

## Research Article

# Long-Term Follow up of Patients Submitted to Argon Plasma Coagulation of Non Dysplastic Barrett's Esophagus after Nissen Fundoplication

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Submitted: 20 June 2016

Accepted: 05 August 2016

Published: 07 August 2016

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**OPEN ACCESS****Keywords**

- Barrett esophagus
- Ablation techniques
- Gastroesophageal reflux

**Abstract**

**Introduction:** The rising incidence of adenocarcinoma in the esophagogastric junction related to the presence of Barrett's esophagus has established a demand for regular endoscopic surveillance. Due to the fact that most patients do not have a complete regression of areas of intestinal metaplasia, even with effective drug therapy and surgery, ablation techniques have been employed for the treatment of mucosal areas in Barrett's esophagus. In 2004 Pinotti published an evaluation of the effect of argon plasma coagulation (APC) after performing Nissen fundoplication in 19 patients with Barrett's esophagus.

**Objective:** In the current study, patients were retrospectively reevaluated for the presence or absence of BE using prior endoscopic surveillance after late follow-up.

**Method:** Retrospective data including the date of the patients' last endoscopy with biopsy were retrieved. Follow-up time was established as the period between argon plasma coagulation and the date of last endoscopy. At each endoscopic exam the presence or absence of the following data were evaluated: columnar epithelium, intestinal metaplasia, dysplasia or adenocarcinoma.

**Results:** Six patients were excluded due to lack of follow-up data. The mean follow-up time was 9 years with a median of 9 years. Return of columnar epithelium and Barrett's esophagus was seen in 3 patients (23.1%). Ten (76.9%) of the 13 reevaluated patients showed complete regression of Barrett's esophagus. None of the studied patients presented dysplasia or adenocarcinoma.

**Discussion:** This study examined the long-term follow-up of patients undergoing ablation of Barrett's esophagus, investigating whether ablation techniques should be better analyzed. Recently a patient with adenocarcinoma located beneath the restored epithelium after APC was referred to our institution and curative esophagectomy was possible. This case led us to reconsider the safety of this procedure. Considering cases of recurrence of dysplasia and progression to intramucosal adenocarcinoma in patients who had undergone successful ablation of columnar epithelium, we are still looking for the proper way to follow these patients.

**Conclusion:** In conclusion, the data suggest a lower risk in developing dysplasia and adenocarcinoma in patients who undergo ablation compared with patients maintained only on endoscopic surveillance. Furthermore, there is not strong enough evidence that supports, even with these results, that these patients can be excluded from frequent endoscopic surveillance or if there is a cost-effectiveness advantage in ablation therapy.

**INTRODUCTION**

The rising incidence of adenocarcinoma in the esophagogastric junction (EGJ) related to the presence of Barrett's esophagus (BE) has established a demand for regular endoscopic surveillance [1,2]

In the last decade, the idea of achieving a definitive treatment of metaplastic columnar epithelium with a subsequent decrease in the risk of recurrence has been very promising [1-7]. The

prevalence of BE in the western population corresponds to 1% to 2% in adults and about 10% in patients with gastroesophageal reflux disease (GERD) [1]. The risk of esophageal adenocarcinoma has decreased over the years. Currently the risk is low and is described as 0.12% per patient per year [2]. However, the possible advantage of definitive control of intestinal metaplasia (IM) remains unclear.

Observations that most patients do not have complete regression from IM areas, even with medical therapy and effective

surgery, led to the use of mucosal ablation techniques of BE areas for treatment. Initially, the use of argon plasma coagulation (APC) was one of the most popular techniques performed by a variety of authors and investigated thoroughly in the literature [1]. Currently, radiofrequency ablation (RFA) with or without endoscopic mucosal resection (EMR) is the most used technique.

Previously, Pinotti AC et al., [3] published results from our institution of APC after performing Nissen fundoplication on 19 non dysplastic BE patients. Our initial evaluation involved a short follow-up time, which varied between 6 to 27 months, and we observed complete restoration of squamous esophageal epithelium in all patients. In that preliminary study, it was believed that surgical anti reflux therapy had great importance in maintaining the clearance of columnar epithelium (CE).

In the current study, we retrospectively evaluated those 19 patients for the presence or absence of BE after a long follow-up and we critically analyzed the indication and results of the BE ablation techniques.

## MATERIALS AND METHODS

In the preliminary study [3], 19 patients with non dysplastic BE were submitted to a laparoscopic Nissen fundoplication followed by APC in an interval of 1 to 3 years after surgery during the period between September 1997 and August 1999. Eleven patients were male (58%). The age ranged from 32 to 72 years (mean 52.3 years; median 52 years). Patients were excluded for the following reasons: disagreement with protocol; esophageal ulcers or strictures; pregnancy or presence of high-grade dysplasia or adenocarcinoma in CE. Patients were also excluded if persistent GERD was present after fundoplication, identified by clinical criteria and 24-hour esophageal pH-metry.

In 4 patients (21%) the complete eradication of BE was reached with one session of APC. In 13 patients (68.42%), two sessions of endoscopic treatment were required. Finally, in 2 patients, 4 and 6 sessions were required due to the greater extent of CE (70 and 90 mm, respectively).

The number of sessions necessary for a complete substitution of CE for normal squamous epithelium varied between 1 and 6. The necessary time to achieve the result varied according to the BE extension, as shown in Table (1) from the original study [3].

There was a complete regeneration of the squamous epithelium of the esophagus in 100% of initial cases. There were no severe complications, only non-cardiac mild chest pain and dysphagia with spontaneous resolution in the first 15 days after the procedure.

Patients were followed by clinical appointments for complaints related to gastroesophageal reflux (GER), in addition to routine endoscopies determined by the outpatient clinic.

The period between the last APC session and the date of the last endoscopy was used to calculate the length of follow-up.

The endoscopic examination of these patients included evaluation of the CE, IM, and integrity of the fundoplication, erosive esophagitis and biopsies of the neo-squamous lining as well as areas suspicious for recurrent columnar metaplastic epithelium, dysplasia or adenocarcinoma.

**Table 1:** Number of sessions of APC needed to achieve CRSE.

Number of sessions	n of patients	CE extension (mm)	Δt to CRSE (mo)
1	4	10 a 25	2 - 3
2	13	20 a 50	4 - 9
4	1	70	13
6	1	90	18

**Abbreviations:** APC: Argon Plasma Coagulation; CRSE: Complete Regeneration of Squamous Epithelium; Δt: Time; MO: Months

## RESULTS AND DISCUSSION

### Results

From the 19 initial patients, 6 were excluded due to lack of follow-up data; of the remaining 13 patients, six were male (43%) and 7 female (57%).

The mean follow-up time was 9 years with a median of 9 years, ranging from 1 to 18 years. There was only one death among those patients caused by pancreatic adenocarcinoma. This patient had endoscopic control after 3 years of APC without evidence CE.

In 5 patients there was a recurrence of CE (38.4%) after 3, 5, 6, 8 and 9 years of follow-up. Two of them, at the 15 and 18 year follow-up endoscopy, had shown complete regression of CE, without any additional intervention. Only one patient had recurrence of IM in CE.

Considering the last endoscopy, 10 (76.9%) of the 13 reevaluated patients showed complete regression of BE. No patients had dysplasia or adenocarcinoma.

A summary of demographic, endoscopic and histologic findings can be seen in Table (2).

### Discussion

In the present study, complete regression of CE and IM was respectively observed in 10 (76.9%) and 12 (83.3%) of 13 patients submitted to APC for ablation of nondysplastic BE after Nissen fundoplication followed by a mean period of 9 years. Similarly, SieCorina et al., [1], published the long-term results of an Australian randomized trial with 129 patients comparing APC versus endoscopic surveillance in the treatment of BE.

In 10 years of follow-up, 70 patients who underwent fundoplication were compared with 59 patients submitted exclusively to medical treatment. Each group was further divided into two separate groups. Of these, one was submitted to APC and the other to endoscopic surveillance. Twenty-one of 32 patients (65.6%) from the APC group maintained at least a 95% reduction of Barrett's esophagus after a follow-up period of 84 months compared with 4 of 27 patients (14.8 %) in the endoscopic surveillance group (P<0.0001). No difference regarding regression of BE was found between those who underwent fundoplication and medical treatment alone. It seems clear that anti reflux treatment does not promote regression of BE. On the other hand, APC ablation promotes sustainable regression of BE in 70% of patients [1].

**Table 2:** Result of long endoscopic follow-up after APC in patients who had underwent Nissen fundoplication.

Patient	Age (years)	Sex	Initial length CE (mm)	n° sessions for CRCE	t CRCE (months)	t FU (months)	CE	IM	Last EDA length CE (mm)	% circ
1	77	F	20	1	16	204	N	N	0	0
2	71	F	20	2	23	60	N	N	0	0
3	78	M	30	2	21	180	N	N	0	0
4	60	F	30	2	20	72	N	N	0	0
5	56	F	40	2	22	192	N	N	0	0
6	76	M	50	2	27	36	Y	N	10	10
7	66	F	30	2	11	216	N	N	0	0
8	38	M	90	6	23	12	N	N	0	0
9	49	M	20	2	19	108	N	N	0	0
10	78	M	40	2	18	108	N	N	0	0
11	52	F	70	4	24	108	Y	Y	90	90
12	58	M	40	2	14	72	Y	N	10	100
13	66	F	30	2	26	36	N	N	0	0

**Abbreviations:** APC: Argon Plasma Coagulation; CE: Columnar Epithelium; CRCE: Complete Regression of Columnar Epithelium; t: Time of/to; FU: Follow-up; IM: Intestinal Metaplasia; % circ: Percentage of Circumferential Presentation of CE.

The adequate control of reflux, either by the use of high doses of proton pump inhibitor (> 60 mg / d) [8-11] or an effective anti-reflux surgery [12,13], seems to be critical for the success of APC ablation of BE. Our patients underwent fundoplication and showed no clinical or endoscopic signs of therapeutic failure of reflux control in the first years after surgery.

Our study showed similar results in relation to reducing the extent of CE in that 10 (76.9%) of the 13 reevaluated patients showed complete regression of BE. The mean and median follow-up of these patients was 9 years. The patient who needed the most number of sessions to eradicate CE (6 sessions in 27 months), with proper control of GERD at that time, showed recurrence after 3 years of follow-up [3]. The effectiveness of surgical treatment, despite being higher than the long-term medical treatment, is not flawless [14].

One advantage of APC ablation is the low standard depth of coagulation, approximately 3 mm, that decreases the chances of perforation, stenosis and other severe complications; in addition, it has a lower cost compared to newer technologies. However, the potential of APC to reduce the number of endoscopic examinations, expand the surveillance interval, or even prevent dysplasia and adenocarcinoma have not been proven yet.

None of the patients in our study presented dysplasia or adenocarcinoma. Although, recently a patient with adenocarcinoma located beneath restored squamous epithelium after APC was referred to our institution and curative esophagectomy was performed. The final staging was pT2 pN0. This case led us to reconsider the safety of this procedure.

In 2000, Van Laethem et al., reported a case of adenocarcinoma in situ beneath the squamous epithelium in the squamocolumnar junction after APC was performed on nondysplastic CE [15]. It has been also reported that a patient with low grade dysplasia in BE who underwent APC progressed to invasive adenocarcinoma with liver metastasis [16].

There are also reports of recurrent IM and progression to dysplasia and adenocarcinoma beneath the squamous epithelium neo-formed after ablation with photodynamic therapy (PDT) [17-19].

In the early 2000's, there was the development of RFA. With the technology came expectations of better results due to greater reproducibility and uniformity of the depth of tissue injury after ablation. Progressively this technique became the most employed and obtained strong relevance in literature for endoscopy treatment of BE. The results of RFA for the treatment of dysplastic Barrett's esophagus are promising with a high dysplasia eradication rate [20,21].

In 2009, Shaheen et al., published the first results of RFA after one year of follow-up. His results showed complete response in the control of IM in 77% of patients, including patients with LGD and HGD, with a low adverse event rate [22]. After 5 years of follow-up, the IM clearance rate was 78% and dysplasia, 91%. These data were confirmed in a systematic review recently conducted by the author [23]. In our study, we had almost the same rate of IM clearance after long-term follow-up (83.3%), the only difference being that we employed APC in non dysplastic patients.

Data from the American Registry of RFA has shown a 20% recurrence rate after 3 years. Patients without dysplasia have a recurrence rate of around 18%, while those with a previous dysplasia have a recurrence rate of 22%; those with intramucosal or invasive adenocarcinoma have slightly higher recurrence rates of 23% and 29%, respectively [24]. Other authors have also described the recurrence of IM and progression to adenocarcinoma in patients undergoing successful RFA [25,26].

A systematic review confirmed the recurrence of CE with IM, dysplasia and adenocarcinoma hidden below the newly formed squamous epithelium in patients undergoing different types of ablation such as APC, PDT or even RFA [27].

These facts emphasize the importance of the continuing surveillance of those patients and the need to evaluate the real effectiveness ablative treatment.

It is worth to mention that in all the studies mentioned the anti-reflux treatment was conducted using proton pump inhibitor (PPI) in standard doses. Some recent studies have suggested that fundoplication might act as a protective factor in preventing the recurrence of IM and progression to dysplasia and adenocarcinoma [28,29].

The long-term follow-up of patients undergoing ablation of BE, regardless of the employed technique should be better analyzed. Considering the various cases of recurrence of dysplasia and progression to intramucosal adenocarcinoma in patients who had undergone successful ablation of CE, the proper way to follow these patients is still under inquiry. Optical coherence tomography and the detection of genetic polymorphisms in neoforced squamous epithelia are amongst the newest technologies under investigation [30].

This study has some limitations. We lost 6 patients in follow-up (31.6%). Their data might have had a substantial impact on the results. The endoscopic images and the histology were not reviewed. We felt that it was unnecessary because there was a group of pathologists and endoscopists dedicated to BE who performed the evaluations following the same standardized protocol.

## CONCLUSION

In conclusion, there was a low rate of recurrence of CE (23.1%) and IM (16.7%) in patients submitted to laparoscopic Nissen fundoplication followed by APC for the treatment of nondysplastic BE. After a mean follow-up of 9 years, the majority of those patients were free of CE and IM.

In sum, there is a lack of studies evaluating whether there is a significant difference in cancer-related dysplasia or long-term follow-up mortality comparing the use or absence of any ablation technique. These data might help to highlight the possible advantage of ablation and justify its indication in a specific group of patients, regarding the expense of spending and morbidity of these procedures when compared with only surveillance. There is not strong enough evidence that supports, even with these results, that those patients can be excluded from frequent endoscopic surveillance or if there is a cost-effectiveness advantage in ablation therapy.

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#### Cite this article

Szachnowicz S, Duarte AF, Filho FM, Bianchi ET, da Costa Seguro FCB, et al. (2016) Long-Term Follow up of Patients Submitted to Argon Plasma Coagulation of Non Dysplastic Barrett's Esophagus after Nissen Fundoplication. *JSM Gastroenterol Hepatol* 4(4): 1066.