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

J. VLIEBERGH (1), P.H. DEPREZ (2), D. DE LOOZE (3), M. FERRANTE (1), H. ORLENT (4), E. MACKEN (5), P. CHRISTIAENS (6), F. MANA (7), G. DE HERTOGH (8), H. WILLEKENS (1), R. BISSCHOPS (1) / [1] University Hospitals Leuven, KU Leuven, Leuven, Belgium, Gastroenterology and Hepatology [2] University Hospitals St-Luc, Brussels, Belgium, Gastroenterology and Hepatology, [3] UZ Ghent, Ghent, Belgium, Gastroenterology,[4] AZ St-Jan, Bruges, Bruges, Belgium, Gastroenterology, [5] UZ Antwerp, Antwerp, Belgium, Gastroenterology, [6] Imelda Hospital Bonheiden, Bonheiden, Belgium, Gastroenterology, [7] UZ Brussels, Jette, Belgium, Gastroenterology, [8] University Hospitals Leuven, Leuven, Belgium, Pathology,

Corresponding Author: J. Vliebergh
Institution: UZ Leuven, Herestraat 49, 3000 Leuven
joke.vliebergh@gmail.com

Abstract

Background and study aims

Radiofrequency ablation (RFA), combined with endoscopic resection (ER), 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 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, from which 295 patients were included for efficacy analysis and achieved CR-IM in 88% and CR-D in 93%. Sustained remission was seen in 65% with a median follow-up of 25 (IQR 12-47) months. No risk factors for recurrent disease were identified. Immediate complications occurred in 4% of all procedures and 6% of all the 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 ER is an efficient treatment for BE with dysplasia or EAC. In the absence of reimbursement more escape treatments are used, not compromising outcome. Since there is recurrent disease after CR-IM in 35%, annually surveillance endoscopy remains necessary.

Introduction

Barrett's esophagus (BE) has been traditionally defined as the visible presence of at least 1 centimeter of metaplastic columnar lined epithelium that replaces the non-keratinized stratified squamous epithelium of the distal esophagus [1][2][3][4]. It is a known premalignant condition typically stepwise and slowly evolving from non-dysplastic IM to dysplasia and eventually esophageal adenocarcinoma (EAC) [1][3][5][6][7].

Over the past two decades treatment of BE dramatically changed since endoscopic resection (ER) replaced esophagectomy as a first line treatment for high grade dysplasia (HGD) [8][9][10]. Endoscopic resection can either be endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), always in combination with ablation since there is a high risk of metachronous disease when only ER is performed [11][12][13]. Since 2008, radiofrequency ablation (RFA) has become available for flat dysplastic Barrett or as add-on after ER 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][17][18]. The good results of combined ER and RFA are worldwide confirmed by large-volume multicenter prospective series that show comparable results for efficacy in the United Kingdom (UK) and the United States [19][20][21]. Analysis from the first two cohorts from the UK RFA registry showed that ER 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 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 centers) of which 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

Inclusion: all patients with undergoing RFA for curative eradication of BE. Exclusion criteria were squamous dysplasia, submucosal invasion (≥T1bsm2), lymphatic/vascular invasion in any of the ER specimens and poorly or undifferentiated lesions (G3, G4) since the higher risk on 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

First step is to assess the need for ER by taking biopsies according to the Seattle protocol and thorough assessment to exclude and resect any visible lesions prior to RFA [24]. The biopsies and ER specimens are always reviewed by at least two expert pathologists. In case of the presence of a duplicated muscularis mucosae, submucosal invasion was diagnosed if the lesion crossed the deepest layer (i.e. the original muscularis mucosae) of the muscularis mucosae [25]. P53 immunostaining was used at all biopsies to confirm dysplasia, the grade of dysplasia was determined by morphological criteria.

Enhanced endoscopic imaging techniques (narrow band imaging, i-scan 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 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.

ER was performed in case of any visible lesion or in case of an histological proof of early adenocarcinoma. Patients without visible abnormalities and a pretreatment diagnosis of dysplasia were directly suitable for primary RFA treatment. If invasive cancer (≥T1bsm2)was demonstrated at the ER specimen, T2 disease or lymfadenopathy was detected, the patient was referred for surgery, which indicated the end of follow-up in the registry. The differentiation between T1a intramucosal and T1b submucosal tumors was based on the anatomopathological findings of the resection specimens. There are no clear endoscopic criteria to differentiate mucosal from submucosal cancers. The main

aspects to refrain from attempt to resect a lesion was a type O-III lesion (clear ulceration), a non-lifting sign and if a lesion could not be aspirated in the resection device.

RFA is performed with either the circumferential ablation device (HALO 360) or with one of the focal devices for shorter non-circumferential areas (HALO 90, HALO 60, Ultra 90, Trough The Scope device) on a three-monthly basis until full CR-IM was obtained or treatment was ceased for another reason (**Figure 1**) (**Figure 2**).

Patients with proven histological 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, entered follow-up. Follow-up endoscopy with four quadrant biopsies under the neo Z-line and neosquamous epithelium of the treated segment happened 3-monthly in the first year, 6-monthly in the second year and annually thereafter. If there was still remaining residual dysplasia at the end of the RFA treatment or in case of recurrence, further endoscopic therapy was offered with either RFA, Argon Plasma Coagulation (APC) or ER depending on histology.

Primary and secondary endpoints

The Belgian RFA registry was analyzed for efficacy and safety outcomes. Primary outcome parameters include 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 dilatation.

Data analysis

Results are reported per protocol (PP) and on an intention-to-treat (ITT) analysis for efficacy. Patients who discontinued treatment early, were included as treatment failures for the ITT analysis and were excluded from the PP analysis. For 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 Square test was performed [17][22]. A p-value less than 0,05 was considered as statistical significant. Possible risk factors for recurrence were assessed with a uni- and multivariate analysis. IBM SPSS software 24.0 was used.

Results

Demographicsf.

A total of 684 procedures in 342 patients were included between February 2008 and January 2017 (**table 1**). Worst pathology prior to start RFA was either the histology of the biopsy before start of RFA, or the histology of the ER specimen. RFA was performed in 54% of patients for HGD, in 37% after resection of EAC, in 7% for low grade dysplasia (LGD) and in 1% for IM. In our series there were 126 patients with a T1a or T1bsm1 adenocarcinoma of which in 46 (37%) there was a duplicated muscularis mucosae. 16 (13%) patients had a normal muscularis mucosae and in 64 (50%) cases

duplication wasn't clearly mentioned. There were no cases of LGD of the foveolar type. The median length of the BE was C2M5. Fifty three% and 7% underwent EMR or ESD, respectively prior to RFA.

Efficacy outcomes

Forty seven of the 342 patients started treatment protocol less than one year ago and were excluded from the efficacy analysis. Within the remaining 295 patients, 19 didn't complete treatment for the following reasons: lost to follow-up (14), non-related comorbidity/death (4) and withdrawal of informed consent (1) (**figure 3**).

- *Complete remission of intestinal metaplasia*

A total of 242 patients achieved CR-IM. Of these patients, 12% (30/242) received a rescue treatment (e.g. additional EMR, ESD, APC of a combination) before achieving CR-IM (Supplementary **table** 1). Treatment failed in 34 patients because of remaining IM (15), remaining dysplasia (11) and need for surgery because of progression to adenocarcinoma (7). There was one death due to invasive adenocarcinoma which was diagnosed on control biopsies after initial treatment of a long segment Barrett with previous histology of only HGD with EMR and RFA (HALO 360) and for which the patient refused any treatment. One year later metastatic disease occurred.

In the ITT analysis CR-IM was obtained in 82%. Correcting for patients not finishing the treatment in a PPanalysis gave a success rate of 88%. Median time to achieve CR-IM, counting from the first RFA treatment is 7 (IQR 4-12) months, with a median number of treatments of 2 (IQR 1-3).

- *Complete remission of dysplasia*

A total of 257 patients achieved CR-D. Of these patients, 13% received a rescue treatment before CR-D. Treatment failures included the same patients as for CR-IM minus 10 patients with remaining IM. In an ITT analysis, CR-D was 87% and in the PP analysis 93%.

- *Durability of response*

From the patients who achieved CR-IM and CR-D, 15 and respectively 18 patients never got a surveillance endoscopy after achieving the endpoint and were lost to follow-up. With a median follow-up time after CR-IM of 25 (IQR 12-47) months, the PP analysis for sustained remission of IM was 65%, which gave a recurrence rate of 35%. Recurrence of IM was most frequently observed (59 patients, 26%), followed by direct recurrence of HGD (14 patients, 6%), LGD (six patients, 2,5%) and adenocarcinoma (one patient, 0,5%). Subanalysis of those with recurrence of IM revealed that in 28 patients (48%) the recurrence wasn't confirmed at later biopsies. On the contrary, in 19 patients (32%) the recurrence of IM wasn't a lonely event with three patients developing HGD and two patients LGD. Thirteen patients (20%) with a recurrence of IM didn't have an endoscopic and histological control yet. Most biopsies with recurrence of IM were taken at the cardia (36%), followed by biopsies from an isle (25%), a tongue (24%) and in 15% the exact place wasn't described in the endoscopy protocol.
The median FU time for patients with CR-D was 23 months (IQR 9-45) and sustained remission was seen in 90% (PP analysis). Recurrence of disease occurred in 23 patients, with the major part having a direct recurrence of HGD.

The median time to recurrence for IM, LGD, HGD and EAC was respectively 14, 7, 10 and 13 months. Kaplan-Meijer analysis of these results was performed (**figure 4**).

- *Risk factors for recurrence*

A univariate analysis of the patients who achieved CR-IM between January 2008 and August 2015 with a follow-up more than 6 months was performed in search for possible factors associated with a higher recurrence rate (**table 2**). LogRank p-values for all data were not significant (supplementary **table 2**), therefore no multivariate analysis could be performed.

- *Academic versus non-academic centers*

24 of the 342 included patients (i.e. 7%) were treated at non-academic centers. CR-IM (PP analysis) was achieved in 64% (9/14) of the patients treated at non-academic centers and in 89% (233/262) of the patients treated in academic centers. There was a significant higher remission rate at the group treated in academic centers (chi square test, p-value <0,01). However no significant difference in sustained remission was seen between patients treated at academic (65%, 141/218) versus non-academic (67%, 6/9) centers (chi square test, p-value 0,9).

Safety outcome

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

- *Immediate adverse events*

There were 24 procedures with immediate complications in 22 different patients (4% of the procedures, 6% of the patients). The majority were minor lacerations of the esophageal mucosa (16), six due to sizing. These lesions were treated conservatively. Seven patients had a bleeding of the esophagus, for which two patients needed an intervention (APC or coagulation). There were no deaths or esophageal perforations (**supplementary table 3**).

- *Late adverse events*

Eighty three events in 69 patients (9% of the procedures, 20% of the patients) were registered as a late complication of which stenosis was the most frequently reported complication. The median number of dilatations needed to improve dysphagia was two (IQR 1-4). Sixteen patients required a prolonged hospitalization, most of them (7/16) due to the development of fever over 38° Celsius. Others reasons were: re-admission because of the development of dysphagia without evidence of oesophageal stenosis (3/16), pneumonia (2/16) and severe thoracic pain (1/16). In three patients the reason of prolonged hospitalization was not specified.

A late bleeding occurred in nine patients for which oneperson needed packed cells and another patient needed endoscopic intervention with clipping. There were three poor healers.From the patients who underwent EMRor ESD prior to RFA, 5% (9/182)and40% (9/23), respectively, developed a stenosis (RR 7.9 (95% CI 3.5-17.9), p<0.0001 Fisher's exact) (**table 3**). .

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-value <0.05), whereas CR-IM is not significantly different (**table 4**). Safety outcomes (stenosis, laceration and bleeding) were not significant different between both [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 safety outcome (stenosis). The only significant difference wasthe 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].

Discussion

This prospective multicenter cohort study reports the Belgian experience treating 342 patients with neoplastic BE using RFA with or without previous ER in a real life clinical setting, in the absence of reimbursement, following an official ablation protocol of 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 variance in practice. Nevertheless through yearly meetings amongst the RFA sites the stratification and harmonization of treatment protocols were discussed.

Our results show that RFA is highly effective at eradicating intestinal metaplasia and dysplasia, with 82% CR-IM (PP 88%) and 87% CR-D (PP 93%). The quite high rate of EMR/ESD (i.e. 53%/7%) prior to initiating RFA is likely to be a contributing factor to these good results. This is supported by the findings of two cohorts of the UK RFA registry (2008-2010 and 2011-2013) that revealed a significant improvement of both CR-IM and CR-D, in the presence of a higher rate of ER prior to RFA [22]. In our setting we had a significant higher number of rescue treatments (additional EMR, ESD, APC or a combination) that 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 since RFA wasn't reimbursed in Belgium until April 2016. Nevertheless, the total outcome was good and almost comparable to study settings. There was a significant difference in comparison of achieving CR-IM in favor of the academic centers, however the total number of patients in non-academic centers is 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 major part of the recurrences was recurrence of IM (26%), which in nearly half of the cases (48%) was a one-time event and wasn't confirmed on later biopsies. The significant recurrence rate is in our view rather due to the fact that control biopsies were also taken at the cardia and the presence of intestinal metaplasia at the cardia was considered as a recurrence whereas in other studies the presence of intestinal metaplasia at the cardia wasn't considered as a recurrence since the meaning of this is not well known at this point yet. Like in the EURO II trial in more than 50% of patients this could not be reconfirmed. Therefore we advise not to restart treatment only based on histological recurrence of IM.

However pertaining IM must be followed up since this can evolve to recurrence of neoplasia, which gives support to the recent position statement of the European society of Gastrointestinal endoscopy[2].

Our recurrence rate is comparable to the recently published 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 can begs the question of persistent residual disease.

These recurrence rates are in contrast with the EURO II trial. Conceptually it may be explained by the systematic ablation of the neo Z-line every time a focal ablation was performed even when only small residual islands were present. This approach was not used in the AIM dysplasia, and probably less stringent in our setting of absence of reimbursement.

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 protocol are similar, but there is a higher rate of CR-D in the EURO II trial [17]. However this reflects real life outcome with inclusion of patients that are sometimes more difficult to treat and would have been excluded from a study protocol because of BE length or too extensive ER and also to some extend due to the absence of reimbursement. Overall, the results are comparable and may reflect that all participating centers 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 –albeit low- real risk of recurrence. Since most recurrences occur within the first year we should suggest for best clinical practice to perform follow-up gastroscopy every three months during the first year, every six months during the second and and yearly thereafter. A recent study of 5 years follow-up showed no recurrences after 4 years of surveillance [27]. However, duration of follow-up probably merely depends on patient's age and co-morbidity. Our univariate analysis couldn’t reveal a possible risk factor to predict recurrence.

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

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

Our study has also several limitations. Inherent to prospective registry, some data were missing, for example there were no data on multifocal dysplasia and maximum depth of invasion in microns from the surface, which 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 there was stroma 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 as 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 performed by as ufficiently trained endoscopist with experience in recognition and resection of small visible BE associated lesions.

Conclusion

The data from this multicenter prospective Belgian registry confirms 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 escape treatments are used with good outcome for the patients. ESD is associated with a higher risk of stenosis when combined with RFA. Since the recurrence rate is 35% after achieving CR-IM, annualsurveillance endoscopy remains necessary. Because of the risk of complications, RFA should not be used in asymptomatic low risk patients with non-dysplastic BE.

References

1. Shaheen NJ, Falk GW, Iyer PG et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016; 111:30–50.
2. Weusten B, Bisschops R, Coron E et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2017;49:191–8.
3. Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014;63:7–42.
4. A Chak, T Lee, M F Kinnard et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. Gut 2002;51:323–328.
5. Desai TK, Krishnan K, Samala N et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut 2012;61:970–6.
6. Hamilton SR, Smith RRL, Cameron JL et al. Prevalence and characteristics of Barrett esophagus in patients with adenocarcinoma of the esophagus or esophagogastric junction. Human Pathology 1988;19:942–948.
7. Thompson JJ, Zinsser KR, Enterline HT. Barrett's metaplasia and adenocarcinoma of the esophagus and gastroesophageal junction. Human Pathology 1983;14:42–61.
8. Spechler SJ. Dysplasia in Barrett's esophagus: limitations of current management strategies. Am J Gastroenterol 2005;100:927–35.
9. Williams VA, Watson TJ, Herbella FA et al. Esophagectomy for high grade dysplasia is safe, curative, and results in good alimentary outcome. J Gastrointestinal Surgery 2007;11:1589–1597.
10. Nasr JY, Schoen RE. Prevalence of adenocarcinoma at esophagectomy for Barrett's esophagus with high grade dysplasia. J Gastrointestinal Oncology 2011;2:34–8.
11. Oliphant Z, Snow A, Knight H et al. Endoscopic resection with or without mucosal ablation of high grade dysplasia and early oesophageal adenocarcinoma - Long term follow up from a regional UK centre. Int J Surg 2014;12:1148–1150.
12. May A, Gossner L, Pech O et al. Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. Eur J Gastroenterology Hepatology 2002;14:1085–1091.
13. Ell C, May A, Pech O et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointestinal Endoscopy 2007;65:3–10.
14. Force SD, Miller DL. Esophageal Radiofrequency Ablation for the Treatment of Intestinal Metaplasia, Low Grade Dysplasia, and High Grade Dysplasia. Semin Thoracic Cardiovascular Surgery 2008;20:305–9.
15. Gaddam S, Sharma P. Advances in endoscopic diagnosis and treatment of Barrett's esophagus. J Digestive Disease 2010;11:323–333.
16. Phoa KN, van Vilsteren FGI, Weusten BLAM et al. Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia. Jama 2014;311:1209-1217.
17. Phoa KN, Pouw RE, Bisschops R et al. Multimodality endoscopic eradication for neoplastic

Barrett oesophagus: results of an European multicentre study (EURO-II). Gut 2016;65:555–562.

18. Cotton CC, Duits LC, Wolf WA et al. Spatial Predisposition of Dysplasia in Barrett's Esophagus Segments: A Pooled Analysis of the SURF and AIM Dysplasia Trials. Am J Gastroenterology2015; 110:1412–1419.
19. Haidry RJ, Dunn JM, Butt MA et al. Radiofrequency ablation and endoscopic mucosal resection for dysplastic Barrett's esophagus and early esophageal adenocarcinoma: Outcomes of the UK national halo RFA registry. Gastroenterology 2013;145:87–95.
20. Ganz RA, Overholt BF, Sharma VK et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicenter registry. Gastrointestinal Endoscopy 2008;68:35–40.
21. Phoa KN, Pouw RE, Van Vilsteren FGI et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: A Netherlands cohort study. Gastroenterology 2013;145:96–104.
22. Haidry RJ, Butt MA, Dunn JM et al. Improvement over time in outcomes for patients undergoing endoscopic therapy for Barrett's oesophagus-related neoplasia: 6-year experience from the first 500 patients treated in the UK patient registry. Gut 2015;64:1192–1199.
23. Manner H, Pech O, Heldmann Y et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surgical Endoscopy Other Interv Tech 2015;29:1888–1896.
24. Levine DS, Blount PL, Rudolph RE et al. Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. Am J Gastroenterol 2000;95:1152–1157.
25. Mandal R V., Forcione DG, Brugge WR et al. Effect of tumor characteristics and duplication of the muscularis mucosae on the endoscopic staging of superficial barrett esophagus-related neoplasia. Am J Surg Pathology 2009;33:620–625.
26. Sharma P, Dent J, Armstrong D et al. The Development and Validation of an Endoscopic Grading System for Barrett's Esophagus: The Prague C & M Criteria. Gastroenterology 2006;131:1392–9.
27. Cotton CC, Wolf WA, Overholt BF et al. Late Recurrence of Barrett's Esophagus After Complete Eradication of Intestinal Metaplasia is Rare: Final Report From Ablation in Intestinal Metaplasia Containing Dysplasia Trial. Gastroenterology 2017;153:681–688.
28. Agoston AT, Dulai PS, Strauss AC et al. Predictors of durable treatment response after radiofrequency ablation for barrett's esophagus associated intramucosal adenocarcinoma. Am J Surg Pathol 2016;40:554–562.

Tables

Number of patients	342
% Male	85 %
Mean age (IQR *)	65 (57-73)
Baseline histology, n (%) • **IM** • **LGD** • **HGD** • **EAC** • **Unknown**	 3 (1%) 23 (7%) 186 (54%) 126 (37%) 4 (1%)
Median BE length C(IQR)M(IQR)	C2 (0-5) M5 (0-7)
EMR prior to RFA, n (%) **ESD prior to RFA, n (%)**	182 (53%) 23 (7%)

Table 1: demographic data and pre-RFA/ER characteristics for all patients. * See alphabetic list of abbreviations

.

Variable	
Female/male (%)	19/139 (12/88)
Median (IQR) age at initiation of therapy (years)	64 (58-73)
Median (IQR) Prague C score	1 (0-4)
Median (IQR) Prague M score	5 (2-6)
Median (IQR) distance diaphragm – Z-line	2 (1-4)
Median (IQR) number of RFA sessions	2 (1-2)
Histology: LGD (%) Histology: HGD (%) Histology: EAC (%)	19/155 (12) 78/155 (50) 58/155 (38)
ER (%)	90/159 (57)
Median (IQR) follow-up	30 (17-45) months
Recurrence (%)	58/159 (36)

Table 2: Characteristics of the patients with a follow-up more than six months after achieving CR-IM

Late adverse event	**Number (% of total RFAor ER/ESD procedures)**
Stenosis	37 (5%)
Bleeding	9 (1%)
Poor healing	3 (0,4%)
Prolonged hospitalisation	16 (2%)
Stenosis post-EMR	9 (5%)
Stenosis post-ESD	9 (40%)

Table 3 : distribution of late adverse events.

	EURO II trial	P-value	Belgian RFA registry	P-value	UK RFA registry (2011-2013)
Efficacy					
• CR-IM (PP)	115/124 (93%)	0.13	242/276 (88%)	0.14	201/242 (83%)
• CR-D (PP)	122/124 (98%)	**0.029**	257/276 (93%)	0.55	222/242 (92%)
• Rescue treatment			30/276 (17%)	0.000024	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%)		

Table 4: comparison of Belgian RFA registry with the EURO II trial and the UK RFA registry cohort 2011-2013.

Supplementary Tables

Type of rescue treatment	CR-IM	CR-D
• APC	6% (17/242)	7% (19/257)
• EMR	5% (11/242)	4% (11/257)
• ESD	0,5% (1/242)	1% (2/257)
• Combination of at least two of the above mentioned procedures	0,5% (1/242)	1% (3/257)
Total	12% (30/242)	13% (35/257)

Supplementary table 1: details of rescue treatments prior to CR-IM and CR-D

Characteristics	Logrank p-value
Female (19/158)	0.561
Age at least 58 years (n=122/159)	0.172
Age at least 65 years (n=78/159)	0.914
Age at least 73 years (n=41/159)	0.610
ER before (n=90/159)	0.196
High grade dysplasia or adca (n=136/155)	0.391
Adenocarcinoma (n=58/155)	0.469
Prague C score at least 1 (n=95/159)	0.674
Prague C score at least 2 (n=79/159	0.409
Prague C score at least 4 (n=46/159)	0.729
Prague M score at least 2 (n=137/159)	0.546
Prague M score at least 5 (n=80/159)	0.473
Prague M score at least 6 (n=51/159)	0.508
Distance diagraphm Z line at least 1 cm	0.481
(n=131/159)	0.353

Distance diagraphm Z line at least 2 cm (n=111/159) Distance diagraphm Z line at least 4 cm (n=44/159)	0.999
At least one RFA session (n=97/159)	0.919
At least two RFA sessions (n=39/159)	0.566

Supplementary table 2 : Univariate analysis

24 immediate complications			
16 lacerations		8 bleedings	
Introduction	1	Biopsy	5
Sizing	9	Ablation	1
Spraying during cleaning	1	Not otherwise specified	2
Ablation	2		
Not otherwise specified	3		

Supplementary table 3: details of the immediate adverse events.

Alphabetic list of abbreviations

APC	Argon plasma coagulation
BE	Barrett's esophagus
CR-D	Complete remission of dysplasia
CR-IM	Complete remission of intestinal metaplasia
EAC	Early adenocarcinoma
EMR	Endoscopic mucosal resection
ER	Endoscopic resection
ESD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasound
FU	Follow-up
HGD	High grade dysplasia
ITT	Intention to treat
IQR	Interquartil range
IM	Intestinal metaplasia
LGD	Low grade dysplasia
PP	Per protocol
RFA	Radiofrequency ablation
UK	United Kingdom

Figures

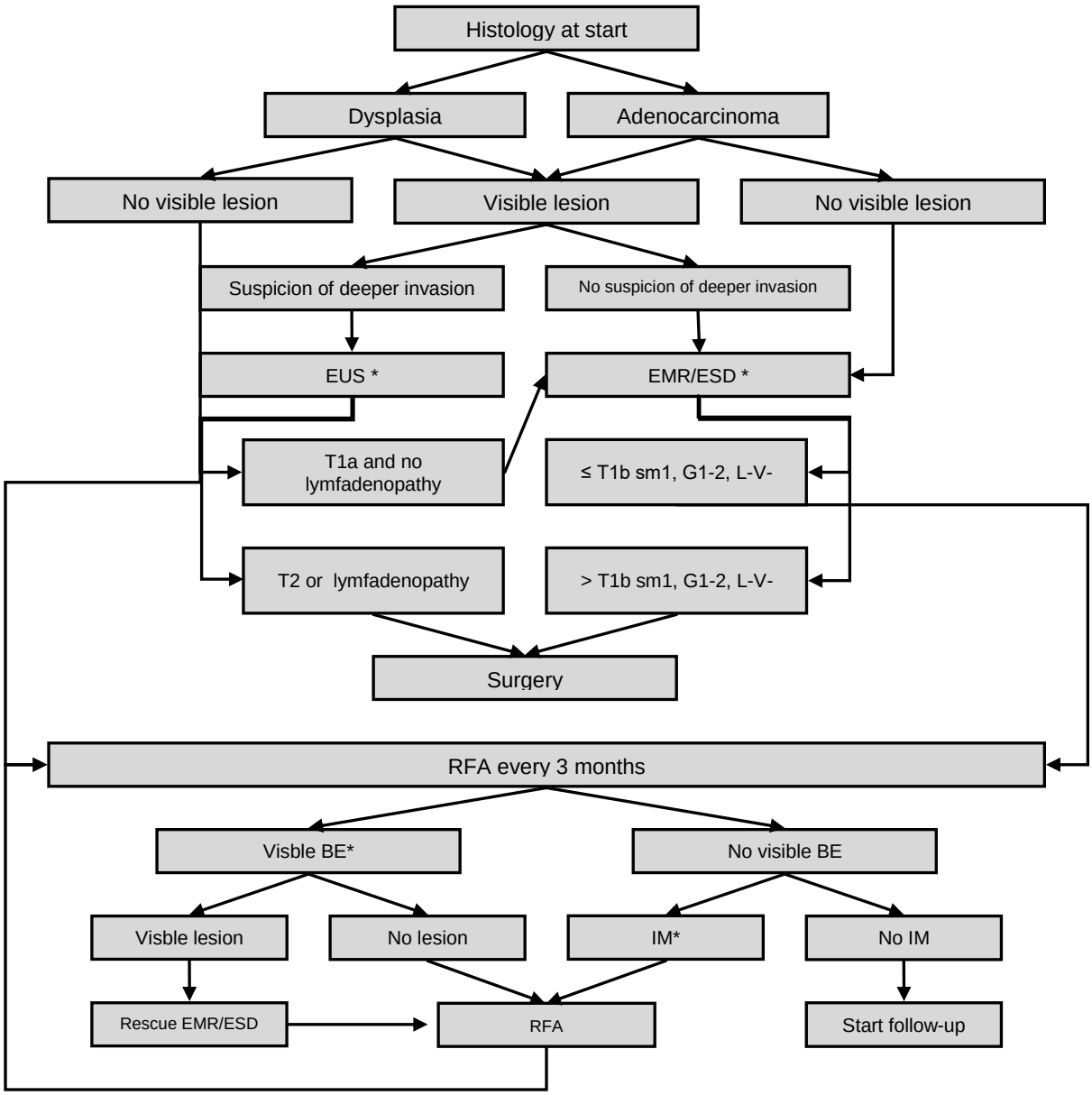


Figure 1: Belgian RFA registry endoscopy protocol.

* See alphabetic list of abbreviations

Figure 2: (cfr. Separated uploaded images)

A. Type 0-IIbBarrett lesion at six o'clock (Paris classification)

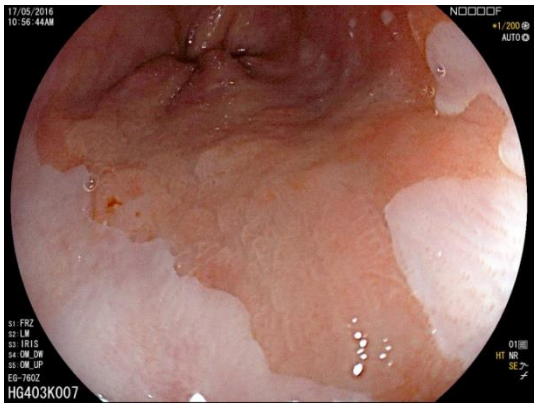
B. Demarcation of the lesion pre EMR

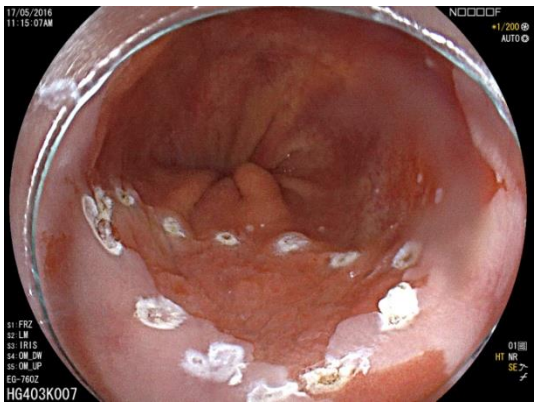
C. Barrett lesion post-EMR

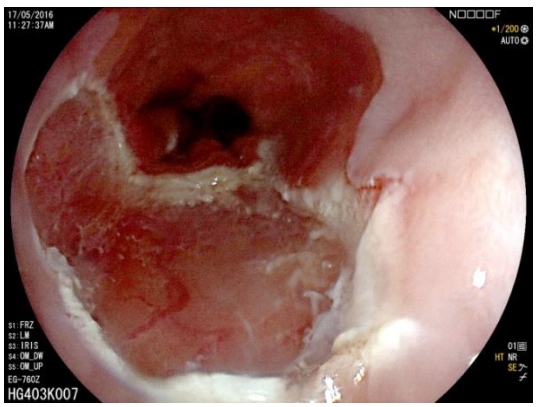
D. Circumferential ablation with HALO 360

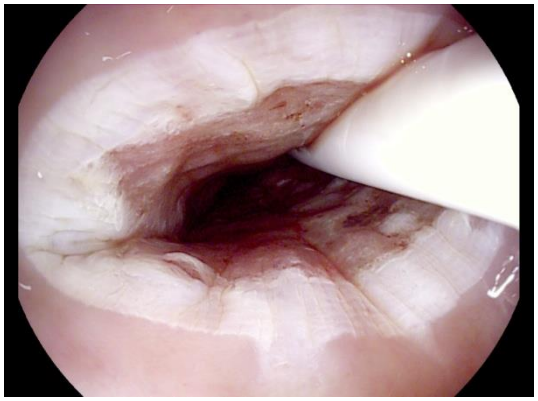
E. Focal ablation with HALO 90

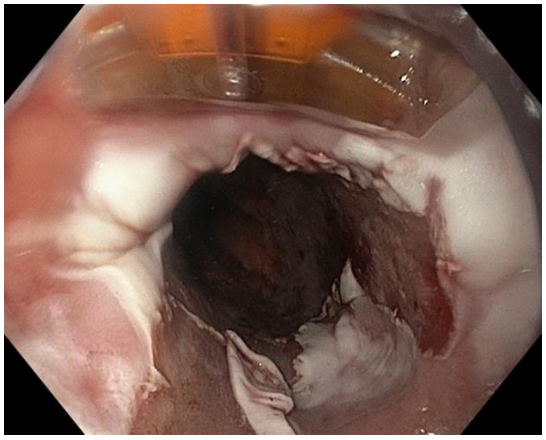
F. Complete regression of the lesion visualized with narrow band imaging

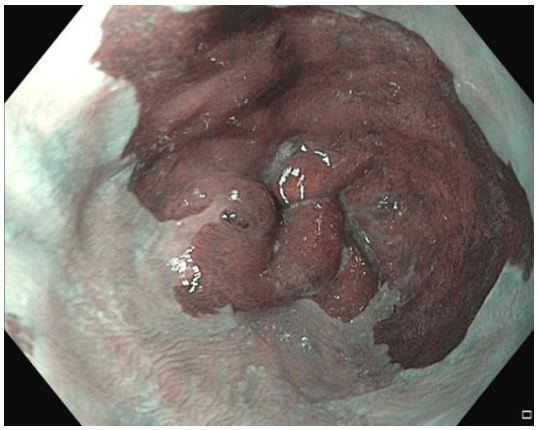
A. 

B. 

C. 

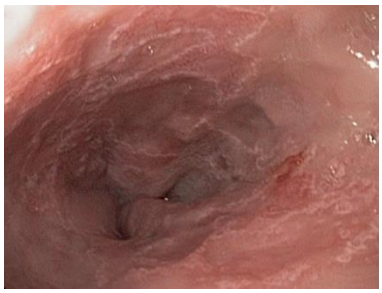
D. 

E. 

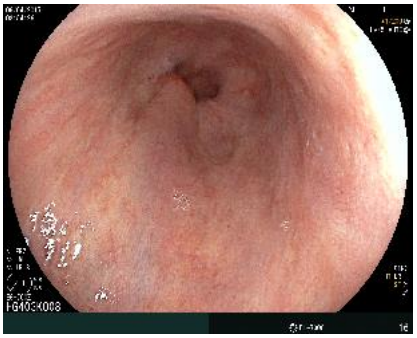
F. 

Alternative Figure 2:

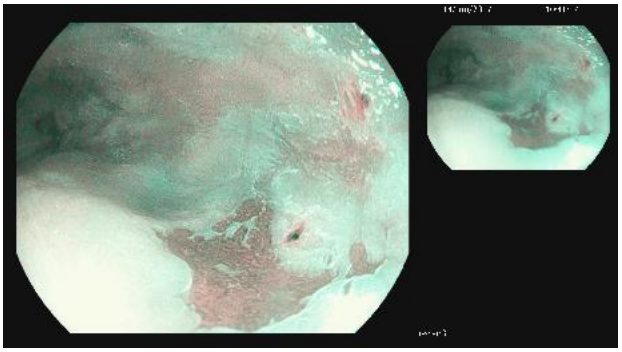
A. Acetic acid staining of C0M4 Barrett with discreet loss of aceto-whitening



B. After RFA



C. Recurrence of BE with i-scan



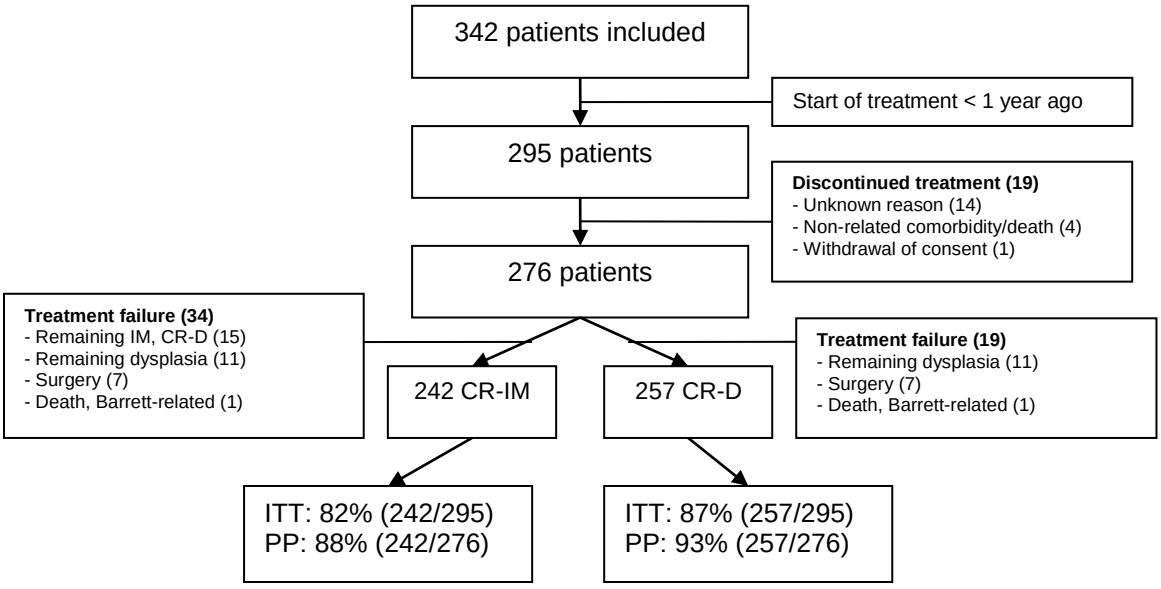


Figure 3: flowdiagram of patients and outcomes for CR-IM and CR-D.

Figure 4: (cfr. Separated uploaded file)

A: Kaplan-Meijer analysis of intestinal metaplasia free survival after achieving CR-IM

B: Kaplan-Meijer analysis of dysplasia free survival after achieving CR-D