sample size calculation. However, this did not influence the conclusion of the primary analysis because there was still >90% of power to assess the noninferiority. After the simple-double arm was closed, the sample size was recalculated with an adjustment of the significance level to .025 because the Bonferroni correction could be omitted because only 2 arms were compared. According to the new sample size calculation there would be 94% power when 36 patients were included per arm.

In conclusion, the results of this international randomized controlled trial are clinically relevant because many endoscopists who have been using the simple-double ablation regimen successfully with the traditional RFA catheter have copied this regimen when using the 360 Express. However, the results of our trial show that the simple-double regimen

is associated with an unacceptable risk of severe stenosis. Furthermore, the results of this study suggest that a single ablation at 10 J/cm² when using the 360 Express results in inferior BE regression at 3 months. We therefore advise using the standard ablation regimen (1–10 J/cm²-clean-1 10 J/cm²) for the 360 Express in treatment of BE, as is recommended in the instructions for use.

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Figure 1. Wrap/unwrap electrode design of the 360 Express radiofrequency ablation balloon catheter. A, The balloon catheter is fully wrapped. B, C, By inflating the balloon the catheter unwraps. D, The balloon is inflated and the catheter is fully unwrapped.

TABLE 1. Definitions of outcome parameters

Outcome parameter	Definition
Percentage of endoscopically visual regression of BE epithelium at 3 months	<p>The mean percentage of BE surface regression of the 2 independent endoscopists blinded to the allocated ablation regimen</p> <p>The percentage of endoscopically visible surface regression was scored by evaluating the still images taken with WLE and optical chromoendoscopy immediately before the 360 Express treatment and at the 3 months follow-up endoscopy</p> <p>When the percentage of BE surface regression in a patient differed $\geq 30\%$ between the endoscopists, a consensus meeting was held to establish a consensus score</p>
Adverse events	<p>Timing: acute, during the procedure; early, ≤ 48 hours; late, > 48 hours</p> <p>Severity: mild, unscheduled hospital admission, hospitalization < 3 days, hemoglobin decrease < 3 g/dL, no need for transfusion; moderate, hospitalization 4–10 days, ≤ 4 units blood transfusion, need for repeat endoscopic intervention, radiologic intervention; severe, hospitalization > 10 days, intensive care unit admission, need for surgery, > 4 units blood transfusion; or in the case of stenosis > 5 dilations, stent placement, or incision therapy; fatal, death attributable to procedure < 30 days or longer with continuous hospitalization</p>
Procedure time	Total procedure time, time from the first introduction until the time of removal of the endoscope; ablation time, the period between the first introduction and the last removal of the 360 Express
Patient discomfort	<p>Retrosternal pain directly after the procedure: immediately after the treatment procedure, the patients' pain was quantified using a VAS score ranging from 0 to 10 (0 no symptoms, 10 unbearable pain)</p> <p>The cumulative daily discomfort score (for 30 days after the procedure): patients were asked to complete a 30-day diary in which they had to score the following 8 symptoms on a 7-point Likert scale (0 no symptoms to 7 unbearable symptoms): retrosternal pain and burning, dysphagia, epigastric pain, decreased appetite, sour throat, nausea, and vomiting. If a patient was free of complaints for 3 days, they could stop completing the questionnaire. The discomfort score is a cumulative score of all 8 symptoms per day (maximum score 56/day)</p>

BE, Barrett's esophagus; WLE, white-light endoscopy; VAS, visual analog scale.

Figure 2. Flowchart of the enrollment. IC, informed consent; m-ITT, modified intention-to-treat analysis; BE, Barrett's esophagus; and ER, endoscopic resection.

TABLE 2. Baseline and clinical characteristics

Characteristics	Standard arm	Simple-single arm	Simple-double arm (arm early closed)
No. of patients	37	38	28
Male:female	29:8	28:10:00	24:04:00
Age (years), median (IQR)	65 (61-72)	67 (63-70)	67 (61-70)
BE (cm), median (IQR)	C4 (2-7), M7 (5-10)	C6 (2-7), M8 (5-10)	C4 (1-5), M6 (4-8)
Active reflux esophagitis at baseline, n (%) [*]	0 (0)	1 (3)	0 (0)
Esophageal narrowing at baseline, n (%) [*]	2 (5)	5 (13)	0 (0)
Worst overall histologic diagnosis before treatment (biopsies or ER specimens), n (%)			
Low-grade dysplasia	11 (30)	15 (39)	11 (39)
High-grade dysplasia	18 (49)	15 (39)	11 (39)
Early cancer	8 (21)	8 (21)	6 (21)
ER before RFA, n (%)	15 (41)	16 (42)	12 (43)
Worst histology of ER specimens, n			
Nondysplastic BE	2	0	1
Low-grade dysplasia	0	2	2
High-grade dysplasia	5	6	3
Early cancer	8	8	6
ER scar regeneration with Barrett's epithelium, n (%) [*]	4 (27)	6 (38)	1 (8)
Worst overall histologic diagnosis before RFA treatment, after ER if applicable, n (%)			
Nondysplastic BE	3 (8)	5 (13)	5 (18)
Low-grade dysplasia	18 (49)	18 (47)	17 (61)
High-grade dysplasia	16 (43)	15 (40)	6 (21)
Months of dysplasia before RFA, median (IQR) [*]	6 (3-9)	7 (4-11)	5 (4-12)
Postablation care			
High-dose PPI þ ranitidine þ sucralfate, n (%)	22 (59)	30 (79)	23 (82)
High-dose PPI þ ranitidine, n (%)	15 (41)	8 (21)	5 (18)

IQR, Interquartile range; BE, Barrett's esophagus; ER, endoscopic resection; RFA, radiofrequency ablation; PPI, proton pump inhibitor.

^{*}Known independent baseline predictors for a poor initial regression response.⁷

Figure 3. Endoscopic images of 4 patients (A-D) with a severe stricture after a single 360 Express treatment using the simple-double regimen.

TABLE 3. Outcomes

Ablation regimen	Standard arm	Simple-single arm	Simple-double arm (arm closed early)
No. of patients	37	38	28
Percentage BE regression at 3 months, median (IQR)	85 (75-94)	73 (46-83)	88 (81-93)
Procedure duration (minutes), median (IQR)	31 (26-35)	17 (13-20)	17 (14-20)
Ablation duration (minutes), median (IQR)	18 (15-22)	6 (5-8)	6 (5-9)
Overall adverse event rate, n (%)	5 (14)	4 (11)	7 (25)
Stricture requiring an intervention, n (%)	0 (0)	0 (0)	6 (21)
Minor laceration, n (%)	4 (11)	3 (8)	0 (0)
Other adverse events, n (%)	Unrelated death: 1 (3)	Retrosternal pain and fever: 1 (3)	Near collapse: 1 (4)

BE, Barrett's esophagus; IQR, interquartile range.

Figure 4. Kaplan-Meier plot showing the duration of discomfort symptoms 30 days after the 360 Express treatment.