Randomized controlled trial comparing the simplified and standard regimen for focal radiofrequency ablation

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## PROTOCOL SUMMARY

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<th><strong>Title</strong></th>
<th>Working title: Optimizing focal ablation therapy for Barrett’s neoplasia: Comparing two different ablation regimens</th>
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<tr>
<td><strong>Design</strong></td>
<td>Prospective randomized study comparing the standard ablation regimen (2x2x15J/cm²) vs. a simplified regimen (3x12J/cm²-no clean), in the treatment of Barrett’s neoplasia using the Barrx90 catheter.</td>
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<td><strong>Objective</strong></td>
<td>To compare the efficacy of the standard protocol against a simplified protocol using the Barrx90 device in the focal treatment of Barrett’s neoplasia.</td>
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<td><strong>Hypothesis</strong></td>
<td>A simplified treatment regimen of 3x12J/cm² without cleaning is non-inferior compared to the standard regimen (2x2x15J/cm²) when evaluating percentage of complete endoscopic remission of IM and neoplasia after 2 focal ablation sessions.</td>
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<td><strong>Primary Endpoint</strong></td>
<td>1. Complete endoscopic and histological remission of IM and dysplasia after 2 focal ablation sessions.</td>
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| **Secondary Endpoints** | 1. Total number of focal RFA sessions to reach complete remission of IM and dysplasia.  
2. Complete endoscopic and histological remission of IM and dysplasia after 3 focal RFA sessions with or without escape treatment.  
3. Rate of esophageal stenosis requiring dilatation, occurring during the focal RFA treatment phase.  
4. Overall complications requiring admission/unplanned endoscopy.  
5. Post-procedural pain immediately after RFA and after 2 days.  
6. Procedure time. |
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| **Collaborating institutions** | Academic Medical Center, Amsterdam, the Netherlands  
Catharina Hospital, Eindhoven, the Netherlands  
Erasmus Medical Center, Rotterdam, the Netherlands  
UZ Gasthuisberg, Leuven, Belgium |
| **Time Course** | November 2014 Submission of study protocol to IRB/EC  
December 2014 Complete submission of protocol in all centers  
January 2015 Start patient enrolment  
June 2015 First treatment of the last patient  
December 2015 Last RFA treatment of last patients  
March 2016 Final follow-up last patient  
April 2016: Analysis and publication |
1. INTRODUCTION AND RATIONALE

In the last three decades, the incidence of esophageal adenocarcinoma (EAC) has increased six-fold, making it the most rapidly rising cancer in the Western world.\(^1\) Presence of a Barrett’s esophagus (BE) is the most important risk factor for developing EAC. In BE, the epithelium of the distal esophagus has been replaced by columnar epithelium containing specialized intestinal metaplasia, due to chronic gastro-esophageal reflux. Malignant transformation of BE is thought to occur in a step-wise fashion from non-dysplastic intestinal metaplasia (IM), to low-grade dysplasia (LGD) then high-grade dysplasia (HGD), and eventually early cancer (EC).\(^2,3\)

Radiofrequency ablation (RFA) is an established endoscopic technique for eradication of Barrett’s esophagus which has been investigated in a variety of study designs.\(^4-8\) Radiofrequency ablation is associated with an acceptable safety profile, high rates of complete eradication of dysplasia and intestinal metaplasia, durability of effect, and a significant relative risk reduction for neoplastic progression.\(^4-8\) As a result, radiofrequency ablation is considered standard of care for patients with high-grade dysplasia, as well as for residual Barrett tissue after endoscopic resection of early cancer.\(^9\)

RFA is usually performed primarily with a balloon based electrode for circumferential ablation (Barrx 360-catheter), followed by focal ablation for smaller areas of residual Barrett’s mucosa, such as residual BE islands, small BE tongues or for treatment of the area just above the gastric folds (i.e. neo-Z-line). In all European RFA studies, standard circumferential treatment of the Z-line is performed during focal ablation procedures for islands or tongues. In this area most recurrences occur and circumferential treatment with the balloon based device may be suboptimal because of poor contact.\(^4\)

The advised treatment regimen in Europe for focal ablation of Barrett’s esophagus consists of two double ablation passes at 15 J/cm\(^2\) with a cleaning phase in between (2x2x15 J/cm\(^2\)). These energy settings were derived from clinical dose escalation studies which were conducted at the AMC Amsterdam in 2007.\(^10,11\) Most US centers however use a regimen with two ablations at 12 J/cm\(^2\) (2x2x12 J/cm\(^2\)), which originates from a randomized controlled trial (AIM-dysplasia study).\(^7\) The AIM-dysplasia study was initiated while the dosimetry studies at the AMC were underway. As a result, the first dose-escalation from 2x12 J/cm\(^2\) to 2x2x12 J/cm\(^2\), which was evaluated at the AMC was included in the AIM-dysplasia trial protocol, but the second step-up in energy dose (from 2x2x12 J/cm\(^2\) to 2x2x15 J/cm\(^2\)) was not. Since then, all RFA studies from the US have used a 2x2x12 J/cm\(^2\) ablation protocol, while all European RFA studies have used 2x2x15 J/cm\(^2\).

Generally focal ablation is performed with the Barrx 90 catheter, which was the first available catheter for focal ablation (previously: Halo 90).\(^10\) Ablation with the Barrx90 catheter is relatively
easy to perform. However, cleaning of the ablation zone and removal of the catheter in order to clean the electrode, followed by reintroduction for the second ablation pass are impractical and uncomfortable for the patient. In a previous randomized study by our group, we studied a simplified ablation regimen for focal ablation of residual Barrett’s islands with the Barrx 90 device. In patients with pairs of islands, one island was ablated with the standard 2x2x15 J/cm² regimen (with cleaning of the ablation zone and electrode) whereas the other island was treated with a simplified 3x15 J/cm² regimen without cleaning. The two settings were found to be comparable for the eradication rate of the islands treated, however we could not evaluate the outcome at a per patient level, as the remaining islands and neo-Z-line were treated with the standard 2x2x15 J/cm² regimen. Although the 3x15 J/cm² regimen requires a reduced number of introductions and is therefore easier to perform, in a prospective series we experienced that this regimen seems to induce more scarring than the standard regimen. If patients undergo the whole focal ablation procedure with this regimen (all islands and circumferential treatment of the neo-Z-line) this may lead to a higher rate of stenosis. Reducing the energy settings to 12 J/cm² when using a triple regimen may be the best compromise between efficacy and an acceptable stenosis percentage. The current focal ablation regimen for squamous neoplasia consists of triple applications at 12 J/cm² with acceptable side effects. By setting the energy dose to 12 J/cm², the focal ablation regimen will be equalized between the US and Europe, and will be comparable with treatment of squamous cell neoplasia.

2. **OBJECTIVE**

The aim of this study is to compare the efficacy of the standard protocol (2x2x15 J/cm²) against a simplified protocol (3x 12J/cm²) using the Barrx90 device in the focal treatment of Barrett’s neoplasia and to evaluate the effect of the simplified protocol on the rate of stenosis and overall complications.

3. **STUDY DESIGN**

This is a prospective randomized study, comparing the standard ablation regimen (2x2x15 J/cm²) against a simplified regimen (3x12 J/cm² – no clean) for focal ablation treatment of Barrett’s neoplasia.

Patients are randomized during the first focal ablation procedure. Patients are randomly assigned in 1:1 ratio to treatment with the standard ablation regimen (standard group) vs. the simplified ablation regimen (simple group). Randomization is performed according to a computer-generated sequence,
which is concealed from the researchers, using variable block randomization per center (4, 6 or 8 patients per block).
Randomization of eligible patients is performed on-site by the study coordinator during the endoscopic procedure after eligibility of the patient is confirmed, using ALEA software. Outcomes are scored after completion of treatment.

4. STUDY POPULATION

4.1 Population base
A patient is eligible for the study, if they have endoscopically visible Barrett’s mucosa. This can be either a short segment BE that is initially treated with the Barrx90-device; residual Barrett’s mucosa after prior ER for visible lesions; residual Barrett’s mucosa after one or two circumferential sessions; or residual Barrett’s mucosa after ER and circumferential RFA.

4.2 Inclusion criteria
1. Patients aged 18-85 years.
2. BE with biopsy proven LGD, HGD or EC confirmed after local expert pathology review, with residual endoscopically visible Barrett’s mucosa, with or without prior ER and/or circumferential RFA.
3. Written informed consent.

4.3 Exclusion criteria
1. Significant esophageal stenosis prior to the first focal RFA treatment, preventing passage of a therapeutic endoscope OR any prior endoscopic dilatation for esophageal stenosis.
2. Presence of esophageal varices.
3. Anti-coagulant therapy (apart from aspirin or NSAID) that cannot be discontinued prior to ER or RFA, OR uncorrectable hemostatic disorders.
4. In case of prior ER: a specimen showing carcinoma with positive vertical resection margins, deep submucosal invasion (>T1sm1), poorly or undifferentiated cancer (G3 or G4), or lymphatic/vascular invasion.
5. In case of prior ER: invasive cancer in any of the biopsies obtained at high-resolution endoscopy after ER.
6. Patients unable to give informed consent.
7. No justification for further treatment due to (unrelated) comorbidity.
4.4 **Sample size calculation**

Based on prior studies we expect the percentage of surface regression of Barrett’s mucosa after 2 focal RFA sessions to be 95%.\(^{12, 15}\) A total of 72 patients (37 per group) is required to demonstrate if a simplified focal Barrx 90 ablation regimen of 3x 12J/cm\(^2\) is non-inferior to the standard ablation regimen of 2x2x 15 J/cm\(^2\), with non-inferiority defined as <15% difference in Barrett’s surface regression after 2 focal ablation sessions (one-sided alpha 2.5%, power 90%).

4.4.1 **Data analysis**

Patient inclusion and treatment is expected to require a period of 12 months. Outcome parameters will be scored at the first post-treatment endoscopy. Final analysis will be performed after all patients have had potentially at least one post-treatment endoscopy.

The primary analysis will be performed on an intention-to-treat basis, defined as all enrolled patients, including treatment failures and drop-outs. To test differences in outcome parameters amongst the standard and simple groups the Mann-Whitney U Test and Chi-square Test will be used when appropriate.

5. **METHODS**

5.1 **Outcome parameters**

5.1.1 **Primary outcome parameters**

1. **Complete endoscopic and histological remission of IM and dysplasia after 2 focal Barrx 90 ablation sessions.**

Complete endoscopic eradication of IM is defined as no suspicion on residual tongues or islands of IM. If there is suspicion on residual IM, the end-point is not reached and additional RFA treatment can be performed, without taking biopsies. Complete histological eradication of IM and neoplasia is defined as absence of IM and/or neoplasia, from neo-Z-line and neosquamous biopsies obtained after 2 focal RFA sessions.

5.1.2 **Secondary outcome parameters**

1. **Total number of focal RFA sessions needed to reach complete remission of IM and dysplasia.**

The protocol allows a total number of 3 focal RFA sessions.

2. **Complete endoscopic and histological remission of IM and dysplasia after 3 focal RFA sessions with or without escape treatment.**
At three months, the first post-treatment endoscopy will be performed with WLE and NBI, with 4-quadrant biopsies obtained from the neo-Z-line and from the neosquamous epithelium. Complete eradication of IM and neoplasia is defined as absence of IM and neoplasia, from neo-Z-line and neosquamous biopsies obtained after 3 focal RFA sessions and/or escape treatment with APC/ER.

3. Rate of esophageal stenosis requiring dilatation, occurring during the focal RFA treatment phase.

Any patient who requires a dilatation session after any of the Barrx 90 procedures, is considered as having an esophageal stenosis. The number of patients with stenosis are documented, and the number of dilatation procedures required to resolve the stenosis are documented.

4. Overall complications requiring admission/unplanned endoscopy.

Number and severity of acute (during the procedure), early (0-48 hours) and late (>48 hours) complications. Complications are only recorded if they are clinically significant and graded as ‘mild’ (unplanned hospital admission, hospitalization <3 days, hemoglobin drop <3 g/dL, no transfusion), ‘moderate’ (4-10 days hospitalization, <4 units blood transfusion, need for unplanned endoscopy), ‘severe’ (hospitalization >10 days, intensive care unit admission, need for surgery, >4 units of blood transfusion) or ‘fatal’ (death attributable to procedure <30 days or longer with continuous hospitalization).

5. Post-procedural pain immediately after RFA and after 2 days.

Post-procedural pain will be recorded using a visual-analogue scale (VAS) immediately after the procedure, as well as after two days by telephone follow-up.

6. Procedure time.

The following time points will be recorded to calculate total procedure time and treatment time: first introduction of the endoscope; first introduction of the Barrx 90 catheter; removal of the endoscope after finishing focal RFA treatment, including time to treat any acute complications occurring during the procedure.

5.2 Study procedures

5.2.1 Radiofrequency ablation using the Barrx 90 device

The Barrx Flex RFA system consists of a generator which can be connected with various ablation devices, such as the circumferential ablation balloon (Barrx 360), and the focal ablation device (Barrx 90). The Barrx Flex energy generator delivers radiofrequency energy in a bipolar mode to the
Simplified focal RFA RCT

ablation probe. The generator measures and displays time, treatment power settings, energy and impedance.

The focal Barrx 90 device consists of an electrode array, which is mounted on an articulated platform, allowing the electrode to move front-to-back and left-to-right, ensuring optimal tissue contact. The electrode array is 20.6 mm long and 13.2 mm wide. After placement at the desired treatment zone, the device is brought into close contact with the mucosa, deflected upward, and activated. Energy is then rapidly delivered, leading to controlled depth ablation of the Barrett’s epithelium. The Barrx Flex energy generator with the Barrx 90 device have a CE mark for use in Europe.

5.2.2 Standard ablation procedure with the Barrx 90 device
The esophagus is evaluated using white light high-resolution endoscopy (WLE) and narrow band imaging (NBI). The Barrx 90 device is attached to the tip of the endoscope at the twelve o’clock position and introduced into the distal esophagus under visual guidance. The endoscope is gently advanced into the esophagus, passing the leading edge of the catheter behind the arytenoids. Residual Barrett’s epithelium is positioned at the 12 o’clock position in the endoscopic video image, corresponding to the position of the electrode. The electrode is brought into close contact with the mucosa, deflected upward, and activated. Without separating the electrode from the esophageal wall, the electrode array is immediately activated two times, resulting in a "double" application of radiofrequency energy at 15 J/cm². After all islands and Z-line have been ablated in this manner, the necrotic debris is cleaned off by a combination of suctioning and irrigating tap water. In addition, the Barrx 90 cap can be used to gently push off the coagulum from the ablation zone. Subsequently, the ablated areas are cleaned by vigorous flushing of water through a spraying catheter. After emptying the stomach, the endoscope is removed, the Barrx 90 electrode is cleaned and then reintroduced to ablate all treated areas again with two times 15 J/cm². After focal ablation of residual BE islands or small BE tongues, the area of the gastric folds (Z-line) will be treated circumferentially with the Barrx 90. Treatment of the Z-line is performed each time the Barrx 90 is introduced to treat residual islands or tongues of BE mucosa, but at least once.

5.2.3 Simplified ablation procedure with the Barrx 90 device
In the simplified Barrx 90 ablation regimen, the target area (i.e. Barrett islands and the circular area of the tops of the gastric folds) is treated with a "triple" application of radiofrequency energy at 12 J/cm², without cleaning in between the ablations. Using this regimen, the Barrx 90 device mounted on the endoscope needs to be introduced only once.
5.2.4 Further treatment
Repeat focal ablation with the designated ablation regimen (standard or simple) will be performed at 3 months intervals with a maximum of three focal RFA sessions. For all patients, treatment of the Z-line is performed each time the Barrx 90 is introduced to treat residual islands or tongues of BE mucosa, but at least once.4

5.2.5 Escape treatment
Escape treatment is allowed to eradicate residual Barrett’s mucosa after the maximum number of three focal RFA sessions, as allowed by the study protocol. Preferably ER is used to remove residual Barrett’s mucosa. However, in the case of small residual islands without visible irregularities, argon plasma coagulation (APC) may be used.

5.2.6 Medication and discharge regimen
All patients will be on a maintenance dose of a proton pump inhibitor (by preference esomeprazole) at a dosage of 40 mg twice a day during the whole treatment period and follow-up. This medication is supplemented with ranitidine 300 mg at bedtime and if available sucralfate suspension three times a day (after each meal and prior to bedtime) for a period of two weeks following all RFA procedures.

5.2.7 Follow-up
In order to evaluate pain after RFA-treatment patients will be contacted by telephone 2 days after the procedure by a dedicated research nurse. A questionnaire will be completed to be able to evaluate if there were any complaints such as a sore throat or retrosternal pain after the procedure. Focal ablation sessions are continued until complete removal of the BE has been achieved upon inspection with high-resolution endoscopy and NBI and no intestinal metaplasia or neoplasia is detected in the biopsies obtained immediately distal to the gastroesophageal junction. When complete eradication of BE is achieved, patients will enter into a surveillance algorithm according to current clinical guidelines. Endoscopists who perform the endoscopies during follow-up will not be blinded for the used treatment protocol during focal ablation.

5.3 Study withdrawal
Any participant who wishes to withdraw from the study on his/her own accord and for whatever reason is entitled to do so without obligation and prejudice to further treatment. In addition, the principal investigator of the study site may decide, for reasons of medical prudence, to withdraw a participant. In either event, the principal investigator will clearly document the date and reason(s) for
the participant’s withdrawal from this study and should indicate whether or not he considers it related to the device.

The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

5.4 **Replacement of individual subjects after withdrawal**
Patients will be recruited until the total number of 72 evaluable patients will be reached.

5.5 **Follow-up of subjects withdrawn from treatment**
The subjects can be monitored by the doctors in charge as part of routine clinical practice.

6. **SAFETY REPORTING**

6.1 **Section 10 WMO event**
In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.2 **Adverse events**
Adverse events (AE) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention.

Adverse events (AEs) may occur during the procedure or during the follow-up phase. AEs occurring prior to the procedure will be documented in the patient’s medical record but will not count as related to the investigational device or procedure. Each AE will be recorded in the corresponding patient’s Case Report form (CRF). Each AE will be judged by the Investigator as to its relationship and level of relatedness to the investigational System and/or investigational procedure. In addition, the Investigator will identify the date of onset, severity and duration. All AEs will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study treatment is not the cause.
6.3 Follow-up of adverse events
All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7 ETHICAL CONSIDERATIONS

7.1 Regulation statement
This study will be conducted according to the principles of the declaration of Helsinki and in accordance with the Medical Research Involving Human Subject Act (WMO). All eligible patients in one of the participating centers will be invited for this trial during a prior consultation and informed consent will be discussed. The person inviting patients for the trial will differ per centre, it will be a physician, (research)nurse or investigator. The patients will have at least 1 week to consider their decision. All eligible patients are required to provide signed informed consent prior to participation. Insurance for subjects participating in medical research is available in accordance with the legal requirements of article 7 of the WMO and Medical Research (Human Subjects) Compulsory Insurance Decree of 23 June 2003.

8.2 Risk assessment: potential benefits
Included patients might have a benefit if randomized to the simple protocol, since in this protocol only one introduction of the endoscope is required, compared to two introductions during the standard protocol. Furthermore, no cleaning step is performed during the simple protocol, which may shorten procedure time.

8.3 Risk assessment: potential risks
Upper endoscopy is an investigation which is performed many times a day in all participating hospitals. The participating endoscopists are skilled and have vast experience in the detection and treatment of early esophageal carcinoma. The risks of upper endoscopy are neglectable, and are mainly associated with the introduction of the endoscope and include sore throat and sedation related side effects such as local bruising or pain at the IV site, allergic reaction to the medications and over sedation requiring sedation reversal medications and longer post-procedure observation. All patients undergoing endoscopy are monitored with continuous pulse oximetry and vital signs assessment (blood pressure) during the procedure. Medications used for conscious sedation are carefully titrated and monitored based on the patients' arousal levels and vital signs.
Radiofrequency ablation is considered a safe treatment (and standard of care) for patients with Barrett’s esophagus. The endoscopists who perform RFA treatment are all trained in performing the procedure. There is a small risk on pain post-treatment, and a sore throat and a very tiny risk on perforation or bleeding. Patients which are treated with the simple protocol might have a slightly elevated risk of stenosis compared to patients which are treated with the standard regimen.

8. ADMINISTRATIVE ASPECTS

8.1 Data registration
Administration of the clinical patient data, including histopathological findings will be registered in a dedicated database. To protect participant confidentiality, the subject’s name is not to appear anywhere on the case record forms or supporting documentation. Each page should be identified with the subject’s case study number, which is comprised of a three-digit site number and a three-digit subject number. A Confidential Patient Log will be maintained in a secure locked location by the Investigator to enable tracing of specific case study numbers to subjects, in the event required. Qualified authorities can get insight in code and data, but only when accompanied by the investigators. Data will be stored 15 years after closure of the trial.

8.2 Annual progress report
The investigator will submit a summary of the progress of the study to the accredited METC of the initiating centre once a year. The accredited METC of the AMC will receive a report about the study subjects that are treated in the AMC. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/serious adverse reactions, other problems, and amendments.

8.3 End of study report
The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.
9. REFERENCES


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