Selected commentary to "Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia. A randomized clinical trial"

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Selected commentary to "Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia. A randomized clinical trial"

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Summary
Background Barrett's esophagus (BE) results from gastroesophageal reflux disease (GERD) and harbors an increased cancer risk. Via low (LGD) and high grade dysplasia (HGD) BE may progress towards cancer (0.5 %–0.75 % annual risk). Radiofrequency ablation (RFA) represents a novel endoscopic method for durable elimination of BE. RFA is effective for cancer prevention persons with HGD. Remains to be questioned the value of RFA in those with LGD.

Methods Critical analysis of the paper by Phoa K et al., published in the recent issue of JAMA. The randomized clinical study compared the effect of surveillance vs. RFA in persons with BE and LGD.

Results After 3 years, RFA was superior vs. surveillance as it significantly inhibited progression to cancer and/or high grade dysplasia (1.5 % vs. 26.5 %). The number necessary to treat to prevent cancer/HGD and cancer was 4.0 and 13.6, respectively.

Conclusions RFA is superior to surveillance to prevent the progression of BE with LGD to HGD/cancer and cancer. Thus RFA should be recommended as the treatment of choice for the management of BE with LGD in those fit for the endoscopic procedure. Future studies will have to elicit the impact of orchestrated therapy of dysplastic BE including anti reflux surgery. Finally the value of RFA for cancer development in those with non-dysplastic BE should be addressed.

Keywords Barrett's esophagus · Esophageal adenocarcinoma · Cancer · Gastroesophageal reflux disease · High-grade dysplasia · Low-grade dysplasia · Radiofrequency ablation

Introduction

Barrett's esophagus (BE) represents the morphological manifestation of gastroesophageal reflux disease (GERD) and affects 20–30 % of reflux symptom-positive individuals (peak 60 years of age for both sexes) [1–3]. Gastroesophageal reflux causes the formation of columnar-lined esophagus (CLE) containing goblet cells, a condition termed BE without dysplasia (i.e., nondysplastic BE (NDBE)) [1–3]. Via low- (LGD) and high-grade dysplasia (HGD), NDBE may progress toward adenocarcinoma of the esophagus [3, 4]. The cancer risk of NDBE ranges between 0.5 and 0.7 % per year, while that of LGD and HGD is increased 10- and 20-fold, respectively [3, 4]. The diagnosis of BE is established by histopathology of biopsies obtained from CLE during esophago-gastroduodenoscopy [3].

Radiofrequency ablation (RFA) represents a novel endoscopic method for the elimination of BE [5–10] (Fig. 1). During endoscopy-guided RFA, the generator-created RF energy is delivered to the tissue via a catheter-mounted balloon (HALO® 360; Fig. 2), endoscope-mounted plates (HALO® 60, 90), or through a novel endoscope device, the so called 'Eagle'. Recent studies have demonstrated that RFA is safe and effective for the elimination of BE without and with dysplasia [4–9]. Following 3–4 RFA treatment session with or without endoscopic resections, clearance of dysplasia and BE without dysplasia is achieved in approximately 80 and 90 % of the cases, respectively [3–9]. If cleared from NDBE, the effect holds in 92 % of the cases after 5 years [9]. Shaheen et al. [5] recently demonstrated the supe-

Phoa K, van Vilsteren FI, Weusten BM, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014;311(12):1209–17.

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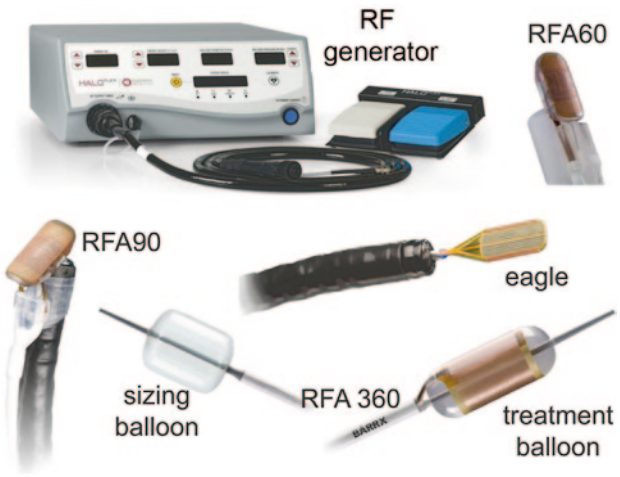

Fig. 1 Equipment for radiofrequency ablation (RFA) includes the RF generator and the RFA 360 sizing and treatment balloon, the endoscope tip-mounted RFA 60, 90, and the trough the endoscope "eagle" device for the delivery of the RF energy pulse to the tissue. (Image provided by GI Solutions, Covidien, USA)

riority of RFA over surveillance for cancer prevention in BE with HGD. The present study by Phoa et al. [11] compared the 2–3 years' effect of RFA with surveillance for LGD-positive BE.

Summary of publication

This multicenter study coming from nine European institutions included GERD symptom-positive patients with BE containing LGD [11]. Diagnosis was reconfirmed by a reference pathologist and a panel of expert pathologists. Patients with endoscopically visible lesions or the diagnosis of HGD or esophageal adenocarcinoma were excluded from randomization. High-resolution endoscopy-guided tissue sampling was performed according to the Seattle four-quadrant multilevel biopsy protocol of CLE. Patients with LGD were randomized in a 1:1 ratio either for RFA or surveillance ($n = 68$ per group) [11]. Due to exclusion criteria (cancer, HGD, comorbidities, etc.), 68 patients per group were randomized of a total number of initially 511 patients.

The protocol for patients in the *RFA group* allowed two subsequent circumferential (HALO 360) and three subsequent focal (HALO 60, 90) ablation sessions. Subsequent treatment sessions were conducted in 3-month intervals until the absence of endoscopically and histopathological BE with or without dysplasia. If clearance of BE with or without dysplasia was not achieved after the allowed number of treatment sessions, patients were allowed to undergo a final single session of endoscopic resection or argon plasma coagulation. After the last RFA treatment session, follow-up endoscopies and biopsy sampling

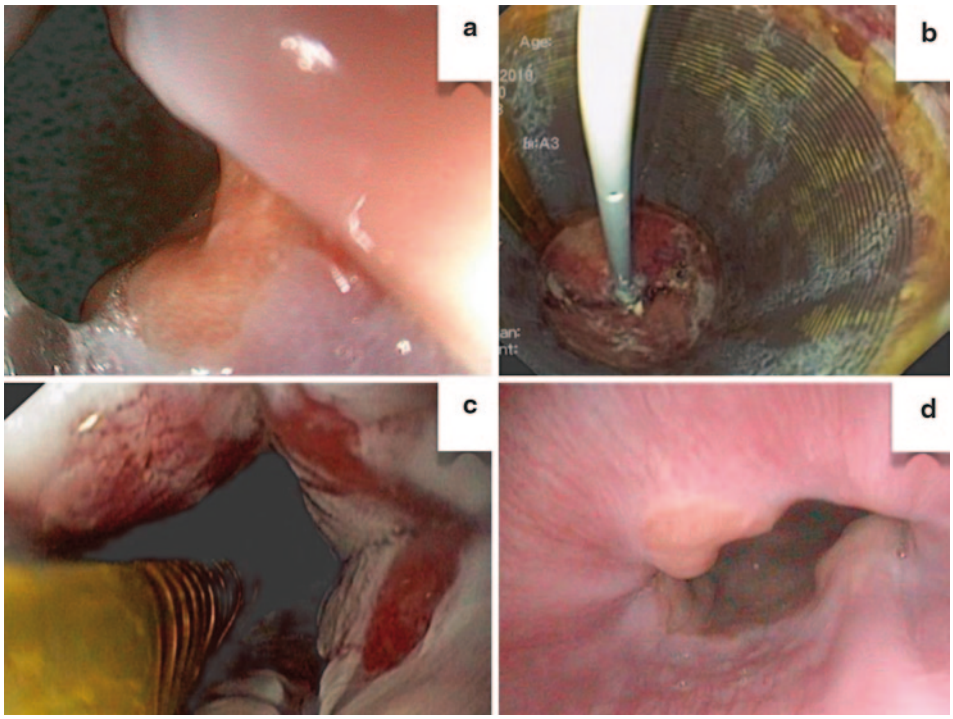

Fig. 2 Antegrade endoscopic images of the distal esophagus before (**a**), during (**b**, **c**), and 3 months after (**d**) radiofrequency ablation (RFA), using the RFA 360 catheter-mounted balloon system, for the treatment of Barrett's esophagus without dysplasia. **a** Irregular squamo-columnar junction within the lower end of the esophagus. **b** Endoscopic view through the treatment balloon during the delivery of the RF energy to the esophageal mucosa. **c** Endoscopic image after the end of the RF energy delivery; note the presence of the white ablated mucosa. **d** Endoscopic image of the squamo-columnar junction 3 months after RFA; histopathology of biopsies assessed absence of Barrett's esophagus. Endoscopic images obtained using Storz (**a**, **d**) and Olympus (**b**, **c**) endoscopy technology

were conducted in 3-month intervals until 3 years after randomization; this translates into 2 years after the end of RFA therapy.

LGD-positive persons of the *control group* underwent diagnostic high-resolution endoscopy and biopsy sampling after 6 and 2 months, and thereafter in 12-month intervals until 3 years after randomization.

All therapeutic or diagnostic endoscopic procedures were conducted in the outpatient setting under sedation (midazolam, fentanyl, pethidine, or propofol). Patients in the RFA group were kept on continuous double-dose proton-pump inhibitor (PPI) therapy and received an H2 blocker during the first 2 weeks after RFA treatment. A reason for this multimedical approach was not presented by the authors. The paper provided no information on the medical therapy of the control group. It seems reasonable that individuals in the control group received PPI therapy.

The major finding of the study was that patients in the control group showed a significantly lower risk of developing HGD and adenocarcinoma, when compared with the control group: 1.5 % ($n=1$) vs 26.5 % ($n=18$) in the RFA vs control group, respectively ($p<0.01$). Risk of developing adenocarcinoma was 1.5 % ($n=1$) vs 8.8 % ($n=6$) for the RFA vs the control group, respectively. These numbers translate into a 25 % risk reduction for the development of HGD and cancer in the RFA group vs surveillance. Numbers necessary to be treated to avoid the development of progression to HGD/cancer and cancer were 4.0 and 13.6, respectively. Complete eradication for dysplasia and intestinal metaplasia was observed in 92.6 and 88.2 % of the cases, respectively. These numbers compare to absence of dysplasia and intestinal metaplasia in 27.9 % vs 0 %, respectively, in the control group. Patients in the RFA group underwent a median of 3 RFA treatments and 3 diagnostic endoscopies (37 biopsies per patient). In the control group, patients required a median of 3 diagnostic endoscopies (32 biopsies per patient).

One patient in the RFA group progressed to cancer and was successfully cleared by endoscopic resection for complete elimination of dysplasia. In the control group, 12 and 6 persons progressed to HGD and adenocarcinoma, respectively. One patient in the control group required esophagectomy for poorly differentiated cancer extending into the submucosa. Surgery was radical, and patient remained disease-free after 37 months of follow-up. The remaining 15 persons with HGD and 5 persons with cancer in the control group underwent endoscopic resection and RFA ($n=9$) or RFA alone ($n=6$). Of these 15 patients, 11 were successfully cleared from dysplasia and intestinal metaplasia; 4 persons are currently treated for HGD or cancer; and 2 patients with HGD are kept on surveillance.

Due to these significant differences regarding the reduction of the risk for HGD and cancer development in the RFA vs the control group, the study was terminated at an earlier time point.

Adverse effects occurred in 13 patients (19.1 %) and included fever, chills, abdominal pain, and slight bleeding and were all managed by medical therapy. A total of 8 patients (11.8 %) developed post-RFA dysphagia due to stricture formation, which resolved after balloon dilatation. Esophageal perforation did not occur. None of such side effects were observed in the control group.

Finally, multivariable statistical analysis examined diagnostic markers predicting the development of HGD/cancer in persons with BE containing LGD. The significant predictors for the progression to HGD/cancer were (1) the number of LGD-positive endoscopies and (2) the length of circumferential BE per centimeter of endoscopically visible LGD-positive CLE. Predictors for absence of LGD could not be assessed.

Table 1 Summary of the paper

What is known
RFA is superior to surveillance to prevent cancer in BE with HGD
What is new
RFA is superior to surveillance to prevent cancer in BE with LGD

RFA radiofrequency ablation, *BE* Barrett's esophagus, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia

Comment

The authors are to be congratulated for this highly motivating and well-designed study, which justifies an important and clear statement in favor of active esophageal cancer prevention. The major finding of the study by Phoa et al. [11] was that RFA significantly reduced the risk for HGD/cancer development in LGD-positive BE, when compared with surveillance (Table 1). Thus, the data extend the superiority of RFA for cancer prevention from HGD- to LGD-positive BE, when compared with surveillance [5, 11]. Therefore, the published literature justifies recommending that BE with LGD and HGD should be treated by RFA. Surveillance should be offered to those with contraindications against RFA, i.e., heart lung disease, blood clotting disorder, pregnancy, or inability to sign written consent [3, 4].

Although using a highly accurate high-resolution endoscopy-guided biopsy sampling protocol, dysplasia disappeared during follow-up in 25 % of the patients in the surveillance group [11]. These data go in line with the observations made in the study by Shaheen et al. [5]. Conceptually, the effect may be explained by the biological insecurities of dysplastic BE [3, 4, 10]. Dysplasia seems to develop and disappear in an unpredictable mosaic pattern. Therefore, it is not known whether the disappearance of dysplasia in the surveillance group is due to the biopsy sampling error or a consequence of the "true" regression of LGD to NDBE. Elimination of CLE with RFA stops the progression to cancer, which also positively affects the life quality of the patient [3]. Future studies will have to elicit the durability of the effect.

The study shows that excellent data can be achieved when RFA and surveillance are performed in highly spe-

cialized centers with adequate technical skills and theoretical background [11]. Furthermore, this contributed to minimize the number and size of complications and assures the presence of adequate complication management. This translates into the recommendation that RFA should be centered to such experienced institutions. In contrast to that, endoscopists outside such centers should focus their accurate attention to identify premalignant BE [2]. BE-, LGD-, and HGD-/cancer-positive individuals should then be offered adequate treatment in expert centers within the setting of interdisciplinary clinical trials involving pathology, radiology, ENT, oncology, gastroenterology, and surgery [3, 4, 11, 12].

Basically, RFA should be offered to those with LGD exhibiting the highest risk to develop cancer. So far, there exists no biochemical/histochemistry/genetic marker for adequate cancer risk prediction. However, the study found that two endoscopic results were associated with an increased risk for progression to HGD/cancer in the surveillance group: the number of LGD-positive endoscopies and the length in centimeter of endoscopically visible circumferential CLE [11]. It remains to be questioned whether these findings may have implications for rethinking the management of NDBE [10]?

Conceptually, cancer prevention works by identifying and eliminating a tissue with known increased cancer risk. Lenglinger et al. [3] and Sikkema et al. [13] recently identified markers that predicted an increased cancer risk of NDBE equaling that of LGD. These markers included the length of NDBE-positive, endoscopically visible CLE > 2.0 cm, esophagitis, hiatal hernia > 3.0 cm, history of NDBE-positive GERD for > 10 years, and a family history positive for esophageal cancer. These findings somehow reflected the cancer risk predictors of LGD, assessed in the study by Phoa et al. [11], i.e., the number of LGD-positive endoscopies and circumferential length of CLE. Thus, it seems justified to consider RFA to NDBE-positive individuals with the aforementioned dysplasia-like cancer risk profile within clinical studies [3, 4].

Taken together, the study by Phoa et al. [11] demonstrates the cancer preventive effect of RFA for LGD-positive BE, when compared with surveillance (Table 1). Thus, the paper extends the observation that RFA is superior to surveillance for HGD- to LGD-positive BE [5, 11]. As a consequence, RFA with or without endoscopic resection should be recommended for the treatment of BE with LGD and HGD/early cancer. To close the gap, future studies will have to question the effect of RFA vs surveillance for NDBE [3, 10]. The problem of this study will of course be the numbers [1–4]. Therefore, it will have to be a large multicenter study, or otherwise we will not be able to visualize the entire size and spectrum of the problem. May the study by Phoa et al. [11] be a motivation to adequately address this issue and contribute to reduce the gap of knowledge. Finally, future trials may also address the impact of RFA and antireflux surgery for the management of BE [3].

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Conflict of interest

The authors declare that there exists no conflict of interest.

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