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# Efficacy and safety of radiofrequency ablation of Barrett's esophagus in the absence of reimbursement: a multicenter prospective Belgian registry

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## ABSTRACT

**Background** Radiofrequency ablation (RFA), combined with endoscopic resection, can be used as a primary treatment for low grade dysplasia, high grade dysplasia, and early esophageal adenocarcinoma (EAC) in Barrett's esophagus (BE). The aim of the Belgian RFA registry is to capture the real-life outcome of endoscopic therapy for BE with RFA and to assess efficacy and safety outside study protocols, in the absence of reimbursement.

**Patients and methods** Between February 2008 and January 2017, data from 7 different expert centers were prospectively collected in the registry. Efficacy outcomes included complete remission of intestinal metaplasia (CR-IM), complete remission of dysplasia (CR-D), and durability of remission. Safety outcomes included immediate and late adverse events.

**Results** 684 RFA procedures in 342 different patients were registered. Of these, 295 patients were included in the efficacy analysis, with CR-IM achieved in 88 % and CR-D in 93 %, in per-protocol analysis; corresponding rates in intention-to-treat analysis were 82 % and 87 %, respectively. Sustained remission was seen in 65 % with a median (interquartile range) follow-up of 25 (12 – 47) months. No risk factors for recurrent disease were identified. Immediate complications occurred in 4 % of all procedures and 6 % of all patients, whereas late complications occurred in 9 % of all procedures and in 20 % of all patients.

**Conclusions** Data from the Belgian registry confirm that RFA in combination with endoscopic resection is an efficient treatment for BE with dysplasia or early EAC. In the absence of reimbursement, more rescue treatments are used, not compromising outcome. Since there is recurrent disease after CR-IM in 35 %, surveillance endoscopy remains necessary.

# Introduction

Barrett's esophagus (BE) has been traditionally defined as the visible presence of at least 1 cm of metaplastic columnar-lined epithelium that replaces the nonkeratinized stratified squamous epithelium of the distal esophagus [1 – 4]. It is a known premalignant condition, typically stepwise and slowly evolving from nondysplastic intestinal metaplasia (IM) to dysplasia and eventually esophageal adenocarcinoma (EAC) [1, 3, 5 – 7].

Over the past two decades treatment of BE has changed dramatically since endoscopic resection replaced esophagectomy as first-line treatment for high grade dysplasia (HGD) [8 – 10]. Endoscopic resection can either be endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), and is always done in combination with ablation as there is a high risk of metachronous disease when only endoscopic resection is performed [11 – 13]. Since 2008, radiofrequency ablation (RFA) has become available for flat dysplastic BE or as an add-on after endoscopic resection of early cancers [14, 15]. Several clinical trials (e. g. SURF, AIM dysplasia, and EURO II) have shown a very high efficacy and safety for eradication of dysplasia and intestinal metaplasia [16 – 18].The good results of combined endoscopic resection and RFA have been confirmed worldwide by large-volume multicenter prospective series, showing comparable results for efficacy in the United Kingdom (UK) and the United States [19 – 21]. Analysis from the first two cohorts from the UK RFA registry showed that endoscopic resection prior to RFA improves treatment outcome [22].

The aim of this prospective multicenter Belgian RFA registry is to capture the real-life outcome of endoscopic therapy for BE with RFA, and to assess efficacy and safety outside study protocols, in the absence of reimbursement.

# Methods

## Data collection

The Belgian RFA registry is a prospective multicenter registry that captures data from 7 expert centers (5 academic and 2 local) where the endoscopists have had the necessary training and support infrastructure. The data were prospectively collected from February 2008 until January 2017 and monitored for demographic variables, histology, treatment before RFA, indication, treatment-specific information, outcomes, and adverse events.

## Inclusion and exclusion criteria

The inclusion criterion was all patients undergoing RFA for curative eradication of BE. Exclusion criteria were presence of squamous dysplasia, submucosal invasion (≥ T1b sm2), lymphatic/vascular invasion in any of the endoscopic resection specimens, and poorly differentiated or undifferentiated lesions (G3, G4) because of the higher risk of lymph node metastasis with these lesions [23].

## Ethical considerations

Written informed consent was obtained and all patients agreed to attend treatment and surveillance procedures at regular intervals. The prospective registry has been approved by the Ethical Committee of the University Hospitals Leuven (S52432).

## Registry endoscopy protocol

The registry protocol is summarized in ▶ **Fig. 1**.

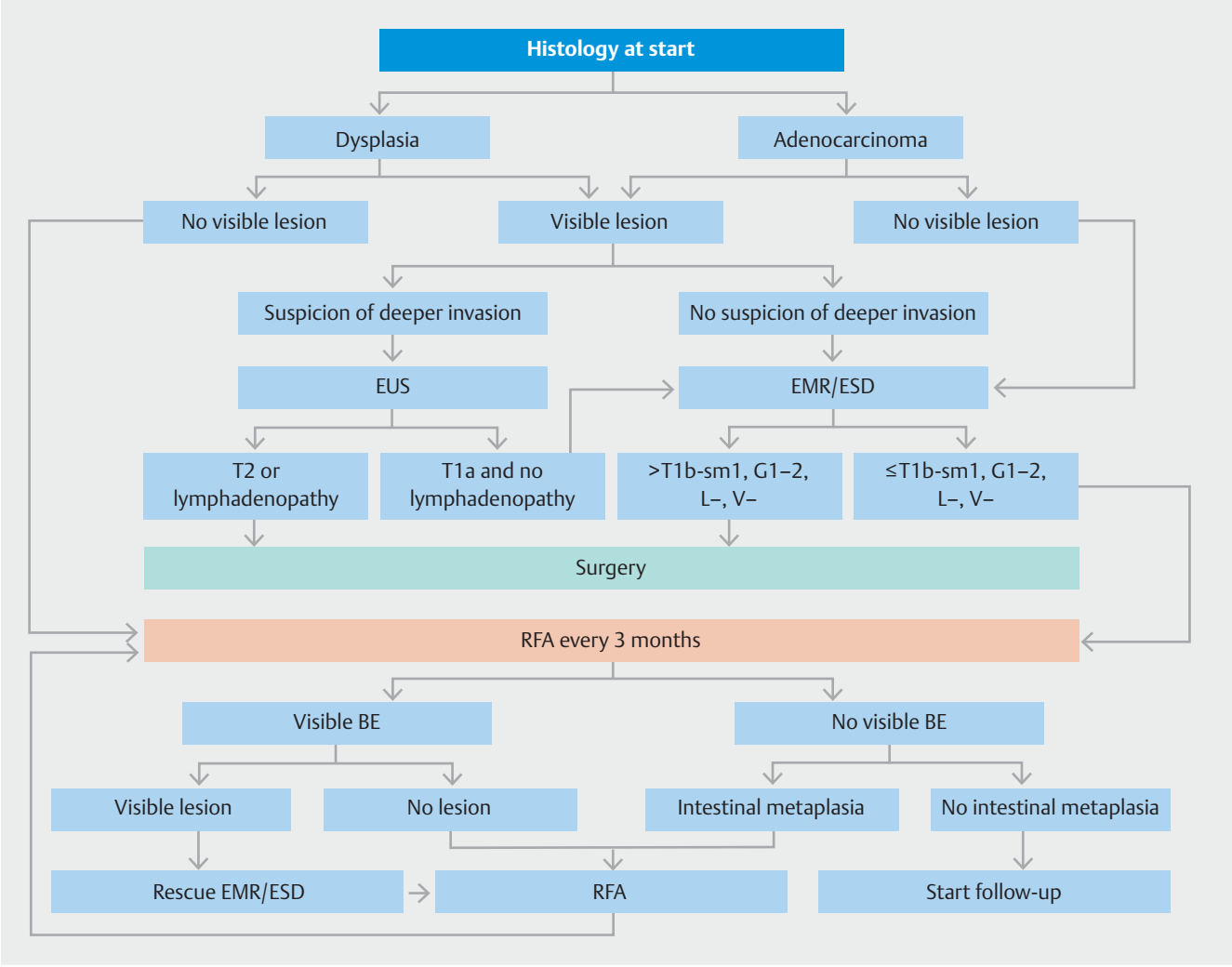
The first step is to assess the need for endoscopic resection by taking biopsies according to the Seattle protocol, and thorough assessment to exclude and resect any visible lesions prior to RFA [24]. The biopsy and endoscopic resection specimens are always reviewed by at least two expert pathologists. When a duplicated muscularis mucosae is present, submucosal invasion is diagnosed if the lesion crosses the deepest layer (i. e., the original muscularis mucosae) of the muscularis mucosae [25]. Immunostaining for p53 is used at all biopsies to confirm dysplasia; the grade of dysplasia is determined by morphological criteria.

Enhanced endoscopic imaging techniques (narrow band imaging, i-SCAN digital contrast, and flexible spectral imaging color enhancement) are used where available and the Barrett segment is measured according to the Prague classification (in centimeters) [26]. In the case of visible lesions with suspicion of deeper invasion, additional imaging with endoscopic ultrasound is often performed to exclude T2 disease and mediastinal lymphadenopathy, which would preclude further endoscopic intervention.

Endoscopic resection is performed in the case of any visible lesion or in the case of histological proof of early adenocarcinoma. Patients without visible abnormalities and with a pretreatment diagnosis of dysplasia are considered directly suitable for primary RFA treatment. If invasive cancer (>T1b sm1) is demonstrated by the endoscopic resection specimen, or T2 disease or lymphadenopathy is detected, the patient is referred for surgery, which indicates the end of follow-up in the registry. The differentiation between T1a intramucosal and T1b submucosal tumors is based on the anatomopathological findings from the resection specimens. There are no clear endoscopic criteria to differentiate mucosal from submucosal cancers. The main reasons for not attempting to resect a lesion are the lesion's being type O-III (clear ulceration), a nonlifting sign, and that a lesion cannot be aspirated into the resection device.

RFA is performed with either the circumferential ablation device (HALO 360) or with one of the focal devices for shorter noncircumferential areas (HALO 90, HALO 60, Ultra 90, through the scope device) (Medtronic, USA). It is done on a 3-monthly basis until full CR-IM is obtained or treatment is ceased for another reason (▶ **Fig. 1**, ▶ **Fig. 2**).

Patients with proven histologically complete remission of intestinal metaplasia (CR-IM) and complete remission of dysplasia (CR-D) in the previously treated Barrett's segment and under the neo-Z-line, enter follow-up. Follow-up endoscopy with four-quadrant biopsies under the neo-Z-line and of the neosquamous epithelium treated segment is done 3-monthly in the first year, 6-monthly in the second year, and annually there-




▶ **Fig. 1** Belgian radiofrequency ablation (RFA) registry endoscopy protocol. BE, Barrett's esophagus; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; G1 – 2, grade 1 to 2; L – ve, no lymphatic invasion; V – ve, no vascular invasion.

after. If there is remaining residual dysplasia at the end of the RFA treatment, or in the case of recurrence, further endoscopic therapy is offered with either RFA, argon plasma coagulation (APC), or endoscopic resection, depending on the histological findings.

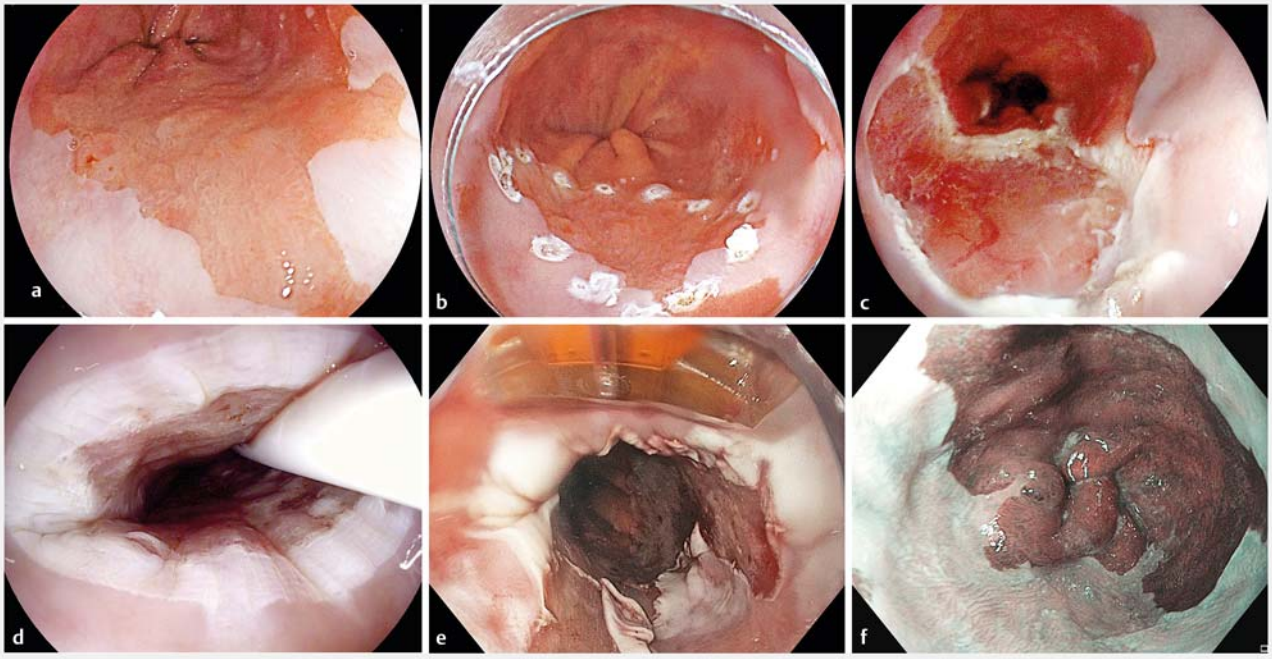
## Primary and secondary endpoints

The data of the Belgian RFA registry were analyzed for efficacy and safety outcomes. The primary outcome parameters included CR-IM and CR-D (endoscopically, and absence of dysplasia or IM under the neo-Z-line). Secondary outcomes were durability of CR-IM and CR-D and safety. Safety outcomes included immediate and late adverse events. Bleeding was considered clinically significant if it required hospitalization, blood transfusion, or an additional endoscopic intervention. A stenosis was defined as narrowing of the esophagus with symptomatic dysphagia requiring dilation.

## Data analysis

Efficacy results are reported in per-protocol and in intention-to-treat (ITT) analyses. Patients who discontinued treatment early were included as treatment failures for the ITT analysis and were excluded from the per-protocol analysis. For the safety analysis, all patients were included.

To compare the results of the Belgian RFA registry with the EURO II trial and the UK RFA registry a chi-squared test was performed [17, 22]. *P* values of less than 0.05 were considered to be statistically significant. Possible risk factors for recurrence were assessed with a univariate and multivariate analysis. IBM SPSS software 24.0 was used.




▶ **Fig. 2** Treatment of Barrett's esophagus with endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA). **a** Type 0-IIb Barrett lesion at six o'clock (Paris classification). **b** Demarcation of the lesion pre-EMR. **c** Barrett lesion post-EMR. **d** Circumferential RFA with HALO 360. **e** Focal ablation with HALO 90. **f** Complete regression of the lesion visualized with narrow band imaging.

# Results

## Clinical data

A total of 684 procedures in 342 patients were included between February 2008 and January 2017 (▶ **Table 1**).

The worst pathology prior to the start of RFA was the histological finding of either the biopsy before start of RFA, or of the endoscopic resection specimen. RFA was performed in 54 % of patients for HGD, in 37 % after resection of early EAC, in 7 % for low grade dysplasia (LGD) and in 1 % for IM. In our series 126 patients had a T1a or T1b sm1 adenocarcinoma, and among these, 46 (37 %) showed a duplicated muscularis mucosae, 16 (13 %) had a normal muscularis mucosae, while in 64 patients (50 %) duplication was not clearly mentioned. There were no cases of LGD of the foveolar type. The median length of the BE was C2M5.

Prior to RFA, 53 % underwent EMR and 7 % ESD.

## Efficacy outcomes

Of the 342 patients, 47 had started the treatment protocol less than 1 year ago and were excluded from the efficacy analysis. Among the remaining 295 patients, 19 did not complete treatment for the following reasons: lost to follow-up (14), nonrelated comorbidity/death (4), and withdrawal of informed consent (1) (▶ **Fig. 3**).

### Complete remission of intestinal metaplasia

CR-IM was achieved in 242 patients achieved. Of these, 12 % (30/242) had received a rescue treatment (e. g. additional EMR, ESD, APC, or a combination of these) before CR-IM was achieved (▶ **Table e2**, available online-only). Treatment failed in 34 patients because of remaining IM (15), remaining dysplasia (11), need for surgery because of progression to adenocarcinoma (7) and there was one death due toe invasive adenocarcinoma. This was diagnosed on control biopsies after initial treatment with EMR and RFA (HALO 360) of long-segment Barrett's with previous histology of only HGD. The patient refused any treatment and metastatic disease occurred 1 year later.

In the ITT analysis, CR-IM was obtained in 82 %. A per-protocol analysis, correcting for patients not finishing the treatment, gave a success rate of 88 %. The median time to achieve CR-IM, counting from the first RFA treatment was 7 months (interquartile range [IQR]) 4 – 12), with median number of treatments 2 (IQR 1 – 3).

### Complete remission of dysplasia

CR-D was achieved in 257 patients. Of these, 13 % received a rescue treatment before CR-D. Treatment failures included the same patients as for CR-IM minus 15 patients with remaining IM. In the ITT analysis, CR-D was 87 % and in the per-protocol analysis it was 93 %.

### Durability of response

Amongst the patients with CR-IM and with CR-D, 15 and 18, respectively, never received a surveillance endoscopy after achieving the end point and were lost to follow-up.

With a median follow-up time after CR-IM of 25 months (IQR 12 – 47), there was sustained remission of IM in 65 %, in a per protocol analysis, giving a recurrence rate of 35 %. Recurrence of IM was most frequently observed (59/227 patients, 26 %), followed by direct recurrence of HGD (14 patients, 6 %), LGD (6 patients, 2.5 %) and adenocarcinoma (1 patient, 0.5 %).

Subanalysis of those with recurrence of IM revealed that in 28 patients (48 %) the recurrence was not confirmed at later biopsies. On the other hand, in 19 patients with confirmation at later biopsies (32 %) recurrence of IM was not an isolated event with 3 patients developing HGD and 2 patients LGD. The remaining 12 patients (20 %) with IM recurrence had not yet received further endoscopic and histological control. Most biopsies showing recurrence of IM were taken at the cardia (36 %), followed by biopsies from islands (25 %), or tongues (24 %), while in 15 % the exact location was not described in the endoscopy report.

The median follow-up time for patients with CR-D was 23 months (interquartile range [IQR] 9 – 45) and sustained remission was seen in 90 % (per-protocol analysis). Recurrence of disease occurred in 23 patients, with the majority having a direct recurrence of HGD.

The median times to recurrence for IM, LGD, HGD, and EAC were, respectively, 14, 7, 10 and 13 months. A Kaplan – Meier analysis of these results was performed (▶ **Fig. 4**).

### Risk factors for recurrence

To search for possible factors associated with higher recurrence, a univariate analysis was done that included patients with CR-IM between January 2008 and August 2015 with follow-up of more than 6 months (▶ **Table 3**). Log rank P values for all data were not significant (▶ **Table e4**); therefore multivariate analysis could not be done.

### Academic versus nonacademic centers

Of the 342 included patients, 24 (7 %) were treated at nonacademic centers. CR-IM (per-protocol analysis) was achieved in 64 % (9/14) of the patients treated at nonacademic centers and in 89 % (233/262) of those treated in academic centers. The remission rate for those treated in academic centers was significantly higher (chi-squared, $P<0.01$). However no significant difference in sustained remission was seen between patients treated at academic versus nonacademic centers (141/218 [65 %] and 6/9 [67 %], respectively; chi-squared, $P=0.9$).

## Safety outcomes

A total of 684 procedures in 342 different patients were registered. Complications that occurred during treatment with RFA were considered to be immediate adverse events. All complications after the RFA procedure were registered as late adverse events.

### Immediate adverse events

There were immediate complications in 24 procedures (4 %) in 22 different patients (6 %) (▶ **Table e5**). The majority were minor lacerations of the esophageal mucosa (16), with 9 due to sizing (measurement of the diameter of the esophagus using a

▶ **Table 1** Demographic data and pre-RFA/endoscopic resection characteristics for all patients.

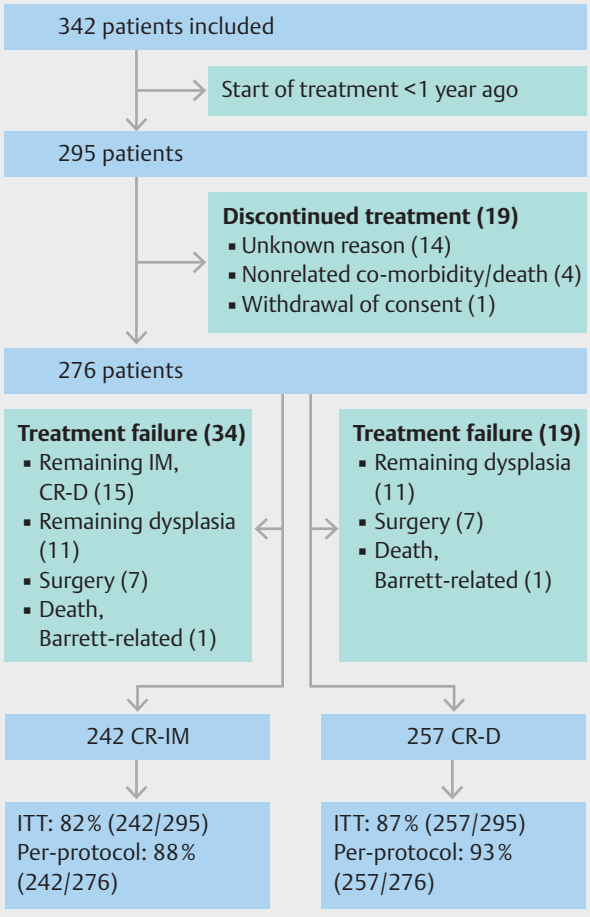
| | |
|---|---|
| Patients, n | 342 |
| % Male | 85 % |
| Age, mean (IQR), years | 65 (57 – 73) |
| Baseline histology, n (%) | |
| ▪ IM | 3 (1 %) |
| ▪ LGD | 23 (7 %) |
| ▪ HGD | 186 (54 %) |
| ▪ EAC | 126 (37 %) |
| ▪ Unknown | 4 (1 %) |
| BE length, median (IQR), cm | |
| ▪ C | 2 (0 – 5) |
| ▪ M | 5 (0 – 7) |
| Endoscopic resection prior to RFA, n (% ) | |
| ▪ EMR | 182 (53 %) |
| ▪ ESD | 23 (7 %) |

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGD, high grade dysplasia; IQR, interquartile range; LGD, low grade dysplasia.

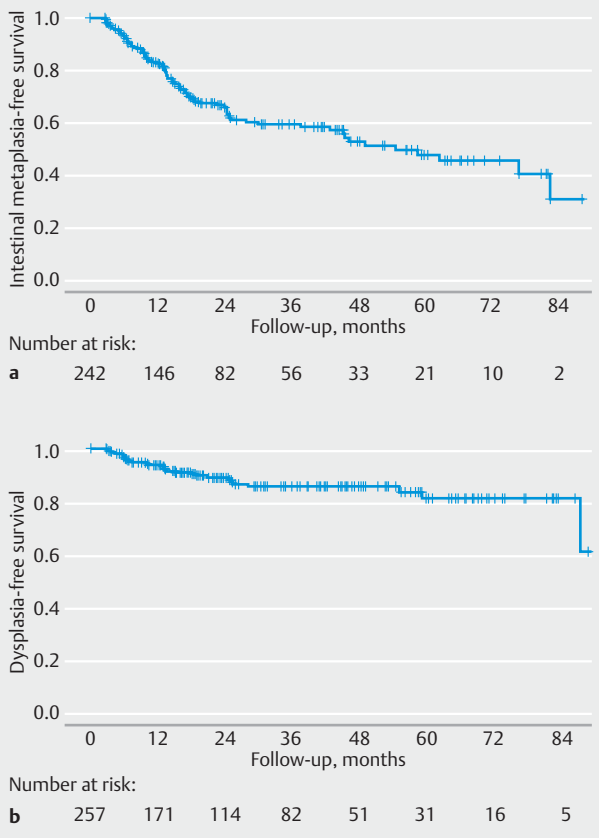
▶ **Table 3** Characteristics of the patients with a follow-up more than 6 months after complete remission of metaplasia (CR-IM) had been achieved.

| Variable | |
|---|---|
| Female/male, n/n (%/%) | 19/139 (12/88) |
| Age at initiation of therapy, median (IQR), years | 64 (58 – 73) |
| Prague C score, median (IQR) | 1 (0 – 4) |
| Prague M score, median (IQR) | 5 (2 – 6) |
| Diaphragm – Z-line distance median (IQR), cm | 2 (1 – 4) |
| RFA sessions, median (IQR), n | 2 (1 – 2) |
| Histology, n/n (%) | |
| ▪ LGD | 19/155 (12) |
| ▪ HGD | 78/155 (50) |
| ▪ EAC | 58/155 (38) |
| Endoscopic resection, n/n (%) | 90/159 (57) |
| Follow-up, median (IQR), months | 30 (17 – 45) |
| Recurrence, n/n (%) | 58/159 (36) |

EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; IQR, interquartile range; LGD, low grade dysplasia




▶ **Fig. 3** Belgian registry for radiofrequency ablation for Barrett's esophagus. Patients and outcomes for complete remission of intestinal metaplasia (CR-IM) and complete remission of dysplasia (CR-D). IM, intestinal metaplasia; ITT, intention-to-treat.




▶ **Fig. 4** Kaplan – Meier analyses, following radiofrequency ablation of Barrett's esophagus: **a** intestinal metaplasia-free survival after complete remission of metaplasia; **b** dysplasia free survival after complete remission of dysplasia.

balloon). These lesions were treated conservatively. There was bleeding of the esophagus in 8 patients, for which 2 patients needed an intervention (APC or coagulation). There were no deaths or esophageal perforations

### Late adverse events

A total of 83 events (9% of procedures) in 69 patients (20%) were registered as late complications, with stenosis being the most frequently reported. The median number of dilations needed to improve dysphagia was 2 (IQR 1 – 4).

Prolonged hospitalization was required in 16 patients, in most cases (7/16) because of the development of fever over 38 °C. Other reasons included readmission because of development of dysphagia without evidence of esophageal stenosis (3/16), pneumonia (2/16), and severe thoracic pain (1/16). In the remaining 3 patients the reason was not specified.

A late bleeding occurred in 9 patients, requiring packed cells in 1 and endoscopic intervention with clipping in 1 other patient. Poor healing occurred in 3 patients. Among the patients who underwent endoscopic resection prior to RFA, stenosis developed in 5% (9/182) of EMR patients and 40% (9/23) of ESD patients (▶ **Table 6**) (relative risk [RR] 7.9, 95% confidence interval [CI] 3.5 – 17.9; $P<0.001$, Fisher's exact test).

## Comparison of the Belgian RFA registry with the EURO II trial and the UK RFA registry

### EURO II trial

Concerning efficacy outcomes, CR-D was significantly higher in the EURO II trial ($P<0.05$), whereas CR-IM was not significantly different (▶ **Table 7**). Safety outcomes (stenosis, laceration, and bleeding) were not significantly different between the Belgian registry and the EURO II trial [17].

### UK RFA registry cohort 2011 – 2013

There was no significant difference between the two registries for efficacy outcomes (CR-IM and CR-D) nor for the safety outcome of stenosis. The only significant difference was in the number of rescue treatments performed to achieve CR-IM or CR-D, with a higher number of rescue treatments in the Belgian RFA registry [22].

▶ **Table 6** Distribution of late adverse events in patients undergoing radiofrequency ablation (RFA).

| Late adverse event | n (% of total RFA or EMR or ESD procedures) |
|---|---|
| Stenosis | 37 (5 % of RFA procedures) |
| Bleeding | 9 (1 % of RFA procedures) |
| Poor healing | 3 (0.4 % of RFA procedures) |
| Prolonged hospitalization | 16 (2 % of RFA procedures) |
| Stenosis post-EMR | 9 (5 % of patients) |
| Stenosis post-ESD | 9 (40 % of patients) |

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

## Discussion

This prospective multicenter cohort study reports the Belgian experience treating 342 patients with neoplastic BE, using RFA with or without previous endoscopic resection in a real-life clinical setting. This was done in the absence of reimbursement and following an official ablation protocol about which all the endoscopists were well informed. In contrast to previously published trials, monitoring of sites was not foreseen nor desired since the goal of this registry is to assess real-life outcomes with variability in practice. Nevertheless, the stratification and harmonization of treatment protocols was discussed through yearly meetings amongst the RFA sites.

Our results show that RFA is highly effective in eradicating intestinal metaplasia and dysplasia, with CR-IM in 82 % (per-protocol 88 %) and CR-D in 87 % (per-protocol 93 %). The fairly high rate of EMR (57 %) or ESD (7 %) prior to initiating RFA is likely to contribute to these good results. This is supported by findings from two cohorts of the UK RFA registry (2008 – 2010 and 2011 – 2013) that revealed a significant improvement in both CR-IM and CR-D in the presence of a higher rate of endoscopic resection prior to RFA [22]. In our setting a significantly higher number of rescue treatments (additional EMR, ESD, APC, or a combination) were performed before achieving remission, in comparison to the UK registry (12 % versus 2 %). This is most likely explained by the lower cost of these rescue treatments, given that RFA was not reimbursed in Belgium until April 2016. Nevertheless, the total outcome was good and almost comparable to study settings. The CR-IM remission rate was significantly higher in the academic centers; however the total number of patients in nonacademic centers was rather low so this analysis is probably underpowered to draw any valid conclusions.

We found a 12 % recurrence of neoplasia after a long-term median follow-up time of 2.4 years. The majority of recurrences were of IM (26 %), and in nearly half of cases (48 %) this was a single event that was not confirmed on later biopsies. In our view, the substantial recurrence rate arises because control biopsies were also taken at the cardia and the presence of intestinal metaplasia at the cardia was considered to be recurrence. However in other studies the presence of intestinal metaplasia at the cardia has not been considered to be recurrence since the implication of this finding is not well understood as yet. As in the EURO II trial, this could not be reconfirmed in more than 50 % of patients. Therefore we advise that treatment should not be restarted only on the basis of histological recurrence of IM. However persisting IM must be followed-up since this can evolve to recurrence of neoplasia, supporting the recent Position Statement of the European Society of Gastrointestinal Endoscopy [2].

Our recurrence rate is comparable to the long-term follow-up data from the AIM dysplasia trial with a recurrence rate of IM in 32 % and of neoplasia in 19 %. Similarly to our series, most recurrences occurred within the first year after eradication [27]. Of course, the fact of an early recurrence begs the question of persistent residual disease.

These recurrence rates are in contrast with those the EURO II trial. Conceptually it may be explained by the systematic ablation, in the EURO II trial, of the neo-Z-line every time a focal ablation was performed even when only small residual islands

▶ **Table 7** Comparison of Belgian radiofrequency ablation (RFA) registry with the EURO II trial and the UK RFA registry cohort 2011 – 2013.

| | EURO II trial | *P*, Belgian vs. EURO II | Belgian RFA registry | *P*, Belgian vs. UK 2011 – 13 | UK RFA registry, 2011 – 13 |
|---|---|---|---|---|---|
| Efficacy | | | | | |
| CR-IM (per-protocol) | 115/124 (93 %) | 0.13 | 242/276 (88 %) | 0.14 | 201/242 (83 %) |
| CR-D (per-protocol) | 122/124 (98 %) | **0.03** | 257/276 (93 %) | 0.55 | 222/242 (92 %) |
| Rescue treatment | | | 30/276 (17 %) | **< 0.001** | 4/242 (2 %) |
| Safety | | | | | |
| Stenosis | 8/132 (6 %) | 0.11 | 37/342 (11 %) | 0.05 | 15/242 (6 %) |
| Laceration | 11 /132 (8 %) | 0.12 | 16/342 (5 %) | | |
| Bleeding | 1/132 (1 %) | 0.26 | 8/342 (2 %) | | |

CR-IM, complete remission of metaplasia; CR-D, complete remission of dysplasia.

were present. This approach was not used in the AIM dysplasia trial, and was probably used less stringently in our setting where RFA was not reimbursed.

Further comparison of our data with the EURO II trial demonstrate that the outcomes for efficacy (CR-IM) and safety of the treatment of mucosal BE neoplasia outside study protocols were similar, but there was a higher rate of CR-D in the EURO II trial [17]. However this reflects real-life outcomes with inclusion of patients who are sometimes more difficult to treat and who would have been excluded from a study protocol because of BE length or too extensive endoscopic resection, and also to some extent because of the absence of reimbursement. Overall, the results are comparable and may reflect that all participating centers in our study were expert centers and all investigators had previously received hands-on training at the coordinating site or elsewhere.

After complete eradication of intestinal metaplasia and dysplasia, surveillance remains important because of the real, albeit low, risk of recurrence. Since most recurrences occur within the first year, we would suggest, for best clinical practice, performance of follow-up gastroscopy every 3 months during the first year, every 6 months during the second year, and annually thereafter. A recent study of 5 years' follow-up showed no recurrences after 4 years of surveillance [27]. However, duration of follow-up probably depends merely on patient age and co-morbidity. Our univariate analysis could not reveal a possible risk factor to predict recurrence.

Immediate and late adverse events occurred, respectively, in 7.5 % and 15 % of patients. Although most complications were mild and no perforation occurred, delayed bleeding especially was severe and possibly life-threatening in 1 % of patients. Stenosis after RFA was the most frequent late adverse event, for which 37 patients required dilations and 5 patients even required temporary stenting. Compared with the EURO II and the UK RFA registry there was a higher rate of stenosis. The fact that 7 % had undergone ESD prior to RFA is probably responsible for this finding, given a significantly higher chance of developing stenosis after ESD in comparison to EMR [17]. Overall we can conclude that, for the correct indication, the risk-benefit balance is favorable for RFA in combination with endoscopic resection as treatment for BE.

There are several strengths to our study. First, all data were prospectively collected on standardized case report forms that were controlled by one trained and experienced study nurse at the coordinating center in Leuven. In addition, it is a genuinely multicenter study with, as well as the participation of five academic centers, the participation also of two local hospitals. Since Belgium has only 11 million inhabitants, the number of 342 patients in this registry suggests that most RFA treatments were captured in our database. Standardization of the procedure and treatment protocol was attempted through several meetings with the centers involved in the registry. Also all endoscopists received proper training through, for instance, the RFA academic community.

Our study has also several limitations. As is inherent to a prospective registry, some data were missing. For example there were no data on multifocal dysplasia and on maximum depth of invasion in microns from the surface; this could have been interesting since intramucosal carcinoma involving >50 % of the metaplastic mucosa is an adverse prognostic indicator for resistance to ablation [28]. The pathology reports of control biopsies specified whether was stroma was included in the biopsy or not, which was the fact in about 10 % of the cases. Since our data are comparable with the EURO II trial, even with a relatively long follow-up, we do not consider this to be a major limitation.

All endoscopies and interventions were performed by the same seven experienced gastroenterologists. Whether or not these results can be generalized to less experienced endoscopists is uncertain. Our data however confirm that a good outcome of RFA for BE can be achieved if it is performed by a sufficiently trained endoscopist with experience in recognition and resection of small visible BE-associated lesions.

## Conclusion

The data from this multicenter prospective Belgian registry confirm that RFA is an efficient and safe treatment for BE with dysplasia or after resection of an early EAC. In the absence of reimbursement more rescue treatments are used, with good outcomes for patients. ESD is associated with a higher risk of stenosis when combined with RFA. Since the recurrence rate is 35 % after achieving CR-IM, surveillance endoscopy remains necessary. Because of the risk of complications, RFA should not be used in asymptomatic low risk patients with nondysplastic BE.

### Competing interests

R. Bisschops has potentially relevant relationships with Medtronic, CDx Diagnostics, Pentax, and Fujifilm; he has received personal payments/honoraria/fees from Boston Scientific, GI Solutions Covidien/Medtronic, Fujifilm, Pentax, Olympus, Norgine, and CDx Diagnostics; he has received research grants from Cook, Pentax, and Fujifilm, and equipment grants from Pentax and Fujifilm. M. Ferrante has received research grants from Takeda and Janssen; he has provided consultancy to Abbvie, Boehringer-Ingelheim, Ferring, Janssen, Mitsubishi Tanabe, MSD, and Pfizer; he has received speaker's fees from Abbvie, Boehringer-Ingelheim, Chiesi, Ferring, Janssen, Mitsubishi Tanabe, MSD, Pfizer, Tillotts, and Zeria.

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