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

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON42316

Source
ToetsingOnline

Brief title
Simplified focal ablation RCT

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
dysplasia in Barrett's esophagus, dysplastic Barrett mucosa

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Barrett's esophagus, Dysplasia, Focal ablation regimen, Radiofrequency ablation

Outcome measures

Primary outcome

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.

Secondary outcome

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.

Study description

Background summary

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 ablation passes at 15 J/cm2 with a cleaning phase in between (2x2x15 J/cm2). 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/cm2 (2x2x12 J/cm2), 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/cm2 to 2x2x12 J/cm2, 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/cm2 to 2x2x15 J/cm2) was not. Since then, all RFA studies from the US have used a 2x2x12 J/cm2 ablation protocol, while all European RFA studies have used 2x2x15 J/cm2. 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.12 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.13 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.14 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.

Study objective

The aim of this study is the efficacy of a simplified triple regimen at an energy setting of 12 J/cm2 instead of 2x2x15 J/cm2, without a cleaning phase in between, and its effect on the rate of stenosis and overall complications when using the Barrx 90 device in eradicating the residual Barrett*s segment and neoplasia.

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), using the Barrx 90 device in the focal ablation treatment of Barrett*s neoplasia.
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 block randomization per center (4 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.

Intervention

Radiofrequency ablation with the BARRX90-device using either the simple regimen, or the standard regimen

Study burden and risks

Possible side-effects of RFA-treatment are pain after treatment (resolving within a few days and fading away with pain medication), sore feeling in the throat and a very small risk for a bleeding or a perforation. Also, a stenosis can develop. We do not know yet if there will be more stenoses after treatment with the simplified regimen. We do not expect the percentage of stenosis after both regimen to be different.
Patients do not undergo additional endoscopies because of this study. They will have to undergo RFA-treatment of their Barrett's esophagus with dysplasia anyway.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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

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.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-04-2015
Enrollment:	60
Type:	Actual

Medical products/devices used

Generic name:	Barrx90-device
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	14-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	11-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL51570.018.14