Endoscopic treatment of Barrett's esophagus by radiofrequency ablation

Gabriel Rahmi, Christophe Cellier
Service d'hépato-gastroentérologie,
Hôpital européen Georges Pompidou,
Paris, France

" Barrett's esophagus (BE) can be associated with the advent of an adenocarcinoma of the lower esophagus, and the detection of a dysplastic section is a predicting factor. The endoscopic treatment of a BE with high-grade dysplasia can be achieved by resection techniques such as endoscopic mucosal resection or submucosal dissection, which must be proposed as a first-line treatment if zones with raised abnormalities are present. However, the treatment of large, circumferential areas may lead to complications, and in particular to the risk of esophageal stricture. The destruction by esophageal radiofrequency ablation of an extended BE with zones of high-grade dysplasia has been evaluated in numerous studies and allows the eradication of the Barrett's mucosa in the short and medium terms, with low morbidity and a very significant reduction in the risk of development of an adenocarcinoma. Treatment of BE with low-grade dysplasia or without dysplasia using this technique is currently being evaluated."

Gastroesophageal reflux can be a contributing factor to the development of Barrett's esophagus (BE), also known as Barrett's mucosa. The prevalence of BE has been estimated at 1% in patients undergoing upper endoscopy, regardless of the indication [1]. BE is a stage with precancerous potential, which can evolve to adenocarcinoma. This risk of malignant transformation is very low in the case of BE without dysplasia (about 0.6% per patient per year) and is also minimal for BE associated with low-grade dysplasia (LGD) (1.7–2% per patient per year). In contrast, it becomes more substantial for high-grade dysplasia (HGD), with a risk determined as 6–10% per patient per year [2-5]. BE with dysplasia can be treated by surgery, but with significant morbidity and mortality, even when performed by highly skilled teams. Endoscopic treatments represent an alternative to surgical treatment. Mucosal resection techniques such as endoscopic mucosal resection or submucosal dissection allow curative treatment and histological analysis but are associated with the onset of esophageal strictures if an extensive resection is performed. Esophageal endoscopic radiofrequency ablation has become the standard treatment for dysplastic BE as it allows the destruction of a large area of the BE without excessive morbidity.

Technique of the esophageal radiofrequency ablation

The treatment is carried out with a radiofrequency catheter and a dedicated generator. The HALO 360 system (BAARx Médical, Covidien, USA) is a method of circumferential thermal destruction of the mucosa using a balloon topped with bipolar electrodes, which is inflated in the esophageal lumen (*figures 1 and 2*).

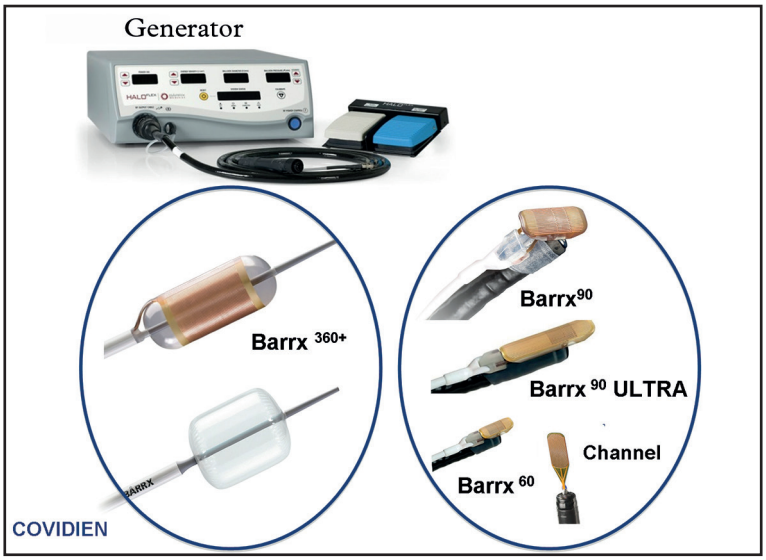

Figure 1. Equipment necessary for esophageal radiofrequency ablation.

The diameter of the balloon is defined through the use of a calibration balloon inflated beforehand in the esophagus. Destruction is homogeneous through the use of a standardized radiofrequency generator. When there is a noncircumferential lesion or a residual island after the first session of radiofrequency ablation, it is possible to use an applicator with bipolar electrodes attached to perform a focal destruction of the mucosa (HALO 90 system) or a smaller radiofrequency catheter inserted through the operating channel (channel catheter). On average, two to three radiofrequency sessions are required to eradicate the entire zone of BE.

The theoretical contraindications of esophageal radiofrequency ablation treatment are: active and/or complicated peptic esophagitis at the time of treatment; an esophagitis due to irradiation; a stricture of the esophagus of any etiology; the presence of esophageal varices; a history of Heller's cardiomyotomy.

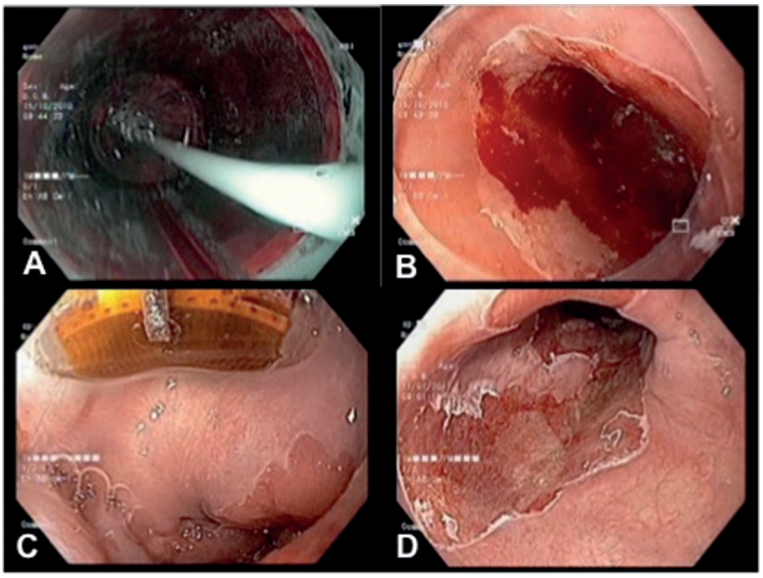

Figure 2. Circumferential radiofrequency ablation treatment with the Barrx 360 system, the balloon being inflated in the esophagus (A and B); and focal ablation treatment with the Barrx 90 system (C and D).

Indications for esophageal radiofrequency ablation

Barrett's esophagus and high-grade dysplasia

Diffuse or multifocal BE in the presence of HGD or of an in situ, non nodular adenocarcinoma is an indication for curative endoscopic radiofrequency ablation that has been well codified and scientifically documented. Macroscopic analysis in white light and with staining (acetic acid or virtual staining) allows the identification of any potential nodular lesion, which should be resected by mucosal resection or submucosal dissection before the remaining BE is treated. In case of doubt regarding a deep malignant invasion, endoscopic ultrasound can be performed beforehand. Only lesions classified as usT1N0 by endoscopic ultrasound can be resected. Histological analysis of the resected section will provide a precise diagnosis of the depth of invasion of the lesion. When the resection is complete and the lesion is intramucosal,

the residual circumferential BE should be destroyed by radiofrequency ablation during a second session of endoscopy (after 2–3 months). When resection is not complete and the depth of invasion reaches the submucosa, a complementary surgical treatment should be proposed. For elderly patients and/or those with significant comorbidities, radiochemotherapy in addition to noncurative endoscopic resection can be discussed.

Barrett's esophagus and low-grade dysplasia

French and international guidelines recommend the monitoring of BE with LGD. This surveillance includes carrying out staged biopsies (Seattle protocol) and biopsies targeted by chromoendoscopy. Radiofrequency ablation treatment in this situation is being evaluated in clinical research protocols that are comparing the evolution of patients treated with radiofrequency ablation with that of patients receiving endoscopic surveillance according to current recommendations. A recent study comparing a group of LGD patients treated with radiofrequency ablation with a control group showed a significant reduction in progression to HGD/cancer in the treated group [6]. In light of the initial results reported in the literature, radiofrequency ablation could be proposed when the presence of LGD is certain (verified after treatment with proton pump inhibitors [PPI], taken at a high dose for 2 months), confirmed (by two different pathologists), multifocal (> 5 LGD crypts in one biopsy; LGD at several levels of the esophagus), and diffuse (> 50% of 200 crypts analyzed show LGD). Other criteria associated with a greater risk of progression are male sex, age 50–75 years, being overweight, and the presence of a hiatus hernia [5].

Barrett's esophagus and intestinal metaplasia (IM)

BE without dysplasia is not an indication for radiofrequency ablation and should just be monitored according to the recommendations currently in place.

Results

A high complete-response rate with few complications

Several studies have demonstrated the effectiveness of radiofrequency ablation in the short and medium terms for the destruction of intestinal metaplasia (IM) and dysplasia in more than 80% of cases [7-10]. Radiofrequency ablation treatment of dysplastic BE also reduces the risk of developing esophageal adenocarcinoma. The first study in the field, by Shaheen et al. [8], showed that neoplastic progression was significantly reduced in the treated group compared with the control group (3.6% versus 16.3%, P = 0.03), with fewer cancers diagnosed (1.2% versus 9.3%, P = 0.045). A meta-analysis including 18 studies and 3,802 patients showed rates for the eradication of intestinal metaplasia and dysplasia of 78% and 91%, respectively [11].
Immediate major complications (hemorrhage, perforation) are extremely rare, whilst minor complications (retrosternal pain, fever, minor bleeding) are rare (between 5% and 10%), with a favorable evolution. The only long-term complication is the occurrence of stenosis, which is observed in 0.5%–10% of cases, depending on the published series. Endoscopic dilation is then an effective treatment. The risk of stenosis is greater in patients with a history of antireflux surgery, and in those who have esophagitis or who are taking oral nonsteroidal anti-inflammatory drugs [12].

Duration of the response and long-term risk of recurrence

The long-term outcomes of esophageal radiofrequency ablation have been less well evaluated, but they appear to persist, both for the eradication of IM and dysplasia [13,14]. Orman et al. [15] analyzed factors predictive of recurrence of dysplasia or IM after a comprehensive and effective radiofrequency ablation treatment in 262 patients. Median follow-up was for 397 days (54–1,668 days). Eight patients had a recurrence and three of these had progression to dysplasia or carcinoma in situ. In this study, the recurrence rates were 4.2% per year for dysplasia and 5.2% per year for IM. A study of 335 patients treated with radiofrequency ablation and endoscopic mucosal resection of nodular zones, for BE with HGD (72%), intramucosal adenocarcinoma (24%), or LGD (4%), showed complete eradication of HGD and IM

in 86% and 62% of patients at 12 months [15]. Phoa et al. reported that in 54 patients treated with radiofrequency ablation, preceded or not by endoscopic mucosal resection, eradication of the HGD or IM persisted in 90% of cases [16]. Finally, in an American study [17], treatment of 448 patients by radiofrequency ablation, for BE with HGD or intramucosal adenocarcinoma (70%), with LGD (15%), or with a simple IM (14%), resulted in complete eradication of the IM in 56% of patients at 24 months, and 71% at 36 months. The recurrence rate for IM at 2 years was 33%. The smaller percentage of eradication rates and the relatively high percentage of IM recurrence in this study could be explained by:

1. the need for two consecutive endoscopies without IM (as opposed to only one in the other studies) to confirm that eradication was complete;
2. the high proportion of BE greater than 8 cm;
3. the systematic collection of biopsies in the region of the gastroesophageal junction (common area of recurrence).

Recurrence of BE could be related to the persistence of glands buried under the squamous neoepithelium after radiofrequency ablation. The prevalence of buried glands varies between different studies. Their histological definition is the presence of a glandular epithelium covered by squamous epithelium, without contact with the esophageal lumen. The Amsterdam group [18] studied the presence of buried glands, as described by the pathologist, in residual BE islands of less than 5 mm. They analyzed biopsies from 69 consecutive patients with follow-up for BE, treated by radiofrequency ablation that was preceded, or not, by mucosal resection. Of 2,515 biopsies of neosquamous epithelium with a normal macroscopic appearance, buried glands were present in 0.1% of cases. Biopsies of the small, residual BE islands showed embedded glands in 21% of cases. These represent, in fact, "pseudo–buried glands" corresponding to the juxtaposition of the glandular epithelium in the BE island and the adjacent squamous epithelium. The authors explain that biopsies of the small BE islands can include an adjacent fragment of squamous epithelium, either because this epithelium partially covers the glandular epithelium or because of the tangential position of the biopsy forceps in the narrow esophageal lumen. This study highlights the risk of false-positive biopsies taken from BE islands. During the endoscopic surveillance of patients treated with radiofrequency ablation, the analysis of the esophageal mucosa

must be scrupulously and precisely performed to be certain to collect biopsies from the neosquamous epithelium and not from residual BE islands, which will be destroyed during the endoscopic follow-up. Nevertheless, these results provide incentive to maintain surveillance, even in patients with complete response after treatment with radiofrequency ablation.

Factors predictive of response to radiofrequency ablation

In the multicenter, prospective study of van Vilsteren et al. [19], independent predictive factors of poor response to circumferential radiofrequency ablation at 3 months (defined as < 50% loss of BE at the surface) were highlighted. In the group of poor responders (n = 36, 13%), the complete-response rates for IM and dysplasia (66% and 86%, respectively) were significantly lower than for good responders (95% and 98%); the average total time necessary to achieve eradication was longer (13 months versus 7 months) and more sessions were required (four versus three). The factors predictive of a poor early response were:

1. active esophagitis despite adequate PPI therapy;
2. Barrett's mucosa on the previous endoscopic resection scar;
3. narrowing of the esophageal lumen before radiofrequency ablation;
4. long-term development of dysplasia prior to treatment.

The presence of esophagitis was the most significant predictive factor and demonstrates the need for control of acid reflux prior to radiofrequency ablation treatment.

Conclusion

BE is a precancerous state that requires endoscopic surveillance to screen for dysplasia. Radiofrequency ablation treatment is indicated for flat esophageal BE with HGD. A rigorous macroscopic endoscopic examination should be performed to identify a possible suspect or nodular infiltration area in a circumferential BE, which can benefit from a prior endoscopic resection by endoscopic mucosal resection or submucosal dissection. The rate of complete response after radiofrequency ablation, in terms of dysplasia and IM, is greater than 80%, and persists after several years. Endoscopic surveillance should, however, be continued, even after complete eradication of BE and dysplasia, in

order to detect any recurrence from buried glands.

Conflicts of interest

None.

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