SYSTEMATIC REVIEW AND META-ANALYSIS

Clin Endosc 2023;56:38-49
https://doi.org/10.5946/ce.2022.179
pISSN: 2234-2400 • eISSN: 2234-2443

Open Access

CLINICAL ENDOSCOPY

# Hybrid argon plasma coagulation in Barrett's esophagus: a systematic review and meta-analysis

**Sagar N. Shah[1], Nabil El Hage Chehade[2], Amirali Tavangar[3], Alyssa Choi[3], Marc Monachese[3], Kenneth J. Chang[3], Jason B. Samarasena[3]**

[1]Department of Internal Medicine, Los Angeles Medical Center, University of California, Los Angeles, CA; [2]Division of Internal Medicine, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH; [3]H.H. Chao Comprehensive Digestive Disease Center and Division of Gastroenterology/Hepatology, University of California, Irvine, CA, USA

**Background/Aims:** Patients with Barrett's esophagus are at increased risk of developing esophageal adenocarcinoma. Endoscopic therapies aim to eradicate dysplastic and metaplastic tissues. Hybrid argon plasma coagulation (hybrid-APC) utilizes submucosal fluid injection to create a protective cushion prior to ablation that shields the submucosa from injury. We performed a pooled meta-analysis to evaluate the safety and efficacy of hybrid-APC.

**Methods:** We conducted a systematic search of major electronic databases in April 2022. Studies that included patients with dysplastic and non-dysplastic Barrett's esophagus undergoing treatment with hybrid-APC were eligible for inclusion. Outcome measures included complete remission of intestinal metaplasia (CR-IM), stricture formation, serious adverse events, and number of sessions necessary to achieve CR-IM.

**Results:** Overall pooled CR-IM rate for patients undergoing hybrid-APC was 90.8% (95% confidence interval [CI], 0.872–0.939; $I^2$=0%). Pooled stricture rate was 2.0% (95% CI, 0.005–0.042; $I^2$=0%). Overall serious adverse event rate was 2.7% (95% CI, 0.007–0.055; $I^2$=0%).

**Conclusions:** Results of the current meta-analysis suggest that hybrid-APC is associated with high rates of CR-IM and a favorable safety profile. Interpretation of these results is limited by the inclusion of retrospective cohort and case series data. Randomized controlled trials that standardize treatment and outcome evaluation protocols are necessary to understand how this treatment option is comparable to the current standards of care.

**Keywords:** Barrett esophagus; Esophageal stenosis; Hybrid argon plasma coagulation

## INTRODUCTION

Barrett's esophagus (BE) is a premalignant condition characterized by metaplastic transformation of stratified squamous to columnar epithelium.[1,2] Patients with BE are at increased risk of developing esophageal adenocarcinoma (EAC).[3] Transformation of the epithelium occurs in a predictable fashion: first to metaplasia, then to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and ultimately EAC. Management of BE is centered on endoscopic therapies aimed at eradicating dysplasia, and ideally metaplasia. Therapy typically combines resection of nodular or visible lesions, followed by ablation of the remaining flat neoplasia.[4-6] Several modalities exist for BE ablation, including argon plasma coagulation (APC), electrocoagulation, photodynamic therapy, cryotherapy, and radiofrequency ablation (RFA). All modalities aim to destroy the BE mucosa, allowing neosquamous epithelial formation. These modalities are limited

**Received:** July 2, 2022 **Revised:** July 28, 2022 **Accepted:** August 1, 2022

**Correspondence:** Jason B. Samarasena
H.H. Chao Comprehensive Digestive Disease Center and Division of Gastroenterology/Hepatology, University of California, Irvine 333 City Blvd West Suite 400, Orange, CA 92868, USA
**E-mail:** jsamaras@hs.uci.edu



 

by the risk of stricture formation, buried gland formation, and need for multiple sessions to achieve remission.[7] Occurrence of these adverse events is associated with the extent of submucosal injury secondary to ablative therapies.[8-10] The ideal therapeutic modality maximizes destruction of metaplastic epithelium down to the muscularis mucosa, while minimizing damage to the underlying submucosa. A new technique called hybrid-APC utilizes submucosal fluid injection to create a protective cushion prior to ablation and shield the submucosa from injury.[11] This technique may allow for the ablation of a larger area to a greater tissue depth with a lower risk of stricture formation and adverse events.

We performed a pooled meta-analysis to evaluate the efficacy and safety of hybrid-APC for the treatment of dysplastic and non-dysplastic BE. Specifically, we evaluated the proportion of patients achieving complete remission of intestinal metaplasia (CR-IM), frequency of stricture formation and adverse event rates, and number of treatment sessions necessary to achieve CR-IM.

## METHODS

### Data sources and searches

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.[12] The study protocol was registered and published in the PROSPERO database. In April 2022, we conducted a systematic search of electronic databases, including PubMed/Medline, Embase, Web of Science, and the Cochrane Library with the assistance of a librarian. Detailed search strategies for each database are included in the Supplementary Material 1. The reference lists of the included studies and relevant systematic reviews were reviewed to supplement the initial literature search. Two investigators (SNS and NEHC) independently reviewed the titles and abstracts to screen studies for relevance to the research question and eligibility for inclusion. Following the initial screening, the remaining studies were reviewed to ensure the availability of the necessary data. Discrepancies or disagreements were resolved through discussion and review by a third author (JBS) until a consensus was reached.

### Study selection

Studies involving human participants with BE who underwent treatment with hybrid-APC were eligible for inclusion. Patients could have non-dysplastic BE and any degree of dysplastic BE or EAC at the baseline. Prior treatment with other ablative modalities prior to hybrid-APC was acceptable. Treatment with hybrid-APC consisted of a submucosal saline injection using a high-pressure water jet system, followed by application of pulsed APC. Power settings were not considered when determining eligibility. Studies must have followed patients until they were evaluated for CR-IM and reported the rates of CR-IM and stricture formation to be eligible for inclusion. Randomized controlled trials (with hybrid-APC arms), cohort studies, and case series were eligible for inclusion. Given that hybrid-APC is a relatively new technique, studies published in abstract form were eligible for inclusion given that they provided sufficient information to meet other inclusion criteria. Single-case studies or video cases were not eligible for inclusion. Only studies written in English were included.

### Outcomes

After nodular lesions are resected, ablative therapies are directed at eradicating the remaining metaplastic and dysplastic tissues. Therefore, we evaluated CR-IM rates. CR-IM was defined as the absence of intestinal metaplasia on biopsy. CR-IM also requires the absence of dysplasia. Tissue damage caused by ablative therapy can lead to stricture formation. We evaluated stricture formation rate, which is defined as the proportion of patients with clinically significant strictures requiring endoscopic therapy (i.e., balloon dilation). Serious adverse events (SAE) were defined as those requiring further interventions, including perforation, stricture, and major bleeding.[13] Finally, we evaluated the number of sessions necessary to achieve CR-IM. When studies did not report the standard deviation for the average number of sessions necessary to achieve CR-IM, the standard deviations were estimated using the range according to the following formula: (maximum-minimum)/4.[14]

### Data extraction and quality assessment

Study-level data and study characteristics were extracted independently by two authors (SNS and NEHC). Quality assessment of the included studies was performed using the Newcastle-Ottawa scale (NOS).[15] For cohort studies, the scale consists of nine questions, each scored up to one point. A total score of 7–9, 4–6, or <4 was suggestive of high quality, high risk of bias, or very high risk of bias, respectively. A modified NOS previously described in the literature was used to evaluate non-comparative, single-arm studies in domains pertinent to this systematic

review.[16,17] The modified scale excludes items related to comparability and adjustment; the scale for non-comparative studies focuses on selection, representativeness, and ascertainment of exposure and outcome. The modified NOS consists of five items requiring a 'yes' or 'no' response. Studies were deemed 'good' quality when all five criteria are fulfilled, 'moderate' quality when four criteria are fulfilled, and 'poor' when three or less criteria are fulfilled. Two authors independently assessed the methodological quality (SNS and NEHC) with disagreements settled by discussion, including a third author (JBS).

### Statistical analysis

We performed a pooled proportion meta-analysis to calculate pooled outcomes. Individual study rates were transformed using the Freeman-Tukey double-arcsine transformation. Pooled proportions were calculated as the back-transformation of the weighted mean (weighting by inverse variance) of the transformed proportions in a restricted maximum likelihood random-effects meta-analysis.[18,19] Heterogeneity was assessed using the $I^2$ statistic. Values greater than 50% or p-values greater than 0.05 were deemed to have significant heterogeneity. In the presence of statistically significant heterogeneity, a leave-one-out sensitivity analysis was performed to evaluate the effects of outlier studies. Furthermore, subgroup analysis by study quality was performed to evaluate the association between methodological quality and outcome. Publication bias was assessed via visual inspection of funnel plots and Egger's regression.[20,21] All statistical analyses were performed in RStudio 2021.09.1 (R Foundation, Vienna, Austria) using metafor and meta packages.[22,23]

## RESULTS

### Study selection

The initial search strategy yielded a total of 67 results. After removing 29 duplicate entries, 38 studies were finally screened. Twelve studies were excluded based on title and abstract screening. A total of 26 records were retrieved. Full texts were accessible for all records sought for retrieval. One study was excluded for overlapping patient cohorts[24] and four studies were excluded due to lack of sufficient outcome data despite relevance to the current systematic review.[25-28] The remaining review articles or case reports were excluded. Seven studies were included in the final analysis.[29-35] The study selection process is summarized in Figure 1.

### Study details

A total of 344 patients across seven studies underwent hybrid-APC treatment for BE (N range=11 to 146). All but one of the included studies were single-arm observational studies. Linn et al.[33] performed a retrospective cohort study using risk factor-matched patients undergoing RFA as a comparator group. Only two studies explicitly stated that consecutively eligible patients were enrolled in the study.[29,30] Four studies included patients with pre-treatment non-dysplastic BE, LGD, HGD and EAC.[30,32,33,35] Kashin et al.[34] treated only patients with LGD. Two studies did not report pre-treatment dysplasia.[29,31]

Four studies specified that all patients were prescribed post-procedural acid-suppression therapy with proton pump inhibitors.[29,30,34,35] None of the included studies reported adherence to acid-suppression therapy. Importantly, only Manner et al.[31] gave an explicit definition for 'stricture'. The other studies reported stricture formation rates without providing a specific definition for this outcome.

Four studies evaluated CR-IM three months after complete macroscopic ablation of BE.[29-32] Kashin et al.[34] evaluated CR-IM at one and three months following macroscopic ablation, and Shimizu et al.[35] evaluated CR-IM at least three months fol-

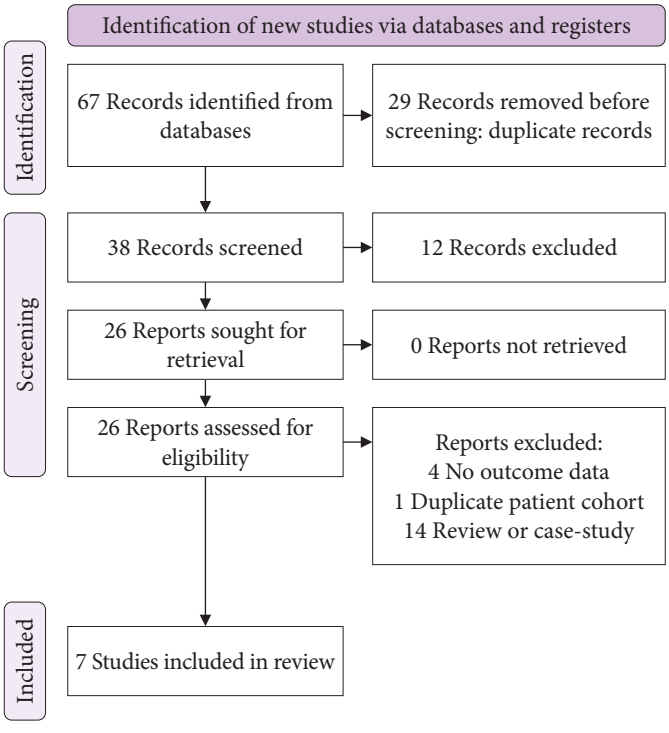


**Fig. 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for study selection process.

lowing completion of therapy. The beginning of the follow-up period and timing of CR-IM evaluation were not specified in the study conducted by Linn et al.[33] Only two studies specified a limit to the number of therapies before classification as a 'treatment failure'.[30,32] Two studies included details regarding buried glands on biopsy results.[31,34] The included studies were performed in the United States, Netherlands, Germany, Russia, and Australia. Prague classifications of pre-treatment Barrett's and hybrid-APC settings are presented in Table 1.[29,30,32-36] The settings were comparable across all studies that reported detailed treatment settings.

### Study quality assessment

Six single-arm observational studies were assessed for bias using the modified NOS for case series (Supplementary Table 1).[15,16,29,30,32-36] Four studies were deemed 'moderate' quality[31,32,34,35] and two studies were deemed 'good' quality.[29,30] Four studies failed to specify how patients were selected for inclusion in their study and whether these patients were consecutively eligible.[31,32,34,35] All studies specified that biopsies were performed prior to treatment to ensure that included patients had dysplastic or non-dysplastic BE. Rösch et al.[32] had a significant portion of the initially enrolled cohort that had not yet completed therapy at the time of abstract publication. All the included studies included data on CR-IM rates and stricture formation.

The study performed by Linn et al.[33] was the only included cohort study and was assessed using the NOS (Supplementary Table 2). The study was deemed 'good' quality, although there was no description of how the treated cohort was derived from the population and it was unclear if pathologists were blinded to the treatment modality.

### Outcomes

All seven studies reported CR-IM and stricture formation rates. Rösch et al.[32] did not report data for adverse events other than stricture formation. Linn et al.[33] did not report the number of sessions necessary to achieve CR-IM. The study-level outcomes are summarized in Table 2.[29,30,32-36] The overall pooled CR-IM rate for patients undergoing hybrid-APC was 90.8% (95% confidence interval [CI], 0.872–0.939; $I^2$=0%) (Fig. 2A). No asymmetry was noted upon visual inspection of the associated funnel plot (Fig. 2B). The pooled stricture rate was 2.0% (95% CI, 0.005–0.042; $I^2$=0%) (Fig. 3A). No asymmetry was noted upon visual inspection of the associated funnel plot (Fig. 3B). The overall SAE rate was 2.7% (95% CI, 0.007–0.055; $I^2$=0%) (Fig. 4A). No asymmetry was noted upon visual inspection of the associated funnel plot (Fig. 4B). There were only two SAE besides stricture formation both reported by Knabe et al.[30]: one patient experienced treatment-related bleeding requiring clipping and one patient experienced perforation requiring clipping. The average mean number of sessions required to achieve CR-IM was 2.59 (95% CI, 2.24–2.94; $I^2$=70%) (Fig. 5A). No asymmetry was noted upon visual inspection of the associated funnel plot (Fig. 5B). For all analyses, no publication bias was detected using Egger's regression (Table 3).

### Evaluation of heterogeneity

Given the presence of statistically significant heterogeneity in the analysis of the average number of sessions required to achieve CR-IM, prespecified leave-one-out sensitivity and subgroup analyses by study quality were performed. With removal of the study performed by Shimizu et al.,[35] the average number of sessions necessary to achieve CR-IM was 2.65 (95% CI, 2.33–2.97; $I^2$=52%).With removal of the study performed by Manner et al.,[31] the average number of sessions necessary to achieve CR-IM was 2.49 (95% CI, 2.24–2.74; $I^2$=61%). There was no statistically significant difference between 'good' and 'moderate' quality studies ($Q_M$=0.18; $p$=0.67).

Unplanned meta-regression analysis of the average Prague classification and year of study publication was performed to further investigate the sources of heterogeneity in the number of sessions needed to achieve CR-IM. There was a correlation between average Prague M length and number of sessions required to achieve CR-IM ($Q_M$=4.70; $R^2$=62%; $p$=0.03) (Fig. 6). There was no correlation between the average Prague C length and number of sessions required to achieve CR-IM ($Q_M$=1.46; $p$=0.23) (Supplementary Fig. 1). There was no correlation between the date of study publication and number of sessions necessary to achieve CR-IM ($Q_M$=0.02; $p$<0.89) (Supplementary Fig. 2).

## DISCUSSION

Given the increasing incidence of EAC, improvements in BE management are of paramount importance. Endoscopic therapies play a significant role in the treatment of BE-related neoplasia, and the innovation and evaluation of new therapeutic modalities impacts a large portion of the population. This study is the first systematic review and meta-analysis to evaluate the

**Table 1.** Select study characteristics

| Study | Year | Study location | Patient (*n*) | Pre-treatment Prague | Pre-treatment dysplasia | Timing of CR-IM evaluation | Treatment failure definition | Buried glands (%) | Post-procedure PPI | Hybrid-APC settings |
|---|---|---|---|---|---|---|---|---|---|---|
| Kashin et al.[34] | 2016 | Russia | 12 | C1, M2 | 100% LGD | 1 and 3 mo after complete macroscopic ablation of BE | None | 0 | Esomeprazole 80 mg/day | Pulsed APC, effect 2, 60 W |
| Manner et al.[31] | 2016 | Germany | 46 | C1.9, M5 | - | 3 mo after complete macroscopic ablation of BE | None | 7 | - | Pulsed APC, effect 2, 60 W; second pass: pulsed APC, effect 2, 40 W |
| Rösch et al.[32] | 2017 | Germany, Netherlands | 80 | - | 0% BE, 21.3% LGD, 15% HGD, 63.8% EAC, 0% indefinite | 3 mo after complete macroscopic ablation of BE | >5 sessions without histologic eradication of IM | - | - | No details provided |
| Shimizu et al.[35] | 2021 | USA | 22 | C0.73, M1.99 | 36.3% BE, 36.3% LGD, 18.1% HGD, 4.5% EAC, 9.1% indefinite | At least 3 mo after complete macroscopic ablation of BE | None | - | Unspecified PPI, 40 mg bid | Pulsed APC, effect 2, 60 W; second pass: pulsed APC, effect 2, 40 W |
| Linn et al.[33] | 2020 | USA | 27 | - | 39% BE, 15% LGD, 8% HGD, 33% no BE, 5% indefinite | 3-6 mo follow-up; does not specify when 'follow-up' period begins | None | - | - | No details provided |
| Staudenmann et al.[29] | 2021 | Australia | 11 | C3.1, M4.5 | - | 3 mo after complete macroscopic ablation of BE | None | - | Pantoprazole 40 mg bid | Pulsed APC, effect 2, 60–70 W |
| Knabe et al.[30] | 2022 | Germany, Netherlands | 146 | C2.09, M4.41 | 67.1% BE, 18.6% LGD, 7.9% HGD, 2.9%, no BE 1.4% | 3 mo after complete macroscopic ablation of BE | >5 sessions without histologic eradication of IM | - | Unspecified PPI, 40 mg bid or tid for 2–3 weeks, followed by 40 mg daily or bid | First pass: 60–70 W; second pass: 40–50 W; additional details not provided |

CR-IM, complete remission of intestinal metaplasia; PPI, proton pump inhibitor; APC, argon plasma coagulation; C, circumferential extent; M, maximal extents; LGD, low-grade dysplasia; BE, Barrett's esophagus; W, Watt; HGD, high-grade dysplasia; EAC, esophageal adenocarcinoma; bid, twice daily; tid, three times daily; -, unavailable.

safety and efficacy of this treatment modality. Hybrid-APC appears to be an effective treatment for eradicating intestinal metaplasia. Pooled stricture and SAE rates in the included studies were low.

Although APC was one of the earliest therapies developed for the treatment of BE, its use is limited by the risk of perforation and stricture formation. While these risks could be mitigated by reducing power settings (thereby reducing the coagulation depth), lower power settings diminished the efficacy of ablative treatments. Previous *ex-vivo* trials have demonstrated that creation of a 'fluid cushion' prior to APC reduces the coagulation depth by half compared to conventional APC using the same wattage and reduces the frequency of submucosal coagulation.[36] Similar results have been demonstrated *in-vivo*, albeit for ablative therapies in the colon.[37] These results provide the theoretical basis for hopes that hybrid-APC may reduce the risk of stricture formation. Indeed, the pooled stricture rate for the included studies was considerably lower than previously reported stricture rates of 5.6% and 6% using RFA.[38,39]

Although the pooled CR-IM rate for hybrid-APC surpassed those reported in previous meta-analyses of RFA while producing less stricture formation,[38-41] the inclusion of retrospective studies and case series may overestimate effectiveness and underestimate true adverse event rates. Notably, only two studies specified that consecutively eligible patients were enrolled.[29,30] Moreover, one prospective study included in the analysis had a stricture rate of 4.1% compared to the pooled rate of 2.0%.[30] The inclusion of retrospective studies and case series, which are more prone to selection bias, lowers the overall quality of

**Table 2.** Summary of study-level outcomes data

| Study | *n* | CR-IM | Stricture | SAE | Session |
|---|---|---|---|---|---|
| Kashin et al.,[34] 2016 | 12 | 12 (100) | 0 (0) | 0 (0) | 2.5 |
| Manner et al.,[31] 2016 | 46 | 39 (84.8) | 1 (2.2) | 1 (2.2) | 3.5 |
| Rösch et al.,[32] 2017 | 80 | 74 (92.5) | 2 (2.5) | - | 2.5 |
| Shimizu et al.,[35] 2021 | 22 | 19 (86.4) | 2 (9.1) | 2 (9.1) | 1.2 |
| Linn et al.,[33] 2020 | 27 | 24 (88.9) | 0 (0) | 0 (0) | - |
| Staudenmann et al.,[29] 2021 | 11 | 11 (100) | 0 (0) | 0 (0) | 2.7 |
| Knabe et al.,[30] 2022 | 146 | 129 (88.4) | 6 (4.1) | 8 (5.5) | 2.96 |

Values are presented as number only or number (%).
CR-IM, complete remission of intestinal metaplasia; SAE, serious adverse event; -, unavailable.

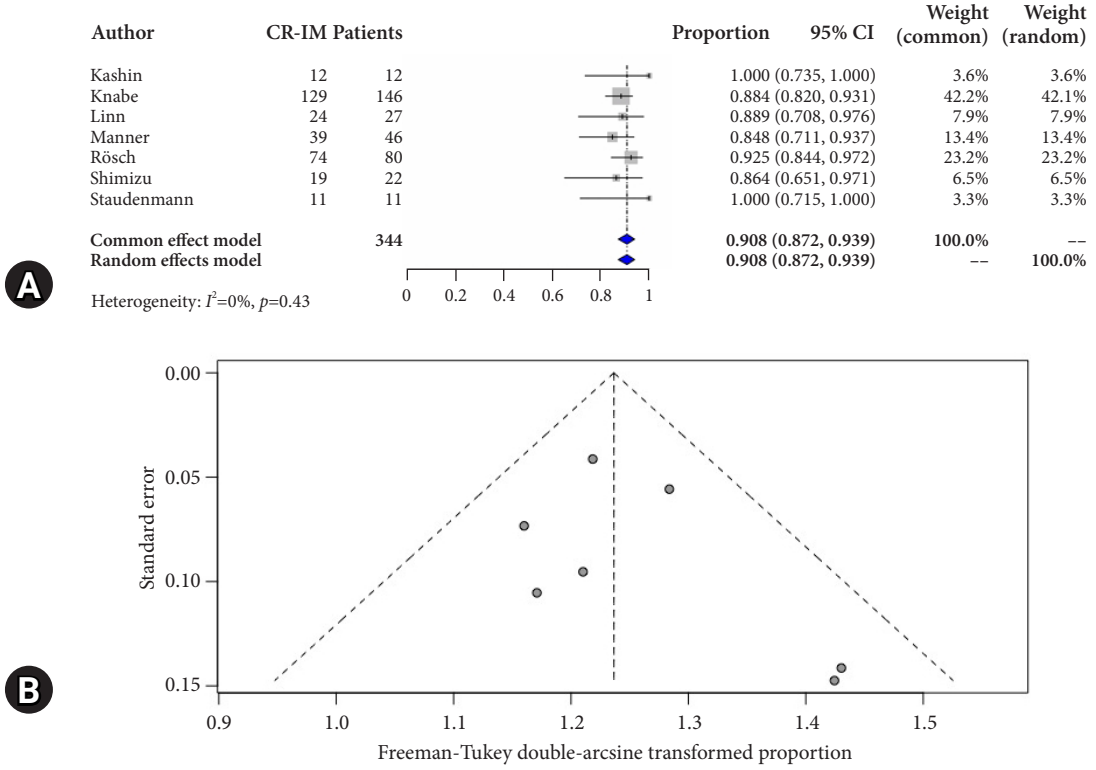


**Fig. 2.** (A) Forest plot of pooled complete remission of intestinal metaplasia (CR-IM) rates for included studies with $I^2$ measure of heterogeneity. (B) Associated funnel plot. CI, confidence interval.

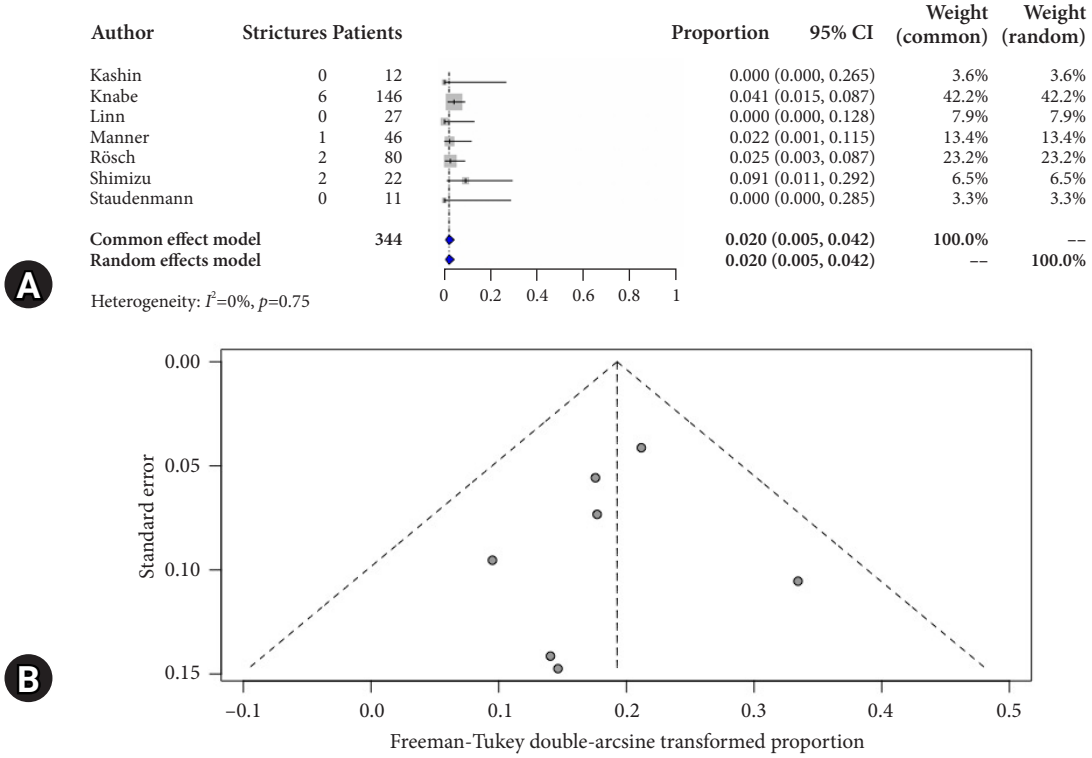


**Fig. 3.** (A) Forest plot of pooled stricture rates for included studies with $I^2$ measure of heterogeneity. (B) Associated funnel plot. CI, confidence interval.

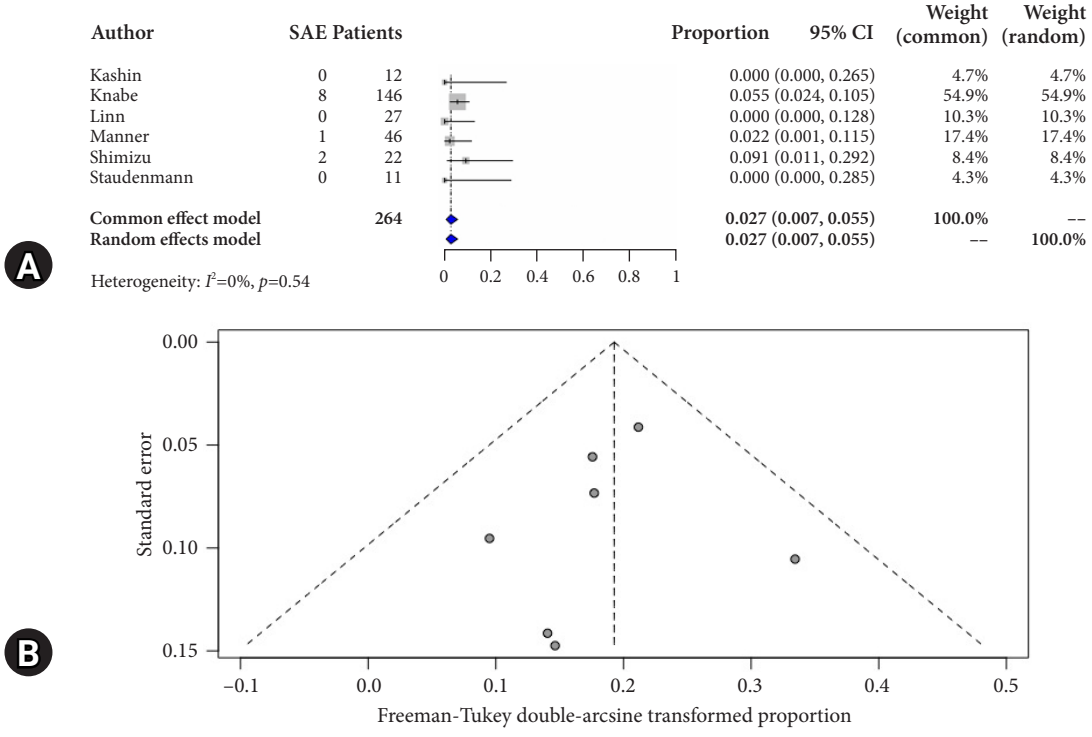


**Fig. 4.** (A) Forest plot of pooled serious adverse event (SAE) rates for included studies with $I^2$ measure of heterogeneity. (B) Associated funnel plot. CI, confidence interval.

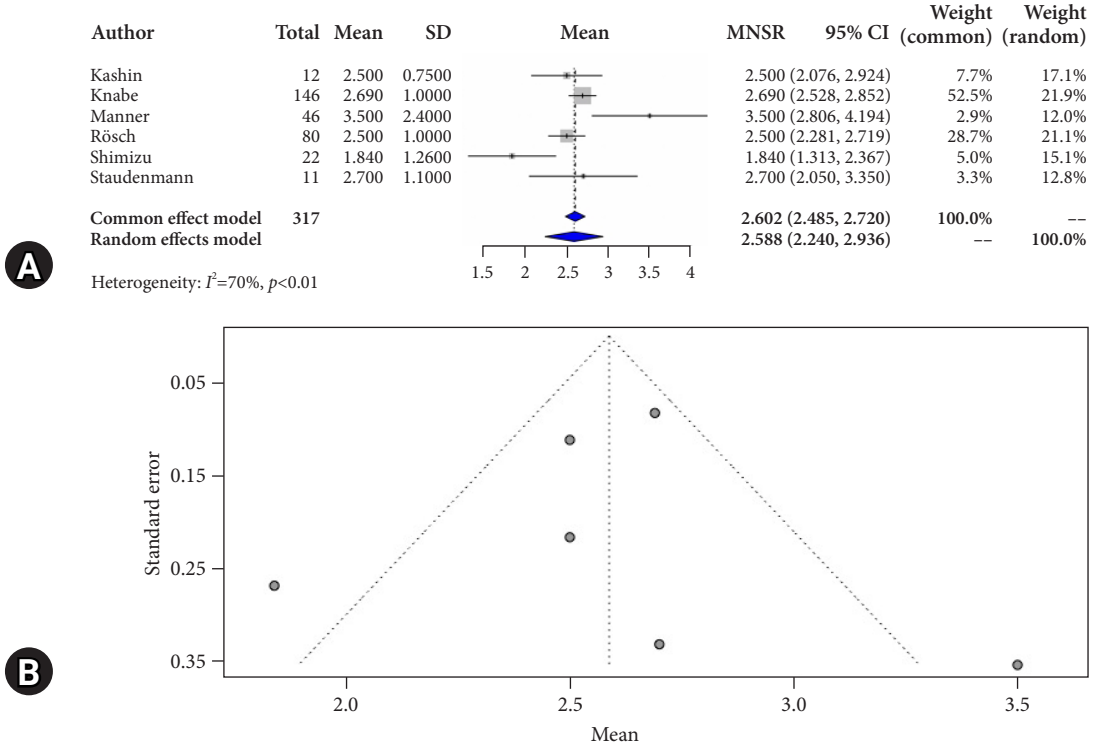


**Fig. 5.** (A) Forest plot of pooled average number of sessions required to achieve complete remission of intestinal metaplasia with $I^2$ measure of heterogeneity. (B) Associated funnel plot. SD, standard deviation; MNSR, mean number of sessions required to achieve CR-IM; CI, confidence interval.

**Table 3.** Summary of pooled results including measures of heterogeneity and publication bias

| Outcome | Pooled rate | Confidence interval | $I^2$ (%) | $B_0$ (Egger's) | $p$-value (Egger's) |
|---|---|---|---|---|---|
| CR-IM | 0.908 | 0.872–0.939 | 0 | 0.91 | 0.36 |
| Stricture | 0.020 | 0.005–0.042 | 0 | –0.35 | 0.66 |
| SAE | 0.027 | 0.007–0.055 | 0 | –0.80 | 0.39 |
| Sessions | 2.59 | 2.24–2.94 | 70 | –0.21 | 0.90 |

CR-IM, complete remission of intestinal metaplasia; SAE, serious adverse event.

evidence. Nonetheless, given that hybrid-APC is in its nascency, the results of this meta-analysis represent the best evidence currently available. Randomized controlled trials are necessary to further assess the comparative safety and efficacy of this new treatment modality.

Removal of the studies performed by Shimizu et al.[35] and Manner et al.[31] on sensitivity analysis considerably reduced the heterogeneity in the number of sessions to achieve CR-IM. This heterogeneity could in part be explained by the extent of BE given meta-regression demonstrated a correlation between the number of treatment sessions necessary and Prague M length. The study performed by Shimizu et al.[35] had the lowest average Prague M length and the study performed by Manner et al.[31] had the highest; these two studies had the lowest and highest average number of treatment sessions necessary to achieve CR-IM, respectively. The lack of a concurrent association between Prague C length and number of sessions may reflect the lower magnitude of variation in the circumferential extent of BE across studies. While lack of familiarity with the procedure in the earliest studies could have led to less aggressive therapy and additional treatment sessions, there was no association between the year of study publication and number of sessions necessary to achieve CR-IM.

Despite the absence of statistical heterogeneity in the CR-IM rates, there were variations in the definitions of treatment success and recurrence across the included studies that affected

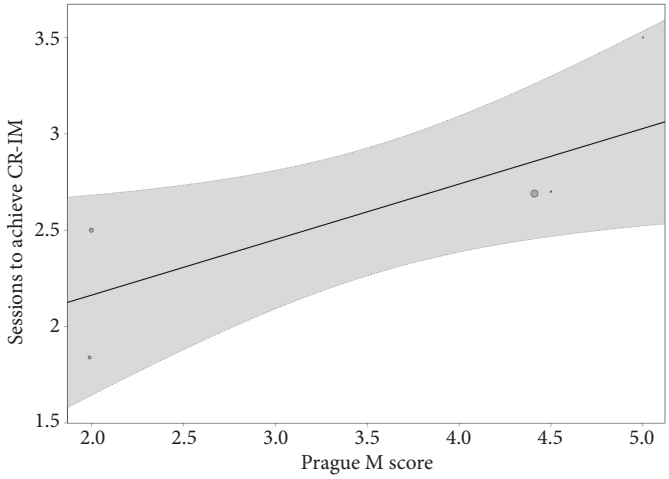


**Fig. 6.** Meta-regression of number of sessions necessary to achieve complete remission of intestinal metaplasia (CR-IM) and average Prague M length with 95% confidence interval bounds.

the measurement of this outcome. Ideally, treatment success should be evaluated at a prespecified time point or after a maximal number of therapies. For example, the studies performed by Knabe et al.[30] and Rösch et al.[32] allowed up to five treatment sessions to achieve success before treatment was considered to have failed. The remaining studies did not specify how many treatments would be allowed prior to a patient being deemed 'treatment failure'. Without a prespecified treatment endpoint, treatment can continue until CR-IM is achieved, rendering it difficult to assess per-treatment effectiveness. Studies have reported the average number of treatments necessary to achieve complete eradication, which was similar to the average number of therapies needed using RFA in previous landmark studies.[42,43]

Furthermore, there was variation in the timing of histologic evaluation of CR-IM. While certain studies evaluated histologic eradication one month after complete macroscopic ablation,[34] others evaluated at three to six months,[33] three months,[30-32] or at least three months[35] following macroscopic eradication. When histologic evaluation is performed, whether the presence of intestinal metaplasia is deemed persistent or recurrent disease affects the evaluation of treatment efficacy. Standardization of this process is important for accurate assessment of new treatment modalities.

The current systematic review was comprehensive, spanning major electronic databases. As the first meta-analysis to evaluate the efficacy of hybrid-APC, our study provides valuable preliminary insight into the utility of this emerging technique. The current study has several limitations. First, many of the included studies were case series, introducing the possibility of preferential inclusion of patients with desirable outcomes or exclusion of those with unfavorable outcomes. We attempted to mitigate the effects of these studies by using rigorous, independent quality assessments. None of the included studies was deemed to be of poor quality. Second, limitations inherent to any meta-analysis of retrospective, non-controlled studies include variations across patient populations and a lack of standardization of interventions. Although there was little heterogeneity, this may be a product of the relatively high CR-IM rates across studies despite systematic differences in methodology. Third, a potential trade-off of reduced coagulation depth using hybrid-APC is the formation of glands and metaplastic cells 'buried' beneath the neosquamous epithelium that forms following ablative therapy.[44] Dysplasia or neoplasia can develop under the squamous epithelium in these areas of intestinal metaplasia.[45] Given the overlying normal tissue, these areas may not be biopsied or detected on subsequent endoscopy. The lower coagulation depth of hybrid-APC could leave behind more intestinal metaplasia in the lamina propria that ultimately becomes buried and evades detection. Only two of the included studies reported the prevalence of buried glands on biopsy following therapy, limiting the analysis of this important consideration. Finally, few of the included studies provided data on long-term follow-up and no studies included data on adherence to post-treatment acid suppression, which could play an important role in post-procedural stricture formation. Evaluation of these outcomes through future studies is necessary to accurately assess the utility of hybrid-APC.

Hybrid-APC is an emerging therapeutic modality for the treatment of dysplastic BE. The results of the current meta-analysis suggest that hybrid-APC is associated with high rates of CR-IM and a favorable safety profile. Randomized controlled trials that standardize the definition of 'treatment success' and 'treatment failure,' as well as the timing of CR-IM evaluation are necessary to understand how this treatment option compares to current standards of care. Particular attention should be paid to the development of buried metaplasia and long-term durable effectiveness using hybrid-APC given the paucity of data on these outcomes in the current literature.

## Supplementary Material

**Supplementary Material 1.** Detailed search strategy for major databases.

**Supplementary Table 1.** Quality assessment of non-comparative studies using modified Newcastle-Ottawa scale.

**Supplementary Table 2.** Quality assessment of cohort study using Newcastle-Ottawa scale.

**Supplementary Fig. 1.** Meta-regression of the number of sessions necessary to achieve complete remission of intestinal metaplasia (CR-IM) and average Prague C length with 95% confidence interval bounds.

**Supplementary Fig. 2.** Meta-regression of the number of sessions necessary to achieve complete remission of intestinal metaplasia (CR-IM) and year of publication with 95% confidence interval bounds.

Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2022.179.

## Ethical Statements

Not applicable.

## Conflicts of Interest

Kenneth Chang is a consultant for Olympus, Cook Medical, endogastric solutions, and ERBE. Jason Samarasena has ownership in Docbot, is a consultant for Neptune Medical, Steris, Microtech, Medtronic, Olympus, and Conmed, has recieved an educational grant from Cook Medical, and has lectured for Mauna Kea Technologies. The other authors have no potential conflicts of interest.

## Funding

None.

## Author Contributions

Conceptualization: SNS, JS; Data curation: SNS, NEHC; Formal analysis: SNS, NEHC; Software: SNS, NEHC; Writing–original draft: all authors; Writing–review & editing: all authors.

## ORCID

Sagar N. Shah https://orcid.org/0000-0002-3592-2270
Nabil El Hage Chehade https://orcid.org/0000-0003-3578-395X
Amirali Tavangar https://orcid.org/0000-0002-5223-5341
Alyssa Choi https://orcid.org/0000-0002-6830-9384
Marc Monachese https://orcid.org/0000-0003-4479-049X
Kenneth J. Chang https://orcid.org/0000-0001-9897-277X
Jason B. Samarasena https://orcid.org/0000-0002-2981-3078

## REFERENCES

1. Burke ZD, Tosh D. Barrett's metaplasia as a paradigm for understanding the development of cancer. Curr Opin Genet Dev 2012;22:494–499.
2. Wang DH, Clemons NJ, Miyashita T, et al. Aberrant epithelial-mesenchymal Hedgehog signaling characterizes Barrett's metaplasia. Gastroenterology 2010;138:1810–1822.
3. Lagergren J, Lagergren P. Recent developments in esophageal adenocarcinoma. CA Cancer J Clin 2013;63:232–248.
4. Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016;111:30–50.
5. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014;146:652–660.
6. Kolb JM, Wani S. Endoscopic eradication therapy for Barrett's oesophagus: state of the art. Curr Opin Gastroenterol 2020;36:351–358.
7. Garman KS, Shaheen NJ. Ablative therapies for Barrett's esophagus. Curr Gastroenterol Rep 2011;13:226–239.
8. Ganz RA, Utley DS, Stern RA, et al. Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus. Gastrointest Endosc 2004;60:1002–1010.
9. Dunkin BJ, Martinez J, Bejarano PA, et al. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. Surg Endosc 2006;20:125–130.
10. van Vilsteren FG, Pouw RE, Seewald S, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. Gut 2011;60:765–773.
11. Kolb JM, Shah S, Chahine A, et al. Hybrid argon plasma coagulation for Barrett's esophagus. VideoGIE 2021;6:339–341.
12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–269.
13. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446–454.
14. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
15. Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in me-

ta-analysis. Ottawa: Ottawa Hospital Research Institute; 2011. p. 1–12.
16. Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23:60–63.
17. Bazerbachi F, Sawas T, Vargas EJ, et al. Metal stents versus plastic stents for the management of pancreatic walled-off necrosis: a systematic review and meta-analysis. Gastrointest Endosc 2018;87:30–42.
18. Lin L, Xu C. Arcsine-based transformations for meta-analysis of proportions: pros, cons, and alternatives. Health Sci Rep 2020;3:e178.
19. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health 2014;72:39.
20. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
21. Easterbrook PJ, Berlin JA, Gopalan R, et al. Publication bias in clinical research. Lancet 1991;337:867–872.
22. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.
23. Barker TH, Migliavaca CB, Stein C, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. BMC Med Res Methodol 2021;21:189.
24. Han J, Shimizu T, Yu A, et al. Efficacy, tolerance, and safety of hybrid argon plasma coagulation for the treatment of Barrett's esophagus: a US pilot study. Am J Gastroenterol 2018;113:S213–S214.
25. Nieto J, Casas D. 935 Salvage hybrid APC after failed radiofrequency ablation and cryotherapy for Barrett's esophagus. Am J Gastroenterol 2019;114:S544–S545.
26. Kroupa R, Dastych M, Konečný Š, et al. Hybrid argon plasma coagulation in the ablation treatment of Barrett's esophagus-long term results. United European Gastroenterol J 2021;9 (Supplement):297.
27. Trindade AJ, Wee D, Wander P, et al. Successful treatment of refractory Barrett's neoplasia with hybrid argon plasma coagulation: a case series. Endoscopy 2020;52:812–813.
28. Arshad HM, Ahsan N, Aldridge T, et al. Safety and efficacy of endoscopic hybridapc for management of Barrett's esophagus. Gastrointest Endosc 2017;85(5 Supplement):AB562–AB563.
29. Staudenmann DA, Skacel EP, Tsoutsman T, et al. Safety and long-term efficacy of hybrid-argon plasma coagulation for the treatment of Barrett's esophagus: an Australian pilot study (with video). Int J Gastrointest Interv 2021;10:128–132.
30. Knabe M, Beyna T, Rösch T, et al. Hybrid APC in combination with resection for the endoscopic treatment of neoplastic Barrett's esophagus: a prospective, multicenter study. Am J Gastroenterol 2022;117:110–119.
31. Manner H, May A, Kouti I, et al. Efficacy and safety of hybrid-APC for the ablation of Barrett's esophagus. Surg Endosc 2016;30:1364–1370.
32. Rösch T, Manner H, May A, et al. Multicenter feasibility study of combined injection and argon plasma coagulation (Hybrid-APC) in the ablation therapy of neoplastic Barrett esophagus. Gastrointest Endosc 2017;85(5 Supplement):AB154.
33. Linn B, Mangels-Dick T, Clemens MA, et al. Hybrid argon plasma coagulation and radiofrequency ablation in Barrett's esophagus. Gastrointest Endosc 2020;91(6 Supplement):AB413.
34. Kashin SV, Kuvaev R, Nadezhin AS, et al. 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(5 Supplement):AB495.
35. Shimizu T, Samarasena JB, Fortinsky KJ, et al. Benefit, tolerance, and safety of hybrid argon plasma coagulation for treatment of Barrett's esophagus: US pilot study. Endosc Int Open 2021;9:E1870–E1876.
36. 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;2:383–390.
37. 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;56:95–99.
38. Qumseya BJ, Wani S, Desai M, et al. Adverse events after radiofrequency ablation in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:1086–1095.
39. 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;50:953–960.
40. 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;11:1245–1255.
41. Desai M, Rösch T, Sundaram S, et al. Systematic review with meta-analysis: the long-term efficacy of Barrett's endoscopic therapy-stringent selection criteria and a proposal for definitions. Aliment Pharmacol Ther 2021;54:222–233.
42. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277–2288.

43. 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;311:1209–1217.
44. Spechler SJ. Buried (but not dead) Barrett's metaplasia: tales from the crypts. Gastrointest Endosc 2012;76:41–43.
45. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. Am J Gastroenterol 2011;106:1899–1908.