Radiofrequency ablation for early esophageal squamous cell neoplasia

Authors

Institutions
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Introduction

Esophageal cancer is the sixth most common cause of cancer death in the world [1]. Over 80% of esophageal cancers occur in developing countries [1], and in these areas, 90% of these cancers are esophageal squamous cell carcinoma (ESCC) [2]. The precursor lesion of ESCC is squamous intraepithelial neoplasia (squamous dysplasia), defined histologically as nuclear atypia (enlargement, pleomorphism, and hyperchromasia), loss of normal cellular polarity, and abnormal tissue maturation [3, 4]. The World Health Organization (WHO) subclasses squamous intraepithelial neoplasia into low-grade intraepithelial neoplasia (LGIN) and high-grade intraepithelial neoplasia (HGIN), depending on the extent of the nuclear atypia and the involvement of the epithelium [4]. In China, where ESCC and its precursors are very common in some areas, a three-tier system is used, including LGIN (mild dysplasia, involving the lower third of the epithelium), medium-grade intraepithelial neoplasia (MGIN, moderate dysplasia, involving the lower two-thirds of the epithelium), and HGIN (severe dysplasia, involving the full thickness of the epithelium) [3]. Follow-up studies in China have shown that the rate of progression to ESCC differs significantly between LGIN (5.3% over 3.5 years), MGIN (26.7%), and HGIN (65.2%), and because of their significant risk of progression, MGIN and HGIN are targets for screening and therapy [5, 6].

Current treatment of esophageal squamous cell neoplasia (ESCN, including squamous intraepithelial neoplasia and invasive squamous cell carcinoma) involves surgery for lesions invading into the deep submucosa or beyond and endoscopic treatment for lesions restricted to the epithelial layer (intraepithelial neoplasia; sm1) or the lamina propria (m2). Lesions invading into the muscularis mucosae (m3) or superficial submucosa (sm1) are considered the “grey zone” between endoscopic and surgical treatment.

One option for endoscopic treatment of early ESCN involves endoscopic resection of unstained lesions (USLs) after Lugol’s chromoscopy, as USLs are predictive for the presence of neoplasia. Endoscopic resection allows for histologic staging of infiltration depth, tumor differentiation, and lymph-vascular invasion, while completely removing the visible lesion. USLs larger than 15 mm require either piecemeal resection with the standard cap-based endoscopic resection techniques or endoscopic submucosal dissection (ESD) for complete resection. Widespread endoscopic resection/ESD, however, is technically demanding, with procedure times of many hours; it is also associated with severe esophageal stenosis for lesions that encompass ≥75% of the circumference and a significant risk for esophageal perforation and bleeding. Complete endoscopic resection is also not necessarily the best approach for all patients with early ESCN. Large flat-type lesions (i.e., type 0-IIb), which carry a very low risk for deeper invasion, can be effectively treated by an endoscopic ablation technique that is much easier to apply and is associated with a very low rate of complications, such as esophageal stenosis. A safe, effective, and technically easy-to-administer ablation method is especially attractive for geographic areas where ESCN is endemic and most endoscopists have a lower level of expertise in endoscopic resection/ESD.

In China, there are many high-risk areas for ESCN, such as the Taihang mountain range in North-Central China and areas in Sichuan, Shandong, Jiangsu, and Fujian Provinces and the Xinjiang Uygur Autonomous Region [7]. These high-risk areas in China are estimated to include a total of over 100 million people, and invasive ESCN occurs here at rates approaching or surpassing 100/100,000 people per year [2], an incidence approximately 30-fold that of Barrett’s-related
esophageal adenocarcinoma in the Western world [8]. The Chinese government is supporting widespread endoscopic screening using Lugol’s chromoscopy in these high-risk areas, and in 2010 it is estimated that 57,000 individuals will undergo such a screening endoscopy. From this screening process, it is estimated that 5% of patients will have MGIN, HGIN, or early cancer limited to the epithelium and will be eligible for endoscopic therapy.

Radiofrequency ablation: technical background and application in Barrett’s esophagus

Radiofrequency ablation (RFA) using the HALO system is a relatively new ablation technique that has been extensively studied in Barrett’s esophagus [9–12]. RFA in Barrett’s esophagus generally involves primary circumferential RFA using a balloon-based bipolar electrode (HALO 360°, Fig. 1), followed after 2–3 months by focal RFA of residual Barrett’s esophagus using the endoscope-mounted HALO 90° catheter (Fig. 2).

For both catheters, an energy generator delivers radiofrequency energy in an automated and controlled manner to the electrode upon activation via a foot switch. Ablative therapy is delivered twice to each area of targeted tissue in the esophagus using a fixed energy and power density. An intervening step of cleaning off any coagulum may be used to improve the ablation effect during the second delivery, although current studies are evaluating double treatment without interval cleaning resulting in shorter total procedure times (< 10 minutes). Uniformity of ablation effect and control of depth of ablation to the muscularis mucosae or superficial submucosa (maximum 1000 microns) is achieved by flattening the mucosa prior to ablation, using a standardized energy density dose, delivering the energy rapidly with high-power density, and using a tightly spaced bipolar electrode array.
to create the electrical field. In this manner, the treatment effect is less operator-dependent. After initial dosimetry studies in the porcine esophagus and human esophagus prior to esophagectomy, a number of prospective clinical studies have evaluated the safety and efficacy of RFA in nondysplastic intestinal metaplasia, LGIN, HGIN, and intramucosal adenocarcinoma developing in Barrett’s esophagus [9–12]. These studies have yielded success rates for eradication of neoplasia and Barrett’s esophagus mucosa of 90%–95%, with remarkably few complications. Further, in a randomized, sham-controlled trial, Shaheen et al. reported that in patients with dysplastic Barrett’s esophagus, RFA was associated with a high rate of complete eradication of both dysplasia and intestinal metaplasia and a reduced risk for disease progression [11]. In addition, RFA in Barrett’s esophagus has been associated with a low rate (<5%) of ablation-related stenosis and the neosquamous mucosa that regenerates after RFA is free of genetic abnormalities, suggesting that it holds no residual malignant potential [9–14].

RFA for early esophageal squamous cell neoplasia

Radiofrequency ablation may also have significant utility for treatment of early ESCN, for several reasons. First, RFA is technically easy to apply, carries a low risk of complications, and is generally performed as an outpatient procedure. This compares favorably with piecemeal endoscopic resection and ESD which require a higher level of endoscopic expertise, long procedure times, and clinical observation for several days, issues that are especially important for the screening programs in the endemic areas mentioned above. Second, circumferential RFA with the HALO360+ has been associated with a low rate of post-RFA stenosis in Barrett’s esophagus, and if this is also true in ESCN then this would enable treatment of widespread or mosaic-like early ESCN for which endoscopic resection or ESD would surely result in severe esophageal strictureing. Third, RFA in Barrett’s esophagus is associated with a complete “reset” of genetic abnormalities, and if this is also true in ESCN it may reduce the rate of late recurrences compared with resection techniques where the resection margin is generally less than 2 mm.

Current experience with RFA of early esophageal squamous cell neoplasia

The clinical experience related to RFA for early ESCN is limited but promising. After a first case report in 2008, a heterogeneous group of 13 patients (with and without prior endoscopic resection, different energy settings) was treated in Amsterdam [15]. Based on these results and a pilot study in Beijing in October 2008, our group initiated a prospective cohort study in Beijing and Feicheng (P. R. China). In this study 60 patients with flat-type ESCN (MGIN, HGIN, T1m2) have been enrolled and the first results will be available later this year. Representative images from this study are shown in Figs. 3-1–3-3.

How to apply RFA in early esophageal squamous cell neoplasia

Consent

Although the HALO systems are FDA cleared and CE marked for esophageal ablation we feel that patients should be informed that limited clinical trial outcomes are available related to the use of this technology for early ESCN. For the same reason, the following guidelines should be regarded as preliminary.

Patient selection

We currently feel that RFA as a single-modality treatment should be restricted to patients with completely flat-type ESCN (type 0-IIb) without nodularity or ulceration, and with a pretreatment biopsy diagnosis of MGIN, HGIN or well-to-moderately differentiated invasive cancer limited to the lamina propria (m2). Type 0-IIa and/or 0-IIc lesions require endoscopic resection/ESD for focal...
Fig. 3 Three cases of early esophageal squamous cell neoplasia before and after radiofrequency ablation treatment, as seen with white light endoscopy, narrow-band imaging, and Lugol’s chromoscopy. 1 a–c Endoscopic view of a semi-circumferential flat type early squamous cell neoplasia containing high-grade intraepithelial neoplasia (HGIN). 1 d–f After primary circumferential ablation there are no signs of residual neoplasia. 2 a–c Mosaic-like flat type squamous cell neoplasia containing HGIN. 2 d–f After primary circumferential ablation and one focal ablation session, only a small unstained area is observed upon Lugol’s chromoscopy showing no dysplasia upon biopsy. 3 a–c A 4-cm-long early squamous cell neoplasia stretching from the 5 – 11 o’clock position and containing HGIN. 3 d–f Primary circumferential ablation and one focal ablation session have resulted in complete removal of the neoplastic lesion. Reproduced with permission of www.endosurgery.eu.
removal and histologic staging; type 0-I and 0-III lesions generally invade into the submucosa and are not eligible for endoscopic treatment.

**Imaging**

Lugol’s chromoscopy (1%–2%) is required in all cases of ESCN. Given the caustic effect of this solution, RFA should not be performed within 2 weeks after Lugol’s chromoscopy, as the Lugol’s solution has been shown to make the epithelium vulnerable to superficial bleeding, which hampers visibility and the proper application of RFA. During the pretreatment chromoendoscopy exam, we place two 0.25 mL tattoos at opposite sites of the esophagus, 1 cm proximal to the most proximal USL and 1 cm distal to the most distal USL. These tattoos serve as permanent markers, allowing easy identification of the treatment area at the actual RFA session (Fig. 1 d,e) and subsequent follow-up sessions.

**Sizing**

Given the mosaic nature of USLs and uncertainties regarding the oncogenetic alterations present in normal staining epithelium, we prefer to perform primary ablation with the circumferential HALO360+ catheter. This enables treatment of the entire field with minimal overlap. Prior to circumferential ablation, sizing of the esophageal inner diameter is required. A sizing catheter is connected to the HALO360 generator, calibrated, and introduced over a guide wire. The sizing procedure is a “blind” procedure using the 1-cm scale on the catheter shaft for reference. For the first measurement the catheter is placed about 4 cm above the most proximal set of tattoos. The measurement cycle is started by pressing the foot switch, which inflates the sizing balloon, and the esophageal inner diameter is automatically calculated for the entire length of the 4-cm-long balloon. This action is repeated for every 1–2 cm of the targeted portion of the esophagus. If any blood is seen on the sizing balloon after removal, endoscopic inspection should be performed to rule out esophageal injury prior to introducing the ablation balloon. If esophageal injury is noted, ablation should be delayed to allow healing.

**Choosing the appropriate ablation catheter**

The HALO360+ ablation balloon is available in five separate outer diameter sizes (18, 22, 25, 28, and 31 mm). The appropriate size is selected based on the smallest single measurement obtained during sizing. If any measurement is less than 18 mm, balloon-based circumferential ablation should not be performed, as the smallest available ablation balloon is 18 mm in outer diameter. Focal ablation using the smaller HALO30 ablation catheter may be considered in these cases, but circumferential treatment with the HALO30 catheter may carry a higher theoretical risk of stenosis due to overlap of adjacent ablation zones.

**Energy setting and cleaning of the ablation zone**

The HALO360+ catheter is introduced over a guide wire and the endoscope is introduced alongside the ablation catheter. Under endoscopic visualization the proximal margin of the electrode is positioned at the level of the most proximal set of tattoos (Fig. 1 e). The balloon is inflated, the esophagus is deflated using endoscope suction to optimize tissue contact, and the electrode is then activated via a foot switch. Energy delivery typically lasts less than 1.5 seconds, after which the balloon is automatically deflated. Moving proximally to distally, the balloon is repositioned, allowing a 5–10-mm overlap with the previous ablation zone. In our initial studies we have used an energy setting of 12 J/cm² with cleaning of the ablation zone after the first ablation pass (Fig. 1 g). These settings were, however, mainly derived from experience with RFA of Barrett’s mucosa. We are currently evaluating delivery of 10 or 12 J/cm² twice to each location, without in-
terval cleaning, which reduces treatment time and minimizes unintended overlap between zones.

Post-RFA patient care
After RFA of Barrett’s esophagus, proper acid-suppressant therapy is very important, not only to minimize patient discomfort, but also to allow the esophagus to heal optimally and regenerate with squamous epithelium. Although the importance of acid-suppressant therapy may be less in ESCN, we prescribe all patients esomепразол 40 mg twice daily for 1 month to optimize the conditions for healing.

In addition, patients are advised to adhere to a liquid diet for 24 hours, gradually progressing to a soft and normal diet at their own discretion. Patients may experience symptoms of chest discomfort, sore throat, difficulty or pain with swallowing and/or nausea, which usually improve each day. Proposed medications consist of an oral antacid/lidocaine mixture for the first 24 hours (e.g. 15 mL every 4 hours), liquid acetaminophen with or without oral codeine on demand, and anti-emetic medication.

Subsequent RFA sessions
Follow-up sessions are scheduled at 2–3-month intervals. The initial treatment area is easily identified by the tattoos and is inspected with standard endoscopy for healing and stenosis followed by Lugol’s chromoxy to identify USLs. As USLs may present reactive changes after RFA or residual ESCN, we obtain biopsies of each USL for histologic analysis followed by immediate ablation using the HALO® catheter (Fig. 2). HALO® ablation is guided by the biopsy sites, with repeated Lugol’s chromoscopy in case of doubt. The target area is positioned at the 12 o'clock position in the endoscopic video image. The electrode is brought into close contact with the mucosa, deflected upward, and activated via a foot switch. While keeping the electrode in place, three sequential ablations at 12 J/cm² are performed without cleaning of the ablation zone.

Combining endoscopic resection and RFA
Many patients with early ESCN have lesions that consist of a large type 0-IIb component as well as one or more focal type 0-IIa/lIc components. As mentioned, RFA is only a suitable treatment strategy for flat-type lesions as it lacks the histologic correlation of endoscopic resection and is not designed to penetrate a thickened raised lesion. Therefore, a combination therapy of endoscopic resection and RFA may combine the best features of these two techniques. Endoscopic resection allows for focal removal of the type 0-IIa/lIc component and enables optimal histologic staging. It also renders the remaining mucosa flat, and thus eligible for subsequent RFA. Our group is currently investigating the optimal timing and combination of these treatments in both animal and human trials. In Barrett’s esophagus the combination of endoscopic resection for staging, followed 8 weeks later by RFA, has been shown to be safe and effective, with a low rate of RFA-related stenosis.[10, 12] It is advised, however, to limit the extent of endoscopic resection to < 50% of the circumference and < 2 cm in length, as focal narrowing after endoscopic resection may make subsequent circumferential RFA more difficult.[12] This issue may be even more relevant for patients with early ESCN, who often have an esophagus with a much smaller inner diameter and reduced compliance compared with Barrett’s patients. Also, it may be more difficult to limit the extent of endoscopic resection of ESCN when using cap-based resection techniques, as the squamous mucosa is more easily sucked into the cap than Barrett’s epithelium, resulting in relatively larger resection areas. Finally, after a prior endoscopic resection, care should be taken not to overestimate the inner esophageal diameter when performing circumferential RFA. The sizing balloon calculates a mean inner diameter based on esophageal wall compliance over a length of 4 cm, which may result in an overestimation of the esophageal inner diameter at the site of the endoscopic resection scar. It is therefore advisable to be conservative when choosing the appropriate diameter of the HALO® catheter, with a low threshold to perform a careful “test-dilation” to avoid overstretching or even lacerating the treatment area with the ablation balloon.

Unresolved issues and future prospects
More studies are underway on the use of RFA for early ESCN. The HALO ablation devices have only recently become available for study in Asia, where early ESCN is more prevalent and more homogeneous cohorts can be studied. Future studies should aim to determine the optimal energy setting and technique for circumferential RFA, the relative roles of HALO® and HALO® as primary treatment tools, the optimal strategy for combined endoscopic resection and RFA treatments, the genetic and other properties of the squamous mucosa that regenerates at the site of the original lesion, and the long-term durability of the treatment outcome.

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