ORIGINAL PAPER

DOI: http://dx.doi.org/ 10.15403/jgld-174

Radiofrequency Ablation in Patients with Barrett's Esophagus-related Neoplasia – Long-Term Outcomes in the Czech National Database

Jana Krajciova[1,2], Martin Janicko[3], Premysl Falt[4,5,6], Jan Gregar[4,5], Stepan Suchanek[7], Ondrej Ngo[8], Marek Kollar [2,9], Ondrej Urban[4,5], Vlastimil Prochazka[4,5], Miroslav Zavoral[7], Julius Spicak[1], Jan Martinek[1,2,10]

1) Depart. of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; 2) Charles University, Institute of Physiology, First Faculty of Medicine, Prague, Czech Republic; 3) 1st Depart. of Internal Medicine, P.J. Safarik University in Kosice, Faculty of Medicine and L. Pasteur University Hospital, Kosice, Slovakia; 4) 2nd Depart. of Internal Medicine, University Hospital, Olomouc, Czech Republic; 5) Faculty of Medicine, Palacky University, Olomouc, Czech Republic; 6) Faculty of Medicine in Hradec Kralove, Charles University, Hradec Kralove, Czech Republic; 7) Depart. of Internal Medicine, 1st Faculty of Medicine, Charles University, Military University Hospital, Prague, Czech Republic
8) Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic; 9) Clinical and Transplant Pathology Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; 10) Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic

Address for correspondence:
Assoc. Prof. **Jan Martinek**, Institute for Clinical and Experimental Medicine Videnska, Prague
jan.martinek@volny.cz

Received: 13.03.2019
Accepted: 01.05.2019

ABSTRACT

Background & Aims: Radiofrequency ablation (RFA) with/without endoscopic resection (ER) is the standard endoscopic treatment modality for Barrett's esophagus (BE) related neoplasia (BORN). The main aim of this study was to assess the long-term outcomes of RFA in patients with BORN.
Methods: We retrospectively analyzed the prospectively collected data from the Czech national database. Main outcomes were: complete remission of neoplasia (CR-N), complete remission of intestinal metaplasia (CR-IM), recurrence of both neoplasia and IM, and safety.
Results: From a total of 170 patients with BORN treated with RFA, 136 patients were analyzed. They were followed up for a median of 27.5 months. Fifty-six patients (41%) had low-grade intraepithelial neoplasia (LGIN), 46 (34%) had high-grade intraepithelial neoplasia (HGIN) and 34 (25%) had early adenocarcinoma (EAC). RFA was combined with previous ER in 65 patients (48%). CR-IM and CR-N were achieved in 77.9% (95% CI 70.0-84.6%) and 98.5% (95% CI 94.8-99.8%). Among 30 patients without CR-IM, 22 (73%) did not have macroscopic signs of BE. Recurrent neoplasia was detected in 4.5% of patients (6/134) and 15% (16/106) experienced a recurrence of IM at the level of the neo-Z-line. Diagnosis of cancer was an independent risk factor for recurrent IM after RFA (OR 7.0, 95% CI 1.6-30.9, p<0.0005).
Conclusion: RFA is highly effective in achieving remission in patients with BORN. A significant proportion of patients did not achieve CR-IM or had a recurrence of IM despite macroscopically absent BE. Recurrence of neoplasia was infrequent but not negligible, thus, patients after successful RFA still require endoscopic surveillance.

Key words: Barrett's esophagus related neoplasia – radiofrequency ablation – neo-Z-line – intestinal metaplasia.

Abbreviations: BE: Barrett's esophagus; BORN: Barrett's esophagus related neoplasia; CR-IM: complete remission of intestinal metaplasia; CR-N: complete remission of neoplasia; EAC: early adenocarcinoma; ER: endoscopic resection; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; HGIN: high-grade intraepithelial neoplasia; IEN: intraepithelial neoplasia; IM: intestinal metaplasia; LGIN: low-grade intraepithelial neoplasia; RFA: radiofrequency ablation.

INTRODUCTION

Barrett's esophagus (BE) is a pre-cancerous condition associated with an increased risk of developing esophageal adenocarcinoma, which has an annual incidence of 0.12-0.2% in patients without intraepithelial neoplasia (IEN) [1-3]. In patients with confirmed low-grade IEN (LGIN), the risk of progression to high-grade IEN (HGIN) or adenocarcinoma rises to 13.4% per year [4] and in patients with high-grade IEN, the risk of developing adenocarcinoma increases to approximately 10% per year [5, 6].

The approach to a patient with BE depends on the presence of IEN. Patients without IEN should be given anti-reflux therapy and should undergo regular endoscopic surveillance [7]. Patients with low- or high-grade IEN are candidates for endoscopic treatment: endoscopic resection (ER) of visible lesions and/or ablation therapy of flat Barrett's mucosa. Endoscopic resection combined with radiofrequency ablation (RFA) is now considered the gold standard for treatment of patients with Barrett's esophagus-related neoplasia (BORN) [7-10]. The aim of this treatment is the complete eradication of both neoplastic and metaplastic mucosa. Radiofrequency

ablation achieves the complete remission of intestinal metaplasia (IM) (CR-IM) in 70-86% and complete remission of neoplasia (CR-N) in 87-95% [5, 11-15]. The question that has not been solved definitely concerns the recurrence of IM and neoplasia. Prospective studies have shown a recurrence rate of IM up to 33% [15] and of neoplasia up to 5% [9, 12, 15]. After successful RFA, patients still need the endoscopic surveillance because of the risk of recurrences. However, the clinical significance of persistent or recurrent IM in patients with normal-appearing neo-squamo-columnar junction is questionable.

The goals of this retrospective analysis from the prospectively maintained Czech national database were to assess the efficacy and safety of RFA for BORN, to assess the durability of CR-IM and CR-N, and to establish the predictors for recurrent IM or neoplasia.

METHODS

This is a retrospective study of all the patients treated with RFA for BORN [LGIN, HGIN or early adenocarcinoma (EAC)] after ER or ESD in the Czech Republic between 2009-2016. A total of 4 referral centers provide treatment with RFA: Institute for Clinical and Experimental Medicine (IKEM), Prague = center A; Military University Hospital, Prague = center B; Vitkovice Hospital, Ostrava = center C; University Hospital, Olomouc = center D, and all centers participated in this study. The creation of the Czech National RFA database and the prospective collection of data was approved by the local institutional review boards and by the Czech Ministry of Health. Neither financial support from industry nor free commercial devices were received.

Patient assessment

We extracted prospectively collected data of all patients who underwent treatment with RFA for BORN between April 2009 – April 2016 (Fig. 1).

Patients older than 18 years with confirmed diagnosis of BE (visible at least 1 cm long segment of metaplastic mucosa with IM) were included. Barrett's esophagus was classified according to C&M Prague classification. We did not treat any patient without IEN. We did not treat patients with esophageal varices and pregnant women. All referred patients underwent a high-resolution endoscopy with Narrow Band Imaging (NBI) and/or chromoendoscopy with acetic acid prior the initial treatment (RFA or ER) to confirm a diagnosis of IEN, or to assess a visible lesion. In patients without a visible lesion, random biopsies according to the Seattle protocol were taken to confirm a diagnosis of IEN; in patients with a visible lesion, biopsies were usually not taken as we considered it to be a clear indication for ER.

All patients signed an informed consent for the treatment and for the anonymous collection of data in the national database.

Treatment protocol and treatment end-points

All patients with macroscopically visible lesions underwent ER (one patient underwent endoscopic submucosal dissection - ESD) that allowed histopathological staging. If the staging did not show an indication for surgery, physicians continued with endoscopic treatment with RFA. Endoscopic resection was performed either by using a cap technique with submucosal injection (EMR Kit, Olympus America, Center Valley, Pennsylvania, USA) or by using a band ligation technique (Six Shooter, Cook Medical, Winston-Salem, North Carolina, USA).

Radiofrequency ablation procedures were performed by experienced endoscopists. Circumferential (HALO360, Covidien, USA) or focal (HALO60 or HALO90, Covidien, USA) ablation was performed to completely remove BE segments. In patients with a long circular segment, we used circumferential ablation and the size of the balloon was chosen according to calibration's result. In patients after previous ER, one-size smaller balloon was selected. Focal therapy was selected in patients with short segment of BE or after circumferential ablation to treat residual metaplastic tongues or islands. In the majority of patients, the conventional RFA protocol (burning – cleaning – burning) was followed, while shortened protocols without cleaning were used exceptionally [16]. The energy dose applied was chosen according to the company recommendation at 12 J/cm^2.

Treatment with RFA was repeated every 2-3 months until the complete eradication of BE segments.

Radiofrequency treatment was finished when a visible clearance of the whole BE was achieved and control biopsies confirmed eradication of IEN. Complete remission of neoplasia was defined as histopathological and endoscopic remission of BORN. Complete remission of IM was defined as histopathological and macroscopic remission of BE and IM (i.e. no IM in biopsies from the GE junction or the esophagus) at two consecutive endoscopies.

Follow-up

The patients underwent regular endoscopic surveillance with multiple biopsies in intervals depending on the initial diagnosis (EAC every 3-6 months during the first 2 years, low-grade and high-grade IEN every 6 months during the first year and then once a year). Patients with a recurrence of BE (visible abnormality with IM) and of IEN were offered endoscopic re-treatment; patients with recurrent IM (if occurring at the level of normal neo-Z-line) continued endoscopic surveillance.

Main endpoints

The primary endpoints were assessment of CR-N, CR-IM and recurrences of both IM and neoplasia. We also assessed risk factors for recurrence of IEN/cancer and of IM and safety parameters.

Statistical analysis

Data is presented as means (+/- standard deviation) or as medians with 5th and 95th percentiles, unless specified otherwise. For statistical comparisons, the Wilcoxon signed rank sum test for paired data, the Mann-Whitney U test, the Fisher exact test, and the chi-squared test with Yates correction were used. Odds ratios were calculated by multivariate logistic regression. Survival curves were produced by Kaplan-Meier procedure with comparison by a log-rank test. A value of $p<0.05$ was considered statistically significant.

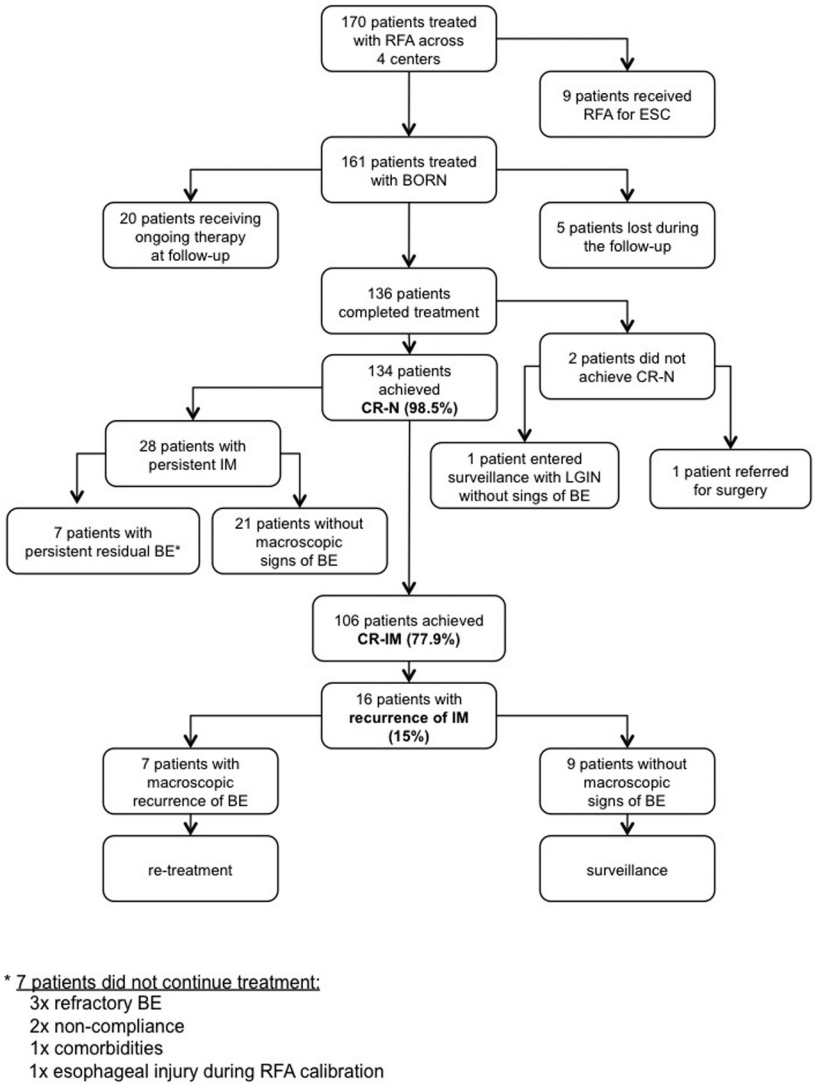

Fig. 1. Flow diagram of all patients treated with RFA.

RESULTS

Patients' characteristics and treatment details

A total of 136 patients (115 males, 21 females, mean age 64, range 22-91 years) completed treatment for BORN with RFA and were included in the analysis (Fig. 1). Fifty-six patients (41%) were diagnosed with LGIN, 46 (34%) patients with HGIN and 34 (25%) with EAC. Mean length of the BE segment was 4.5 cm (range 1-13 cm). The baseline characteristics are shown in Table I.

Table I. Baseline characteristics of patients.

	A (IKEM)	B (Military h.)	C (Ostrava)	D (Olomouc)	Total
	n = 69	n = 11	n = 37	n = 19	n = 136
Male : Female	59 : 10	10 : 1	28 : 9	18 : 1	115 : 21
Mean age - years (+/- SD, range)	65 (22 - 91)	59 (37 - 75)	64 (40 - 87)	60 (43 - 73)	64 (22 - 91)
Median BE length - cm (IQR)	C1M4 (C0-13, M1-13)	C0M3 (C0-10, M2-11)	C1M5 (C0-11, M1-12)	C2M4 (C1-5, M2-10)	C1M4 (C0-13, M1-13)
Diagnosis:					
LGIN	19 (28%)	11 (100%)	11 (30%)	15 (79%)	56 (41%)
HGIN	22 (32%)	0	20 (54%)	4 (21%)	46 (34%)
EAC	28 (40%)	0	6 (16%)	0	34 (25%)
Median follow-up - months (range)	36 (4 - 70)	18 (5 - 20)	18 (2 - 80)	28 (4 - 65)	27.5 (2 - 80)

BE: Barrett esophagus; HGIN: high grade intraepithelial neoplasia; LGIN: low grade intraepithelial neoplasia; EAC: early adenocarcinoma

Table II. Differences in selected parameters between patients who did and did not develop recurrent intestinal metaplasia.

		CR-IM	Recurrent IM	p
Age (years)		62.4 ± 11.9	69.6 ± 12.5	0.096⁺
Gender				0.277*
	Male	74 (83.1%)	15 (93.8 %)	
	Female	15 (16.9%)	1 (6.3 %)	
Primary diagnosis				< 0.0005$
	EAC	15 (16.9%)	10 (62.5%)	
	HGIN	31 (34.8%)	3 (18.8%)	
	LGIN	43 (48.3%)	3 (18.8%)	
BE length (cm)		4.0 ± 2.9	5.1 ± 3.4	0.201⁺
No. of treatment sessions				0.196$
	1	38 (42.7%)	7 (43.8%)	
	2	38 (42.7%)	4 (25.0%)	
	3 or more	13 (14.6%)	5 (31.3%)	

BE: Barrett's esophagus; CR-IM: complete remission of intestinal metaplasia; EAC: early adenocarcinoma; HGIN: high grade intraepithelial neoplasia; LGIN: low grade intraepithelial neoplasia; ⁺ Mann-Whitney, *Fisher exact, $Chi-squared with Yates correction.

In 71 patients (52%), RFA was a single treatment modality, while in 65 patients (48%) RFA was combined with ER or ESD of all visible lesions. A total of 251 sessions with RFA were performed, 73 with HALO360 system and 178 with HALO60 or HALO90 systems. The median number of RFA sessions was 2 (range: 1-6).

Treatment efficacy

Complete remission of IM and CR-N was achieved in 77.9% (95% CI 70.0-84.6%) and 98.5% (95%CI 94.8-99.8%), respectively. Among 30 patients without CR-IM (22%), 22 (73%) did not have macroscopic signs of BE. Out of 8 patients, who had persistent BE, 3 patients had refractory BE, 2 patients were discarded due to their non-compliance, 1 patient could not continue with RFA due to comorbidities and 1 due to adverse events during the treatment.

Recurrences

During the follow-up, 6 patients (4.5%, 6/134 pts) had recurrent neoplasia (5x LGIN, 1x HGIN), from these 2 patients had persistent IM and 3 patients had macroscopic recurrence of BE with recurrent IM (after its previous successful eradication). The recurrences of IEN occurred within a median of 37 months (range 24-53) after the RFA treatment.

Intestinal metaplasia recurred in 16 patients (15%, 16/106) and in all of them, recurrence occurred at the level of neo-Z-line. In 9 of these patients (56%) there were no signs of macroscopic recurrence of BE. The differences in selected parameters between patients who did and did not develop recurrent IM are shown in Table II.

A total of 7 patients had macroscopic recurrence of BE; all had persistent or recurrent IM. In 3 of them, recurrent IEN was diagnosed.

The majority of patients with macroscopic recurrence of BE and/or with recurrent IEN underwent successful endoscopic re-treatment consisting of re-RFA (n= 4), ER (n=2) or „escape" argon plasma coagulation (n=3). In one patient with recurrent BE without IEN, re-treatment was not indicated due to his age and comorbidities.

In the multivariate logistic regression analysis adjusted for age, gender and the length of the original BE segment, the diagnosis of cancer was an independent risk factor for recurrent IM after RFA (OR 7.0, 95% CI 1.6-30.9, p < 0.0005) (Fig. 2). We did not find any other risk factors or predictors for persistent or recurrent IM (gender, age, body mass index, length of BE, presence/absence of hiatal hernia, primary diagnosis of LGIN or HGIN, number of treatment sessions).

We observed no difference in selected parameters between patients who did and did not develop recurrent neoplasia (Table III). Similarly, the logistic regression analysis did not detect any significant risk factor for recurrent neoplasia. These results are probably biased by the low number of recurrent neoplasia cases (n = 6). However, there was a trend (p=0.083)

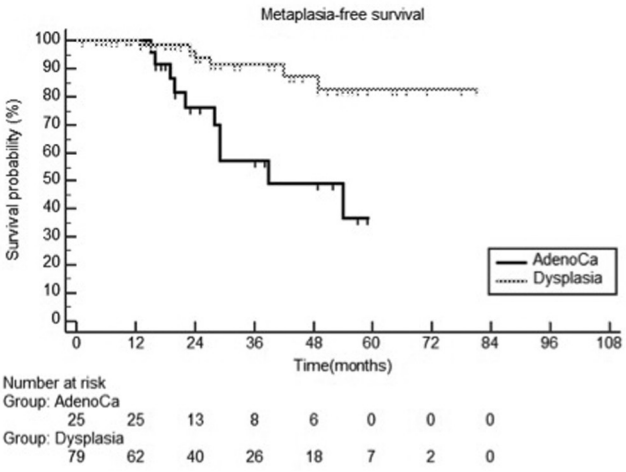

Fig. 2. Kaplan-Meier analysis of durability of complete remission of intestinal metaplasia according to the primary diagnosis.

Table III. Differences in selected parameters between patients who did and did not develop recurrent neoplasia.

		CR-N	Recurrent neoplasia	p
Age (years)		63.9 ± 11.6	65.7 ± 11.0	0.722⁺
Gender				0.589*
	Male	105 (83.3%)	6 (100%)	
	Female	21 (16.7%)	0	
Primary diagnosis				0.083$
	EAC	31 (24.4%)	2 (33.3%)	
	HGIN	40 (31.5%)	4 (66.7%)	
	LGIN	56 (44.1%)	0	
BE length (cm)		4.6 ± 3.2	2.7 ± 1.8	0.149⁺
No. of treatment sessions				0.356$
	1	53 (42.1%)	4 (66.7%)	
	2	47 (37.3%)	2 (33.3%)	
	3 or more	26 (20.6%)	0	
CR-IM		94 (74.6%)	5 (83.3%)	1.0*

BE: Barrett's esophagus; CR-IM: complete remission of intestinal metaplasia; CR-N: complete remission of neoplasia, EAC: early adenocarcinoma; HGIN: high grade intraepithelial neoplasia; LGIN: low grade intraepithelial neoplasia. ⁺ Mann-Whitney, *Fisher exact, $Chi-squared with Yates correction.

for an increased risk of recurrent neoplasia in patients with the initial diagnosis of cancer or HGIN (vs. LGIN). Of note, all patients with recurrent neoplasia had either persistent or recurrent IM.

We did not detect persistent/recurrent IM or neoplasia beneath the neo-squamous epithelium ("buried glands") in any patient.

Safety

We noticed treatment-related adverse events (AEs) in 23 patients (17%): 13 had chest pain, 8 developed stricture, 1 had mild injury of a tongue (mucosal tear) and 1 had esophageal submucosal tear after balloon calibration. One patient with esophageal stricture experienced perforation during balloon dilatation and had to undergo esophagectomy. All the remaining strictures were successfully managed endoscopically.

DISCUSSION

In this retrospective analysis we found that among patients with BORN who had undergone endoscopic treatment consisting of RFA with or without ER (or ESD), 98.5% patients achieved CR-N and 77.9% patients achieved CR-IM. After a median of 27.5 months of follow-up, IEN recurred in 4.5% of patients and recurrence of IM was observed in 15%. In our cohort, no patient experienced a recurrence of or post-treatment progression to adenocarcinoma.

The majority of the patients who did not achieve CR-IM, or who experienced recurrent IM, had macroscopically a normal neo-Z-line. Importantly, we did not detect any patient with buried glands beneath the neo-squamous epithelium. Procedure related adverse events were observed in 17% of the patients, among them strictures in 6%.

In our hands, RFA effectiveness was similar to that reported in several other studies, having achieved CR-N above 90-95% with its low recurrence rate of 1-3% [5, 9, 10, 12, 13]. In our study, only 2 patients did not achieve CR-N. One patient with initial diagnosis of low-grade IEN entered endoscopic surveillance and has not progressed yet. The second patient with multifocal high-grade IEN underwent esophagectomy. During the follow up, a total of 6 patients (4.5%) had a recurrence of IEN and all were successfully treated endoscopically. The rate of recurrent neoplasia was similar to other studies [17-20]. However, a recent final analysis of AIM dysplasia trial showed a higher recurrence of neoplasia (17%) [21]. There was a greater probability of recurrence in the first year following CR-IM than in the following 4 years combined. The higher rate of recurrent IEN in this study compared to our results might be, at least partially, explained by the different histopathological criteria used by the pathologists (Europe vs. USA) to diagnose LGIN. In our study, all recurrences of IEN occurred mainly within 2-4 years following RFA treatment. Because of the low number of patients with recurrent neoplasia, we were not able to find risk factors for recurrent neoplasia; however, we found a non-significant trend for an increased risk of IEN recurrence in patients with an initial diagnosis of cancer or HGIN compared to patients with LGIN (p= 0.083).

Detection of post-RFA cancer may suggest an inappropriate identification of the esophageal lesions, and thus, an inappropriate indication for RFA. In several reports, post-treatment cancers, even rare, have been described [5, 9, 11, 19, 20]. Post-RFA cancers most probably originate from buried glands, or from the remnants of initially unrecognized cancer, which was mistakenly ablated instead of resection therapy. Or, cancers can progress from persistent/recurrent dysplasia [13]. For example, in the UK RFA registry, overall post-treatment progression to cancer occurred in 2.1% [10]. Data from the US

RFA registry shows very low incidence of post-RFA cancers (6.1 per 1000 patient-year) [22]. Barrett's esophagus length, baseline histological grade and subsquamous buried glands were independently associated with the development of post-RFA cancer [23]. As we did not experience any recurrent cancer, it shows that all four Czech centers conscientiously perform diagnostic endoscopy before a definitive decision about the subsequent treatment and our diagnostic process and indication for either ER or RFA seem appropriate [24]. Of note, the frequency of prior ER increased according to the UK registry from an early stage of 48% to a current rate of 60% [25].

Together with CR-N, a CR-IM is nowadays considered as another target of endoscopic treatment of BORN. Persistent IM might be a risk factor for recurrence or the progression to a more severe type of neoplasia. In one study, the recurrence of neoplasia was as high as 32% in patients in whom IM persisted after ablation therapy and was significantly lower in those without persistent IM (9%) [26]. Other studies as well as our study did not show that persistent or recurrent IM at the level of macroscopically normal neo-Z-line is a risk factor for progression or neoplasia recurrence. There is no doubt, however, that persistent or recurrent IM in a macroscopically visible segment of BE represents a risk for further progression and these patients should undergo endoscopic re-treatment.

There are discrepancies among studies with regard to both a complete remission of IM and a recurrence of IM. In some studies, remission of IM was achieved in 93% of the patients (Euro II trial) [9], while a meta-analysis showed CR-IM in only 78% (CI 95% 70-86) of the patients. Our rate of CR-IM (78%) lies in-between these data and we found that an initial diagnosis of cancer was a significant risk factor for recurrent IM after treatment.

Recurrence of IM occurred in 7-32% in published studies [9, 11, 12, 17, 19, 20, 27]. We found a 15% rate of IM recurrence. The longer follow-up and strict biopsy protocol might be responsible for a higher rate of IM recurrence in our study as compared to some other reports [9, 17, 19, 20]. The majority of our IM recurrences occurred in patients with macroscopically normal neo-Z-line. As the persistence or recurrence of IM at the level of macroscopically normal neo-Z-line probably does not carry an increased risk of progression, RFA re-treatment is not indicated in these patients. Pouw et al. [28] showed that among 43 patients with CR-IM following RFA for HGIN (or early cancer), 12% had a histological recurrence of IM without any macroscopic abnormality within the neo-Z-line. None of them experienced recurrent neoplasia.

In another multicenter trial, the recurrence of IM in those patients, who achieved CR-IM, was 13% [13] and none had recurrent neoplasia. In our study, neoplasia recurred in 6 patients (4.5%): from these, 5 patients had recurrent IM and 3 patients had macroscopically normal neo Z-line. One of the highest rates of recurrent IM was reported by Vaccaro et al. [29], who found recurrent IM in 32% (15/47 pts) of the patients and four of these patients had also recurrent neoplasia.

Thus, it seems that reporting of persistent or recurrent IM in several previous studies did not differentiate between patients with or without recurrence (or persistent) BE (= macroscopically visible abnormality). Persistent or recurrent IM within a macroscopically normal neo-Z-line does not seem to represent a significant risk factor for neoplasia or cancer recurrence, but exceptions may occur. Nevertheless, as some cases of progression have been reported, the patients after successful endoscopic treatment of BORN still need endoscopic surveillance. Intervals of this surveillance are not defined and should probably depend on the initial diagnosis, as progression is most frequent in patients with cancer.

Radiofrequency ablation is not free of complications. In a systematic review and meta-analysis, Qumseya et al. [30] showed an adverse event rate of 8.8%. The most common side effect was stricture (5.6%), followed by bleeding - 1%, and a low rate of perforation - 0.6%. In our analysis, we noticed adverse events in 17% of patients, among them strictures in 6%. All strictures, except one, were successfully managed endoscopically.

CONCLUSIONS

We confirmed that RFA is effective in achieving remission of Barrett's esophagus-related neoplasia. The recurrence rates of IM or neoplasia were low but not negligible. After successful RFA for BORN, the patients still need endoscopic surveillance. Diagnosis of cancer was a risk factor for recurrent IM after RFA.

Conflicts of interest: None to declare.

Authors' contributions: J.K. collected and analyzed the data, performed follow-up endoscopies, drafted the manuscript. M. J. performed the statistics, data analysis and critical review of the manuscript. P.F., J.G., S.S., V.P., M.Z performed the procedures and collected data. O.N. administered the national database, and performed the statistics. M.K. assessed the histopathological slides, O.U., J.S. performed the procedures. J.M. designed the study design, performed the procedures. O.N., M.K., O.U., J.S. and J.M. critically revised the manuscript.

Acknowledgements: The study was partially supported by grants No.16-27648A, Progres Q28/LF1 and MO 1012.

REFERENCES

1. Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. New Engl J Med 2011;365:1375-1383. doi:10.1056/NEJMoa1103042
2. Martinek J, Benes M, Brandtl P, et al. Low incidence of adenocarcinoma and high-grade intraepithelial neoplasia in patients with Barrett's esophagus: a prospective cohort study. Endoscopy 2008;40:711-716. doi:10.1055/s-2008-1077502
3. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst 2011;103:1049-1057. doi:10.1093/jnci/djr203
4. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol 2010;105:1523-1530. doi:10.1038/ajg.2010.171
5. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. New Engl J Med 2009;360:2277-2288. doi:10.1056/NEJMoa0808145

6. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc 2008;67:394-398. doi:10.1016/j.gie.2007.07.019
7. 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. doi:10.1136/gutjnl-2013-305372
8. Bennett C, Vakil N, Bergman J, et al. Consensus Statements for Management of Barrett's Dysplasia and Early-Stage Esophageal Adenocarcinoma, Based on a Delphi Process. Gastroenterology 2012;143:336-346. doi:10.1053/j.gastro.2012.04.032
9. 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. doi:10.1136/gutjnl-2015-309298
10. 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. doi:10.1053/j.gastro.2013.03.045
11. Orman ES, Li N, Shaheen NJ. Efficacy and Durability of Radiofrequency Ablation for Barrett's Esophagus: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2013;11:1245-1255. doi:10.1016/j.cgh.2013.03.039
12. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy 2010;42:781-789. doi:10.1055/s-0030-1255779
13. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol 2010;8:23-29. doi:10.1016/j.cgh.2009.07.003
14. Gupta M, Iyer PG, Lutzke L, et al. Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US Multicenter Consortium. Gastroenterology 2013;145:79-86. doi:10.1053/j.gastro.2013.03.008
15. Alvarez Herrero L, van Vilsteren FG, Pouw RE, et al. Endoscopic radiofrequency ablation combined with endoscopic resection for early neoplasia in Barrett's esophagus longer than 10 cm. Gastrointest Endosc 2011;73:682-690. doi:10.1016/j.gie.2010.11.016
16. van Vilsteren FG, Phoa KN, Herrero L, et al. A simplified regimen for focal radiofrequency ablation of Barrett's mucosa: a randomized multicenter trial comparing two ablation regimens. Gastrointest Endosc 2013;78:30-38. doi:10.1016/j.gie.2013.02.002
17. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology 2011;141:460-468. doi:10.1053/j.gastro.2011.04.061
18. Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. Clin Gastroenterol Hepatol 2014;12:1840-1847. doi:10.1016/j.cgh.2014.04.034
19. 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. doi:10.1053/j.gastro.2013.03.046
20. Orman ES, Kim HP, Bulsiewicz WJ, et al. Intestinal metaplasia recurs infrequently in patients successfully treated for Barrett's esophagus with radiofrequency ablation. Am J Gastroenterol 2013;108:187-195.
21. 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. doi:10.1053/j.gastro.2017.05.044
22. Wolf WA, Pasricha S, Cotton C, et al. Incidence of Esophageal Adenocarcinoma and Causes of Mortality After Radiofrequency Ablation of Barrett's Esophagus. Gastroenterology 2015;149:1752-1961. doi:10.1053/j.gastro.2015.08.048
23. Ortiz-Fernandez-Sordo J, Sami S, Mansilla-Vivar R, De Caestecker J, Cole A, Ragunath K. Incidence of metachronous visible lesions in patients referred for radiofrequency ablation (RFA) therapy for early Barrett's neoplasia: a single-centre experience. Frontline Gastroenterol 2016;7:24-29. doi:10.1136/flgastro-2015-100561
24. Pasricha S, Cotton C, Hathorn KE, et al. Effects of the Learning Curve on Efficacy of Radiofrequency Ablation for Barrett's Esophagus. Gastroenterology 2015;149:890-896. doi:10.1053/j.gastro.2015.06.012
25. 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. doi:10.1136/gutjnl-2014-308501
26. Guarner-Argente C, Buoncristiano T, Furth EE, Falk GW, Ginsberg GG. Long-term outcomes of patients with Barrett's esophagus and high-grade dysplasia or early cancer treated with endoluminal therapies with intention to complete eradication. Gastrointest Endosc 2013;77:190-199. doi:10.1016/j.gie.2012.10.013
27. Krishnamoorthi R, Singh S, Ragunathan K, Katzka DA, Wang KK, Iyer PG. Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. Gastrointest Endosc 2016;83:1090-1106. doi:10.1016/j.gie.2016.02.009
28. Pouw RE, Gondrie JJ, Sondermeijer CM, et al. Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. J Gastrointest Surg 2008;12:1627-1636. doi:10.1007/s11605-008-0629-1
29. Vaccaro BJ, Gonzalez S, Poneros JM, et al. Detection of Intestinal Metaplasia After Successful Eradication of Barrett's Esophagus with Radiofrequency Ablation. Dig Dis Sci 2011;56:1996-2000. doi:10.1007/s10620-011-1680-4
30. Qumseya BJ, Wani S, Desai M, et al. Adverse Events After Radiofrequency Ablation in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2016;14:1086-1095. doi:10.1016/j.cgh.2016.04.001