Review Article

Novel endoscopic therapies in Barrett's esophagus: narrative review

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Abstract: In the last decade, the management of Barrett's esophagus (BE) has been broadly updated. Among the endoscopic ablative techniques, radiofrequency ablation (RFA) is highly effective and currently represents the standard of care for the eradication of BE after endoscopic resection of visible dysplastic lesions. Newly, some thermal and non-thermal endoscopic modalities have been investigated for treating BE, also as first-line in case of dysplasia. Data on the safety and efficacy of cryotherapy, hybrid argon plasma coagulation (APC) and EndoRotor resection have been recently reported in the literature. We aimed to review current evidence on novel endoscopic technologies emerging with the indication of treating BE, and to discuss their limitations, advantages and potential implementation in routine clinical practice as well as in clinical trials. A PubMed search was conducted up to August 2020 to identify relevant studies. Efficacy rates, in terms of dysplasia and metaplasia eradication, assessed for the emerging thermal and non-thermal endoscopic modalities are promising and similar to RFA. According to the present data, post-treatment stricture occurrence appears to be low especially after Hybrid-APC and EndoRotor. The current evidence on novel endoscopic techniques needs further endorsement by randomized clinical trials and meta-analysis. The comparison of these modalities to the traditional care by the ongoing clinical trials, particularly in naïve patients is highly warranted.

Keywords: Barrett's esophagus (BE); cryotherapy; hybrid argon plasma coagulation (hybrid-APC); outcomes; EndoRotor

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Introduction

Barrett's esophagus (BE) identifies the replacement of the esophageal squamous mucosa with a metaplastic specialized intestinal columnar type epithelium, extending at least one centimeter above the gastroesophageal junction (1,2). It is thought to occur as a consequence of chronic injury, likely mediated by acidic reflux from the stomach.

The significance of BE lies in being the strongest risk factor and precursor of esophageal adenocarcinoma (EAC), arising as the end result of a stepwise transformation from metaplasia to dysplasia (low grade and high grade) to adenocarcinoma. Dysplasia is defined as neoplastic epithelium that is confined to the basement membrane and the use of the descriptors "low grade" or "high grade" is based upon the severity of architectural distortion, seen histologically. Advancing age, increasing Barrett's segment length, and endoscopic irregularities of the mucosa (e.g., nodules, ulcers) are risk factors for dysplasia (1,2).

The risk of EAC is proportional to the degree of

Table 1 Current recommendations for surveillance and treatment of Barrett's esophagus

BE	Surveillance interval	Treatment
Non-dysplastic BE		
≥1, ≤3 cm	5 years	Not indicated
≥3, ≤10 cm	3 years	Not indicated
Dysplastic BE		
LGD visible lesion	–	Endoscopic resection (EMR, ESD)
LGD without visible lesions	Re-evaluation after 6 months, if confirmed treatment is indicated	Endoscopic ablation (i.e., RFA)
HGD visible lesion	–	Endoscopic resection (EMR, ESD)
HGD without visible lesions	Re-biopsy, if confirmed treatment is indicated	Endoscopic ablation (i.e., RFA)

LGD, low-grade dysplasia; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; RFA, radiofrequency ablation.

dysplasia, and survival in EAC is stage-dependent. Patients with non-dysplastic (ND) BE or low-grade dysplasia (LGD) were enrolled in a prospective Dutch multicenter study that aimed to identify predisposing factors for the onset of EAC on BE and it emerged that the risk of developing EAC is predominantly determined by the presence of LGD. In fact, patients with ND Barrett esophagus and no other risk factors (esophagitis, BE longer >10 cm and BE >10 years) had a risk of malignant progression of <1%, whereas those with LGD and at least one other risk factor had a risk of developing high-grade dysplasia (HGD) or EAC of 18–40% (3).

Afterwards, another Dutch multi-center study confirmed that the presence of LGD in BE is associated with a markedly increased risk of malignant progression. In particular, it has been reported that, for patients with BE with confirmed LGD, the risk of HGD/EAC was 9.1% per patient-year, while patients with ND BE had a malignant progression risk of 0.6% and 0.9 % for patient-year, respectively (4).

Based on this evidence, which has been confirmed in other studies (5-7), medical societies currently recommend no treatment but regular endoscopic surveillance at intervals of 3 to 5 years for ND BE with the aim of identifying suspicious areas for dysplasia and acquiring histological confirmation. (8,9). The currently available international guidelines recommend ablative treatment in the case of LGD or HGD on random biopsies of BE without visible lesions aiming to reduce the risk of progression towards EAC (8,9). *Table 1* summarizes current recommendations for surveillance and treatment of BE.

In addition, ablative treatment is also recommended in the case of residual BE after endoscopic removal [by endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)] of visible dysplastic lesions, with the objective of preventing recurrence and/or metachronous neoplastic lesions (8,9).

Among ablative treatments for BE, at present, radiofrequency ablation (RFA) is the most widely available and used technique. A specific catheter applies the radiofrequency, which heats intracellular water to induce cell necrosis of the target mucosa. Catheters can have a balloon or a pad on the tip and are available in different sizes. Some RFA generators deliver power in a "stepwise" algorithm that provides lower starting power that increases (i.e., from 5 to 10 W/min) gradually. As concerns technical aspects, there are several FDA-approved RFA devices on the market: the main differences are the power of the generator, the technique used to maximize treatment volumes, size of the needles, and the electrical parameters that can be monitored. The rate of efficacy of RFA, in terms of complete eradication of dysplasia (CE-D), varies from 90% to 95% (10-14); while minimally lower rates are observed with respect to complete eradication of intestinal metaplasia (CE-IM) (10-14). The most common adverse event (AE) reported is esophageal stricture formation, followed by bleeding, retrosternal chest pain and perforation. Stricture formation after RFA occurs in around 5% of the patients and often requires subsequent endoscopic dilatation (14). Cases of buried glands with evidence of sub-squamous IM on surveillance biopsy have also been reported in a few studies (10-14).

To date, RFA is not able to guarantee a complete ablation success and a certain amount of patients, estimated to be

around 10%, does not reach the CE-IM (10-14).

Recently, further endoscopic techniques that employ thermic energy to remove the metaplastic tissue, such as argon plasma coagulation (APC) and cryotherapy, and others, such as hot avulsion and EndoRotor, are emerging as alternative treatments. Their efficacy with the particular indication of treating BE is under investigation and, beyond treatment success, the potential risk of post-therapeutic AEs, in particular stenosis, is yet to be evaluated.

We aim to provide a review of the current evidence about the novel endoscopic technologies in the treatment of BE, focusing on new ablative techniques, and to discuss their limitations, advantages and potential implementation.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aoe-20-76).

Methods

A PubMed search was conducted up to August 2020 to identify relevant studies about novel ablation techniques for BE.

The search for studies of relevance was performed using the following text words and corresponding Medical Subject Heading/Entree terms when possible: "Barrett's esophagus", "argon plasma coagulation", "hybrid-argon plasma coagulation", "treatment of Barrett's esophagus", "Endorotor", "hot avulsion", "cryotherapy". Studies reporting data animal models were not also considered for data presentation and discussion. Studies not published in the English language were excluded. All papers presented in our review have been published between 2008 and 2019.

Discussion

Hybrid-APC (H-APC)

APC is an alternative ablative technique for residual BE and is effective in reducing neoplasia recurrences, compared to surveillance alone over a follow-up of 2 years, as demonstrated by randomized clinical trials (RCTs) (15). However, the development of post-treatment strictures requiring endoscopic dilatation is a relevant major AE, occurring in about 9% of patients (15). Furthermore, after APC, as well as after RFA, a certain rate of buried Barrett's glands that remain below the newly formed squamous epithelium has been reported (16). These glands are associated with a potential risk of neoplastic progression (16).

H-APC is a new arising technique that involves submucosal fluid injection (e.g., 0.9% sodium chloride solution, with or without supplementation of epinephrine) prior to performing APC. It was first reported by Norton *et al.* and Fujishiro *et al.* as an alternative technique for BE ablation, aiming to reduce the depth of thermal injury (17-19). Usually, the technique involves a high pressure needleless submucosal injection of saline via a built-in water jet within the APC catheter itself. In an initial randomized ex-vivo study evaluating the tissue effect after H-APC, the coagulation depth was halved compared with standard APC and no thermal injury to the proper muscle layer was observed (20).

So far, literature data and studies on H-APC, both as a primary modality and after RFA failure, are mostly derived from small cohorts. In their pilot study, Manner *et al.* included patients treated with H-APC who had a residual non-neoplastic Barrett's segment of at least 1 cm after endoscopic resection of early neoplasia. The authors assessed a macroscopically complete remission of 96% and a histological eradication of dysplasia of 78%, after a median of 3.5 sessions of H-APC. Furthermore, in this study the rate of stricture formation was estimated at 2%, and buried Barrett's glands were observed in 7% of patients. Minor AEs of H-APC were observed in 22% of patients (e.g., retrosternal pressure/pain, heartburn and odynophagia) (21). Effectiveness and safety of H-APC has been also investigated prospectively in a small cohort in Russia. Twelve patients (mean age 54 years; range, 40–68 years) with BE (median length C1/M2) with LGD were selected for H-APC. Complete macroscopic BE ablation was achieved after a mean of 3.4 treatment sessions; the rate of histologically complete Barrett's ablation was 100% after a mean follow-up of 4.5 months. No perforations, no uncontrollable bleeding, or strictures occurred (22).

In a US series of patients with BE refractory after Barrx RFA, the investigators performed H-APC, reaching a complete eradication in 5 of 6 patients (23). None of the patients developed immediate (e.g., bleeding and perforation) or late complications, such as dysphagia or strictures (23). From the above-mentioned preliminary data, H-APC appears safe and effective in the treatment of RFA refractory Barrett's mucosa (23,24).

In a more recent cohort pilot study, the efficacy of H-APC in the treatment of BE was evaluated both in naïve and previously treated patients (59% prior RFA, 18% EMR, 12% cryotherapy and 35% naive) (25). The treatment

protocol was different from previous reports as they used an EMR-cap to allow stability, better visibility and a more precise focal distance for APC application. Moreover, after submucosal injection, APC was applied to all visible Barrett's areas; coagulated tissue was removed with the cap and water jet and then a second application of APC at a lower energy setting was carried out. In the short-term follow-up, 17 of 22 patients (77%) achieved CE-IM and there were two treatment-related strictures (9%) that required a single balloon dilation with no other complications (25). The investigators concluded that H-APC showed efficacy, tolerability and a safety profile similar to RFA ablation (25). Taking into account the differences in terms of expense between H-APC and other modalities for Barrett's ablation, this technique may represent a favorable cost-effective profile (25).

Currently, in Germany and in the Netherlands, a multi-center study is evaluating if the safety profile and the promising effectiveness of H-APC observed in the pilot study of Manner *et al.* can be confirmed. An abstract of the first 3 months follow-up data has been presented at United European Gastroenterology Week 2018. Patients diagnosed with visible lesions and/or cancer underwent a combination of resection (EMR/ESD) plus a maximum of five H-APC sessions, while ablation was performed exclusively on patients with neoplastic BE (LGIN/HGIN) without visible lesions. After a 3-month follow-up 126 of 164 included patients (109 males, mean age 64 years) have completed therapy, and short-term eradication rates were 92% [116/126]. Some immediate complications occurred, such as bleeding in five patients and one case of perforation treated conservatively by clipping. There were six reported cases of strictures that required a single balloon dilation. Despite a relatively short follow-up, H-APC appears to be feasible and safe and may have a similar effectiveness and safety profile as RFA ablation with a short-term efficacy of around 90% (26).

The final results of this large prospective study are pending; in addition, RCTs directly comparing H-APC and RFA are required to validate these emerging data. In this respect, a US multi-center RCT (clinicaltrials.gov NCT03621319) is in progress in patients with BE after EMR of visible lesions, with the aim of comparing H-APC and RFA in terms of rate of stricture-free eradication of dysplastic BE at 12 months follow-up, post- operative pain (7 days after procedure) and cost-effectiveness.

To date, a direct comparison with RFA is available only for standard APC in patients with BE and HGD or EAC: this study has reported similar dysplasia and BE clearance at one-year of follow-up (CE-D 83.8% *vs.* 79.4% and CE-IM 48.3% *vs.* 55.8%, respectively). As concerns adverse effects, stricture rate was documented by 8.3% and by 8.1% for RFA and APC, respectively, while, buried BE glands were observed in 6.1% and 13.3% of the patients, treated with RFA and APC, respectively. Finally, the study authors performed a cost analysis of these two procedures and estimated RFA-costs to be over $27,000 per case more than APC (RFA mean cost $33,170 *vs.* APC mean cost $5,678) (27).

Cryotherapy

As an alternative ablative technique, or in case of BE refractory to RFA, cryotherapy represents one of the modalities of choice. In contrast to RFA, which directly applies heat, cryotherapy induces necrosis of the target tissue through the employment of a cryogen. The application of cryogens causes multiple cycles of freezing and thawing, inducing immediate cell injury by intracellular and extracellular ice formation. Delayed effects include microvascular injury, with subsequent anoxia and stimulation of cytotoxic T-cells leading to apoptosis and cell death (28).

Currently, the available cryogens used in clinical practice are liquid nitrogen (LN) (TrueFreeze Cryospray, CSA Medical, Lexington, Massachusetts, USA) and nitrous oxide (NO) (Coldplay CryoBalloon Focal Ablation System, C2 Therapeutics, Redwood City, California, USA). In terms of costs, cryotherapy is comparable to RFA. Moreover the cryotherapy delivery systems are a rather easy technology for physicians: 5 to 10 treatment sessions allow for a physician to become comfortable performing this ablative treatment.

In 2016 the production of cryotherapy platforms that used liquid carbon dioxide as a cryogen (Polar wand, GI Supply, Camp Hill, PA, USA) ceased; therefore data related to this technique will not be reported in this review.

Liquid nitrogen

LN is delivered through a catheter passing through the operative channel of the endoscope. The LN rapidly expands into a gas and freezes tissues at temperatures down to –196 ℃. The site is frozen for a total of two cycles that last for 20 seconds each, with 45 seconds of pauses between each cycle, which allows for re-cooling. The non-contact delivery enables the ablation of areas with an irregular

surface such as nodules, masses and plaques.

Data about the efficacy of LN-cryospray (LNC)-based ablation have been endorsed by meta-analysis, both for first-line treatment and rescue treatment after failure of RFA. A recent systematic review with meta-analysis including 12 studies (n=386) assessed a pooled rate of CE-IM at 56.5% (95% CI: 48.5–64.2%) (29), while the estimated pooled CE-D rate and complete eradication of HGD (CE-HGD) were 83.5% (95% CI: 78.3–87.7%) and 86.5% (95% CI: 64.4–95.8%), respectively (29). These outcomes were achieved both in naïve and non-naïve patients, with slightly higher rates in the subgroup of naïve patients. Cryotherapy has been also demonstrated to be effective as a rescue therapy in patients with previous failure of RFA (CE-IM 58.4%, 95% CI: 47.2–68.8%) (29). In this analysis the pooled rate of AEs was calculated at 4.7% (95% CI: 1.6–12.9%), with esophageal stricture and chest pain the most reported AEs, confirming the safety profile of this technique (29).

Currently, few retrospective studies have been published regarding the long-term clinical success and the safety of cryotherapy.

Gosain *et al.* retrospectively observed 100% [32/32] of CE-D and 84.4% [27/32] of CE-IM at 2-year follow-up in patients treated with LNC every 8 weeks until CE-HGD and CE-IM. At a median last follow-up of 37 months (range, 24–57 months), the authors assessed CE-D and CE-IM at 97% and 81%, respectively (30). In this study, complete eradication of both metaplasia and dysplasia were similar to those estimated for a 2-year follow-up after RFA (30).

Moreover, in a further retrospective single-center study, the efficacy of LNC was evaluated in terms of CE-HGD, dysplasia and intestinal metaplasia at 5-year follow-up in patients with BE-HGD/intramucosal adenocarcinoma. Among the 40 patients included, complete CE-HGD, CE-D and CE-IM were seen in 93%, 88% and 75% of the patients respectively. Incidence rates of recurrent intestinal metaplasia, dysplasia and HGD/EAC per person-year of follow-up after initial CE-IM were 12.2%, 4.0% and 1.4%, each, and most of the recurrences were observed immediately below the neo squamocolumnar junction. These results underline the efficacy of LNC in the treatment of BE over the long-term, which is a fundamental feature for the management of eventual recurrences (31).

Robust evidence from clinical trials and meta-analysis has established RFA as a safe and highly effective endoscopic ablation for BE, with the consequent need to compare any other ablative therapy with RFA.

At present, data are sparse and do not allow for establishing cryo-ablative modalities as inferior or superior to RFA, especially in treatment-naive patients. A head-to-head prospective trial aiming to directly compare RFA and cryotherapy is warranted. To date, an RCT (clinicaltrials.gov NCT01961778) comparing Barrx RFA *vs.* LNC (TrueFreeze Cryospray) in patients with HGD/EAC BE is ongoing and is investigating both treatment success (defined as CE-IM) and safety.

Among the available data, a retrospective analysis including 154 patients (73 RFA and 81 cryotherapy), comparing cryotherapy (LN cryotherapy) and RFA for Barrett's dysplasia or IMC was conducted by Thota *et al.* The authors assessed a superior efficacy of RFA since, on multivariate analysis, patients in the RFA group had a threefold increased odd of having CE-IM than those who underwent LN cryotherapy [odds ratio (OR) 2.9, 95% confidence interval (CI): 1.4–6.0, P=0.004]. However, in this study CE-D were comparable in the two treatment groups (OR 1.7, 95% CI: 0.66–4.3, P=0.28). A possible selection bias might explain these results, as the patients treated with cryotherapy were older and less likely to have undergone EMR (32).

Finally, a possible technical advantage of cryotherapy that may find a specific indication in the future is the ease of use in a dilated esophagus.

Nitrous oxide

Newly arising as an implementation of the traditional cryotherapy technique, the cryoballoon focal ablation system employs NO; the cryogen contacts the balloon resulting in the freezing of the targeted mucosa.

The balloon catheter, measuring 3.7 mm, is passed through the operative channel of the endoscope and attached to a handle that contains a cartridge with liquid NO. When pressing the trigger, the balloon is insufflated, and the cryogen is delivered to the ablation site for 10 seconds, cooling the tissue at temperatures up to –85 ℃. Looking through the transparent balloon enables the treatment of multiple visible BE areas with targeted focal ablations that can be, in this way, delivered under endoscopic guidance with a distal to proximal progression from the gastro-esophageal junction.

Results from a recent clinical trial, including both treatment-naïve and previously ablated patients with BE dysplasia, showed an overall CE-D and CE-IM rates at 1-year of 95% and 88%, respectively, with no difference between patients with or without prior endoscopic ablation (33).

Importantly, no esophageal perforations and no progression to esophageal cancer were observed in this study; while 9.7% of the patients developed strictures and 2% had minor bleeding (33). These results suggest cryoballoon focal ablation as a comparable modality in terms of efficacy and safety with LCN, with even higher CE-D and CE-IM rates.

As concerns the current research on CryoBallon, the European Multicenter EURO-COLDPLAY study (clinicalTrials.gov NCT02514525) is prospectively evaluating the efficacy and safety of the Focal C2 CryoBalloon™ Ablation System in untreated patients with BE-related neoplasia.

Hot avulsion

Hot avulsion with hot biopsy forceps is a technique that has been proposed to resect Barrett esophagus in case of residual focal areas <1 cm, not suspected for dysplasia, following previous endoscopic treatment for dysplasia or intramucosal cancer.

In the only published retrospective study, data from 35 patients harboring 124 residual areas were analyzed with a mean follow-up of 17.4 months. All patients achieved complete eradication of residual focal BE and only one of the patients required a second hot avulsion treatment. A limitation of this technique observed in the study was that, although hot avulsion provided samples in all cases, due to a cautery artifact, a proper microscopic assessment of dysplasia was possible only in 20.2% of the cases (34).

Further studies are required before this technique can be incorporated into routine clinical practice.

EndoRotor

An additional promising device for refractory BE is the EndoRotor (Endoscopic Resection System, Interscope Medical, Inc., Whitinsville, MA, USA), originally intended for the endoscopic treatment of colonic adenomatous lesions and, to date, FDA-approved for removal of remaining tissue of the margins after EMR. EndoRotor consists of an automated, exclusively mechanical, resection system: the absence of thermal delivery is a potential strength in terms of lowering the occurrence of post-treatment strictures. The main components of the EndoRotor system are a console with the motor drive, the peristaltic pump and the vacuum regulation, a catheter with the cutting device that is activated by the foot pedal, and a dedicated trap for specimen collection.

This technique has been investigated by Knabe *et al.* in their pilot study, in which 14 patients with remaining Barrett's mucosa after ER of early mucosal adenocarcinoma (pT1a) underwent treatment with EndoRotor (35). All the patients were successfully treated after a 3-month follow-up; the authors observed intra-procedural bleeding requiring endoscopic hemostasis in 42.9% of the cases (6/14 patients) (35). In this pilot study, of note, no post-therapeutic stenosis occurred within a 3-month follow-up (35). From these preliminary data, the non-thermal resection with EndoRotor appears to have a higher bleeding rate compared with RFA, where it is estimated to be around 1% (36). Randomized multi-center studies are required to support the indications of this technique in the treatment of BE and to compare it to the currently established ablative modalities.

To date, an ongoing prospective, randomized trial (clinicaltrials.gov NCT03364114) aims to compare the safety and performance of the EndoRotor mucosal resection system with continued ablative therapy in dysplastic BE refractory after 3 failed RFAs. The primary outcome will be the complete removal of Barrett's metaplasia after no more than two treatments. The results of this study are avidly awaited.

Conclusions

Endoscopic ablative therapy is indicated after effective endoscopic resection of any visible lesion of BE histologically confirmed with dysplasia or early cancer. The ablative treatment aims to eradicate non-visible dysplasia in these patients, reducing the risk of recurrence of dysplasia and the occurrence of cancer (8,10). At present, RFA represents the gold standard as ablative therapy, being the most validated with endorsed evidence from meta-analysis (13,14).

This review highlights the novel emerging endoscopic therapies that appear very promising, both in the treatment of residual Barrett's after ER of visible lesions and in case of dysplastic BE without visible lesions. *Table 2* summarizes the results of the studies presented in our review.

Among the potential advantages of these techniques over RFA, especially regarding H-APC and EndoRotor, there is a reduced risk of post-therapeutic strictures. As from the preliminary data exposed in this review, the rate of stricture formation has been estimated at 2% and at 0% for H-APC and EndoRotor, respectively (20,21,35). Still, it appears clear that these data need confirmation. Concerning EndoRotor, such a low risk of post-procedural stricture might be related to a short surface of removed

Table 2 Evidence on novel endoscopic treatments for Barrett's esophagus

Reference	Study design	Technique	Efficacy	Notes
Manner H, *et al.* (21)	Prospective (N=50)	Hybrid-APC	After a median of 3.5 H-APC sessions, 96% of the patients achieved macroscopically complete remission. Histopathological remission observed in 39/50 patients (78%)	–
Mohan BP, *et al.* (29)	Systematic review with meta-analysis (N=386)	Liquid nitrogen cryospray	Pooled CE-IM was 56.5%; pooled CE-D was 83.5%; pooled CE-HGD was 86.5% In patients with RFA-failure, pooled CE-IM was 58.4%, Pooled CE-D was 81.9%	Estimated rate of AEs was 4.7%; LNC can be considered as rescue option after RFA failure
Gosain S, *et al.* (30)	Retrospective (N=32)	Liquid nitrogen cryospray	At 2-years follow-up, CE-HGD was 100% [32/32], CE-IM was 84% [27/32]	–
Ramay FH, *et al.* (31)	Retrospective (N=40)	Liquid nitrogen cryospray	At 5 years follow-up, CE-HGD was 93% [37/40], CE-D was 88% [35/40], CE-IM was 75% [30/40]	Patients with precious endoscopic resection were included
Canto MI, *et al.* (33)	Prospective (N=41)	Cryoballoon focal ablation	Overall 1-year CE-D and CE-IM rates were assessed by 95% and 88%, respectively	Patients with or without prior ablation included; previous EMR for nodular lesions included
Knabe M, *et al.* (35)	Prospective (N=14)	EndoRotor	100% of treatment success	Treatment of residual Barrett's after EMR; intra-procedural bleeding occurred 37.5%; no post-therapeutic stenosis observed

CE-IM, complete eradication of intestinal metaplasia; CE-D, complete eradication of dysplasia; CE-HGD, complete eradication of high-grade dysplasia; EMR, endoscopic mucosal resection; APC, argon plasma coagulation.

Barrett's mucosa: the application of EndoRotor to a whole circumference would necessarily increase the strictures' occurrence rate. The proper length of safely removable tissue through EndoRotor requires further investigation. Favorable characteristics of the novel endoscopic treatments presented in our review are exposed in *Table 3*. Notably, post-procedural pain is unremarkable after cryotherapy (29,30) but no data are available with this respect for EndoRotor or hot avulsion.

A relevant limitation of conventional thermal ablation therapy (i.e., RFA and APC/H-APC) is the progression to dysplasia/neoplasia of the buried glands: non-thermal techniques such as EndoRotor theoretically carry a lower risk of buried dysplasia, that needs dedicated inquiry.

Beyond safety, the proper indication of any of these endoscopic modalities needs further clarification; if the efficacy rates assessed for naïve patients will be confirmed by future data, the algorithm of treatment will anticipate less expensive techniques (i.e., cryotherapy or H-APC) and those that imply the possibility of an histological assessment (i.e., hot avulsion or EndoRotor). Of critical importance is that the efficacy and safety of these new treatments in previously treated patients (e.g., prior RFA) needs to be thoroughly evaluated: this would allow physicians and medical societies to establish the most correct sequence of treatments and customize it depending on thermal/non-thermal techniques and on the possibility of an histological assessment, which is unavoidable in high-risk or highly pre-treated patients.

Notably, in the future, some of the presented endoscopic techniques might be designated as treatment of choice in particular cases such as short-segment BE, residual BE area on squamocolumnar junction, need for focal "touch-up" treatments, or, in case of a dilated esophagus: conditions, that are extremely challenging to be approached with RFA alone.

Prospective randomized trials properly designed to compare RFA with novel ablative techniques are currently ongoing with warranted results, in order to confirm the efficacy and safety of these treatments.

Table 3 Arguments in favor of novel endoscopic treatments for Barrett's esophagus against RFA

Technique	Advantages	Disadvantages
Hybrid-APC	Short-term efficacy around 90% (26)	Higher buried glans rate than RFA (to be confirmed by ongoing RCTs)
	Reduced costs ($25,000 per case less than RFA) (27)	
	Lower post-treatment stricture rate	
Cryotherapy		
Liquid nitrogen	Low/absent post-procedural pain	Longer learning curve (5 to 10 sessions); comparable costs
	Applicable in dilated esophagus	
	Effective as rescue therapy in patients with previous failure of RFA	
	Long-term CE-D and CE-IM of 97% and 81%, respectively (30)	
	Safety (pooled AEs rate by 4.7% (29)	
Nitrous oxide	CE-D and CE-IM rates of 95% and 88% at 1 year, respectively (33)	–
	Absents or extremely low risk of perforations or progression to cancer	
EndoRotor	Absent or extremely risk of post-therapeutic strictures (0%) (35)	Very limited data
	Histologic assessment	
Hot avulsion	Histologic assessment	Proper microscopic assessment is possible in a minority of cases
		Proposed for Barrett's areas <1 cm
		Very limited data

RFA, radiofrequency ablation; APC, argon plasma coagulation; CE-D, complete eradication of dysplasia; CE-IM, complete eradication of intestinal metaplasia; AEs, adverse events.

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References

1. Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med 2014;371:836-45.
2. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology 2011;140:e18-52; quiz e13.
3. Sikkema M, Looman CW, Steyerberg EW, et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. Am J Gastroenterol 2011;106:1231-8.
4. Duits LC, Phoa KN, Curvers WL, et al. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. Gut 2015;64:700-6.
5. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. JAMA 2013;310:627-36.
6. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut 2012;61:970-6.
7. Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc 2008;67:394-8.
8. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointest Endosc (ESGE) Position Statement. Endoscopy 2017;49:191-8.
9. ASGE Standards of Practice Committee; Qumseya B, Sultan S, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointest Endosc 2019;90:335-359.e2.
10. Standards of Practice Committee; Wani S, Qumseya B, et al. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. Gastrointest Endosc 2018;87:907-931.e9.
11. Guthikonda A, Cotton CC, Madanick RD, et al. Clinical outcomes following recurrence of intestinal metaplasia after successful treatment of Barrett's esophagus with radiofrequency ablation. Am J Gastroenterol 2017;112:87-94.
12. Gupta M, Iyer PG, Lutzke L, et al. Recurrence of esophageal intestinal metaplasia after endoscopic mucosal resection and radiofrequency ablation of Barrett's esophagus: results from a US multicenter consortium. Gastroenterology 2013;145:79-86.e1.
13. Pandey G, Mulla M, Lewis WG, et al. Systematic review and meta-analysis of the effectiveness of radiofrequency ablation in low grade dysplastic Barrett's esophagus. Endoscopy 2018;50:953-60.
14. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:1245-55.
15. Manner H, Rabenstein T, Pech O, et al. Ablation of residual Barrett's epithelium after endoscopic resection: a randomized long-term follow-up study of argon plasma coagulation vs. surveillance (APE study). Endoscopy 2014;46:6-12.
16. Rees JR, Lao-Sirieix P, Wong A, et al. Treatment for Barrett's esophagus. Cochrane Database Syst Rev 2010;1:CD004060.
17. Norton ID, Wang L, Levine SA, et al. Efficacy of colonic submucosal saline solution injection for the reduction of iatrogenic thermal injury. Gastrointest Endosc 2002;56:95-9.
18. Fujishiro M, Yahagi N, Nakamura M, et al Submucosal injection of normal saline may prevent tissue damage from argon plasma coagulation: an experimental study using resected porcine esophagus, stomach, and colon. Surg Laparosc Endosc Percutan Tech 2006;16:307-11.
19. Fujishiro M, Kodashima S, Ono S, et al Submucosal injection of normal saline can prevent unexpected deep thermal injury of argon plasma coagulation in the in vivo porcine stomach. Gut Liver 2008;2:95-8.
20. Manner H, Neugebauer A, Scharpf M, et al. The tissue effect of argon-plasma coagulation with prior submucosal injection (Hybrid-APC) versus standard APC: A randomized ex-vivo study. United European Gastroenterol J 2014;2:383-90.
21. Manner H, May A, Kouti I, et al. Efficacy and Safety of Hybrid-APC for the Ablation of Barrett's Esophagus. Surg Endosc 2016;30:1364-70.
22. Kashin SV, Kuvaev R, Nadezhin AS, et al. Mo2016 The New Hybrid Argon Plasma Coagulation (Hybrid APC) for Endoscopic Ablation of Barrett's Esophagus (BE): the Results of the Pilot Trial. Gastrointest Endosc 2016;83:AB495.

23. Arshad HMS, Ahsan N, Aldridge T, et al. Safety and Efficacy of Endoscopic Hybrid-APC for Management of Barrett's Esophagus. Gastrointest Endosc 2017;85:AB562-AB563.
24. Arshad HMS, Ahsan N, Aldridge T, et al. Tu1161 Safety and Efficacy of Endoscopic Hybridapc for Management of Barrett's Esophagus. Gastrointest Endosc 2017;85:AB562-AB563.
25. Shimizu T, Samarasena J, Fortinsky KJ, et al. Efficacy, tolerance, and safety of Hybrid Argon Plasma Coagulation for the treatment of Barrett's Esophagus: A single center pilot study. Gastroinest Endosc 2018;87:AB292.
26. Rösch T, Manner H, May A, et al. 1151 Multicenter Feasibility Study of Combined Injection and Argon Plasma Coagulation (Hybrid-APC) in the Ablation Therapy of Neoplastic Barrett Esophagus. Gastrointest Endosc 2018;85:AB154.
27. Peerally MF, Bhandari P, Ragunath K, et al. Radiofrequency ablation compared with argon plasma coagulation after endoscopic resection of high-grade dysplasia or stage T1 adenocarcinoma in Barrett's esophagus: a randomized pilot study (BRIDE). Gastrointest Endosc 2019;89:680-9.
28. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. Cryobiology 1998;37:171-86.
29. Mohan BP, Krishnamoorthi R, Ponnada S, et al. Liquid Nitrogen Spray Cryotherapy in Treatment of Barrett's Esophagus, where do we stand? A Systematic Review and Meta-Analysis. Dis Esophagus 2019;32:doy130.
30. Gosain S, Mercer K, Twaddell WS, et al. Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. Gastrointest Endosc 2013;78:260-5.
31. Ramay FH, Cui Q, Greenwald BD. Outcomes after liquid nitrogen spray cryotherapy in Barrett's esophagus-associated high-grade dysplasia and intramucosal adenocarcinoma: 5-year follow-up. Gastrointest Endosc 2017;86:626-32.
32. Thota PN, Arora Z, Dumot JA, et al. Cryotherapy and Radiofrequency Ablation for Eradication of Barrett's Esophagus with Dysplasia or Intramucosal Cancer. Dig Dis Sci 2018;63:1311-9.
33. Canto MI, Shaheen NJ, Almario JA, et al. Multifocal nitrous oxide cryoballoon ablation with or without EMR for treatment of neoplastic Barrett's esophagus (with video). Gastrointest Endosc 2018;88:438-446.e2.
34. Aranda-Hernández J, Shimamura Y, Grin A, et al. Hot avulsion may be effective as salvage treatment for focal Barrett's esophagus remaining after endoscopic therapy for dysplasia or early cancer: a preliminary study. Endoscopy 2018;50:8-13.
35. Knabe M, Blößer S, Wetzka J, et al. Non-thermal ablation of non-neoplastic Barrett's esophagus with the novel EndoRotor® resection device. United European Gastroenterol J 2018;6:678-83.
36. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: A randomized clinical trial. JAMA 2014;311:1209-17.

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