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Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus

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Abstract

Background—Radiofrequency ablation (RFA) is safe and effective for eradicating neoplasia in Barrett's esophagus.

Objective—Evaluate RFA for eradicating early esophageal squamous cell neoplasia (ESCN) defined as moderate- and high-grade squamous intraepithelial neoplasia (MGIN, HGIN) and early flat-type esophageal squamous cell carcinoma (ESCC).

Design—Prospective cohort study.

Setting—Tertiary referral center.

Patients—Esophageal unstained lesions (USLs) were identified using Lugol's chromoendoscopy. Inclusion: at least 1 flat (type 0-IIb) USL ≥ 3mm, USL-bearing esophagus ≥ 12 cm, and a consensus diagnosis of MGIN, HGIN, or ESCC by two expert GI pathologists. Exclusion: prior endoscopic resection or ablation, stricture, or any non-flat mucosa.

Interventions—Circumferential RFA creating a continuous treatment area (TA) including all USLs. At 3-month intervals thereafter, chromoendoscopy with biopsies, followed by focal RFA of USLs, if present.

Main outcome measures—Complete response (CR) at 12 months, defined as absence of MGIN, HGIN or ESCC in TA; CR after one RFA session; neoplastic progression from baseline; and adverse events.

Results—29 patients (14 male, mean age 60.3 years) with MGIN (18), HGIN (10), or ESCC (1) participated. Mean USL length was 6.2 cm (TA 8.2 cm). At 3-months, after one RFA session, 86% of patients (25/29) were CR. At 12-months, 97% (28/29) of patients were CR. There was no neoplastic progression. There were 4 strictures, all dilated to resolution.

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Competing interests

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Limitations—Single center study with limited number of patients.

Conclusions—In patients with early ESCN (MGIN, HGIN, flat-type ESCC), RFA was associated with a high rate of histological complete response (97% of patients), no neoplastic progression, and an acceptable adverse event profile.

Introduction

Esophageal cancer is the sixth most common cause of cancer death worldwide, with an estimated 406,000 deaths in 2008 [1, 2]. Most esophageal cancers (80%) occur in developing countries, and most of these (90%) are esophageal squamous cell carcinoma (ESCC) [1, 3]. China, central Asia, northeastern Iran, eastern and southern Africa, and northern France have the highest incidence rates for ESCC [1, 4]. Nearly half of worldwide ESCC cases occur in China, where ESCC is the fourth leading cause of cancer-related death [5].

Several factors may influence the development of ESCC, including tobacco use, heavy consumption of alcohol, drinking hot liquids, exposure to nitrosamines, acetaldehyde, mycotoxins and polycyclic aromatic hydrocarbons, nutritional deficiencies, poor oral health, achalasia and low socioeconomic status [6]. In high-risk regions, such as China and Iran, exposure to polycyclic aromatic hydrocarbons, acetaldehyde, and nitrosamines and drinking hot liquids are primary contributors to ESCC development [7–15]. In lower-risk regions, such as the U.S., tobacco and alcohol are primary contributors to ESCC development [16–18].

While ESCC may present with raised or ulcerated lesions that are visible upon white light endoscopy, identification of flat precursor lesions [intraepithelial neoplasia (IEN) and early flat cancer] requires chromoendoscopy with Lugol's solution (1–3% iodine). Non-neoplastic esophageal squamous epithelium contains intracellular glycogen which reversibly binds to iodine, rendering the mucosa visibly "brown", while neoplastic esophageal squamous epithelium contains relatively little glycogen and therefore appears "unstained." Unstained lesions (USLs) have a high sensitivity for IEN and early flat ESCC, thus enabling targeted biopsy, histopathological evaluation, and treatment [19].

In China, intraepithelial squamous neoplasia of the esophagus is graded according to the proportion of the epithelial thickness containing neoplasia: 1/3 (low-grade intraepithelial neoplasia, LGIN, mild dysplasia), 2/3 (moderate-grade, MGIN, moderate dysplasia), or 3/3 (high-grade, HGIN, severe dysplasia) [20]. The rate of progression to invasive ESCC varies according to the baseline grade of neoplasia: LGIN (5% incident ESCC within 3.5 years, 24% incident ESCC within 13.5 years), MGIN (27% and 50%, respectively) and HGIN (65% and 74%, respectively) [21, 22]. Because of their high risk for developing invasive ESCC, MGIN and HGIN are considered clinically meaningful IEN and are targets for screening and endoscopic therapy.

Endoscopic radiofrequency ablation (RFA) for esophageal neoplasia refers to delivery of a 465 KHz energy waveform via a bipolar electrode array mounted on the outside of a balloon or on an articulated platform on the distal end of an endoscope (HALO System, BÂRRX Medical, Sunnyvale, CA, USA). RFA is safe and effective for eradicating early neoplasia in Barrett's esophagus, the precursor to esophageal adenocarcinoma [23–26]. A randomized, sham-controlled trial showed that RFA resulted in a high rate of complete eradication of neoplasia and a reduction in the rate of neoplastic progression [23]. This evidence base suggests that RFA may also have utility for eradicating early esophageal squamous cell neoplasia (ESCN). Therefore, we evaluated the effectiveness and safety of endoscopic RFA for eradicating MGIN, HGIN, and early flat-type (type 0-IIb) ESCC.

Patients and Methods

This was a prospective study conducted at the Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CICAMS) from October 2008 to April 2009. The CICAMS IRB approved the study protocol and the patient informed consent form. All participants signed an informed consent form. A data and safety monitoring committee monitored the trial. The reading of coded biopsy slides was exempted from review by the Office of Human Subjects Research of the National Institutes of Health, allowing the participation of NIH personnel (SD) in the research team.

Patients

Patients were eligible if they met all of the following inclusion criteria; 1) age 18–85 years; 2) high resolution (HR) Lugol's chromoendoscopy performed within 3 months prior to primary ablation showing at least one USL ≥ 3 cm containing MGIN, HGIN or early flat (type 0-IIb) ESCC (limited to T1m2); 3) length of USL-bearing esophagus ≥ 12 cm; 4) endoscopic ultrasound (EUS) with no submucosal invasion or lymphadenopathy; 5) CT chest/abdomen (HGIN/ESCC patients) with no metastasis or lymphadenopathy, and 6) subject neither pregnant nor intending to become pregnant during the study.

Patients were excluded if any one of the following exclusion criteria was present; 1) esophageal stricture preventing passage of therapeutic endoscope, 2) prior endoscopic resection (ER), 3) any non-flat esophageal mucosa, 4) esophageal dilation in past 12 months, 5) history of non-squamous cell cancer of the esophagus, or history of ESCC (any stage) prior to 3 months before enrollment, 6) ESCC with T1m3 or worse invasion, G3 or worse differentiation, or lymphatic or vascular invasion, 7) N or M positive ESCC, 8) previous ablation or radiation to the esophagus, or 9) previous esophageal surgery, except fundoplication.

Study Devices

Circumferential ablation was performed using the HALO³⁶⁰ system, consisting of balloon-based sizing and ablation catheters. The ablation catheter balloon is encircled by a 3 cm long bipolar array, which delivers short duration (~1 second) RFA at 40 W/cm² and 10–12 J/cm². Focal ablation was performed using the HALO⁹⁰ system, consisting an endoscope mounted ablation device. RFA is delivered at 40 W/cm² and 12 J/cm² via a 13 × 20 mm electrode.

Endoscopy procedures were performed with Olympus GIF-H260, GIF-H260Z, or GIF-H260J (Olympus, Tokyo, Japan) high-resolution endoscopes (Lucera systems). EUS was performed using a mechanical radial ultrasonic gastrovideoscope (GF-UM2000, Olympus, Tokyo, Japan).

Baseline Qualifying Examination

Patients underwent a baseline qualifying HR chromoendoscopy (1.25% Lugol's) to identify all USLs. If USLs met the study criteria, tattoos were placed 1 cm above and below the USL-bearing portion of the esophagus, defining the treatment area (TA). The location and size of each USL were recorded followed by collecting biopsies from each USL and from the normal staining portion of the TA. The worst grade of neoplasia detected at this visit served as the entry diagnosis for the patient. All patients underwent EUS, and those patients with HGIN/ESCC further underwent CT chest/abdomen with contrast.

Patient Flow

Within 3-months of the baseline qualifying endoscopy, patients underwent primary RFA of the TA (Figure 1). Participants returned 3-months later for HR chromoendoscopy. If no

USLs were seen, patients underwent biopsy of the TA as delineated by tattoos. If USLs were present, biopsies were obtained from each USL followed by focal ablation of each USL. Biopsies were also obtained from the normal staining portion of the TA. The 3-month pathology results determined whether the patient would return for a 6-month visit or be discharged to the 12-month visit. At the 12-month (primary endpoint) visit, patients underwent HR chromoendoscopy with biopsy.

Endoscopy Procedure Patient Sedation

Endoscopy procedures were performed using conscious sedation with midazolam, fentanyl, and/or propofol.

Ablation Procedures

All primary ablations were performed circumferentially using the HALO³⁶⁰ System. The TA was treated with 2 applications of energy (10 or 12 J/cm²) encompassing all tissue between the proximal and distal tattoos. According to dose-assignment, coagulum was or was not cleaned from the TA between ablation passes (Table 2). Secondary ablations were performed focally using the HALO⁹⁰ System. If USL(s) were identified at follow-up, the USL(s) were biopsied and then ablated three times in succession (12 J/cm²) with no cleaning.

Post-ablation discharge instructions

After ablation, patients were provided with omeprazole (20 mg po bid, 1 month), liquid acetaminophen with narcotic po prn, liquid antacid and lidocaine po prn, and sucralfate po prn.

Post-ablation symptom monitoring

Patients completed a standardized (unvalidated) daily diary assessing chest pain, dysphagia, throat pain, odynophagia, and abdominal pain at baseline and for the 14 days following any primary or secondary RFA procedure [23]. The diary entries utilized a 0–100 point visual analogue scale (VAS).

Esophageal Tissue Specimen Procurement and Processing

All esophageal biopsy specimens were procured in a pre-defined manner using large capacity biopsy forceps (FB-25k-1, 4.8 mm, Olympus, Japan). At the baseline qualifying examination and 3-, 6-, and 9-month follow-up visits, each USL was sampled with 1 biopsy per 1 cm of USL dimension, and the normal staining mucosa in the TA was sampled with 2 biopsies per 2 cm of TA length. At the 12-month visit, more frequent biopsies were obtained from the TA (4 biopsies per 2 cm of TA length). Each specimen was removed from the forceps using a toothpick, spread flat, attached to filter paper, and placed flat into a specimen jar (maximum 2 specimens from each location per jar). Each jar was numbered so it could be matched via a case report form to the biopsy location and mucosal staining characteristics (stained vs. unstained). After fixation, the filter paper was removed and the specimens embedded in a paraffin block with the flat surfaces oriented perpendicular to the cut surface of the block. The maximum number of specimens per block was two. Sections were applied to slides and stained with hematoxylin and eosin.

Histopathology Interpretation

Two expert GI pathologists (NL, SMD) independently reviewed specimens from baseline qualifying and 12-month examinations. The pathologists were blinded to patient history, treatment regimen, and prior histology results. Each specimen was graded as squamous epithelium: without intra-epithelial neoplasia, with LGIN, with MGIN, with HGIN, or with

invasive ESCC (depth and grade determined where possible based upon biopsy depth). The most advanced diagnosis from a visit was the histology status for that visit. If there was concordance between the independent reviews for the most advanced diagnosis, no further review was performed. Discordance was resolved by joint review. The study site GI pathologist (NL) singly interpreted specimens from the 3-, 6-, or 9-month examinations.

Outcome Measures

The primary endpoint was the proportion of patients with a histological complete response (CR) at 12 months, defined as absence of MGIN, HGIN or ESCC from any biopsy in the TA. The secondary endpoints were: 1) proportion of patients with CR at 3-months; 2) proportion of patients demonstrating neoplastic progression, defined as detection of ESCN of a more severe histological grade than study entry grade at any examination; 3) subject discomfort after ablation; and 4) adverse events.

Results

Patients

Twenty-nine patients were enrolled: 18 had a baseline diagnosis of MGIN, 10 had HGIN, and 1 had ESCC (T1m2). Baseline characteristics of the patients are shown in Table 1.

Disease Outcomes

At 3-months after circumferential RFA, 25 of the 29 patients (86%) were CR (1 LGIN, 24 no IEN) (Table 2). Of these 25 CR patients, 8 had no USLs and underwent biopsy only (8 no IEN), while 17 had USL(s) that were biopsied and then treated with focal RFA (1 LGIN, 16 no IEN). The remaining 4 patients (14%) had USL(s), were biopsied (2 HGIN, 2 MGIN) and treated with focal RFA. These 4 patients subsequently achieved CR at 6 or 9 months (1 LGIN, 3 no IEN) before being released to a 12-month follow-up.

At the 12-month follow-up endoscopy, 28 of the 29 patients (97%) were CR (4 LGIN, 24 no IEN) (Table 2). Of these 28 CR patients, 19 had no USLs (2 LGIN, 17 no IEN) and 9 had USL(s) (2 LGIN, 7 no IEN).

The single treatment failure at 12 months had a study entry diagnosis of ESCC and USLs involving 12 cm of the esophagus. At 3-months, the extensive USLs had been reduced to four USLs (each < 1 cm) with MGIN (treated with focal RFA.) At 6-months, the single remaining USL was biopsied and treated with focal RFA, but the biopsy showed no IEN, so the patient was released to the 12-month follow-up, at which time biopsy from the USL showed HGIN (study failure). The USL was removed with a single ER and showed HGIN with negative deep and lateral margins.

No patient exhibited neoplastic progression at any study visit.

Safety and Side Effects

All primary ablations were circumferential (n=29, median procedure time 39 min, IQR 32–55), while all secondary ablations were focal (22 procedures in 18 patients, median procedure time 11 min, IQR 10–12). There were no serious adverse events such as perforation, infection, bleeding or death. There was one mucosal laceration after sizing, which required no intervention. This patient underwent circumferential ablation 3-months later and achieved CR at the 3- and 12-month study visits.

Symptoms after circumferential RFA peaked on day 1 and returned to “0” by day 8, while symptoms after focal RFA were less severe, peaking on day 1 and returning to “0” by day 4 (Figure 3).

Stricture was noted in 4 patients (14%) after circumferential RFA. One stricture was graded as “mild” (non-circumferential scarring) and 3 as “moderate” (circumferential scarring allowing passage of therapeutic endoscope). All strictures resolved with dilation (median 2.5 sessions, IQR 2–4). All stricture patients achieved CR at 12 months.

Utility of Lugol’s mucosal staining for detection of neoplasia post-RFA

We performed a *post-hoc* analysis comparing Lugol’s mucosal staining patterns versus the associated histopathology for each post-RFA biopsy. In follow-up specimens obtained from normal staining mucosa (496 specimens), no findings of MGIN or worse were observed (a 100% negative predictive value), while for specimens from USLs (96 specimens), 13 exhibited MGIN or worse (a 14% positive predictive value). The sensitivity and specificity of a post-RFA USL for containing MGIN or worse were 100% and 86%, respectively (Table 3).

Discussion

In this prospective trial, 29 patients with early ESCN (MGIN, HGIN, or flat-type ESCC) underwent RFA and 97% (28/29) achieved CR at 12 months.

Prior to this study, Pouw et al. described outcomes from RFA in a 66-year-old male with a 35-mm, flat-type ESCC with adjacent HGIN who was ineligible for surgery or ER. One circumferential RFA treatment resulted in complete eradication of HGIN and ESCC [27]. Existing management strategies for early ESCN include ER, endoscopic submucosal dissection (ESD), and esophagectomy. While ER is associated with 90% curative resection rates, recurrence occurs in up to 26% of patients [28–32]. Piecemeal (vs. *en bloc*) ER, larger lesions, deeper invasion, and the presence of multiple USLs are associated with increased recurrence [28–29, 33.] ESD results in higher rates of *en bloc* resection and lower rates of recurrence compared to ER, but is more technically demanding and has higher complication rates [34, 35]. Furthermore, ER and ESD for extensive USLs, such as those treated with RFA in this study, are quite difficult to perform and are complicated by even higher local recurrence and stricture rates [27, 34, 36, 37]. While historically regarded as a gold standard for curative resection, esophagectomy has relatively higher morbidity and mortality rates [38, 39].

In this trial, stricture occurred in 14% of patients, all after circumferential RFA. This rate is somewhat higher than rates of stricture after RFA for Barrett’s (0–9%) [23–26, 40–41]. In the Barrett’s RFA literature, prior ER or stricture and long segment length may increase stricture risk [25, 40–41]. Our patients did not have prior ER or stricture, but did have long treatment length (median 8.2 cm). Technique and dose may also contribute to stricture formation when using RFA for early ESCN. We evaluated four regimens, including the regimen presently used for treating Barrett’s esophagus (12 J/cm²-clean-12 J/cm²), varying energy density (10 or 12 J/cm²) and cleaning of coagulum (Table 2). Two regimens contained all 4 of the strictures (12 J/cm²-clean-12 J/cm² (19%) and 12 J/cm²-x2 without cleaning (14%)), while the other two regimens, with arguably lower energy density (12J/cm²-clean-10J/cm² and 10J/cm²-x2 without cleaning), had no strictures. While the size of each dosimetry group is too small to draw conclusions about the relationship between energy density and stricture rate, squamous epithelium may be more sensitive to RFA than is Barrett’s epithelium. Further dosimetry work is underway to preserve our high CR while reducing the stricture rate.

Comparing our CR rates for early ESCN patients to those observed for Barrett's esophagus, the majority of our patients (86%) achieved CR after one primary circumferential ablation and 97% achieved CR after a mean of 1.7 ablations, less than the 2–4 sessions usually needed to achieve CR in Barrett's [23–26, 40–41].

Strengths of this study include its prospective design, its histology-based primary outcome, expert pathologists with blinded review, and the experience of the investigator group in the management of esophageal neoplasia.

Limitations of this study include its small patient sample size, the lack of a control group, inclusion of only one patient with ESCC, four circumferential dose-groups, and the possibility that sampling error during follow-up overestimated the CR rate. Regarding the single case of ESCC at baseline, caution should be used in generalizing these trial results to all patients with an eligible T1m2 lesion until outcomes involving more patients are available. Regarding the dosimetry, we evaluated four regimens to allow us to begin optimizing these variables for future trials. Regarding the potential for sampling error in follow-up visits, it is unlikely that we missed significant neoplasia in the normal staining TA, since all 496 biopsy specimens from this mucosa were negative. It is possible that we missed some neoplasia within a biopsied USL, but all USLs were focally treated with RFA and then biopsied 3-months later and again at the 12-month visit. In this study we performed circumferential RFA to the entire TA as the primary treatment, based on the hypothesis that occult neoplasia and/or oncogenetic abnormalities may exist independent of the USLs. While we will persist in this approach in future studies, the fact that all 496 post-RFA biopsy specimens from normal staining TA had no MGIN or worse disease may allow us to obtain fewer or no biopsies from normal staining tissue after RFA, at least at interim visits prior to the primary endpoint endoscopy. Also, post-RFA USLs in this study were biopsied and treated empirically with focal RFA, because such USLs in untreated patients may have significant neoplasia and we wanted to avoid the need for patients to return for an additional ablation endoscopy. We think that this is proper practice in this situation, even though only 13 of 96 such biopsies (14%) contained MGIN or worse disease.

Our results suggest that RFA has utility in the treatment of appropriately selected patients with early ESCN. Our selection criteria included patients with MGIN and HGIN because of their very high near-term risk for developing invasive cancer (27% and 65% over 3.5 years, respectively) [21]. We also included one patient with flat-type ESCC, because the rate of lymph node metastasis is low and the depth of RFA injury is adequate to remove such lesions. We excluded patients with non-flat mucosal lesions, as such lesions require ER for accurate diagnosis and staging. ER followed by RFA is safe and effective in studies of Barrett's neoplasia, so future studies combining ER and RFA in ESCN are underway [25–26, 40, 42]. In conclusion, in this prospective study of RFA in patients with early flat-type esophageal squamous cell neoplasia (MGIN, HGIN, ESCC), RFA was associated with a high rate of histological complete response (97% of patients), no neoplastic progression, and an acceptable adverse event profile.

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Abbreviations

CR	complete response
ER	endoscopic resection
ESCC	esophageal squamous cell carcinoma
ESCN	esophageal squamous cell neoplasia
ESD	endoscopic mucosal dissection
HGIN	high grade intraepithelial neoplasia
HR	high resolution
IEN	intraepithelial neoplasia
IQR	interquartile range
LGIN	low grade intraepithelial neoplasia
MGIN	moderate grade intraepithelial neoplasia
RFA	radiofrequency ablation
TA	treatment area
USL	unstained lesion

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010; 127:2893–2917. [PubMed: 21351269]
2. Garcia, M.; Jemal, A.; Ward, EM.; Center, MM.; Hao, Y.; Siegel, RL.; Thun, MJ. *Global Cancer Facts & Figures 2007*. Atlanta, GA: American Cancer Society; 2007.
3. Blot, WJ.; McLaughlin, JK.; Fraumeni, JF, Jr. Esophageal cancer. In: Schottenfeld, D.; Fraumeni, JF., Jr, editors. *Cancer epidemiology and prevention*. 3. Oxford: Oxford University Press; 2006. p. 697-706.
4. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. *Semin Radiat Oncol*. 2006; 17:2–9. [PubMed: 17185192]
5. Lu XJ, Chen ZF, Guo CL, Li SS, et al. Endoscopic survey of esophageal cancer in a high-risk area of China. *World J Gastroenterol*. 2004; 10:2931–2935. [PubMed: 15378767]
6. Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. *Gastroenterol Clin North Am*. 2009; 38:27, 57, vii. [PubMed: 19327566]
7. Tran GD, Sun XD, Abnet CC, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*. 2005; 113:456–463. [PubMed: 15455378]
8. Roth M, Qiao Y, Rothman N, et al. High urine 1-hydroxypyrene glucuronide concentration in Linxian, China, an area of high risk for squamous oesophageal cancer. *Biomarkers*. 2001; 6:381–386.
9. Abnet CC, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Prospective study of tooth loss and incident esophageal and gastric cancers in China. *Cancer Causes Control*. 2001; 12:847–854. [PubMed: 11714113]
10. Pourshams A, Khademi H, Malekshah A, Islami F, Nouraei M, Sadjadi A, et al. Cohort profile: the Golestan cohort study - a prospective study of esophageal cancer in northern Iran. *Int J Epidemiol*. 2010; 39:52–59. [PubMed: 19332502]

11. Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer*. 2008; 98:1857–1863. [PubMed: 18475303]
12. Islami F, Ren JS, Taylor PR, Kamangar F. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. *Br J Cancer*. 2009; 101:1641–1647. [PubMed: 19862003]
13. Kamangar F, Strickland PT, Pourshams A, Malekzadeh R, Boffetta P, Roth MJ, et al. High exposure to polycyclic aromatic hydrocarbons may contribute to high risk of esophageal cancer in northeastern Iran. *Anticancer Res*. 2005; 25:425–428. [PubMed: 15816606]
14. Islami F, Kamangar F, Aghcheli K, et al. Epidemiologic features of upper gastrointestinal tract cancers in Northeastern Iran. *Br J Cancer*. 2004; 90:1402–1406. [PubMed: 15054463]
15. Abnet CC, Kamangar F, Islami F, Nasrollahzadeh D, Brennan P, Aghcheli K, et al. Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2008; 17:3062–3068. [PubMed: 18990747]
16. Brown LM, Hoover RN, Greenberg RS, Schoenberg JB, Schwartz AG, Swanson GM, et al. Are racial differences in squamous cell esophageal cancer explained by alcohol and tobacco use? *J Natl Cancer Inst*. 1994; 86:1340–1345. [PubMed: 8064893]
17. Brown LM, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM, et al. Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. *Am J Epidemiol*. 2001; 153:114–122. [PubMed: 11159155]
18. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol*. 2007; 165:1424–1433. [PubMed: 17420181]
19. Dawsey SM, Fleischer DE, Wang GQ, et al. Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. *Cancer*. 1998; 83:220–231. [PubMed: 9669803]
20. Dawsey SM, Lewin KJ, Liu FS, Wang GQ, Shen Q. Esophageal morphology from Linxian, China. Squamous histologic findings in 754 patients. *Cancer*. 1994; 73:2027–2037. [PubMed: 8156507]
21. Dawsey SM, Lewin KJ, Wang G-Q, 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; 74:1686–1692. [PubMed: 8082069]
22. 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; 54:187–192. [PubMed: 15647178]
23. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009; 360:2277–2288. [PubMed: 19474425]
24. Sharma VK, Kim HJ, Das A, et al. Circumferential and focal ablation of Barrett's esophagus containing dysplasia. *Am J Gastroenterol*. 2009; 104:310–317. [PubMed: 19174783]
25. Pouw RE, Gondrie JJ, Sondermeijer CM, et al. Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. *J Gastrointest Surg*. 2008; 12:1627–1636. [PubMed: 18704598]
26. 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. [PubMed: 18355819]
27. Pouw RE, Gondrie JJ, Curvers WL, et al. Successful balloon-based radiofrequency ablation of a widespread early squamous cell carcinoma and high-grade dysplasia of the esophagus: a case report. *Gastrointest Endosc*. 2008; 68:537–541. [PubMed: 18760181]
28. Esaki M, Matsumoto T, Hirakawa K, et al. Risk factors for local recurrence of superficial esophageal cancer after treatment by endoscopic mucosal resection. *Endoscopy*. 2007; 39:41–45. [PubMed: 17252459]
29. Katada C, Muto M, Manabe T, et al. Local recurrence of squamous cell carcinoma of the esophagus after EMR. *Gastrointest Endosc*. 2005; 61:219–225. [PubMed: 15729229]
30. Ciocirlan M, Lapalus MG, Hervieu V, et al. Endoscopic mucosal resection for squamous premalignant and early malignant lesions of the esophagus. *Endoscopy*. 2007; 39:24–29. [PubMed: 17252456]

31. Takahashi H, Arimura Y, Masao H, et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). *Gastrointest Endosc.* 2010; 72:255–264. [PubMed: 20541198]
32. Pech O, May A, Gossner L, et al. Curative endoscopic therapy in patients with early esophageal squamous-cell carcinoma or high-grade intraepithelial neoplasia. *Endoscopy.* 2007; 39:30–35. [PubMed: 17252457]
33. Ishihara R, Iishi H, Takeuchi Y, et al. Local recurrence of large squamous-cell carcinoma of the esophagus after endoscopic resection. *Gastrointest Endosc.* 2008; 67:799–804. [PubMed: 18158151]
34. Ishii N, Horiki N, Itoh T, et al. Endoscopic submucosal dissection with a combination of small-caliber-tip transparent hood and flex knife is a safe and effective treatment for superficial esophageal neoplasias. *Surg Endosc.* 2010; 24:335–342. [PubMed: 19517169]
35. Fujishiro M, Yahagi N, Kakushima N, et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. *Clin Gastroenterol Hepatol.* 2006; 4:688–694. [PubMed: 16713746]
36. Katada C, Muto M, Manabe T, et al. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. *Gastrointest Endosc.* 2003 Feb; 57:165–169. [PubMed: 12556777]
37. Mizuta H, Nishimori I, Kuratani Y, et al. Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. *Dis Esophagus.* 2009; 22:626–631. [PubMed: 19302207]
38. Barreto JC, Posner MC. Transhiatal versus transthoracic esophagectomy for esophageal cancer. *World J Gastroenterol.* 2010; 16:3804–3810. [PubMed: 20698043]
39. Goan YG, Chang HC, Hsu HK, Chou YP. An audit of surgical outcomes of esophageal squamous cell carcinoma. *Eur J Cardiothorac Surg.* 2007; 31:536–544. [PubMed: 17222561]
40. Vassiliou MC, von Renteln D, Wiener DC, et al. Treatment of ultralong-segment Barrett's using focal and balloon-based radiofrequency ablation. *Surg Endosc.* 2010; 24:786–791. [PubMed: 19711128]
41. Velanovich V. Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus: initial results and lessons learned. *Surg Endosc.* 2009; 23:2175–2180. [PubMed: 19263139]
42. Zhang YM, Bergman JJ, Weusten B, et al. Radiofrequency ablation for early esophageal squamous cell neoplasia. *Endoscopy.* 2010; 42:327–333. [PubMed: 20235007]

Figure 1.

After enrollment, patients underwent primary circumferential radiofrequency ablation (RFA) of the treatment area (TA). Patients returned at 3-month intervals for endoscopy with Lugol's to identify residual USLs. Flow diagram depicts decision tree at each visit based upon endoscopic findings and subsequent histology results. Once a patient demonstrated a histological complete response (CR) defined as absence of MGIN, HGIN and ESCC in all biopsies obtained at a follow-up visit, they were released to the 12-month primary endpoint endoscopy visit.

Figure 2.

Circumferential and focal radiofrequency ablation (RFA) of a 5-cm long flat-type early squamous cell neoplasia with high-grade intraepithelial neoplasia (HGIN). Patient achieved complete response (absence of MGIN, HGIN and ESCC in the treatment area) at 12-month primary outcome.

A. Pre-treatment white light endoscopy image showing a more reddish colored area at the lower half of the image;

B. Corresponding image with narrow band imaging;

C. Corresponding image with Lugol's chromoendoscopy demonstrating a flat type unstained lesion, biopsies showed HGIN;

- D. Circumferential ablation catheter placed in the esophagus prior to the first ablation pass;
- E. Appearance of the mucosa after first circumferential ablation pass and after cleaning the ablation zone;
- F. Circumferential ablation catheter placed in the esophagus prior to the second ablation pass;
- G. 3-month visit. White light endoscopy image showing the treatment area;
- H. Corresponding image with Lugol's chromoendoscopy demonstrating an unstained lesion at 5:00;
- I. Appearance of the mucosa immediately after focal ablation of the unstained lesion, the ablation catheter can be seen at the top of the endoscopic image;
- J, K, L. 12-month primary endpoint visit. White light endoscopy and Lugol's HR chromoendoscopy images demonstrate no evidence of residual squamous neoplasia. Biopsies confirmed complete response.

Figure 3.

(a–b). Patient-reported 14-day diary scores after: a) circumferential RFA, and b) focal RFA. Visual analog scale (0–100) with “0” representing no symptoms and “100” representing severe symptoms.

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Table 1

Baseline characteristics of the patients *

Variable	Value
Patients – no.	29
Age - years	
Mean	60.3 ± 6.2
Range	43 – 73
Sex – no. (%)	
Male	14 (48)
Female	15 (52)
Body Mass Index (kg/m ²)	
Mean	23.2 ± 2.8
Range	18.4 – 28.6
Chinese Ethnicity – no. (%) **	29 (100)
Current use of tobacco – no. (%)	6 (21)
Years of tobacco use in users	36.2 ± 4.9
Cigarettes per day in users	14.2 ± 6.6
Current use of alcohol – no. (%)	8 (28%)
Years of alcohol use in users	34.4 ± 7.3
Number of drinks per week in users	17.6 ± 13.8
History of any cancer in a first-degree relative – no. (%)	11 (38)
Grade of esophageal neoplasia at study entry –no. (%)	
MGIN	18 (62)
HGIN	10 (34)
ESCC	1 (4)
Length of unstained lesions – cm	
Mean	6.2 ± 3.1
Range	2 – 12
Length of treatment area – cm	
Mean	8.2 ± 3.1
Range	4 – 14

* Plus-minus values are means ± SD

** Ethnicity was self-reported

MGIN: moderate-grade intraepithelial neoplasia

HGIN: high-grade intraepithelial neoplasia

ESCC: esophageal squamous cell carcinoma

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Table 2

Patient outcomes

Treatment Regimen			Patients	CR after primary RFA no. (%)	Stricture no. (%)	CR 12 mo no. (%)
First Pass Dose (J/cm ²)	Cleaning	Second Pass Dose (J/cm ²)				
12	Yes	12	16	14 (88%)	3 (19%)	16 (100%)
12	Yes	10	4	4 (100%)	0 (0%)	4 (100%)
12	No	12	7	6 (86%)	1 (14%)	6 (86%)
10	No	10	2	1 (50%)	0 (0%)	2 (100%)
			29	25 (86%)	4 (14%)	28 (97%)

Treatment regimen refers to the primary circumferential ablation only.

All patients had two applications of energy at the primary ablation session.

Cleaning (yes/no) denotes cleaning of coagulum from the treatment area between the 1st and 2nd energy applications.

CR is the proportion of patients with histological complete response at interim or 12 month visit, defined as no MGIN, HGIN, or ESCC on biopsy from treatment area.

J/cm²: Joules per square centimeter

RFA: radiofrequency ablation

Table 3

Correlation of endoscopic mucosal staining and histopathology in the follow-up endoscopy visits

	Biopsy specimens with MGIN or worse no. (%)	Biopsy specimens with less than MGIN no. (%)	Total
Unstained Mucosa	13 (14% [*])	83 (86%)	96
Stained Mucosa	0 (0%)	496 (100%)	496
Total	13	579	592

MGIN: moderate-grade intraepithelial neoplasia

* All percentages are row percentages