Role of ablative therapy for squamous cell neoplasia of esophagus

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Abstract: Esophageal squamous cell neoplasia (ESCN) is the histologic precursor to esophageal squamous cell carcinoma (ESCC), which causes a large burden of disease across the world. Over the past years, on account of the rapid development of endoscopic techniques with highly effectiveness and less invasiveness, the management of ESCN had changed from radical esophagectomy towards endoscopic therapeutics, including endoscopic resection (ER) and ablation techniques. Compared with ER, ablative techniques offer more convenient and safe modality, showing a reasonable efficacy and promising results in eradicating ESCN. Two most widely used ablative therapies for ESCN are radiofrequency ablation and cryoablation. Radiofrequency ablation ablates tissue through heat, while cryoablation coagulates tissue through cold. Recent data show that radiofrequency ablation is highly effective and durable in the removal of early ESCN, and demonstrates a lower rate of stenosis in treating large and extensive ESCN. Meanwhile, cryoablation also demonstrates relatively satisfactory short-term outcome in eradicating ESCN. However, there is still a risk of recurrence and residual lesions for both RFA and cryoablation when treating ESCN. Considering that complete tissue destruction of ablation does not allow histological assessment, staging the neoplasia and deciding which patient may be an ablation candidate before treatment is of great importance, and endoscopic surveillance with Lugol's chromoendoscopy is also necessary to detect any recurrence and metachronous lesions. Moreover, a combination approach of ER with ablation therapies has promising results in selected patients, and may provide minimally invasive and effective treatment. This review mainly focuses on the role of ablative therapy in practice for squamous cell neoplasia of esophagus.

Keywords: Esophageal squamous cell neoplasia (ESCN); radiofrequency ablation; cryoablation

Introduction

As one of eight major cancers in the world and six major causes of cancer-related death, esophageal cancer has a poor overall 5-year survival rate of 10–15% (1). More than 80% of esophageal cancer occurs in developing countries, and among them, over 90% of patients suffer from esophageal squamous cell carcinoma (ESCC) (2). Especially in China, the burden of the disease is heavy, and almost half of new cases and deaths of ESCC in the world occur in China (1,3).

The presence of esophageal squamous cell neoplasia (ESCN) is the essential risk factor in progressing to ESCC (4). Although the prognosis of patients with advanced ESCC is poor, ESCN can be clinically cured endoscopically with a perfect prognosis while preserving the esophagus. With no symptom usually, ESCN can be detected through endoscopic screening using Lugol's chromoendoscopy. Recent advances in endoscopic imaging techniques have

aided our ability to detect ESCN (5).

In China, ESCNs are classified histologically in three progressive stages: low-grade intra-epithelial neoplasia (LGIN), moderate-grade intra-epithelial neoplasia (MGIN) and high-grade intra-epithelial neoplasia (HGIN) with 1/3, 2/3 and 3/3 of the epithelium containing neoplasia, respectively (6). The degeneration of ESCC is a gradual process: from normal squamous epithelium to LGIN, to MGIN, to HGIN, and eventually progressing to invasive carcinoma. According to the follow-up studies in the high-risk areas of China, there is a significant difference between LGIN (24% at 13.5 years follow-up), MGIN (50%) and HGIN (74%) in the rate of progression to ESCC, which indicates that MGIN and HGIN are regarded as indications for treatment due to the possibility of progression to cancer, while LGIN only needs follow-up monitoring (7,8).

The endoscopic treatment techniques of ESCN are mainly divided into two categories: endoscopic resection (ER) and endoscopic ablation. please define methods, including endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), enable *en bloc* resection of the neoplasia, thereby allowing adequate pathological assessment of the resected specimen to evaluate the prognosis and the situation that may require additional treatment (9-11). However, ER is a complicated procedure which requires a high level of endoscopic expertise and has a long learning curve, especially for ESD which is associated with a risk for complications (9,12,13). In addition, widespread ER has been reported to be associated with esophageal stenosis that may be difficult to treat endoscopically and decreases patients' quality of life (12).

In contrast to ER, endoscopic ablation therapies offer more convenient and safe tehcniques and might have more advantages in the selected patients. Multiple studies have suggested that ablation is highly effective and safe in removing dysplasia in cases of Barrett's esophagus (BE) (14-16). As for squamous dysplasia of esophagus, a growing number of clinical studies have demonstrated the potential of ablation to eradicate ESCN. Traditional ablation methods including photodynamic therapy (PDT) or argon plasma coagulation (APC) lost the valuable role in clinical practice because of uncomplete ablation and high risk of complications (17,18). Radiofrequency ablation (RFA) and cryotherapy are the currently two most widely accepted techniques used for ESCN. The aim of this review is to highlight these advances, with special focus on the role of ablation in practice of squamous dysplasia of esophagus.

Radiofrequency ablation (RFA)

RFA system

Esophageal RFA therapy has been widely known as a thermal ablative technique using a HALO-ablation system (Medtronic, Sunnyvale, California) which requires a specific catheter to apply the radiofrequency ablation to the mucosa of esophagus. The HALO system emits radiofrequency energy (RF) to coagulate (ablate) the thin layer of diseased squamous epithelium of the esophagus. The heat generated by RF delivery can achieve 60–100 ℃ to result in tissue vaporization or coagulation and inactivate tumor cells. Owing to the fixed energy transmission device along with a bipolar ablation catheter, RFA can control the depth of coagulation to be limited to 500–1,000 microns (19), thus reducing the risk of complications related with damage of mucosal structure, such as postoperative stenosis.

There are two kinds of HALO systems with different ablation catheters playing a specific role in the treatment of ESCN, respectively. First, HALO[360] System, a kind of circumferential ablation system, includes a balloon-based catheter wrapped with a 3 cm long electrode having tightly spaced bipolar electrode bands, resulting in a circumferential ablation. An energy generator is used to inflate a sizing balloon positioned within the esophageal body to measure the internal diameter of the esophagus at the target lesion. Upon determination of the inner diameter size, an appropriate sized balloon-based ablation catheter is selected for ablation. The generator inflates the ablation catheter within the esophagus and delivers the controlled amount of RF energy to achieve the desired ablation effect. Given the ablation of circumference of esophagus, HALO[360] is mainly designed for multifocal and circumferential lesions. Currently, a newly introduced and listed HALO[360] device of second generation called BARRX[TM] 360 Express integrates sizing and ablation into one catheter featuring the self-adaption to the esophageal lumen, which helps to simplify and reduce procedure time.

The second system is focal ablation including HALO[90], HALO[90] Ultra and HALO[60], using a cap-based electrode installed on the tail end of an endoscope. The device is introduced with the endoscope to provide more focally targeted ablation of small areas of dysplasia, either primary or secondary therapy. The focal ablation device is substantially equivalent to the HALO[360] device in terms of energy delivery and ablation depth, having the same electrode design. The difference is that its superficial area is smaller, allowing more focal selective ablation, and

this device is designed to be a cap-based, attached to the endoscope. Recently, a new kind of focal ablation device called BARRX™ Channel has been introduced with an endoscopic catheter which could pass through the working channel of endoscope. The new device is mainly applied to esophagus with stenosis that obstructs other focal ablation catheters.

Treatment efficacy of RFA for ESCN

A great number of RCTs and observation studies suggest that RFA is highly effective and durable in the removal of Barrett's mucosa and related dysplasia (14,20-23). In recent years, researchers have paid more and more attentions to RFA for eradication of esophageal squamous neoplasia. A research group of National Cancer Center of China conducted a series of studies to evaluate its potential to treat ESCN since 2008. The security and efficacy of RFA in the eradication of ESCN in patients suffering from flat-MGIN, HGIN and early ESCC (24,25) were assessed in a prospective trial. Among 96 enrolled patients in total (45 MGIN, 42 HGIN, 9 early ESCC), 84% (81/96) cases were remitted completely (CR; absence of MGIN+ in biopsies) at 12 months and showed no serious adverse events such as infection, perforation or death. Stenosis was observed in 20 (21 %) patients who accepted circumferential RFA, and all resolved with a median of 4 dilations (25). van Vilsteren and colleagues treated 13 ESCN patients (10 HGIN, three mucosal ESCC) with complete remission after median 2 RFA procedures, and no recurrence after 17 months in median follow-up visit (26). Wang *et al.* (27) reported their results in 7 patients with ultralong and extensive ESCNs with a mean length of 12.4 cm and more than half of the circumference (3 patients had circumferential extension), 6 of whom achieved a complete response at 6 months. In a retrospective study, Wang *et al.* (28) enrolled 65 ESCN patients with length more than 3 cm and extending more than 1/2 of the circumference of esophagus, 18 ESCN patients received the treatment of RFA, and 47 patients received the treatment of ESD. According to the results, RFA and ESD have the same effect in the short-term treatment of early flat large ESCN, and the treatment duration of RFA was greatly shorter than that of ESD (126.6 *vs.* 34.8 min; P<0.001); ESD was correlated with a higher incidence of esophageal stenosis (83% *vs.* 27%, P=0.01), and more sessions of dilatation were required to relieve the symptoms (median, 13 *vs.* 3, P=0.04). These

results of studies of RFA for early ESCN demonstrated satisfactory short-term outcome.

More importantly, our group firstly reported the 5-year effectiveness of RFA for the eradication of MGIN, HGIN and early flat ESCC in the aforementioned trial (29). In the 78 patients eradicated completely at 12 months after baseline RFA, the vast majority (86%) remained completely relieved for 5 years after the first treatment. A few patients (9%) were recurrent, and repeated focal RFA could be used to cure them. All non-flat lesions or diagnosis with severer histological grade than baseline was defined as progressive disease, which developed in 5% patients, and ESD could be used to cure half of the lesions. In a word, among patients suffering from ESCN, RFA led to a sustained eradication of lesion in the majority of patients during 5 years of follow-up.

In contrast, 12 patients who unsuccessfully eradicated ESCN at the 12-month showed relatively poor results (29), which demonstrated that patients suffering from ESCN residues at 12 months more possibly progress to invasive disease. Hence, we suggested that patients with unsuccessful eradication of ESCN at 12 months should receive the treatment of EMR or ESD in order to have a complete histological examination and even further clinical treatment. In the second place, considering the recurrence rate in the treatment region and the appearance of metachronous lesions in other area of esophagus, it is necessary to make strict endoscopic follow-up visit with Lugol's chromoendoscopy after RFA of ESCN. All Unstained lesion (USL) shall be biopsied for histological diagnosis after Lugol's staining.

Third, our study found that Pink-color sign (HR 3.66, 95% CI: 1.59–8.41) was an independent risk factor failing to realize or maintain CR within 5 years after initial RFA. Previous studies showed RFA should be restricted to patients with lesions limited to epithelial, i.e., MGIN or HGIN. RFA can play its ablation effect over the epithelium, which is deficient for invasive tumor (i.e., ESCC) (30-32). However, these failure cases highlighted the limitations of Paris classification and endoscopic biopsies in staging patients and deciding who may be an RFA candidate. Pink-color sign refers to the change of red or rose-pink color within 2 to 3 minutes after Lugol's staining, which seemingly is an easily recognizable feature of ESCC and advanced stages of ESCN (33-35). Therefore, we advise to add pink-color sign after Lugol's chromoscopy as additional endoscopic exclusion criteria for RFA treatment.

In our study, we found two patients with subepithelial

ESCC developing a non-flat lesion with normal epithelium in white light, NBI and after Lugol's endoscopy, but histologically showed ESCC infiltrated into submucosa and covered by normal squamous epithelium. ESCN extends downward to the existing ducts of submucosal glands, which is seemingly related to the residual ESCN after RFA if the ablation is very superficial. Given the potential of residual lesions progress to squamous cancer, we would suggest cautiously using RFA only for flat MIGN and HIGN without any invasive neoplasia, and several "lessons learned" had been suggested to optimize RFA procedure in our publication (29).

Adverse events after RFA

Adverse events related to RFA include stenosis, mucosal lacerations, hemorrhage, and chest pain. Our prospective study reported that mucosal lacerations were observed during esophagus diameter sizing in 4 patients (4%), but no clinical intervention required. Stenosis of esophageal was observed in 20 patients (21%), with circumferential RFA and all resolved with median 4 sessions of dilations (25). No new stenosis was observed during the follow-up period (29). Wang *et al.* (27) reported stenosis was developed in 2 of 7 patients with ultralong and extensive ESCNs with a mean length of 12.4 cm and more than half of the circumference, and required balloon dilation for 2 and 8 sessions, respectively. It has been reported that the incidence of stenosis in patients with circumferential extension of more than 75% can reach 88–100% when treated with ESD (36-38). In the retrospectively comparative study, Wang *et al.* (28) reported that for lesions covering more than 3 quarters of the circumference, RFA was superior to ESD with a shorter procedure time and lower stenosis rate following removal of larger lesions (27% *vs.* 83%, P=0.01). Based on these observations, compared with ER methods, RFA demonstrated a lower rate of strictures in treating large and extensive ESCNs.

Combination with ER

There are many early ESCNs consisting of a large flat type lesion as well as one or more focal non-flat type component. As mentioned, the ablation of RFA covers the epithelium of esophagus, which is seemingly deficient for eradication of non-flat lesions (30-32), and the complete tissue destruction does not allow histological assessment after procedure. ER has the advantage of providing whole resected specimens for accurate histological evaluation, but is also associated with higher rates of stenosis for extensive lesions. Regarding as extensive and multifocal ESCNs including non-flat lesions, endoscopists must consider the advantages of each technique in order to achieve optimal treatment efficacy and reduce the incidence of adverse event. A combination of ER and RFA may integrate the optimal characteristics of the two methods, playing an increasing role in the treatment of patients with multifocal ESCN.

As for the treatment of Barrett's esophagus, the combination of ER and RFA has been reported to lead to a good treatment result (39,40). Alvarez Herrero *et al.* (40) reported that RFA allied with ER for visible abnormalities is also an effective and secure treatment method for Barrett's esophagus longer than 10cm in length containing neoplasia. Becker *et al.* (41) firstly reported the application of multimodal endoscopic therapy in 6 consecutive patients with multifocal intraepithelial neoplasia and superficial squamous cell carcinoma of the esophagus. All endoscopically visible lesions received the treatment of ER to obtain specimens for histological assessment and to reduce the thickness of tumor. Then, RFA was performed to the remaining tumor area and the surrounding 3 cm of mucosa to eliminate residual or synchronous lesions. During the follow-up period, all patients showed no recurrence or metastasis. Our group also reported the eradication effect of RFA combined with ER on the treatment of early widespread non-flat type ESCN (42). Four patients with early non-flat ESCC and precancerous lesions occupied more than 3/4 circumference were retrospectively analyzed. Three cases were CR at 3-month, 1 year and 5 years after operation; one case developed HGIN at 3-month and MGIN at 1-year and 3-year, and achieved CR after repeated RFA. Stenosis occurred in 4 cases, 2 of which were mild without treatment, and the other 2 cases were severe and relieved by dilation for 5–8 (mean 6.5) times. These studies demonstrated that a combined approach of ER with RFA has promising results in selected patients, and may provide minimally invasive and effective treatment. Prospective study involving a larger number of patients is still needed to evaluate long-term validity and find the optimal strategy of the technique combination.

Cryoablation

Cryoablation systems and efficacy

Endoscopic cryoablation is another ablative modality recently

attracting emerging attentions for the treatment of ESCN. RFA ablates tissue through heat, while cryoablation relies on the quick cooling and thawing to destruct tissue with a cryogen, such as liquid nitrogen or carbon dioxide (43). These rapid temperature changes lead to the destruction of cell membranes and thrombosis in the blood vessels resulting in apoptosis and ischemia (44). Approved by United States Food and Drug Administration, two kinds of systems are currently available in clinical practice. Using liquid nitrogen as the cryogen, the TruFreeze system (CSA Medical, Lexington, Mass) is delivered via a low-pressure, flexible 7-French spray catheter via the endoscopic working channel and results in flash freezing the mucosa to –196 ℃. While a stomach tube is necessary to provide venting channel for continuous decompression of the rapidly expansional nitrogen to prevent mucosal perforation. Cryospray ablation using liquid nitrogen mainly involves in the management of BE associated dysplasia in majority of the studies (45,46) and is used as palliative treatment of ESCC (47), but there is no data for the treatment of early ESCN.

Another system applying liquid nitrous oxide as the cryogen is called cryoballoon focal ablation system (CbFAS, C2 Therapeutics, Redwood, California), which consists of a small hand-held controller and a through-the-scope catheter with a self-sizing balloon. The catheter can rotate 360 degrees by applying the handheld controller and deliver liquid nitrous oxide into an inflated balloon to freeze the targeted mucosa to –85 ℃. CbFAS has several advantages over the TruFreeze system, including the unnecessary of decompression channel, the targeted equally delivery of the cryogen and being easy to carry and operate (44). Previous studies showed promising ability of CbFAS to eliminate BE (48,49). Canto *et al.* (50) firstly reported the possibility of treating early ESCN with the CbFAS. Ten patients suffering from LGIN (n=2), HGIN (n=7), or ESCC (n=1, after EMR) in 24 USLs showed no major adverse events, and all patients achieved complete remission after 3 months of follow-up. Furthermore, a larger prospective study was performed to measure the efficacy and safety of CbFAS for treatment of early ESCN (51) by our group. We enrolled 80 flat-type ESCNs (59MGIN, 21HGIN) lack of pink-color sign with a median USL length of 3cm and circumferential extent of 60 degrees. Seventy-nine patients were ablated successfully with focal cryoballoon ablation and the cryogen was delivered for 10 seconds at each ablation site. After the first single treatment, among 78 patients, 70 patients (90%) achieved CR, and 1 did not make follow-up visit. The remaining 8 patients suffering from residual USLs received

the re-treatment of CbFAS, and all exhibited CR after the second ablation. At the 12th month after the first ablation, among 78 patients (97%), 76 patients sustained CR and recurrent MGIN occurred in 2 (3%) patients. No stenosis or other serious adverse events were observed. Superficial mucosal lacerations occurred in four patients (5%) when balloon inflation, and none of patients need further clinical intervention. Our short-term outcomes demonstrated that CbFAS is secure and effective in eradicating ESCN with small size and no pink-color sign. Moreover, long-term follow-up data and more studies of larger lesions are necessary to evaluate the effect of cryoballoon ablation in the treatment of ESCN.

Depth of ablation, cryoablation vs. RFA

Scholvinck *et al.* described the short-term and long-term histopathological effects and security of the CbFAS in porcine and human models. Four patients scheduled to undergo esophagectomy received eight 6-second cryoablations. In the acute phase, necrosis was confined to the mucosa or muscularis mucosa, and then extended to the submucosa at 4 days. The 6-second cryoablation resulted in necrosis in the mucosa and submucosa at median 2 mm from the mucosa surface. Hence, the depth of necrosis introduced by CbFAS has been claimed to be deeper than that of RFA (limited to 0.5–1 mm), and may be more sufficient for successful ablation of ESCN. However, comparative study between cryoablation and RFA are necessary to assess the security and efficacy in the treatment of ESCN.

Further perspectives in ablation for ESCN

Over the last few years, it has been proved that ablation therapy is highly effective, convenient and safe in eradicating ESCN, and recently claims its important role in clinical practice. However, given the lack of histological evaluation, careful selection of patients before ablation is important when regard it as primary treatment tools, and endoscopic surveillance should be continued to detect any recurrence. More studies aiming at the optimal treatment and follow-up protocol, long-term durability results, comparison with other methods will help us better understand the role of ablation. Furthermore, combination of ablation therapy and ER will be more effective for the management of ESCN in the future, and studies of the optimal combined treatment regimens are necessary.

Footnote

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015;64:381-7.
3. Lin Y, Totsuka Y, He Y, et al. Epidemiology of esophageal cancer in Japan and China. J Epidemiol 2013;23:233-42.
4. Taylor PR, Abnet CC, Dawsey SM. Squamous dysplasia--the precursor lesion for esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2013;22:540-52.
5. Lee CT, Chang CY, Lee YC, et al. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. Endoscopy 2010;42:613-9.
6. Dawsey SM, Lewin KJ, Liu FS, et al. Esophageal morphology from Linxian, China. Squamous histologic findings in 754 patients. Cancer 1994;73:2027-37.
7. Dawsey SM, Lewin KJ, Wang GQ, et al. Squamous esophageal histology and subsequent risk of squamous cell carcinoma of the esophagus. A prospective follow-up study from Linxian, China. Cancer 1994;74:1686-92.
8. Wang GQ, Abnet CC, Shen Q, et al. Histological precursors of oesophageal squamous cell carcinoma: results from a 13 year prospective follow up study in a high risk population. Gut 2005;54:187-92.
9. Ono S, Fujishiro M, Niimi K, et al. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. Gastrointest Endosc 2009;70:860-6.
10. Oyama T, Tomori A, Hotta K, et al. Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol 2005;3:S67-70.
11. Fujishiro M, Yahagi N, Kakushima N, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. Clin Gastroenterol Hepatol 2006;4:688-94.
12. Sgourakis G, Gockel I, Lang H. Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. World J Gastroenterol 2013;19:1424-37.
13. Lee CT, Chang CY, Tai CM, et al. Endoscopic submucosal dissection for early esophageal neoplasia: a single center experience in South Taiwan. J Formos Med Assoc 2012;111:132-9.
14. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277-88.
15. 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.

16. Ganz RA, Overholt BF, Sharma VK, et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. Multicenter Registry. Gastrointest Endosc 2008;68:35-40.

17. Van Laethem JL, Jagodzinski R, Peny MO, et al. Argon plasma coagulation in the treatment of Barrett's high-grade dysplasia and in situ adenocarcinoma. Endoscopy 2001;33:257-61.

18. Overholt BF, Panjehpour M, Halberg DL. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. Gastrointest Endosc 2003;58:183-8.

19. Belghazi K, Bergman J, Pouw RE. Endoscopic Resection and Radiofrequency Ablation for Early Esophageal Neoplasia. Dig Dis 2016;34:469-75.

20. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. Gastrointest Endosc 2008;68:867-76.

21. Sharma VK, Wang KK, Overholt BF, et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc 2007;65:185-95.

22. Sharma VK, Jae Kim H, Das A, et al. Circumferential and focal ablation of Barrett's esophagus containing dysplasia. Am J Gastroenterol 2009;104:310-7.

23. Gondrie JJ, Pouw RE, Sondermeijer CM, et al. Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. Endoscopy 2008;40:370-9.

24. Bergman JJ, Zhang YM, He S, et al. Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus. Gastrointest Endosc 2011;74:1181-90.

25. He S, Bergman J, Zhang Y, et al. Endoscopic radiofrequency ablation for early esophageal squamous cell neoplasia: report of safety and effectiveness from a large prospective trial. Endoscopy 2015;47:398-408.

26. van Vilsteren FG, Alvarez Herrero L, Pouw RE, et al. Radiofrequency ablation for the endoscopic eradication of esophageal squamous high grade intraepithelial neoplasia and mucosal squamous cell carcinoma. Endoscopy 2011;43:282-90.

27. Wang WL, Chang IW, Chang CY, et al. Circumferential balloon-based radiofrequency ablation for ultralong and extensive flat esophageal squamous neoplasia. Gastrointest Endosc 2014;80:1185-9.

28. Wang WL, Chang IW, Chen CC, et al. Radiofrequency Ablation Versus Endoscopic Submucosal Dissection in Treating Large Early Esophageal Squamous Cell Neoplasia. Medicine 2015;94:e2240.

29. Yu X, van Munster SN, Zhang Y, et al. Durability of radiofrequency ablation for treatment of esophageal squamous cell neoplasia: 5-year follow-up of a treated cohort in China. Gastrointest Endosc 2019;89:736-48.e2.

30. 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;60:1002-10.

31. Dunkin BJ, Martinez J, Bejarano PA, et al. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. Surg Endosc 2006;20:125-30.

32. Smith CD, Bejarano PA, Melvin WS, et al. Endoscopic ablation of intestinal metaplasia containing high-grade dysplasia in esophagectomy patients using a balloon-based ablation system. Surg Endosc 2007;21:560-9.

33. Shimizu Y, Omori T, Yokoyama A, et al. Endoscopic diagnosis of early squamous neoplasia of the esophagus with iodine staining: high-grade intra-epithelial neoplasia turns pink within a few minutes. J Gastroenterol Hepatol 2008;23:546-50.

34. Ishihara R, Kanzaki H, Iishi H, et al. Pink-color sign in esophageal squamous neoplasia, and speculation regarding the underlying mechanism. World J Gastroenterol 2013;19:4300-8.

35. Goda K, Dobashi A, Yoshimura N, et al. Narrow-Band Imaging Magnifying Endoscopy versus Lugol Chromoendoscopy with Pink-Color Sign Assessment in the Diagnosis of Superficial Esophageal Squamous Neoplasms: A Randomised Noninferiority Trial. Gastroenterol Res Pract 2015;2015:639462.

36. Katada C, Muto M, Manabe T, et al. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. Gastrointest Endosc 2003;57:165-9.

37. Ono S, Fujishiro M, Niimi K, et al. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. Endoscopy 2009;41:661-5.

38. Shi Q, Ju H, Yao LQ, et al. Risk factors for postoperative stricture after endoscopic submucosal dissection for superficial esophageal carcinoma. Endoscopy 2014;46:640-4.

39. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic

resection for barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol 2010;8:23-9.

40. Alvarez Herrero L, van Vilsteren FG, Pouw RE, et al. Endoscopic radiofrequency ablation combined with endoscopic resection for early neoplasia in Barrett's esophagus longer than 10 cm. Gastrointest Endosc 2011;73:682-90.

41. Becker V, Bajbouj M, Schmid RM, et al. Multimodal endoscopic therapy for multifocal intraepithelial neoplasia and superficial esophageal squamous cell carcinoma - a case series. Endoscopy 2011;43:360-4.

42. Zhang Y, Bergman JJ, Xue L, et al. Preliminary study on efficacy of radiofrequency ablation combined with endoscopic resection for eradicating widespread early non-flat type esophageal squamous cell carcinoma. Zhonghua Wei Chang Wai Ke Za Zhi 2015;18:875-80.

43. Johnston CM, Schoenfeld LP, Mysore JV, et al. Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. Gastrointest Endosc 1999;50:86-92.

44. Lal P, Thota PN. Cryotherapy in the management of premalignant and malignant conditions of the esophagus. World J Gastroenterol 2018;24:4862-9.

45. Greenwald BD, Dumot JA, Horwhat JD, et al. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. Dis Esophagus 2010;23:13-9.

46. Ghorbani S, Tsai FC, Greenwald BD, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's dysplasia: results of the National Cryospray Registry. Dis Esophagus 2016;29:241-7.

47. Cash BD, Johnston LR, Johnston MH. Cryospray ablation (CSA) in the palliative treatment of squamous cell carcinoma of the esophagus. World J Surg Oncol 2007;5:34.

48. Schölvinck DW, Künzli HT, Kestens C, et al. Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study. Endoscopy 2015;47:1106-12.

49. Künzli HT, Schölvinck DW, Meijer SL, et al. Efficacy of the CryoBalloon Focal Ablation System for the eradication of dysplastic Barrett's esophagus islands. Endoscopy 2017;49:169-75.

50. Canto MI, Abrams JA, Kunzli HT, et al. Nitrous oxide cryotherapy for treatment of esophageal squamous cell neoplasia: initial multicenter international experience with a novel portable cryoballoon ablation system (with video). Gastrointest Endosc 2018;87:574-81.

51. Ke Y, van Munster SN, Xue L, et al. Prospective study of endoscopic focal cryoballoon ablation for esophageal squamous cell neoplasia in China. Gastrointest Endosc 2019;90:204-12.