Endoscopic ablation of Barrett’s esophagus using high power setting argon plasma coagulation: A prospective study

Corrado Pedrazzani, Filippo Catalano, Mara Festini, Germana Zerman, Anna Tomezzoli, Andrea Ruzzenente, Alfredo Guglielmi, Giovanni de Manzoni

INTRODUCTION

While the incidence of the adenocarcinoma of the distal esophagus and gastric cardia is rising rapidly,[1,2] long-term prognosis of surgically treated patients remains poor.[3] The principal risk factor for the development of esophageal adenocarcinoma is Barrett’s esophagus (BE). Although the exact estimation of this hazard has not been assessed yet, it is estimated that BE leads to an increased risk of 30-125 times compared to the general population.[4,5] Many questions remain regarding the best management of BE, since routine endoscopic follow-up is not definitely accepted[6,7] and medical therapies as well as anti-reflux surgery have not proven to induce the regression of BE.[8,9]

Argon plasma coagulation (APC) is one of the several endoscopic approaches that have been proposed in order to reverse BE and to induce squamous re-epithelialization. This technique allows to ablate large areas of specialized intestinal metaplasia with a limited depth of injury that minimizes the risk of stricture and perforation. Conversely, the chance of having isolated microfoci of metaplastic mucosa beneath the new squamous epithelium points out the importance of eliminating the totality of BE.[10,11] Although APC has been reported in many series with different power settings (30-60 W), few studies reported high level of energy (70-90 W).[12,13]

The aim of this prospective study was to evaluate the effectiveness of 90 W APC for the ablation of BE.

MATERIALS AND METHODS

Study population

The study includes 25 patients observed at the First Department of General Surgery, University of Verona, Italy, between October 2000 and October 2003 who underwent APC for histologically proven BE.
**Definition and inclusion criteria**

BE was diagnosed if specialized intestinal metaplasia was observed in biopsy specimens obtained from the tubular esophagus above the gastro-esophageal junction. Long-segment BE was defined as the occurrence of intestinal metaplasia extending more than 3 cm from the gastro-esophageal junction. Short-segment BE was considered when the columnar lining was less than 3 cm \[^{[13]}\].

The most important inclusion criteria were: histologically proven BE, age ranging from 18 to 75 years old, possibility of follow-up with a life expectancy longer than 5 years, informed consent, absence of previous malignancies or intercurrent diseases precluding the prognosis under study. Patients with low grade dysplasia were included while no patient underwent APC for high grade dysplasia.

**Endoscopy and biopsy protocol**

A baseline endoscopic examination was performed in all the cases with a Pentax EG endoscope (series 2901-2940) to allow precise measurement of the BE segment length and to classify it according to the presence of tongues (type I), islands (type II) or circumferential (type III) metaplastic mucosa.

Gastro-esophageal junction was defined by the end of the tubular esophagus or, in the presence of hiatal hernia, by the proximal extent of the gastric rugal folds. The length of BE was routinely evaluated considering the distance from the incisors on the basis of markings on the endoscope shaft while the endoscope was being withdrawn. Four 7-mm biopsy specimens were taken every 2 cm of BE segment. Further four biopsy specimens were taken just over the proximal margin of BE and four just below the GEJ. Additionally, specific biopsies were taken on any mucosal abnormality \[^{[14]}\].

**Ablation technique**

APC was carried out as a day-case procedure under intravenous sedation with midazolam in all the cases. Heart rate, blood pressure and pulse oximetry were routinely monitored. Ablation was performed using the ERBE ‘Argon Beamer 2’ device (ERBE Electromedizin, Tübingen, Germany) with a power setting of 90 W and a gas flow of 2 L/min. After esophageal intubation the APC probe was moved forward for 1 cm from the endoscope and positioned at 1-2 mm from the mucosa. A longitudinal strip was ablated starting from the gastro-esophageal junction withdrawing the endoscope till the end of BE. The procedure was then repeated on the adjacent mucosa. When the length of BE was longer than 4 cm, its ablation was carried out in two or more sessions. Any remaining islands of metaplastic mucosa were treated in a final procedure.

No post-operative blood or instrumental examinations were routinely performed. A tepid semiliquid diet was advised on the day of intervention, while no particular dietary restrictions (except usual GERD rules) were prescribed for the following days. All patients were established on high dose PPI regimens (pantoprazole or esomeprazole 40 mg×2) starting one week before the planned treatment and continuing till the confirmation of the complete ablation of the BE (usually one month). Thereafter prolonged medical therapy with standard PPI doses (pantoprazole or esomeprazole 20 mg) was recommended in any case except one who had undergone previous anti-reflux surgery.

**Follow-up**

After the completion of APC treatment and the complete BE eradication, confirmed histologically at one month, the patients were followed up at 6 mo, at 1 and 2 years and thereafter at two-year intervals. The follow-up protocol requires endoscopic examination as previously described and multiple 7-mm biopsy specimens taken according to the four quadrant technique considering the previously assessed length of metaplastic mucosa.

**RESULTS**

Patients’ clinical characteristics are shown in Table 1. Twenty-five patients underwent APC, 11 had a long-segment BE while in 14 the length of metaplastic mucosa was inferior to 3 cm. The mean BE length was 34 mm (median 25 mm, range 10–130 mm). Among the 25 patients only 3 cases had a previous histological diagnosis of low grade dysplasia.

Data on APC treatment are available in Table 2. The ablation treatment was completed in all the patients but one (patient n. 16, table 2) who required an additional session. The mean (range) number of ablation sessions was 1.6 (40). APC treatment was completed in 24 (96) patients. The mean (range) length of BE was 34 mm (10–130 mm). Among the 25 patients, 11 had a long-segment BE and 14 a short-segment BE. Six patients had a short-segment BE \(^{[13]}\).

**Table 1 Clincial characteristics of the 25 patients**

| Parameter                              | Number represented in parenthesis are percentages |
|----------------------------------------|--------------------------------------------------|
| Age (yr)                               | 61.7 (34-74)                                     |
| Male:Female                            | 18:7                                             |
| Presence of GERD symptoms              | 15 (60)                                          |
| Presence of hiatal hernia              | 24 (96)                                          |
| Length of BE (mm)                      | 34 (10-130)                                      |
| Type of BE                             |                                                  |
| Long-segment BE                        | 11 (44)                                          |
| Short-segment BE                       | 14 (56)                                          |
| Type I                                 | 3 (12)                                           |
| Type II                                | 4 (16)                                           |
| Type III                               | 8 (32)                                           |
| Presence of low grade dysplasia        | 3 (12)                                           |

\(^{1}\)Number represented in parenthesis are percentages. \(^{2}\)Mean (range).

**Table 2 Results of ablation treatment in the 25 patients**

| Parameter                              | APC treatment |
|----------------------------------------|---------------|
| Treatment completed                    | 24 (96)       |
| No. of APC sessions                    | 1.6 (40)      |
| Single                                 | 15 (60)       |
| Two                                    | 6 (24)        |
| Three or more                          | 4 (16)        |
| Treatment-related morbidity            | 17 (42.5)     |
| Retrosternal pain                      | 9 (22.5)      |
| Fever                                  | 7 (17.5)      |
| Dysphagia                              | 2 (5)         |
| Ulcer formation                        | 2 (5)         |
| Eradication completed                  | 23 (92)       |

\(^{3}\)Number represented in parenthesis are percentages. \(^{4}\)Mean (total). **Morbidity** calculated on the total number of treatment sessions. \(^{5}\)In one case, ulcer formation was a cause of severe hemorrhage that required admission and endoscopic sclerosis.
has not been clearly demonstrated of BE, since the efficacy of routine endoscopic follow-up and Western Europe has never exceeded 38 °C. Two cases suffered from temporary dysphagia that resolved without any adjunctive treatment. Ulcer formation was observed in two cases, one of which needed urgent endoscopic sclerosis and re-admission for severe hemorrhage 7 d after the second APC session. The subsequent recovery was uneventful and the patient was discharged after three days without any blood transfusion.

None of the patients was lost to follow-up with an overall mean period of 26.3 mo (median 23 mo, range 9-45 mo). Twenty-one patients (84%) had a follow-up period longer than 12 mo. The patient who underwent incomplete ablation of his 130-mm BE was excluded from the subsequent analysis. The total number of endoscopic follow-up examinations for the remaining 24 patients was 82 with a mean number of 3.4 per patient (median 3 per patient, range 2-6 per patient).

Only one case out of the 24 patients (4.2%) with a complete regression of metaplastic mucosa showed a relapse of BE. This was the first treated patient who recurred one year after the completion of the treatment of a long-segment BE (35 mm). A further APC session was hence performed and, at the moment, there is no evidence of intestinal metaplasia after 33 mo.

**DISCUSSION**

Epidemiological studies clearly indicate that there has been a rising prevalence of adenocarcinoma of the distal esophagus and gastro-esophageal junction not only in United States and Western Europe but also in some Oriental regions. BE is considered the strongest risk factor for esophageal adenocarcinoma, but an association with cardiac cancer is also reported. Long as well as short-segment BE seem to be related to this risk and are hence managed similarly.

The exact hazard assessment has not been calculated yet and the reported increase of 30-125 times is perhaps overestimated.

Many questions remain regarding the best management of BE, since the efficacy of routine endoscopic follow-up has not been clearly demonstrated and medical therapies as well as anti-reflux surgery have not proven to induce regression of BE.

In the attempt to reduce the risk for esophageal adenocarcinoma several endoscopic ablative treatments such as Nd:YAG laser, multipolar electrocoagulation, photodynamic therapy and APC have been proposed in order to induce squamous re-epithelialization of BE. One of the most popular treatments is APC, a technique that involves the application of a high frequency current carried to the tissue through a flow of ionized argon gas that allows to ablate metaplastic mucosa with a limited depth of injury. It has been estimated that the depth of injury necessary to completely eradicate the metaplastic mucosa is 0.6 mm and this is obtained by APC. Many studies analyzed APC with power settings of 30-60 W, but few studies reported higher level of energy (70-90 W) or the 96.9% reported by Schulz who used 90 W. In our experience, 42.5% of the treatment sessions were complicated (66% of the patients). These percentages are similar to literature results, accomplished with usual power settings and are consistent with the 98.6% reported by Pereira-Lima who used 65-70 W and with the 96.9% reported by Schulz who used 90 W.

Theoretically, the use of a powered wattage leads to an increased risk of complications such as stenosis and perforations. In our experience, 42.5% of the treatment sessions were complicated (66% of the patients). These percentages are similar to literature results with a lower number of major complications. As already reported the most frequent complications were retrosternal pain (22.5%) and fever (17.5%). Transient dysphagia as well as ulcer formation was observed in a minority of patients (5%).

In conclusion, APC with high power setting (90 W) showed to be safe and effective. The effects persist at a mean follow-up period of two years with a comparable cost in term of complications with respect to standard
power settings. Long-term follow-up with a greater number of patients is required to assess if ablation of BE can reduce the incidence of malignant progression and if high power setting has a role in it.

REFERENCES

1 Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265: 1287-1289
2 de Manzoni G, Pedrazzani C, Pasini F, Di Leo A, Durante E, Castaldini G, Cordiano C. Results of surgical treatment of adenocarcinoma of the gastric cardia. Ann Thorac Surg 2002; 73: 1035-1040
3 Wijnhoven BP, Siersma PD, Hop WC, van Dekken H, Talus HW. Adenocarcinomas of the distal oesophagus and gastric cardia are one clinical entity. Rotterdam Oesophageal Tumour Study Group. Br J Surg 1999; 86: 529-535
4 Falk GW, Richter JE. Reflux disease and Barrett’s esophagus. Endoscopy 1998; 30: 61-72
5 Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett’s esophagus: a prospective study of 170 patients followed 4.8 years. Am J Gastroenterol 1997; 92: 212-215
6 Morales TG, Sampliner RE. Barrett’s esophagus: update on screening, surveillance, and treatment. Arch Intern Med 1999; 159: 1411-1416
7 Macdonald CE, Wicks AC, Playford RJ. Ten years’ experience of screening patients with Barrett’s oesophagus in a university teaching hospital. Gut 1997; 41: 303-307
8 Parrilla P, Martinez de Haro LF, Ortiz A, Munitiz V, Molina J, Bermejo J, Canteras M. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett’s esophagus. Ann Surg 2003; 237: 291-298
9 Hofstetter WL, Peters JH, DeMeester TR, Hagen JA, DeMeester SR, Crookes PF, Tsai P, Banki F, Bremner CG. Long-term outcome of antireflux surgery in patients with Barrett’s esophagus. Ann Surg 2001; 234: 532-538; discussion 538-539
10 Sharma P, Bhattacharyya A, Garewal HS, Sampliner RE. Durability of new squamous epithelium after endoscopic reversal of Barrett’s esophagus. Gastrointest Endosc 1999; 50: 159-164
11 Pereira-Lima JC, Busnello JV, Saul C, Toneloto EB, Lopes CV, Rynkowski CB, Blaya C. High power setting argon plasma coagulation for the eradication of Barrett’s esophagus. Am J Gastroenterol 2000; 95: 1661-1668
12 Schulz H, Mielhke S, Antos D, Schentke KU, Vieth M, Stolte M, Bayerdorffer E. Ablation of Barrett’s epithelium by endoscopic argon plasma coagulation in combination with high-dose omeprazole. Gastrointest Endosc 2000; 51: 659-663
13 Spechler SJ, Goyal RK. Barrett’s esophagus. N Engl J Med 1986; 315: 362-371
14 Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett’s esophagus. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1998; 93: 1028-1032
15 Dolan K, Sutton R, Walker SJ, Morris AI, Campbell F, Williams EM. New classification of oesophageal and gastric carcinomas derived from changing patterns in epidemiology. Br J Cancer 1999; 80: 834-842
16 Zhang H, Chen SH, Li YM. Epidemiological investigation of oesophageal carcinoma. World J Gastroenterol 2004; 10: 1834-1835
17 Rudolph RE, Vaughan TL, Storer BE, Haggitt RC, Rabinovitch PS, Levine DS, Reid BJ. Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. Ann Intern Med 2000; 132: 612-620
18 Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett’s esophagus? Gastroenterology 2000; 119: 333-338
19 Byrne JP, Armstrong GR, Attwood SE. Restoration of the normal squamous lining in Barrett’s esophagus by argon beam plasma coagulation. Am J Gastroenterol 1998; 93: 1810-1815
20 Wahab PJ, Mulder CJ, den Hartog G, Thies JE. Argon plasma coagulation in flexible gastrointestinal endoscopy: pilot experiences. Endoscopy 1997; 29: 176-181
21 Ackroyd R, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW. Ablation treatment for Barrett oesophagus: what depth of tissue destruction is needed? J Clin Pathol 1999; 52: 509-512
22 Van Laethem JL, Cremer M, Peny MO, Delhaye M, Deviere J. Eradication of Barrett’s mucosa with argon plasma coagulation and acid suppression: immediate and mid term results. Gut 1998; 43: 747-751
23 Vargo JJ. Clinical applications of the argon plasma coagulator. Gastrointest Endosc 2004; 59: 81-88

Science Editor Guo SY  Language Editor Elsevier HK