
Argon Plasma Coagulation in Barrett's Esophagus: The Most Widely Available Technique

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Summary

Argon plasma coagulation (APC) is the most widely available technique for ablation of Barrett's esophagus. When the argon plasma is applied, thermal injury to the epithelium results. The depth of injury is the function of the voltage, the gas flow, and the pressure applied to the probe. A series of 32 patients with high-grade dysplasia were treated with APC with 34 months of follow-up. Dysplasia

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reversed in 78% of patients and cancer prevented in 87%. APC has been used as a primary form of therapy for early invasive cancer, as adjunct to other therapy such as endoscopic mucosal resection.

Key Words: Argon plasma coagulation, High-grade dysplasia, Esophageal, Adenocarcinoma

INTRODUCTION

Argon beam plasma coagulation (ABPC) consists of a high-frequency monopolar probe that delivers electrical energy through an ionized plasma of argon gas to the target tissue causing tissue surface coagulation [1]. The technology of plasma coagulation using argon relies on the physical principle that argon gas (like other gases) can be charged with electrons and the gas particles can carry that charge through the air and release the charge at the point of contact with a conducting surface (see Fig. 1). As a consequence, the resulting flow of electricity has some special and useful properties for use in medical applications. ABPC can be used in open surgery [2] laparoscopic surgery and at flexible endoscopy [3, 4]. For each application there is a dedicated applicator, and for endoscopy this is a flexible tube (carrying the argon gas) with a ceramic tip (for charging the gas molecules with electrons). The fundamental difference between ordinary electrical current and that which flows from argon plasma is the way in which the electrons travel. In a copper-conducting wire electrons flow from one metal atom to another at the speed of light and the amount of electricity that can be transmitted is huge. In a gas plasma the amount of electricity that can be transmitted is limited by the number of gas particles that are traveling across the gap between application and tissue surface, with one electron being delivered for each gas particle. The transfer of electricity can be increased by increasing the gas flow or by increasing the charge up to a point where 100% of the gas molecules are charged. In endoscopic practice argon is delivered between 2 and 6 l/min and the charge ranges from 20 to 80 W of energy [5–7]. As with all electrosurgical techniques an electrical plate is required on the patient to complete the electrical circuit. The application is contact free – with the probe carrying the argon being placed 1–3 mm off the surface of the tissue to be ablated (see Figs. 2 and 3).

An interesting effect of the limited electrical charge carried is the effect of tissue resistance. Once the surface of the tissue has been charred and dries it becomes resistant to the flow of current. The argon gas molecule then holds its electron until it finds a new area of conducting tissue – usually the tissue adjacent to the first area of ablation. The effect then of prolonged application is to widen the surface area of

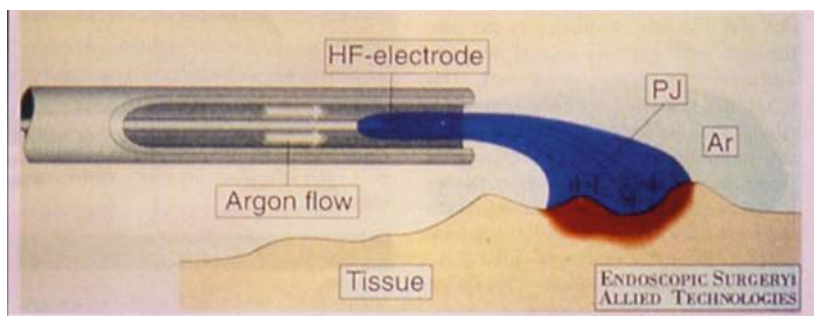


Fig. 1. Physics of the argon beam plasma coagulator.

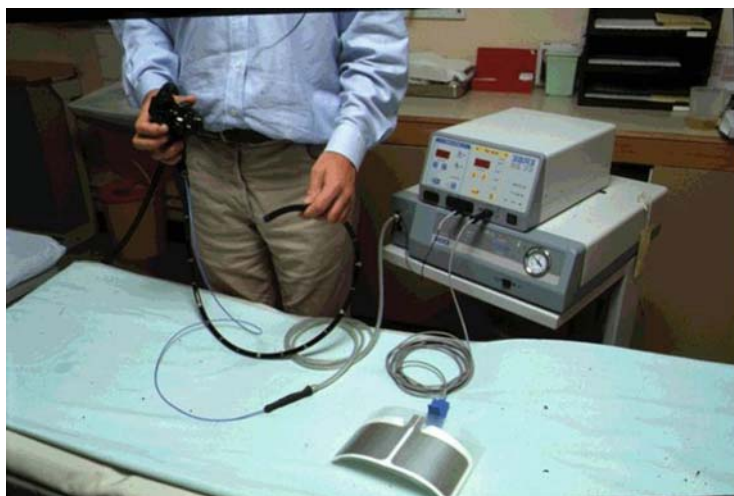


Fig. 2. The endoscopic technology for applying ABPC includes a standard endoscope, a delivery tube for the argon, a diathermy machine with pump, and completion of the electrical circuit with an electrical plate.

injury or ablation, and not to deepen it. The initial depth depends on the current (which depends on the gas flow and wattage) but not the time of application. The longer the application the wider the surface area of injury and this makes argon plasma beams useful for wide surface area ablation as would be required for Barrett's esophagus. When applied in Barrett's esophagus, ABPC generates a white coagulum and is best applied using the technique of endoscope withdrawal while applying the argon which results in longitudinal strips of ablation [8]. (see Fig. 4)

Some workers consider the depth of injury to be less predictable than alternative modalities of ablation. Ackroyd et al. looked at the depth of



Fig. 3. ERBE diathermy with argon gas delivery system.

injury and considered the depth of injury to be 75 mm in their hands [9]. Deeper tissue ablations can be achieved using higher degrees of wattage, and using forced current or the new APC-2 development. The amount of pressure applied to the ABPC probe by the endoscopist can also affect the depth of injury. The problem with insufficient depth in the circumstance of Barrett's ablation has been the concern about the remnant glands that might grow underneath the new squamous lining that grows in place of the ablated Barrett's. In our center all patients grew a macroscopically normal-looking squamous mucosa after 3–6 weeks

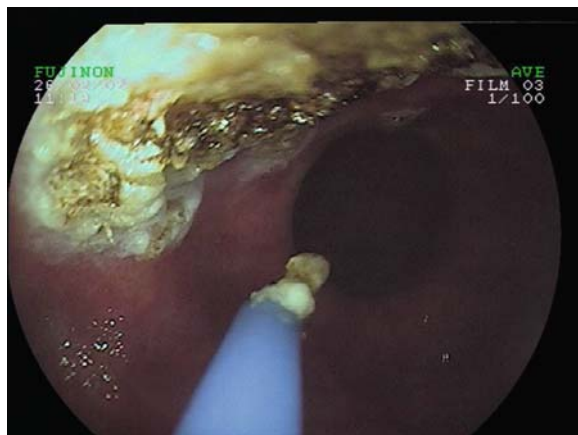


Fig. 4. Appearance of ablated mucosa after ABPC.

and areas of endoscopic gaps could easily be filled in by repeat treatments. On microscopy the squamous epithelium looked normal except for the presence of scattered buried glands of intestinal metaplasia seen in a significant proportion (30%) of the patients. Whether these glands represent a risk for cancer is very difficult to assess and this has not occurred in our series. The progression to cancer after argon beam ablation has been reported [10] where a focus of adenocarcinoma has grown underneath the surface squamous epithelium.

In clinical circumstances where deeper tissue debulking is required – as with tumors of the esophagus or stomach requiring debulking to allow the passage of food, or in the case of stents blocked by ingrowths of tumor, or tumor growing below or above the margins of stent then the electrical properties of the tissue can be manipulated by wetting the surface after each ablation using a saline wash and this allows a repeat application of devitalizing current which will penetrate deeper into the tissue. Argon is easy to use in this situation up to 1-cm deep to the original surface and is therefore an effective way of dealing with some circumstances of obstructing upper gastro-intestinal malignancy. In practice stents are more effective in first-line treatment of dysphagia palliation rather than using the argon beam *de novo*.

The reduced risk of deep injury makes the complication of stricture very rare, (compared to some other technologies such as PDT) and perforation is also very rare. The technology is relatively easy to apply and there are no special precautions above those usually applied for any electrosurgical technique. No special laser eye protection is needed. The availability of argon is wide and the gas relatively cheap. The appli-

cation is usually performed with a sedated patient to allow prolonged endoscopic operating times relative to a simple diagnostic endoscopy but there is no absolute need for sedation or anesthesia because the patient is not usually aware of the ablating burn (Table 1).

Table 1

The advantages of the physical properties of argon beam plasma coagulation

- Requires no special operator precautions (in contrast to laser)
 - Useful after EMR to stop bleeding from the underlying submucosa as well as dealing with the surface epithelium adjacent to the excised mucosal specimen
 - Deep injury to muscle layers does not occur and strictures very uncommon
 - Widely available in operating rooms and endoscopy rooms as it is used for other purposes
 - Relatively cheap to set up
-

The application of argon beam achieves a number of other surgical aims. It is useful for tissue devitalization as in Barrett's epithelium, gastric antral vascular ectasia (GAVE) syndrome, and postpolypectomy therapy. It is also useful for hemostasis of peptic ulcer bleeding [11], angiodysplasia, radiation proctitis, and bleeding after polypectomy.

Sensation of argon ablation: Argon beam ablation is remarkably comfortable from the patient's perspective. Eickhoff et al. have described the lack of direct pain effect with argon in their prospective assessment of the pain sensation in 152 applications [12]. The only exception is in the distal anal canal where skin sensors do pick up pain from argon application. The esophagus does not transmit pain sensation during argon therapy. Indirectly the distension of the stomach (or the colon) creates abdominal tension, pain on breathing, and tachycardia but this is minimized by venting the argon gas – achieved either by a naso-gastric tube placed to vent the gas, or by using a double lumen endoscope and sucking out the gas immediately after filling the organ with argon. If a single channel scope is used the operator must remove the applicator probe from the working channel of the scope to allow the suction the release the accumulated gas. Some patients belch the gas spontaneously but it is more comfortable to releasing it for the patient (using a double lumen scope and suction) before this stage to ensure their comfort. Occasionally, retrosternal pain has occurred after Barrett's ablation [13–15] and this posttreatment discomfort responds to simple analgesics, supplementing the acid suppression with proton

pump inhibitors (PPI) which is essential in patients having ablation of Barrett's esophagus.

There have been occasional reports of Neuromuscular Stimulation (NMS) with argon gas and this was seen in 10% of patients by Eikhoff et al. [12], usually mild in nature but occasionally manifesting as a feeling of tingling or electrical shock as the muscle involved contracts involuntarily. As a result of the minimal effect on comfort we have used argon with simple midazolam sedation which usually allows a patient to remain relaxed for up to 15 or 20 min of application. For wider surface areas of Barrett's epithelium this allows time to deal with up to 5 cm of esophageal length at one sitting (Table 2).

Table 2
Potential complications of argon
beam plasma coagulation

- | |
|------------------------------|
| 1. Subcutaneous emphysema |
| 2. Neuromuscular Stimulation |
| 3. Vagal symptoms |
| 4. Stricture |
| 5. Bleeding |
| 6. Fever |
| 7. Fistula |
| 8. Perforation |

Complications of ABPC include strictures, fever, bleeding, or even more rarely perforation, with one death reported in the literature. Perforation and strictures were associated early during the pilot studies and at the beginning of the learning curve. Strictures were also associated with higher powers of ABPC settings and needed balloon dilatations. Blood transfusion was needed only in one setting due to delayed detachment of a scar tissue. One study reported the presence of pleural effusions and fever which might be related to micro-perforations [14, 16].

TREATMENT OF BARRETT'S ESOPHAGUS WITH ARGON PLASMA COAGULATION

The clinical value of using argon beam ablation was initially assessed in a pilot study of patients with Barrett's esophagus. In 1997, we published a pilot study on the restoration of the normal squamous lining in Barrett's esophagus by ABPC [17]. This study aimed to establish the feasibility of ABPC, in conjunction with control of gastro-esophageal

reflux, to restore a squamous lining. Thirty patients (18 men and 12 women), median age 59 years were recruited. The median length of the Barrett's segment was 5 cm (range 3–17 cm). Control of gastro-esophageal reflux was achieved with antireflux surgery in 5 patients, proton pump inhibitors at standard dose in 20 patients and double dose in 5 patients. A total of 88 ABPC procedures were performed. Twenty-seven patients completed treatment with ABPC. One had to discontinue treatment due to excess co-morbidities (rheumatoid arthritis, chronic respiratory disease). All patients had a reduction in the length of columnar mucosa to <3 cm. Sixteen patients did not have any evidence of macroscopic intestinal metaplasia, nine had a 1-cm segment and two patients who originally had 10- and 17-cm segments had only 2-cm segments. When reflux was controlled adequately a reduction in length of 2–3 cm per treatment session was achieved. All 27 patients who had been followed up for a median of 7 months had histological confirmation of replacement of the columnar lining by squamous epithelium. No underlying intestinal metaplasia was seen in 70% of the patients. In 30% of the patients, squamous epithelium was seen to overlie persistent intestinal type glands. The two patients with high-grade dysplasia (HGD) had histologically confirmed replacement with normal squamous lining with no recurrence of Barrett's either microscopically or macroscopically after 1-year follow-up. Neither of these patients had underlying glandular epithelium beneath the squamous epithelium.

The medium-term follow-up of this pilot study looked at the outcomes after a median of just over 3 years [18]. Fifty-five patients with ablated long-segment BE (more than 3 cm) were followed up for a mean of 38 months. Patients with HGD and low-grade dysplasia (LGD) were included. All patients with dysplasia underwent thorough endoscopic biopsy before ablation to exclude invasive adenocarcinoma and the diagnosis of HGD was confirmed by a second pathologist. Nine patients had LGD, nine others had HGD, and the remainder had metaplasia only. Twelve patients had reflux control by antireflux surgery and the remaining patients had maintenance PPI therapy. No adenocarcinomas developed in any of the patients following ablation. No patient with initial benign metaplasia progressed to dysplasia. All patients with initial dysplasia who completed treatment with ablation therapy had regression of the dysplasia with no subsequent recurrence.

The mean length of the Barrett's epithelium in this series before ablation was 6 cm. Barrett's epithelium was ablated to within 1 cm of the GE junction in all but four patients (mean reduction in length of Barrett's was 5 cm). The mean number of treatment sessions required was three. Sixteen (30%) of the 53 patients have had areas of intestinal metaplasia

detected beneath the neosquamous epithelium on routine histological examination of the biopsies taken from the ablated epithelium.

Two patients had esophageal perforation. Both patients had mediastinal emphysema and chest pain associated with a tachycardia immediately after ABPC treatment. The first underwent drainage via a thoracotomy but died from respiratory failure shortly afterwards. This patient had chronic obstructive airways disease and severe respiratory failure before the procedure, had high-grade dysplasia and would not have been fit for esophagectomy. The second one was treated conservatively with parenteral nutrition and kept nil-by-mouth for 5 days and made an uneventful recovery. The latter patient showed a regrowth of squamous mucosa to within 1 cm of the gastro-esophageal junction. One further patient required readmission to hospital with chest pain following the initial treatment. From these studies we concluded that ABPC was an effective method of ablating wide areas of Barrett's epithelium, with a long-lasting effect at restoring a new squamous lining that persisted as long as effective antireflux therapy was administered. The studies were too small to identify a benefit in relation to cancer prevention.

TREATMENT OF HIGH-GRADE DYSPLASIA IN BARRETT'S WITH ARGON PLASMA COAGULATION

The potential value of ABPC in preventing cancer is easier to measure in a group where the risk of acquiring cancer is much higher than in benign Barrett's. Patients with high-grade dysplasia are either likely to have invasive cancer in up to 50% (if nodularity is present) or develop invasive cancer at a cumulative rate of 10% per annum. This is an ideal group to assess if ABPC confers clinical benefit, especially in patients who are unfit for esophagectomy, or who do not want to submit themselves to this major surgery until invasive cancer has been diagnosed. The study of Van Laethem [10] examined 10 patients (7 men and 3 women) with HGD or in situ adenocarcinoma associated with BE with a mean segment length 5.8 ± 2.7 cm (range 3–12) who were unfit for surgery because of general contraindications or age ($n = 8$) or had clearly refused surgical intervention ($n = 2$) in the period between 1996 and 1999.

Complete eradication of HGD and in situ adenocarcinoma was achieved in 8 out of the 10 patients after a mean of 3.3 ± 1.5 sessions of ABPC. EUS staging in all patients categorized all patients as stage T0N0. One stricture with significant dysphagia occurred after two sessions of ABPC and required balloon dilatation. At endoscopy there were neither visible lesions nor residual Barrett's islands. Complete

histologically confirmed neosquamous re-epithelization was, however, observed in 5/10 patients (50%) only because of residual metaplastic but not dysplastic glands under the new squamous layer. HGD or tumor-in situ areas were completely eradicated in 8/10 patients (80%). One patient with initial HGD showed only partial regression of his lesion, with HGD persisting even 30 months after ABPC treatment; EUS and CT Chest did not reveal any invasive neoplasia. No additional therapy was proposed and the patient was thought to have stable disease. One patient showed a regression from HGD to LGD but a local recurrence consisting of invasive carcinoma was observed after only 3 months of endotherapy, suggesting that the initial staging was probably underestimated. Surgery was again rejected because of this patient's general condition. Additional therapy consisted of PDT but without successful ablation of the neoplastic lesion and the patient died 2 years later from neoplastic disease.

This study demonstrated that ABPC was effective in patients with HGD and superficial adenocarcinoma only in the absence of recognized mucosal lesions i.e., mucosal thickening or nodules, in the absence of abnormalities detected under EUS and in the absence of invasion of muscularis mucosae on biopsy.

The largest series of HGD treated by ABPC comes from Lewis et al. [19] Thirty-two patients with a histological diagnosis of HGD over a 7-year period. All patients underwent ABPC with an ERBE "Beamer 2" electro-surgery unit set at a 2 l/min gas flow and 70 W output. Repeat endoscopies with further ablative therapies were performed at 4- to 8-week intervals. Completion of treatment was regarded when ablation of the total area of HGD was achieved with no histological evidence of HGD on subsequent biopsy. All patients were taking acid suppression using proton pump inhibitors and were followed up with regular gastroscopies at 3, 6, and 12 months postprocedure.

After a mean follow-up period of 34 months (range 3–78 months) with eight patients at 5 years; HGD was seen to resolve in 25 patients (78%) and 22 of these had complete regression of dysplasia to neosquamous esophageal mucosa. Two persisted with HGD and one with LGD after 1 year of follow-up following commencement of treatment. Four patients (13%) progressed on to developing adenocarcinoma in a total follow-up time of 92 patient years. One patient died of an unrelated cause, while the other three continued ABPC treatment to their cancer, one of which had no residual lesion on follow-up endoscopy and biopsy. Three patients went on to subsequent esophageal resection of persistent HGD with good survival. No patients died of esophageal cancer. (see Fig. 5)

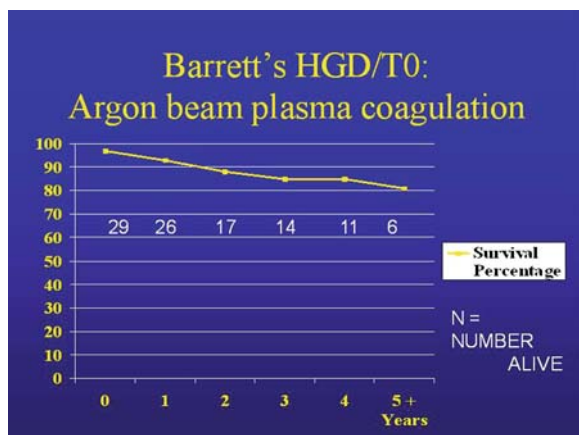


Fig. 5. Kaplan Meyer survival curve after argon beam ablation of patients with high-grade dysplasia in Barrett's esophagus.

The total number of ABPC procedures in this group was 105, with a median of two treatments per patient (range 1–13). Normal diet was restored at 24 h in all patients without dysphagia or odynophagia. No other patients required re-admission, opiate analgesia, or overnight stay. The follow-up data was analyzed and a Kaplan Meyer survival estimate calculated with 95% confidence interval (CI). A further survival curve was created and compared to the standard UK population of comparable age. The Kaplan Meyer survival curve showed that the survival of patients was comparable to the standard United Kingdom population of a similar age over the long term. As a result of this study we consider that ABPC is a safe and effective treatment for HGD in BE (Fig. 4).

A similar series of patients was treated by Ell et al. who described a series of 120 patients in whom the treatment offered initially was endoscopic mucosal resection (EMR) for early cancer or HGD, complemented by argon beam coagulation [20]. Ell discovered cancer progression in 14% of the patients after a mean follow-up of 12 months, compared to 13% after a mean period of 34-month follow-up in the study by Lewis et al. [19]. The morbidity was the same. This demonstrates that in comparison to EMR, ABPC is a realistic procedure that should be considered in patients with HGD who are of questionable fitness for surgery. The main advantage of EMR initially is the ability to examine the pathology in detail. If the patient is fit for surgical resection then this is a useful strategy. If not then simple ablation may be easier and more cost-effective.

TREATMENT OF CANCER IN BARRETT'S WITH ARGON PLASMA COAGULATION

ABPC therapy has significant value in the palliative treatment of invasive adenocarcinoma in patients unfit for resection [21]. ABPC was used in 16 patients with localized tumors who were deemed unfit for surgical resection and achieved a cure in a majority of these, who would otherwise have been left to have progressive cancer without specific therapy. ABPC was also used in the palliation of 18 patients with advanced esophago-gastric cancers for bleeding, obstruction and to prevent obstruction and as well as another 14 patients with dysphagia due to stent overgrowth. Data from these patients were collected prospectively. A total of 110 sessions of ABPC were performed for esophageal and gastric cancer. All 16 patients with early localized cancers were alive, and four at the end of a follow-up period of 21 months were disease free. Four patients, three gastric and one esophageal, had no endoscopic recurrence after the first treatment at 20, 24, 29, and 42 months, respectively. In these patients no histological evidence of tumor recurrence was obtained even after aggressive searching. Seven patients who had biopsy proven residual or recurrent disease after the first ABPC treatment required two to five treatments. Despite these persistent or recurrent tumors, all of them have remained asymptomatic. Three patients with localized carcinoma arising in Barrett's mucosa received more than five treatments. These patients were asymptomatic at 26, 30 and 32 months respectively since the start of treatment. Eighteen patients with advanced cancer underwent a median of one treatment and had a median survival of 5 months after treatment initiation. Eight patients with esophageal cancer had minimal initial dysphagia; local tumor control meant that they did not require stent insertion till late in their disease. In one of these patients with dysphagia and a short stricture ABPC was successful. Luminal patency was not restored in the other two cases and stenting was required shortly after the procedure. Complete control of bleeding was obtained in three of five bleeding gastric cancers, with partial response in the other two, both of whom died within 6 weeks. Two patients with impending gastric outlet obstruction were managed successfully by endoscopic ablation/coagulation and did not obstruct. In 13 of the 14 patients with esophageal stents, ABPC treatment was successful in controlling over- and undergrowth as well as tumor ingrowth through the stent wall. In all these patients, stent patency was restored during the first treatment. Three patients required a second treatment, and one patient required insertion of a second stent. ABPC contributed to the management of 10% of patients with esophago-gastric malignancy managed

in our unit. The reason for such a small proportion of patients to be treated by ABPC is that palliative surgery is the treatment of choice for advanced gastric cancers and stenting is used for dysphagia in advanced esophageal cancer and palliative chemotherapy is an option in a small group of them.

Early cancers in the unfit were the most encouraging to treat in this study since we avoided a major resection and achieved an apparent "cure" in 4 of 14 patients, while the rest of the group remains asymptomatic. Photodynamic therapy [22] and EMR [23] have also been described in the management of early esophago-gastric malignancy, with encouraging initial results for both modalities. However, photodynamic therapy is associated with stricture formation in up to one-third of patients, severe stricture is seen in approximately 10% and photosensitivity occurred for up to 1 month after the procedure. Variable results were obtained with ABPC in patients with advanced cancer. It was useful adjunct in all stented patients with dysphagia due to tumor ingrowth/overgrowth. ABPC also controlled bleeding from tumor, as measured by the requirement for further transfusion in three of five cases; it also controlled it partially in a further two cases. Like Robertson et al. [24] we have found ABPC effective in restoring the esophageal lumen in patients with obstructed stents, although laser therapy has also shown to be effective [25]. Even though occasionally it took 30 min to ablate the diffuse infiltration of the tumor through the wall of the stent, we were able to perform all of the procedures under sedation.

COMPARISONS OF ARGON PLASMA COAGULATION WITH OTHER ABLATIVE TECHNOLOGIES

Argon Versus Multipolar Electro Coagulation (MPEC)

MPEC probes deliver thermal energy through the operator channel of the endoscope and is readily available and inexpensive. It requires multiple treatment sessions to achieve success and seems to be associated with a higher frequency of dysphagia after Barrett's ablation. Kovacs et al. reported an 80% reversal of BE in 27 patients treated via MPEC on PPI; however, 4 had remaining islands with the appearance of BE [26]. Forty-one percent of patients on this study experienced dysphagia, odynophagia, or chest pain lasting up to 4 days. In addition, the success of ablation decreased significantly once the length of BE exceeded 4 cm, such that only 25% had eradication at this length or longer.

Dulai et al. [27] compared argon plasma coagulation with multipolar electrocoagulation for ablation of BE [27]. The selected 52 patients

were randomized. The mean length of Barrett's esophagus was 3.1 cm in the MPEC group versus 4.0 cm in the APC group ($p = 0.03$). The mean number of treatment sessions required for endoscopic ablation was 2.9 for MPEC versus 3.8 for APC ($p = 0.04$) in an intention-to-treat analysis ($p = 0.249$, after adjustment for the difference in length of Barrett's esophagus). The proportion of patients in which ablation was endoscopically achieved proximal to the gastro-esophageal junction was 88% for the MPEC group versus 81% for the APC group ($p = 0.68$) and histologically achieved in 81% for MPEC versus 65% for APC ($p = 0.21$). The mean time required for the first treatment session was 6 min with MPEC versus 10 min with APC ($p = 0.01$) in per protocol analysis. There was no serious adverse event, but transient moderate to severe upper-GI symptoms occurred after MPEC in 8% versus 13% after APC ($p = 0.64$). The study concluded that there were no statistically significant differences between ablation of Barrett's esophagus with pantoprazole and MPEC and endoscopic and histologic ablation with pantoprazole and APC.

Argon Versus Laser

Various lasers have been used in gastroenterology for mucosal ablation, including the neodymium (Nd):yttrium-aluminum-garnet (YAG) laser, the potassium titanyl phosphate (KTP) laser, the KTP:YAG laser, and the argon laser. The ablative depth of injury depends on the type of laser and is about 3–4 mm with the Nd:YAG laser [28, 29]. In 1999, Gossner et al. treated 10 patients with BE, of which 4 had HGD. This group described a "complete response" in all patients, with a mean follow-up of 10.6 months. Subsquamous SIM (specialized intraepithelial neoplasia) was reported in 20% although no other complications were documented. The longest outcome after Barrett's ablation comes from the laser ablations of Salo, in Finland who has demonstrated a long-lasting effect of ablation in restoring a squamous lining to the lower esophagus of patient with Barrett's esophagus [30, 31]. The esophageal stricture rate is higher than with MPEC [32] and thus significantly higher than with argon. The special precautions required for laser, the higher stricture rate and the learning curve for application make laser an unlikely long-term modality for the future ablation of Barrett's esophagus.

Argon Versus Photodynamic Therapy

The administration of a chemical photosensitizer gives PDT its effectiveness while at the same time causing sufficient side effect to make PDT unlikely to be the surviving technology of choice for ablation

of Barrett's. The accumulation of protoporphyrin in the stroma causes significant stricturing effect in the submucosal layers after laser light application [33]. The only approved photosensitizer in North America, Europe, and Japan is porfimer sodium (Photofrin® [Axcan Pharma Inc, Birmingham, AL]). Photofrin® is given intravenously, results in deep injury and is associated with significant morbidity [34]. The drug remains in the skin for up to 2 months and can result in severe sunburn if standard sunlight precautions are not observed. Alternative topical chemical sensitizers such as 5-aminolevulinic acid, m-tetra (hydroxyphenyl) chlorine and benzoporphyrin derivative monoacid ring. A result in more-superficial injury and because of their lack of deep penetration are unlikely to be effective against high-grade dysplasia [35].

Overholt et al. [22] have published extensively regarding their experience of using PDT in 103 patients, most of whom had HGD. The mean follow-up in this group is over 4 years. Of the 65 patients with HGD, 78% had their HGD eliminated. On the basis of an intention-to-treat analysis, 54% had no residual BE. This is very similar in percentage terms to the outcome of the 50 patients treated with argon beam by Lewis et al. [19]. The overall stricture rate for patients treated with PDT was 30%, but for those who required more than one PDT treatment it was 50%. Other side effects reported with PDT include chest pain, dysphagia, odynophagia, pleural effusions, and atrial fibrillation [22]. Subsquamous, nondysplastic SIM occurred in 4.9% of patients, but more importantly 3 patients (4.6%) developed subsquamous adenocarcinoma. The occurrence of subsquamous SIM is reported in virtually all studies using PDT: in detailed pathology studies the prevalence is reported to be as high as 51.5% [36].

Argon Versus Endoscopic Mucosal Resection or Mucosectomy

It is most likely that the use of argon in the future will be to complement the use of endoscopic mucosal resection rather than compete with it. Endoscopic mucosal resection (EMR) or more correctly Endoscopic Resection (ER), removes mucosa and submucosa by resecting through the middle or deeper part of the submucosa. Unlike the other ablative techniques, a tissue specimen is obtained that can be evaluated for staging and histology. Ell et al. prospectively evaluated the role of EMR in 64 patients with BE: 61 with early cancer and 3 with HGD. The patients were divided into two groups. Group A had lesions ≤ 2 cm or macroscopic type I, IIA, IIB, IIC lesions ≤ 1 cm; well-differentiated or moderately differentiated adenocarcinoma or HGD; and lesions limited to the mucosa. Group B had lesions >2 cm limited to the

mucosa and/or macroscopically type III lesions; poorly differentiated adenocarcinoma; or infiltration of the submucosa. All patients were treated with an intravenous PPI infusion for 48 h. Complete local remission was achieved in 97% of the patients in group A and in 59% of those in group B. Recurrent metachronous carcinomas occurred in 17% of patients in group A and 14% of patients in group B during a mean follow-up of 12 months [20].

Seewald et al. described ablation of BE in 12 patients after circumferential EMR. Five patients had multifocal lesions and seven had none. The median number of EMR sessions was 2.5 with an average number of 5 snare resections per EMR session. During a 9 month follow-up there was no recurrence of BE or malignancy; however, minor bleeding occurred during 4 of the 31 EMR sessions, and 2 of the 12 patients developed strictures that required dilation [37]. The use of ABPC is comparable to EMR in relation to the number of treatment sessions, patient outcomes, and recovery but is easier to perform and has a shorter learning curve.

Argon Versus Radiofrequency Ablation (RFA)

There is little comparative study between the argon and the new balloon-based, bipolar radiofrequency ablation (Stellartech Research Coagulation System, manufactured for BARRx, Inc, Sunnyvale, CA). Radiofrequency ablation requires the use of sizing balloons to determine the inner diameter of the targeted portion of the esophagus. This is followed by placement of a balloon-based electrode with a 3-cm-long treatment area that incorporates tightly spaced, bipolar electrodes that alternate in polarity. The electrode is then attached to a radiofrequency generator and a preselected amount of energy is delivered in less than 1 s at 350 W [35]. In a recent study settings of 10 or 12 J/cm² at 260 or 350 W, respectively, were used, achieving full-thickness ablation of epithelium without direct injury to the submucosa.

Pouw et al. studied the effect of RFA on BE with early neoplasia [38]. Patients who had BE \leq 12 cm with early neoplasia were included in this study. Visible lesions were endoscopically resected. A balloon-based catheter was used for circumferential ablation and an endoscope-based catheter for focal ablation. Ablation was repeated every 2 months until the entire Barrett epithelium was endoscopically and histologically eradicated. Forty-four patients were included (35 men, median age 68 years, median BE 7 cm). Thirty-one patients first underwent endoscopic resection [early cancer ($n = 16$), high-grade dysplasia ($n = 12$), low-grade dysplasia ($n = 3$)]. The worst histology remaining after resection was high-grade ($n = 32$), low-grade ($n = 10$), or no ($n = 2$) dysplasia.

After ablation, complete histological eradication of all dysplasia and intestinal metaplasia was achieved in 43 patients (98%). Complications following ablation were mucosal laceration at resection site ($n = 3$) and transient dysphagia ($n = 4$). After 21 months of follow-up (interquartile range 10–27), no dysplasia had recurred. The study concluded that RFA, with or without prior endoscopic resection for visible abnormalities, is effective and safe in eradicating BE and associated neoplasia [38]. It appears from the above results that RFA is likely to be successful in ablating Barrett's but it requires dedicated technology and many centers may already have argon beam technology available in their endoscopy suites and further studies including randomized controlled trials will be needed to allow us to use such specialized instruments and technology, just for the purpose of Barrett's ablation.

Antireflux Therapy as Adjunct to Ablative Therapy

It is now universally agreed that GERD is the strongest risk factor for development of BE and in any patient with Barrett's or adenocarcinoma of the esophagus treatment with full-dose proton pump inhibitor is important to complement the ABPC and facilitate healing by minimizing acid reflux. In our experience there are a few patients who having avoided resection for HGD in their 40s or 50s then requested anti reflux surgery for their reflux control and this has been successful in selected cases. PPI therapy in conjunction with ABPC is the most effective method of restoring a squamous lining. Although acid suppression effectively controls symptoms of GERD and can also lead to the appearance of squamous islands within columnar-lined epithelium, it does not cause regression of the overall length of BE [39]. Sharma and co-workers have similarly demonstrated that despite the increase in number of squamous islands there was no overall change in length of the BE over an average of 5.7 years follow-up [40]. Sampliner et al. have shown convincingly that treatment with high-dose proton pump inhibitors does not markedly decrease Barrett's metaplasia [41].

The Problem of Buried Barret's Glands Underneath the Neosquamous Lining

The occurrence of subsquamous SIM postablation occurs with all modalities. It occurs in 20–30% of argon-treated Barrett's esophagus [42, 43]. The significance of this finding may not be as great as first considered. The genetic structure of the buried glands and the neosquamous mucosa is a stable phenotype not linked with markers of potential malignancy [43]. The development of intramucosal adenocarcinoma arising under neosquamous epithelium, however, has been reported

despite apparent macroscopic and microscopic clearance [10, 44] but these are isolated cases, and analysis of survival curves, particularly in the treatment of high-grade dysplasia, shows excellent results in cancer prevention [19].

CONCLUSION

The Place of ABPC Ablation in Benign Barrett's Esophagus

ABPC is of unproven value for nondysplastic Barrett's and in low-grade dysplasia. The concerns raised about buried glands and the persistent risk of cancer also discourage many therapeutic endoscopists from adopting argon in this situation. It is possible that the radiofrequency Halo device may have a safety profile that makes ablation in nondysplastic Barrett's worth considering.

The Place of ABPC Ablation in High-Grade Dysplasia

The very low invasive cancer development after treatment of high-grade dysplasia with argon encourages its use to avoid esophagectomy, especially in the unfit. The combination of EMR (to carefully check for evidence of invasive cancer) and argon seems the safest and most effective way of managing HGD with the best quality of life and long-term outcome. Good-quality reflux control is essential to deal with the underlying driving force of malignant change in the esophagus.

The Place of ABPC Ablation of Barrett's in Malignancy

The place of ablation of Barrett's esophagus in advanced malignancy relates only to the palliative treatment of the tumor and thus as an adjunct to stenting (unblocking or dealing with growth above or below the margins of a stent) or dealing with bleeding in a palliative setting.

The lessons learned from the introduction and development of argon ablation of Barrett's have informed and assisted the wider development of ablation technologies. This will support assessments of new technologies, particularly that of the radiofrequency device currently under clinical trials. Meanwhile, units that have argon available may find it as a useful adjunct to EMR and an option in the treatment of HGD or early cancer in patients unfit for surgical resection or those who wish to avoid the detrimental effects of esophagectomy on their quality of life.

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