Argon plasma coagulation for Barrett's esophagus with low-grade dysplasia: a randomized trial with long-term follow-up on the impact of power setting and proton pump inhibitor dose

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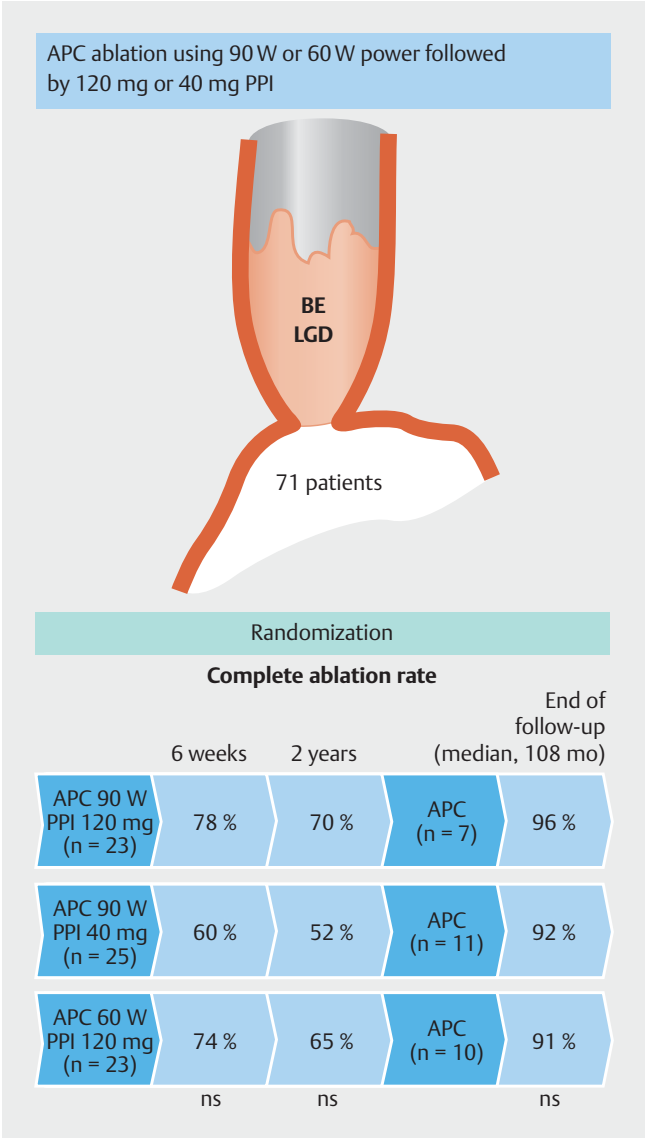
ABSTRACT

Background This study evaluated the impact of power setting and proton pump inhibitor (PPI) dose on efficacy and safety of argon plasma coagulation (APC) of Barrett's esophagus (BE) with low-grade dysplasia (LGD).

Methods 71 patients were randomized to APC with power set at 90 W or 60 W followed by 120 mg or 40 mg omeprazole. The primary outcome was the rate of complete (endoscopic and histologic) ablation of BE at 6 weeks. Secondary outcomes included safety and long-term efficacy.

GRAPHICAL ABSTRACT



Results Complete ablation rate in the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg groups was 78 % (18/23; 95 % confidence interval [CI] 61–95), 60 % (15/25; 95 %CI 41–79), 74 % (17/23; 95 %CI 56–92), respectively, at 6 weeks and 70 % (16/23; 95 %CI 51–88), 52 % (13/25; 95 %CI 32–72), and 65 % (15/23; 95 %CI 46–85) at 2 years post-treatment (differences not significant). Additional APC was required in 28 patients (23 residual and 5 recurrent BE). At median follow-up of 108 months, 66/71 patients (93 %; 95 %CI 87–99) maintained complete ablation. No high-grade dysplasia or adenocarcinoma developed. Overall, adverse events (97 % mild) did not differ significantly between groups. Chest pain/discomfort was more frequent in patients receiving 90 W vs. 60 W power ($P<0.001$). One patient had esophageal perforation and two developed stenosis.

Conclusions APC power setting and PPI dose did not impact efficacy and safety of BE ablation. Complete ablation of BE with LGD was durable in >90 % of patients, without any evidence of neoplasia progression in the long term.

Introduction

Barrett's esophagus (BE) is a premalignant condition associated with progression to esophageal adenocarcinoma that involves a multi-step process from nondysplastic Barrett's metaplasia through low-grade (LGD) and high-grade dysplasia (HGD) to cancer [1]. Endoscopic ablation of Barrett's mucosa followed by squamous re-epithelialization can stop this process and reduce the risk of cancer, and is therefore recommended in individuals with Barrett's dysplasia [2–7]. The main methods used in endoscopic ablation of BE are radiofrequency ablation (RFA) and argon plasma coagulation (APC); both have been shown to reduce the risk of neoplastic progression in randomized controlled trials (RCT) [8–15]. A recent RCT directly comparing RFA and APC showed similar efficacy of these methods in ablation of Barrett's metaplasia and dysplasia, and similar safety; however, the cost of APC was substantially lower [16].

Whereas efficacy and safety of APC for the ablation of BE have been proven, the treatment protocol has not been standardized for factors that may affect results, such as the APC power used for ablation and the dose of proton pump inhibitor (PPI) administered after ablation to promote healing of the mucosa and squamous re-epithelialization. In addition, long-term efficacy data are limited to a few studies evaluating exclusively or predominantly patients with nondysplastic BE [13, 17–20].

The aim of this randomized study was to evaluate the impact of APC power setting (90 vs. 60 W) and PPI dose (120 vs. 40 mg omeprazole per day) on the efficacy and safety of APC in individuals with BE and LGD. The long-term outcomes of APC for BE ablation were also prospectively evaluated.

Methods

Study design and settings

This investigator-initiated, single-center, parallel-group RCT was conducted in a tertiary referral center in Poland. The research proposal was reviewed and approved by the institutional review board at the Center of Postgraduate Medical Education. The study was registered in the ClinicalTrials.gov registry (NCT04154748).

Patient enrollment and allocation

Consecutive adult patients with LGD in flat Barrett's mucosa referred for endoscopic treatment were eligible for the study. Excluded patients were those with HGD or adenocarcinoma, visible lesions (nodules, ulcerations) in Barrett's mucosa, serious comorbidities and short life expectancy, coagulopathy, pregnancy or lactation, and psychiatric disorders. All participants signed an informed consent form to participate in the study.

BE diagnosis was based on endoscopic evidence of columnar mucosa extending ≥ 1 cm above the proximal margin of the gastric folds and histologic evidence of intestinal metaplasia in biopsy specimens [21]. The diagnosis of BE and LGD had to be confirmed in all cases by an expert pathologist involved in the study.

Recruited participants were randomly allocated in a 1:1:1 ratio to one of three groups:

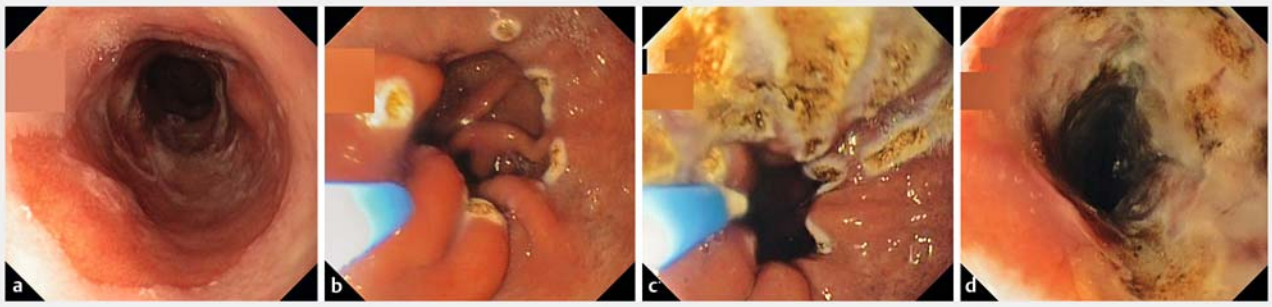
1. 90 W/120 mg group, who received treatment with high-power APC (90 W) followed by acid suppression with high-dose oral omeprazole (40 mg three times daily).
2. 90 W/40 mg group, who received treatment with high-power APC (90 W) followed by acid suppression with low-dose oral omeprazole (40 mg once daily).
3. 60 W/120 mg, who received treatment with low-power APC (60 W) followed by acid suppression with high-dose oral omeprazole (40 mg three times daily).

The randomization code was generated at the clinical trials administration office at the authors' institution.

Treatments

APC ablation

Endoscopic APC ablation was carried out on an inpatient basis, under intravenous analgosedation with propofol, midazolam, and fentanyl supervised by an anesthesiologist. A standard gastroscope (Olympus Europa, Hamburg, Germany) and electrosurgical generator (ICC 200; Erbe Elektromedizin, Tübingen, Germany) were used. The power was set at 60 W or 90 W according to the randomization group and the gas flow was 2 L/min. APC was applied with forward-firing probe (Erbe), maintaining it at a short distance from the mucosa and creating linear strips during withdrawal (paint-stroke technique), starting at the gas-



▶ **Fig. 1** Argon plasma coagulation (APC) of Barrett's esophagus. **a** Long-segment Barrett's esophagus before treatment. **b** Markings at the distal margin of the Barrett's segment. **c** Ablation of Barrett's mucosa with APC using forward-firing probe and paint-stroke technique. **d** Status after ablation of the whole Barrett's segment.

troesophageal junction and continuing proximally (▶ **Fig. 1**). All ablations were performed by a single, experienced endoscopist.

A maximum length of 4 cm of circumferential BE was ablated during one treatment session; in patients with longer Barrett's segments, repeat sessions were performed using the same settings and technique until no Barrett's mucosa was visible endoscopically. APC was not reapplied on the areas successfully ablated during previous sessions. After APC, patients stayed for at least one night in the hospital and were observed for occurrence of adverse events.

Acid suppression therapy

Throughout the entire APC treatment period and 6 weeks thereafter, patients received omeprazole in a high (40 mg three times daily) or low (40 mg once daily) dose, according to the randomization group. Subsequently, patients continued PPI at doses required to control reflux symptoms.

Assessment of treatment effects

Treatment efficacy was assessed during outpatient visits at 6 weeks and then 6, 12, and 24 months after the last APC session. The assessment included endoscopic evaluation of the postablation area with multiple biopsies from neosquamous mucosa and from visible abnormalities suggesting residual Barrett's mucosa. Complete ablation was defined as no endoscopic and histologic evidence of Barrett's mucosa, dysplasia, and buried metaplastic glands. In case of incomplete ablation, no additional APC ablation was offered in the first two years of observation, but it was allowed after this time point. Subsequent follow-up examinations took place at yearly intervals up to 5 years and every 2 years thereafter. Patients were followed for a minimum of 4 years. BE recurrence was defined as endoscopic and histologic detection of Barrett's mucosa in a patient with prior complete ablation.

Adverse events were assessed during each hospitalization for APC and during an outpatient visit 6 weeks after the last APC session. The type and severity of adverse events, time of their occurrence and resolution, and details on their management were recorded by a physician. Based on these data, for the purpose of the final analysis, the adverse events were reclassified according to the American Society for Gastrointestinal Endoscopy lexicon for adverse events [22].

Outcomes

The primary outcome was the complete ablation rate at 6 weeks after APC treatment. Secondary outcomes were: 1) adverse event rate during APC treatment and within the 6-week post-treatment period; 2) complete ablation rate 2 years after APC treatment and at the end of follow-up; 3) recurrence rate, defined as the percentage of patients with complete ablation in whom endoscopic and histologic evidence of BE was found during follow-up.

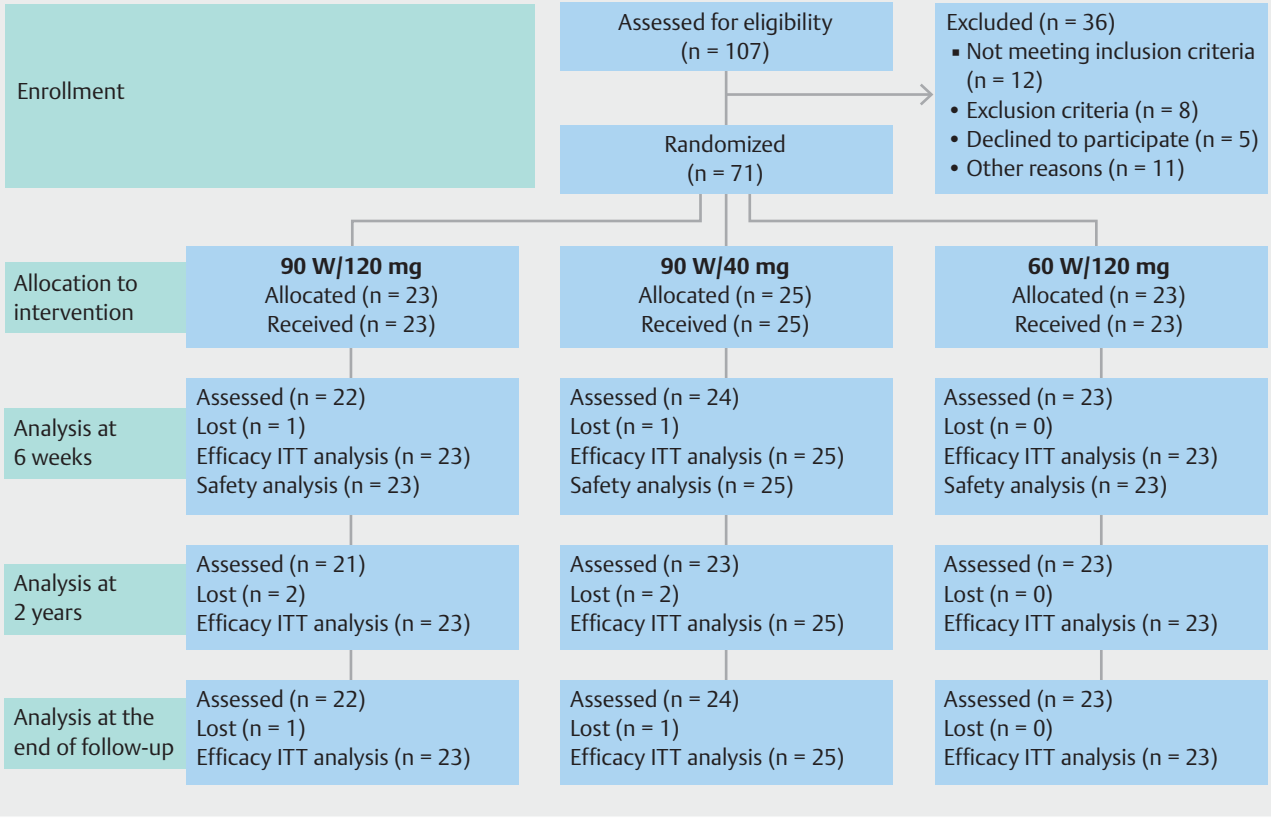
Blinding

Patients were blinded to the power settings used for APC, but knew the PPI dose they received. The endoscopist performing APC ablation was blinded to participant allocation and APC power setting (the power was set by an assistant and the power display remained covered during the entire procedure). The endoscopist and pathologist involved in efficacy assessment were blinded to participant allocation.

Sample size and statistical methods

It was assumed that two pairwise comparisons would be performed (90 W/40 mg group vs. 90 W/120 mg group and 60 W/120 mg group vs. 90 W/120 mg group) and that the complete ablation rate would be 60 % in 90 W/40 mg and 60 W/120 mg groups, and 98 % in the 90 W/120 mg group [23–25]. To detect such a difference with 80 % power and 0.025 significance level (Bonferroni correction for pairwise comparison) and allowing for a dropout rate of 10 %, a minimum sample size of 23 patients in each group was required.

Categorical variables were compared using Fisher's exact test or chi-squared test depending on the frequency of the events. Continuous variables were checked for normality of the distribution using histograms. As none of the variables followed normal distribution, Kruskal–Wallis test was used to compare the groups. Overall *P* values of less than 0.05 were considered to denote statistically significant difference. For



▶ **Fig. 2** The CONSORT flow-diagram of the study (www.consort-statement.org).

pairwise comparisons, Bonferroni correction for significance level was used (*P* value of 0.025). Primary analysis was conducted on an intention-to-treat (ITT) basis. Because the study was designed to compare 90 W/40 mg group vs. 90 W/120 mg group and 60 W/120 mg group vs. 90 W/120 mg group, *P* values for pairwise comparisons were reported, even if the test comparing all three groups did not detect significant differences in the study end points.

Statistical analysis was conducted using Stata software, version 15.1, (StataCorp, College Station, Texas, USA).

Results

Enrollment and allocation

A total of 107 patients were assessed for eligibility from June 2002 to November 2014; 36 were not included because they declined to participate (n = 5), did not meet inclusion criteria (no LGD confirmed, n = 12), met exclusion criteria (HGD or adenocarcinoma, n = 5; coagulopathy, n = 3) or because of organizational reasons (n = 11). The remaining 71 patients were included and randomly assigned to the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg groups (23, 25, and 23 patients, respectively). ▶ **Fig. 2** shows patient flow through the study.

▶ **Table 1** summarizes the baseline demographic and clinical characteristics of study groups. The groups were comparable in terms of patient sex and age, length of BE, presence of circumferential BE segment, presence of hiatal hernia, and history of antireflux surgery.

Primary outcome

Of the 71 patients randomized, all received the allocated intervention. The number of APC treatment sessions per patient did not differ significantly between the groups (median of 2, 1, and 2 sessions per patient, in the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg groups, respectively). Complete endoscopic and histologic ablation at 6 weeks after APC therapy was confirmed in 50 patients (70 %; 95 % confidence interval [CI] 60–81) with no statistically significant differences between the groups: 18 (78 %; 95 %CI 61–95), 15 (60 %; 95 %CI 41–79), and 17 (74 %; 95 %CI 56–92) patients in the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg groups, respectively. A total of 19 patients (27 %) had residual BE (4 [17 %], 9 [36 %], and 6 [26 %] patients, respectively). Two patients (3 %) were lost to assessment: one patient in the 90 W/120 mg group had esophageal perforation requiring surgery after the APC procedure and one patient in the 90 W/40 mg group declined to undergo endoscopic evaluation at 6 weeks. Data on treatment efficacy at 6 weeks are summarized in ▶ **Table 2**.

▶ **Table 1** Baseline characteristics of study groups.

Characteristic	APC 90 W PPI 120 mg	APC 90 W PPI 40 mg	APC 60 W PPI 120 mg	*P* value[1]
No. of patients	23	25	23	
Male sex, n (%)	16 (70)	23 (92)	15 (65)	0.05
Age, median (IQR), years	62 (52.5–72)	60 (51–65)	62 (55.5–68.5)	0.28
BE length, median (IQR), cm	4 (3–5.5)	4 (3–7)	3 (3–5)	0.74
Circumferential BE segment, n (%)	15 (65)	16 (64)	12 (52)	0.60
Hiatal hernia, n (%)	15 (65)	22 (88)	15 (65)	0.11
History of antireflux surgery, n (%)	2 (9)	0 (0)	2 (9)	0.38

APC, argon plasma coagulation; PPI, proton pump inhibitor IQR, interquartile range; BE, Barrett's esophagus.
[1] For comparison between all three groups.

▶ **Table 2** Treatment efficacy at 6 weeks.

Outcome	All patients (n = 71)	APC 90 W PPI 120 mg (n = 23)	APC 90 W PPI 40 mg (n = 25)	APC 60 W PPI 120 mg (n = 23)	*P* value[1]	*P* value[2]	*P* value[3]
Treatment efficacy, n (%) [95 %CI]					0.49	0.36	0.72
▪ Complete ablation	50 (70) [60–81]	18 (78) [61–95]	15 (60) [41–79]	17 (74) [56–92]			
▪ Residual BE	19 (27)	4 (17)	9 (36)	6 (26)			
▪ Lost to assessment	2 (3)	1 (4)	1 (4)	0 (0)			
No. of APC sessions					0.82	0.58	0.76
▪ Median (IQR)	2 (1–2)	2 (1–2)	1 (1–3)	2 (1–2)			
▪ Range	1–7	1–6	1–7	1–4			
Total APC procedure time per patient, minutes					0.76	0.43	0.64
▪ Median (IQR)	17 (10–30)	13 (6–30)	17 (12–32)	18 (11–26)			
▪ Range	2–74	2–50	3–74	5–40			

APC, argon plasma coagulation; PPI, proton pump inhibitor; CI, confidence interval; BE, Barrett's esophagus; IQR, interquartile range.
[1] For comparison between all three groups.
[2] For comparison between APC 90 W/PPI 120 mg vs. APC 90 W/PPI 40 mg (effect of PPI).
[3] For comparison between APC 90 W/PPI 120 mg vs. APC 60 W/PPI 120 mg (effect of power).

Secondary outcomes

Treatment safety

A total of 124 adverse events occurred after 143 APC sessions; the majority of adverse events were mild in severity (97 %) and post-procedural (94 %). Adverse events were noted in 19 patients (83 %) in the 90 W/120 mg group, in 18 patients (72 %) in the 90 W/40 mg group, and in 11 patients (48 %) in the 60 W/120 mg group, with a nonsignificant trend toward higher adverse event rates in groups treated with 90 W power APC (▶ **Table 3**). The most common adverse event was chest pain or discomfort; it was noted more frequently in patients who were treated with 90 W power than in those treated with 60 W power (19 [83 %], 17 [68 %], and 9 [39 %] patients in the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg groups, respectively; $P < 0.001$). A few patients in each group experienced transient dysphagia, odynophagia, fever, or anesthesia-related adverse events (hypotension, tachycardia, or desaturation). There was one severe and three moderate adverse events. One patient (4 %) in the 90 W/120 mg group had an esophageal perforation after the first APC session and required esophagectomy. Two patients (one in the 90 W/40 mg group [4 %] and one in the 60 W/120 mg group [4 %]), developed symptomatic esophageal strictures and underwent successful endoscopic dilation. One patient in the 90 W/120 mg group experienced pleural effusion with significant C-reactive protein elevation, without signs of perforation on computed tomography, which resolved under

▶ **Table 3** Treatment safety.

Outcome	APC 90 W PPI 120 mg (n = 23)	APC 90 W PPI 40 mg (n = 25)	APC 60 W PPI 120 mg (n = 23)	*P* value[1]	*P* value[2]	*P* value[3]
Patients with adverse event, n (%)	19 (83)	18 (72)	11 (48)	0.04	0.50	0.03
Patients with chest pain/discomfort, n (%)	19 (83)	17 (68)	9 (39)	< 0.001	0.32	< 0.001
Total adverse events, n	54	38	32			
Adverse event severity grade, n (%)				> 0.99	> 0.99	> 0.99
▪ Mild	52 (96)	37 (97)	31 (97)			
▪ Moderate	1 (2)	1 (3)	1 (3)			
▪ Severe	1 (2)	0 (0)	0 (0)			
▪ Fatal	0 (0)	0 (0)	0 (0)			
Adverse event timing, n (%)				0.64	0.39	> 0.99
▪ Intraprocedure	3 (6)	0 (0)	2 (6)			
▪ Post-procedure (≤ 14 days)	50 (93)	37 (97)	29 (91)			
▪ Late (> 14 days)	1 (2)	1 (3)	1 (3)			
Adverse event type, n (%)				0.44	0.37	0.74
▪ Chest pain/discomfort	29 (54)	28 (74)	15 (47)			
▪ Dysphagia	8 (15)	2 (5)	3 (9)			
▪ Odynophagia	7 (13)	4 (11)	6 (19)			
▪ Fever > 38 °C	6 (11)	3 (8)	3 (9)			
▪ Perforation	1 (2)	0 (0)	0 (0)			
▪ Stenosis	0 (0)	1 (3)	1 (3)			
▪ Anesthesia related	2 (4)	0 (0)	2 (6)			
▪ Other[4]	1 (2)	0 (0)	2 (6)			

APC, argon plasma coagulation; PPI, proton pump inhibitor.
[1] For comparison between all three groups.
[2] For comparison between APC 90 W/PPI 120 mg vs. APC 90 W/PPI 40 mg (effect of PPI).
[3] For comparison between APC 90 W/PPI 120 mg vs. APC 60 W/PPI 120 mg (effect of power).
[4] Pleural effusion (n = 1), vomiting (n = 1), abdominal discomfort/bloating (n = 1).

treatment with antibiotics. None of the patients evaluated in the study died in relation to the applied treatment.

Long-term efficacy

Long-term outcomes are summarized in ▶ **Table 4**. Complete endoscopic and histologic response at 2 years after therapy was confirmed in 44 patients (62 %; 95 %CI 51–73) with no statistically significant differences between the groups (16 [70 %; 95 %CI 51–88], 13 [52 %; 95 %CI 32–72], and 15 [65 %; 95 %CI 46–85] patients in the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg group, respectively). A total of 23 patients (32 %) had residual BE: 5 (22 %), 10 (40 %), and 8 (35 %), respectively. Four patients (6 %) were lost to assessment (2 [9 %], 2 [8 %], and 0 [0 %], respectively). This group included the two patients who were lost to assessment at 6 weeks (described above), and two patients in whom only 1-year follow-up was available (one patient in the 90 W/40 mg group died of unrelated causes and one patient in the 90 W/120 mg group declined to undergo further follow-up).

A total of 23 patients with residual BE and 5 patients with recurrent BE were treated with additional APC. The number of patients who required additional APC for residual or recurrent BE did not differ significantly between groups (▶ **Table 4**). Buried metaplastic glands were detected in seven patients (10 %) at various time points during the observation.

A total of 69 patients (97 %) completed at least 1 year of follow-up, 67 patients (94 %) at least 2 years' follow-up, and 65 patients (92 %) at least 4 years' follow-up. The median length of follow-up in the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg groups was 105.5, 109, and 113 months, respectively, and 108 months in the whole cohort. Complete response at the end of follow-up was confirmed in 66 patients (93 %; 95 %CI 87–99), with no statistically significant differences between the groups (22 [96 %; 95 %CI 87–100], 23 [92 %; 95 %CI 81–100], and 21

▶ **Table 4** Long-term outcomes.

Outcome	All patients (n = 71)	APC 90 W PPI 120 mg (n = 23)	APC 90 W PPI 40 mg (n = 25)	APC 60 W PPI 120 mg (n = 23)	*P* value[1]	*P* value[2]	*P* value[3]
Status at 2 years, n (%) [95 %CI]					0.42	0.33	0.35
▪ Complete ablation	44 (62) [51–73]	16 (70) [51–88]	13 (52) [32–72]	15 (65) [46–85]			
▪ Residual BE	23 (32)	5 (22)	10 (40)	8 (35)			
▪ Lost to assessment	4 (6)	2 (9)	2 (8)	0 (0)			
Patients requiring APC for residual or recurrent BE, n (%)	28 (39)	7 (30)	11 (44)	10 (43)	0.56	0.33	0.36
Status at the end of follow-up, n (%) [95 %CI]					0.76	> 0.99	0.49
▪ Complete ablation	66 (93) [87–99]	22 (96) [87–100]	23 (92) [81–100]	21 (91) [80–100]			
▪ Residual BE	3 (4)	0 (0)	1 (4)	2 (9)			
▪ Lost to assessment	2 (3)	1 (4)	1 (4)	0 (0)			
Length of follow-up, months					0.67	0.59	0.38
▪ Median (IQR)	108 (61–145)	105.5 (60–144)	109 (72–147)	113 (67.5–157)			
▪ Range	12–202	12–160	12–176	48–202			

APC, argon plasma coagulation; PPI, proton pump inhibitor; CI, confidence interval; BE, Barrett's esophagus; IQR, interquartile range.
[1] For comparison between all three groups.
[2] For comparison between APC 90 W/PPI 120 mg vs. APC 90 W/PPI 40 mg (effect of PPI).
[3] For comparison between APC 90 W/PPI 120 mg vs. APC 60 W/PPI 120 mg (effect of power).

[91 %; 95 %CI 80–100] patients in the 90 W/120 mg, 90 W/40 mg, and 60 W/120 mg, respectively). Three patients (4 %) had residual BE at the end of follow-up (0 [0 %], 1 [4 %], and 2 [9 %], respectively). No HGD or esophageal adenocarcinoma developed in any of the patients evaluated in the study.

Discussion

This is the first randomized study to evaluate the impact of power settings and PPI dose on the efficacy and safety of APC in patients with BE. The study also provides unique data on the long-term efficacy of APC ablation of BE with LGD.

Previous studies on the efficacy of APC of BE reported variable results. Complete ablation was achieved in 39 %–98 % of patients in the short term (up to 1 year); long-term success rates were usually lower due to BE recurrence [11, 17, 18, 23–30]. It has been suggested that the differences in efficacy might be explained by APC power settings used for ablation and the dose of PPI administered after ablation to promote healing and squamous re-epithelialization of the mucosa. These suggestions were mainly based on the excellent results reported by Schulz et al., who used high APC power (90 W) followed by high omeprazole dose (120 mg) for 6 weeks to achieve complete squamous regeneration in 69 of 70 (98.6 %) patients with nondysplastic BE and did not observe relapse during a median follow-up of 12 months [25].

The same protocol used in one of the groups in the present study (90 W/120 mg) resulted in a complete ablation rate of only 78 %. Moreover, the study did not find significant differences in APC efficacy in patients allocated to treatments using different power settings and PPI doses. The complete ablation rate at 6 weeks (the primary outcome of the study) in compared groups was in the 60 %–78 % range and did not differ significantly between patients treated with high (90 W) or low (60 W) APC power and between patients who received high (120 mg) or low (40 mg) PPI dose during and after APC treatment (▶ **Table 2**). In addition, no significant differences in the efficacy were observed 2 years after APC treatment and at the end of long-term follow-up (▶ **Table 4**). Similar results (a complete remission rate of 77 % at a mean of 14 months) were reported from the multicenter APBANEX study using high-power APC (90 W) in combination with esomeprazole 80 mg per day [29]. These data indicate that increasing the power used for ablation and subsequent PPI dose is not a simple solution for improving APC efficacy.

The present study provides unique data on the long-term outcomes of APC treatment of BE with LGD. Other long-term observations available in the literature included exclusively or predominantly patients with nondysplastic BE [13, 17–20]. With median follow-up of 108 months, the present study offers one of the longest follow-up datasets available. The median follow-up in previous studies ranged from 36 to 51 months, and

only the study by Milashka et al. reported longer follow-up [17–20]. The follow-up in the present study was thorough; 97 % of patients completed 12 months of follow-up and 92 % were followed for at least 48 months.

BE recurrence occurred in only five patients (7 %) and was treated easily with additional APC. Overall, 93 % of patients were free of BE and LGD at the end of follow-up without significant differences between the study groups. None of the patients developed cancer or HGD. This latter finding is noteworthy because some previous studies observed that cancer may develop in 4 %–9 % of patients during long-term follow-up after APC ablation of mainly nondysplastic BE [17, 19]. Cancer development may have been due to the presence of buried metaplastic glands and/or incomplete ablation; however, the numbers were insufficient to allow for a meaningful analysis [17, 19]. The difference between these studies and the present study is that in the present study incomplete ablation or BE recurrence were actively sought and re-treated. In total, 28 patients required a median of one additional APC to treat residual or recurrent BE. Buried metaplastic glands were detected in 10 % of patients, a rate similar or less than that reported by others [14, 19, 29, 31, 32]. The results of the present study indicate that APC of BE with LGD is oncologically safe, provided that patients for this treatment are selected carefully and treated and followed according to a strict protocol.

In the present study, 68 % of patients experienced adverse events of APC treatment and this rate is in the middle of the range reported from other series (0 %–91 %) [11, 25, 27, 29–31]. The vast majority of adverse events (97 %) were mild in severity (▶ **Table 3**) and did not have clinically significant consequences. The most common adverse event of chest pain or discomfort was observed two times more frequently after high (90 W) vs. low (60 W) power APC, which may suggest a possible effect of deeper tissue injury ($P < 0.001$).

Moderately severe adverse events included two cases of symptomatic stenosis that were successfully dilated endoscopically and a case of pleural effusion treated with intravenous antibiotics. One patient had a severe adverse event, an esophageal perforation that required esophagectomy. The incidence of perforation and stenosis combined (4 %; 3/71) was in the lower range reported by other authors (1 %–11 %) [13, 16, 19, 25, 27, 29, 33]. Three out of four moderate-to-severe adverse events occurred in patients treated with high (90 W) power APC; however, the numbers were too low to evaluate association with the power setting.

This is the largest study evaluating both short- and long-term outcomes of APC ablation of BE with LGD. The study evaluated a well-defined and uniform group of consecutive patients with BE and LGD confirmed by an expert pathologist. Treatment efficacy was assessed using a strict definition of treatment success and was analyzed on an ITT basis. The endoscopist and pathologist involved in the treatment and efficacy assessment were blinded to participant allocation. The length of follow-up in this study ranks among the longest available in the literature and is highly complete. All the data were collected prospectively.

The following limitations should be recognized. First, the study was conducted at a single center and all the APC treatments were performed by a single experienced endoscopist, which limits the generalizability of the findings. Second, the recruitment period was long because of a relatively low number of BE patients with confirmed LGD available for inclusion. Third, the trial was powered to detect a relatively large effect (60 % vs. 98 % difference in complete ablation rate at 6 weeks) and, hence, may not have been adequately powered to detect more modest differences. Fourth, patients were not blinded to PPI dose they received. Bias from this source cannot be excluded; however, it would be rather small and limited to adverse event assessment, without an impact on efficacy assessment as this was based on endoscopic and histologic criteria. The endoscopist performing APC treatment was blinded to APC power settings; however, the blinding might not have been completely effective because it is possible that experienced operators could recognize whether they are working with higher or lower APC power. Again, bias from this source is unlikely because the endoscopic assessment of treatment efficacy took place 6 weeks after the APC treatment and had to be confirmed by histologic evaluation. Fifth, a group treated with low power APC (60 W) and low dose PPI (40 mg) was not included because of concerns related to a low expected treatment effect. It should be emphasized that the current guidelines recommend double PPI dose after BE ablation. Sixth, the APC power settings of the Erbe ICC 200 generator used in the study are difficult to translate into the settings available on newer APC generators; however, the conclusion that they do not have a significant impact on efficacy and safety of APC treatment remain valid.

Finally, the fact that the study evaluated APC, a technique that is no longer considered the first-line ablative therapy for BE, may seem to be a limitation. However, at the time the study was designed and started, techniques such as RFA, currently recommended for BE ablation, or hybrid APC, currently under evaluation, were not available. In addition, although the role of RFA for ablation of BE is well established based on confirmed efficacy and safety [8–10, 34], there is no strong evidence in favor of this method over APC, and both techniques share common limitations. Similarly to APC, the RFA protocol for ablation is not fully standardized, multiple treatment sessions are often required to achieve complete ablation, cases of serious adverse events have been reported, and long-term follow-up data are limited [35]. Conversely, APC is widely available in endoscopy units, easy to perform, safe, and inexpensive. A recent pilot RCT comparing RFA and APC for ablation of BE after endoscopic resection of HGD or adenocarcinoma suggested similar efficacy and safety but a cost difference of $ 27 491 per case treated favoring APC [16]. These data indicate that APC remains a valid option in the management of BE.

Conclusions

In conclusion, this randomized study did not confirm the hypothesis that APC power setting (90 W or 60 W) or PPI dose (120 mg or 40 mg) have an impact on the efficacy and overall safety of BE ablation; however, chest pain or discomfort occurred more frequently after APC using 90 W power. Irrespective of

treatment protocol, complete endoscopic and histologic ablation of BE with LGD after APC and acid suppression was durable in over 90 % of patients, without any evidence of neoplasia progression in the long term. These results indicate that APC is a valid option in the management of BE with LGD.

Competing interests

The authors declare that they have no conflicts of interest.

Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT0415474 | Type of study: prospective, randomized study

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CORRECTION

Argon plasma coagulation for Barrett's esophagus with lowgrade dysplasia: a randomized trial with long-term follow-up on the impact of power setting and proton pump inhibitor dose

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In the above-mentioned article, Fig. 2 has been corrected. This was corrected in the online version on October 1, 2020.