

• BRIEF REPORTS •

Long-term follow-up after complete ablation of Barrett's esophagus with argon plasma coagulation

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Abstract

AIM: To report the long-term outcome of patients after complete ablation of non-neoplastic Barrett's esophagus (BE) with respect to BE relapse and development of intraepithelial neoplasia or esophageal adenocarcinoma.

METHODS: In 70 patients with histologically proven non-neoplastic BE, complete BE ablation was achieved by argon plasma coagulation (APC) and high-dose proton pump inhibitor therapy (120 mg omeprazole daily). Sixty-six patients (94.4%) underwent further surveillance endoscopy. At each surveillance endoscopy four-quadrant biopsies were taken from the neo-squamous epithelium at 2 cm intervals depending on the pre-treatment length of BE mucosa beginning at the neo-Z-line, and from any endoscopically suspicious lesion.

RESULTS: The median follow-up of 66 patients was 51 mo (range 9-85 mo) giving a total of 280.5 patient years. A mean of 6 biopsies were taken during surveillance endoscopies. In 13 patients (19.7%) tongues or islands suspicious for BE were found during endoscopy. In 8 of these patients (12.1%) non-neoplastic BE relapse was confirmed histologically giving a histological relapse rate of 3% per year. In none of the patients, intraepithelial neoplasia nor an esophageal adenocarcinoma was detected. Logistic regression analysis identified endoscopic detection of islands or tongues as the only positive predictor of BE relapse ($P = 0.0004$).

CONCLUSION: The long-term relapse rate of non-

neoplastic BE following complete ablation with high-power APC is low (3% per year).

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Key words: Barrett's esophagus; Argon plasma coagulation; Esophageal adenocarcinoma

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INTRODUCTION

Barrett's esophagus (BE) is a metaplastic replacement of the normal squamous epithelium by specialized intestinal columnar epithelium. BE is considered as a premalignant condition arising in patients with chronic gastroesophageal reflux disease (GERD)^[1,2]. Approximately 6-12% of patients with symptoms of GERD develop this condition^[2,3]. Gerson *et al*^[4] reported a BE prevalence of 25% in asymptomatic male veterans older than 50 years of age undergoing screening sigmoidoscopy for colorectal cancer. BE is a well-recognized risk factor for esophageal adenocarcinoma. Patients with BE have a 30- to 125-fold increased risk of developing adenocarcinoma compared to the general population^[3,5,6]. Proton pump inhibitor (PPI) therapy, even at high doses, does not result in complete regression of BE^[7-10]. Thus, there have been made many efforts to develop effective endoscopic treatments such as photodynamic therapy^[11,12] and laser therapy^[13] in order to ablate BE.

In recent years, argon plasma coagulation (APC) has been suggested as an effective technique for the ablation of BE^[7,14-16]. APC is a thermal cautery device that involves the transmission of a high-frequency current via a constant flow of ionized argon gas. The depth of tissue destruction is limited to 2-3 mm. Short- and mid-term efficacy data of APC treatment are promising^[15-17]. However, long-term follow-up studies investigating the risk of BE relapse or development of neoplasia after APC treatment are sparse. So far, only two studies have assessed the long-term outcome of patients with BE after APC treatment reporting a high endoscopic and histological relapse rate of 30 and 62% during a mean follow-up period of 3 years^[18,19].

We have previously described a large cohort of patients with non-neoplastic BE who underwent ablation of BE by

high-power APC^[16]. Here, we report the long-term outcome of patients after complete ablation of BE with respect to BE relapse and the development of intraepithelial neoplasia or esophageal adenocarcinoma.

MATERIALS AND METHODS

Patients

In an outpatient setting, consecutive patients undergoing endoscopy for the evaluation of GERD symptoms were evaluated between 1994 and 1998. Patients were eligible for the study if BE without intraepithelial neoplasia was histologically confirmed and written informed consent was given, particularly regarding the experimental nature of the APC procedure. Patients were excluded from the study if they were younger than 18 years of age and if any serious gastrointestinal or extraintestinal disease or BE with any kind of intraepithelial neoplasia was present.

Endoscopy and APC treatment

At baseline endoscopy the macroscopic extent of BE was determined by measuring the distance between the most proximal point of columnar mucosa and the proximal end of gastric folds as referenced to the distance from the incisions. For the APC procedure, patients received intravenous sedation with 10-mg midazolam. Circumferential areas of BE were ablated by using an argon beamer device (APC300, ERBOTOM ICC200; Erbe Medizintechnik, Tübingen, Germany), using a gas flow of 2 L/min at a power setting of 90 W. Ablation was initiated at the gastroesophageal transition zone and proceeded longitudinally toward the proximal epithelial junction with squamous epithelium. All APC treatments were carried out by a single experienced gastroenterologist (H.S.) at intervals of 2-3 wk and continued until macroscopic and histological complete reepithelialization with squamous epithelium.

Biopsy protocol and histological assessment

Before the APC procedure, four-quadrant biopsies were obtained every 2 cm along the visible length of BE by using a spiked biopsy forceps with an open diameter of 7 mm (MTW Endoskopie, Wesel, Germany). Additional specimens were obtained from any abnormal area as recommended by Levine *et al.*^[30].

After macroscopic complete ablation of BE, regeneration of squamous epithelium was confirmed by quadrant biopsies every 2 cm. Thereafter, during surveillance endoscopies, two to four biopsies were routinely taken from the neosquamous epithelium and additional biopsies from any endoscopically suspected BE or other suspicious lesions.

The histological examination included staining with hematoxylin and eosin, and PAS-alcian-blue at pH 2.5. The histologic diagnosis of BE was established only when specialized intestinal columnar epithelium was detected. Complete intestinal metaplasia of normal or inflammatory cardia mucosa was not classified as BE. All biopsies were examined by two experienced pathologists (M.S. and M.V.).

BE relapse was defined either as endoscopically suspected and histologically confirmed BE, or as random detection of BE by biopsies from exactly below the Z-line and/or

underneath neosquamous epithelium (buried glands).

Antireflux therapy during follow-up

During the entire APC treatment period, 40 mg omeprazole was given three times daily in order to achieve maximum acid suppression. After completion of APC treatment the omeprazole dose was reduced to 20 mg or continued with 40 mg daily as maintenance therapy depending on the results of pH monitoring and reflux symptoms (cumulative reflux time [pH less than 4] less than 7% per 24 h). After 12 mo of follow-up, PPI therapy was continued depending on the presence of reflux symptoms or if esophagitis was detected during surveillance endoscopy. Antireflux surgery was considered in eligible patients.

RESULTS

APC treatment

Seventy-three patients (45 men, mean age 55±12 years, range 28-77 years) with histologically proven non-neoplastic BE and at least moderate to severe gastroesophageal reflux symptoms for more than one year were enrolled in the initial study^[16]. The median length of BE was 4 cm (range 1-12 cm), 56 patients (76.7%) had a BE longer than 2 cm. Three patients were lost during APC treatment due to unwillingness to continue and therefore, excluded from this analysis. In 69 of 70 patients complete squamous regeneration was achieved after a median of two APC sessions. In one patient (extent of BE 8 cm) 6 sessions of APC were necessary during the first 12 mo to achieve complete ablation except for a persistent small island of residual BE without intraepithelial neoplasia. After repeated sessions of APC treatment, this patient also achieved complete ablation and was included in the long-term follow-up study.

The APC procedures were generally well tolerated^[22]. No severe complications such as bleeding or perforation occurred. Three patients developed mild esophageal strictures that were successfully treated by a single bougie dilatation.

Long-term follow-up

Sixty-six out of 70 patients (94.3%) underwent further surveillance endoscopy approximately every 12 mo. The clinical characteristics of these 66 patients are summarized in Table 1. In these patients, the median follow-up period ranged from 9 to 85 mo with a median of 51 mo giving a total of 280.5 patient years. During the entire follow-up period, 220 endoscopies were performed (mean 3.3 endoscopies per patient) with a mean of six biopsies taken during endoscopy.

The remaining four patients who did not undergo further surveillance endoscopy after the initial follow-up of 12 mo were interviewed (M.A.) by telephone at mo 84, 75, 61 and 78, respectively, after complete APC ablation of BE. None of them reported having any symptoms of dysphagia or having a diagnosis of upper gastrointestinal tract carcinoma.

Thirty-three patients (50%) received further PPI therapy with symptom-adjusted doses. Based upon patients' willingness, 22 patients (33.3%) underwent laparoscopic fundoplication after complete BE ablation. Eight patients who underwent laparoscopic fundoplication required further PPI therapy. Eleven patients were free of reflux symptoms and had no further antireflux therapy.

Table 1 Baseline characteristics of patients with continuous surveillance endoscopy

Variable	
Patients (<i>n</i>)	66
Length of BE >3 cm, <i>n</i> (%)	37 (56)
APC applications (mean)	2 ¹
APC energy (W)	90 ¹
Median follow-up (mo)	51
Hiatal hernia, <i>n</i> (%)	26 (39)
Sustained PPI-therapy, <i>n</i> (%)	33 (50)
Laparoscopic fundoplication, <i>n</i> (%)	22 (33)

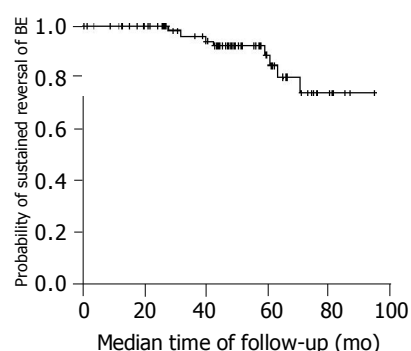
¹Initial study^[16].

BE relapse

In 13 of the 66 patients (19.7%) islands or tongues of BE was identified during surveillance endoscopy. The macroscopic features of suspicious BE are summarized in Table 2. In 8 of the 13 patients, BE was histologically confirmed. Therefore, the cumulative relapse rate of histologically confirmed BE during the entire long-term follow-up was 12.1% giving an annual relapse rate of approximately 3%. The probability of sustained absence of BE after complete ablation by APC is shown in Figure 1.

Table 2 Endoscopically suspicious and histologically confirmed BE relapse rates for 66 patients

	Endoscopically suspicious BE Number of patients (%)	Histologically confirmed BE Number of patients (%)
Endoscopic finding	13 (19.7)	8 (12.1)
Tongues >3 cm	1 (1.6)	1 (1.6)
Tongues >1 cm	5 (7.5)	3 (4.5)
Tongues <1 cm	4 (6.1)	2 (3)
Small islands	3 (4.5)	2 (3)

**Figure 1** Probability of sustained absence of BE after complete ablation by APC.

Seven of the 8 patients with BE relapse received antireflux therapy during follow-up (laparoscopic fundoplication, *n* = 3; PPI therapy, *n* = 4). One BE relapse occurred in a patient without further antireflux therapy. All patients with histologically confirmed BE relapse were retreated with one session of high-power APC treatment.

Logistic regression analysis identified the endoscopic

detection suspicious for BE as the only predictor of histological BE relapse. Other potential factors such as hiatal hernia, antireflux therapy or initial length of BE were not predictive for BE relapse (Table 3).

Table 3 Variables as predictors of BE relapse in 66 patients treated with APC and analyzed using logistic regression analysis

Variable	Multivariate analysis <i>P</i>
Age (yr)	0.57
Gender	0.11
Hiatal hernia	0.15
Number of APC sessions	0.22
Length of BE	0.10
Endoscopically islands or tongues of suspicious BE	0.0004
PPI therapy	0.96
Antireflux surgery	0.73

Importantly, neither intraepithelial neoplasia nor esophageal adenocarcinoma was detected in our patient cohort during the entire follow-up period.

DISCUSSION

The presence of BE as the most serious complication of GERD is associated with an increased risk of developing adenocarcinoma of the esophagus^[1-6]. Thus, besides surveillance strategies many efforts have been made to develop new effective therapeutic endoscopic therapy for the ablation of BE such as thermal laser ablation or photodynamic therapy and APC^[8,11-13,20].

The results of our long-term follow-up study suggest that endoscopic APC is effective and safe for the ablation of BE without neoplasia. To our knowledge the present study currently represents the largest series with the longest follow-up of patients. During a median follow-up of 51 mo we observed a low BE relapse rate of 12.1% after a complete BE ablation, which represents a BE relapse rate of approximately 3% per year. In our patient population neither intraepithelial neoplasia nor esophageal adenocarcinoma was detected.

Since the use of APC was described in a case report^[21], several controlled studies with a larger number of patients have been fully published with a short- and mid-term follow-up^[14,15,18,17,22,23,25]. The results of these studies are contradictory regarding both the initial success rate of complete ablation and relapse rate of BE. In four studies a complete ablation of BE between 87 and 100% is achieved^[15-17,22]. Other studies showed only complete reversal of BE in 61-70% of patients^[14,18,23,25]. The reported number of APC sessions (range 2-4) and the mean length of BE (4-6 cm) prior to the treatment were comparable in all studies. In contrast to all other published studies, in our study the highest level of energy (90 W) was applied during the APC treatment. This difference might be one reason for the higher rate of squamous reepithelialization in our study. Pereira-Lima *et al*^[15] and Tigges *et al*^[22] used APC at a power setting of up to 70 W and achieved a complete BE reversal in 96 and 91% of patients, respectively. We also used a higher dose of

omeprazole (40 mg three times daily) to suppress acid during the APC treatment period than all other studies.

Since most studies reported a low complication rate, APC can be regarded as a safe endoscopic method^[24]. However, severe complications have been reported in four patients suffering from perforation^[18,25], two patients died due to these complications. Although we used a high energy level in our study, only three patients (4.3%) developed a mild esophageal stricture, that was resolved after a single session of bougie dilatation. Since the long-term benefit of this procedure has not been sufficiently investigated, APC treatment should be still used primarily in experienced centers and within controlled trials.

Based upon the incidence of adenocarcinoma in patients with BE (estimated 0.5-1% per year)^[1] we would have expected to observe up to three adenocarcinomas in our cohort. However, our data are certainly underpowered for valid incidence rates of adenocarcinoma after APC ablation of BE, or for the assessment of possible risk reduction of carcinoma development. In contrast to other studies we did not include patients with any kind of intraepithelial neoplasia in our study. Others have shown that in some cases adenocarcinoma might develop under the new regenerated squamous epithelium after APC treatment^[26,27] although that was not the case in our study. This fact supports the current hypothesis that BE arises from pluripotential stem cells present in the basal layer of esophageal mucosa^[28-34]. There are concerns that buried glands could remain beneath the new regenerated squamous epithelium after APC treatment and would not be detected by biopsies. However, it is still unknown whether buried glands relapse or still remain in BE due to incomplete ablation. Based upon our long-term follow-up data, this phenomenon appears not to be a clinically relevant problem, since we did not detect any buried glands in our cohort. Nevertheless, sampling cannot definitely rule out BE.

There are only two studies with long-term follow-up data after APC treatment of BE (Table 2). Kahaleh *et al.*^[19] published a study of 39 patients with BE, 7 of them with low-grade intraepithelial neoplasia and received APC treatment. After a complete ablation rate, they demonstrated a high BE relapse rate of 62% during a median follow-up period of 36 mo. Five out of seven patients with a low-grade intraepithelial neoplasia at baseline had recurrence of BE, one developed low-grade intraepithelial neoplasia again. In two patients of this cohort an esophageal adenocarcinoma was detected after a follow-up of 12 and 18 mo, respectively. Based upon these results, Kahaleh *et al.*^[19] concluded that APC cannot be recommended as an effective ablation method for BE. There are, however, some limitations in this study. First, it has to be considered that Kahaleh *et al.*^[19] showed a short-term relapse rate of 44% after 1 mo, thus it appears that in their study about 44% were incompletely ablated rather than relapsed. Weinstein^[35] suggested that the reason for the low rate of complete ablation at baseline may be due to technical factors such as use of energy or acid suppression agents and demand of more vigorous ablation especially in longer-segment BE coupled with more potent acid suppression. Morris *et al.*^[18] described a cohort of 55 patients undergoing APC treatment of BE followed

up a mean period of 36 mo. After a complete ablation rate of 70% no BE relapse was observed during the long-term follow-up. As in our initial report^[16], we speculate that incomplete acid suppression and the lower level of energy may be the main reasons for the lower success rates of APC and remaining BE.

Several studies suggested short length of BE (<3 cm) and the normalization of acid exposure can be used as positive predictors of long-term reversal of BE^[14,19]. Our regression analysis only identified the endoscopically detected suspicious BE as a positive predictor of histological BE relapse, whereas other factors such as the length of BE, hiatal hernia or previous antireflux therapy had no statistical impact on the sustained reversal of BE. In contrast to other studies^[18,19] in which endoscopically suspicious BE was always confirmed histologically, we found endoscopically suspicious but not histologically confirmed BE in five patients. That means minimal endoscopic findings may not be equivalent to BE unless histologically confirmed.

In conclusion this study suggests that endoscopic APC is an effective method for the ablation of BE without neoplasia. The long-term relapse rate of BE is low. Nevertheless, APC treatment of BE does not replace surveillance endoscopy at present although cost-utility analysis has shown that subsequent surveillance of patients with BE but no neoplasia, even at 5-year intervals, is an expensive practice^[36].

Although the present cohort was followed up for over 4 years without any evidence for intraepithelial neoplasia or adenocarcinoma, further long-term studies are warranted to determine whether risk reduction of malignancy can be achieved by APC ablation of BE.

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