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Austrian expert panel recommendation for radiofrequency ablation of Barrett's esophagus

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Summary
Background Barrett's esophagus (BE) represents the premalignant manifestation of gastroesophageal reflux disease and includes columnar lined esophagus with intestinal metaplasia, low-grade dysplasia, high-grade dysplasia and cancer.

Methods An Austrian panel of expert meeting was held at the Medical University Vienna, June 2015, to establish and define recommendations for the *endoscopic treatment* of BE with and without dysplasia and cancer. Recommendations are based on critical analysis of published evidence. Statistics were not applied.

Results Diagnosis of cancer and dysplasia is to be reconfirmed by a second expert pathologist. Advanced cancer (>T1a) requires surgical resection±adjuvant therapies. Treatment of T1a early cancer, high- and low-grade dysplasia should include endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA). In the presence of increased cancer risk, BE without dysplasia should be treated by RFA within clinical studies only. Elimination of any early cancer, dysplasia and IM defines complete response, that is, post RFA histopathology shows squamous, cardiac or oxyntocardiac mucosa lined esophagus (*Chandrasoma* classification). Follow-up endoscopies are timed according to the base line histopathology. Down grade from cancer to dysplasia or from dysplasia to non-dysplastic BE defines partial response, respectively. Based on esophageal function testing, reflux is treated by medical or surgical therapy.

Conclusion In Austria, RFA±EMR is recommended for BE containing early cancer or dysplasia. Non-dysplastic BE with an increased cancer risk should be offered RFA within clinical trials to assess the efficacy for cancer prevention in this group of patients.

Keywords Barrett's esophagus · Dysplasia · Esophageal cancer · Radiofrequency ablation

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Introduction

Barrett's esophagus (BE) is the morphological manifestation of gastroesophageal reflux disease (GERD) [1]. Through low- (LGD) and high-grade dysplasia (HGD), BE may progress toward esophageal cancer (0.15–0.5% annual cancer risk) [2, 3]. Diagnosis of BE is established by endoscopy and histopathology of biopsies obtained from columnar lined esophagus (CLE) (Fig. 1).

Radiofrequency ablation (RFA) represents a novel endoscopic therapy for durable elimination of BE. In LGD, HGD and early cancer RFA is conducted after endoscopic mucosal resection. Discrepancy exists regarding the therapy of non-dysplastic BE (NDBE). So far there exists no multidisciplinary recommendation for the treatment of BE in Austria. Therefore the present paper aims to summarize the Austrian expert panel recommendations for the endoscopic management of BE with and without early cancer and dysplasia.

Methods

The expert panel conducted a critical analysis of the published literature to examine the role of RFA and mucosal resection for the endoscopic management of BE with and without dysplasia and early cancer. Based on the published evidence the expert panel orchestrated the recommendations. Statistics were not applied.

Results

Based on the critical analysis of the published literature the expert panel summarizes recommendations regarding the epidemiology, diagnosis, and treatment of BE in Austria. BE is an important risk factor for esophageal carcinoma and it's incidence is probably rising during the last 20 years in Europe including Austria [4, 5]. Esophageal adenocarcinoma, one of the two main types of esophageal cancer, is rapidly increasing in incidence with a prognosis of fewer than 15% of individuals surviving beyond 5 years when treated for it [6, 7]. In Austria the esophageal cancer incidence is 2.6 cases per 100,000 population each year [8]. Even in symptomatic NDBE a cancer risk comparable to LGD was shown; the annual progression rate from NDBE to LGD is 4.3% [3].

Diagnosis of BE is established by endoscopy and histopathology of biopsies obtained from CLE. Presence of goblet cells within CLE defines Barrett's esophagus without dysplasia. Potentially, via low- and high-grade dysplasia, BE progresses toward esophageal cancer. Diagnosis of cancer and dysplasia is to be reconfirmed by a second expert pathologist [9].

The scope of the Austrian guideline is to provide a national, practical, clinical and evidence-based standard for managing RFA treatment in patients with BE and related neoplasia.

The Austrian Society of Gastroenterology and Hepatology (ÖGGH), the Austrian Society of Surgery (ÖCG) and the Austrian Society of Oncological Society (ACO ASSO) officially support that guideline.

The Austrian expert panel found, following 1–4 treatment sessions, RFA provides a complete response rate of 90%, which remained over a surveillance period of 5 years (complete eradication of intestinal metaplasia and complete eradication of neoplasia) in patients with high-grade intraepithelial neoplasia and/or early-stage cancer [10, 11]. Furthermore in patients with LGD a complete response rate of 93% was observed which remained over a surveillance period of 3 years [10, 12–14].

RFA is a safe procedure with 0.2% and 5% rate for severe and minor complications, respectively [15–17] (Fig. 2).

Based on the published technical, safety, durability and efficacy aspects the Austrian guideline recommends RFA (±prior endoscopic mucosal resection or submucosal dissection) for BE containing LGD, HGD, and early T1a cancer (Table 1). In these indications, RFA significantly fostered cancer prevention, when compared to surveillance.

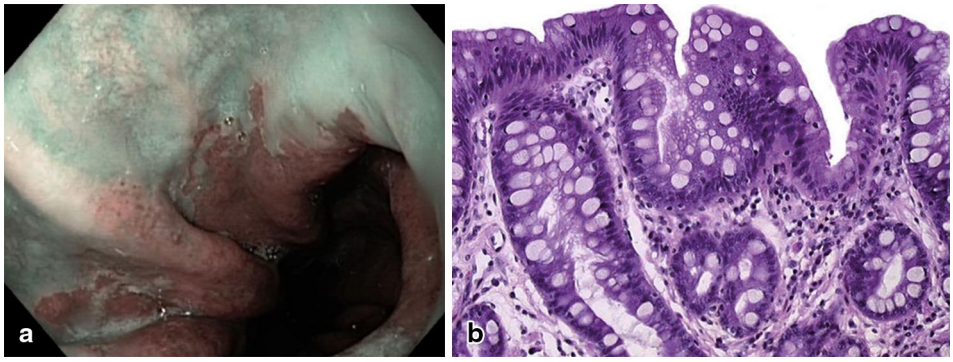

Fig. 1 **a** Antegrade endoscopic image of columnar lined esophagus (CLE) within the distal esophagus. Histopathology of biopsies obtained from CLE demonstrated Barrett's esophagus with low-grade dysplasia (LGD). **b** Histopathology of Barrett's esophagus, showing columnar lined esophagus containing typical goblet cells, that is, the hallmark for Barrett's esophagus, magnification 50×, H&E stain

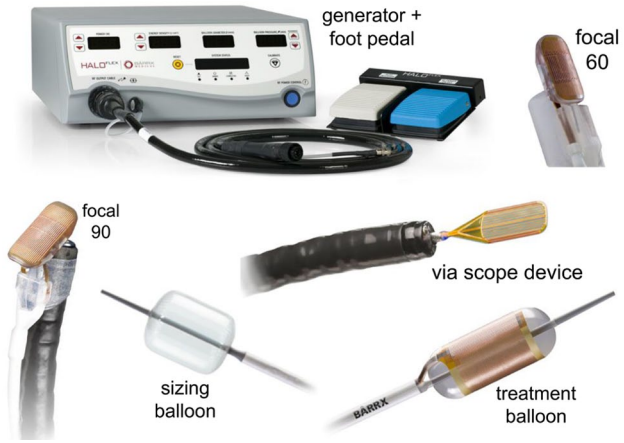

Fig. 2 Equipment for radiofrequency ablation (RFA) including the generator, sizing, treatment balloon, endoscope tip mounted and via the scope electrodes

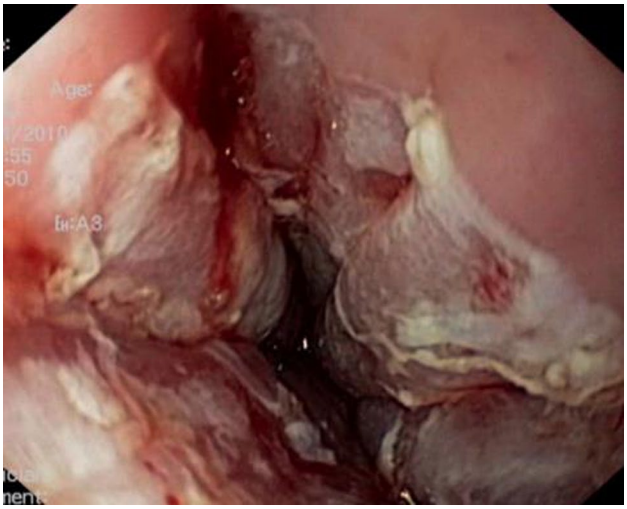

Fig. 3 Endoscopic image after radiofrequency ablation (RFA) showing the white layer of cell detritus covering the esophagus

The ablation treatment is contraindicated in persons with prior radiation therapy to the esophagus, esophageal varices are at risk for bleeding, prior Heller myotomy, eosinophilic esophagitis and pregnancy. In the presence of esophageal stenosis or stricture of the esophagus RFA is also not recommended. The role of endoscopic submucosal dissection in contrast to endoscopic mucosal resection in the treatment of BE and its dysplastic forms will be discussed in another consensus statement in detail.

In the presence of an increased cancer risk profile, RFA may also be considered for the treatment of NDBE within clinical trials. Increased cancer risk includes: long standing GERD (>10 years), hiatal hernia >3.0 cm, esophagitis, length of BE, history of BE with dysplasia, positive family history for esophageal and gastrointestinal cancer and obesity with an intraabdominal fat distribution [18–22]. RFA of NDBE should be conducted in specialized centers within clinical trials [23, 24].

According to the baseline histopathology, RFA treatment is scheduled using the *Chandrasoma classification* (see Table 1). In general a synchronized second opinion from a reference pathology center should be demanded for carcinoma or dysplasia. For cancer (T1a and >T1a) an interdisciplinary tumor board should be added and involved in patient management strategy. LGD and HGD can be handled according to multidisciplinary institutional guidelines.

The 1st RFA treatment is recommended to be conducted as circumferential ablation (using Barrx 360) (Fig. 3), afterwards according to diagnostic findings during the follow-up endoscopy and may apply circumferential (Barrx 360) or focal ablation (Barrx 90, 60 or "Eagle" (via the endoscope), respectively.

Of note comorbidities may contribute to delay or decline of the 1st ablation (RFA).

Esophagogastroduodenoscopy surveillance recommendation

Treatment response after RFA is assessed using a combination of endoscopic evaluation and histological examination. The eradication of any HGD, LGD and IM defines *complete response* after RFA, that is, esophagus is lined by squamous epithelium, cardiac or oxyntocardiac

Table 1 Recommended indications for radiofrequency ablation in Barrett's esophagus (BE)

Carcinoma[a]		HGD[a]	LGD[a]	NDBE
>T1a	T1a			
Surgical resection ± neo-adjuvant chemotherapy/radiation	EMR + RFA or ESD + RFA	EMR + RFA or ESD + RFA	(EMR) + RFA	RFA only within the scope of controlled clinical trials/registries Individually in patients with elevated risk profile[b]

1st RFA using Barrx 360, afterwards according to diagnostic findings Barrx 360, 90, 60 or "Eagle" (via endoscope), respectively
The location in the esophagus itself is insubstantial for Barrett esophagus with dysplasia treatment
HGD high-grade dysplasia, *LGD* low-grade dysplasia, *NDBE* non-dysplastic Barrett's esophagus, *RFA* radiofrequency ablation, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection
[a]T1a and >T1a ad interdisciplinary tumor board; LGD and HGD institutional guidelines Caution: obtain reference pathology center's second opinion for CA/Dysplasia—Histology (academic institutions: MUW, MUI, MUG, etc.), *Chandrasoma classification*
[b]Risk factors for adenocarcinoma: GERD >10 years, family history of gastrointestinal tumors (esophagus, stomach, colon, rectum, pancreas, liver, bile), hiatus hernia >3.0 cm, length of BE, esophagitis and obesity as described in the text

Table 2 Recommended EGD interval after RFA based on histologic report

Histologic result	EGD interval (months)
T1a/HGD	3
HGD	3
LGD	3–6
IM	12–36[a]
CM, OCM	12–36[a]

T1a = early cancer
HGD high-grade dysplasia, *LGD* low-grade dysplasia, *IM* intestinal metaplasia, *CM* cardiac mucosa, *OCM* oxyntocardiac mucosa, *EGD* esophagogastroduodenoscopy
[a]Endoscopy, biopsy sampling and histopathology were conducted as described in the text according to the study protocol

mucosa, and there is absence of so-called buried glands. Down staging from higher to lower grades of dysplasia (i.e., HGD to LGD; LGD to BE without dysplasia, defines *partial response*. Therefore post RFA biopsies obtained from the treated area and the neo-squamocolumnar junction are mandatory for the histopathologic confirmation of CLE types and the exclusion of buried glands. In case of partial response, follow-up RFA treatments are recommended.

An average of three RFA sessions (range 1–5) are recommended as essential quantity ablations (±EMR) until effective elimination of Barrett±LGD, HGD, T1a-Ca is sustainable. The maximal quantity of RFA treatments per patient is seven RFA sessions (expert communication with Prof. Dr. George Triadafilopoulos, Stanford, CA, USA). The recommended interval for maintenance esophagogastroduodenoscopy after RFA depends on the histological report and varies between 3 and 6 months (further details see Table 2).

With regard to validity of the histologic assessment it is important to distinguish the interval between intervention, that is, RFA and biopsy sampling (<3 months), as the presence of inflammatory cells within the mucosa might lead to misinterpretation.

As a maintenance treatment after RFA high dose, proton pump inhibitor (PPI) therapy is recommended (double standard dose over 12 months after intervention). For patients indicated to surgical anti-reflux treatment, impedance pH reflux monitoring and high resolution impedance—manometry are recommended. After 12 months, PPI treatment should be tailored according to the response, that is, dose required for relief of GERD symptoms [25, 26].

Discussion

For the first time, this paper reports a multidisciplinary recommendation for the management of BE in Austria. Based on published evidence a panel of experts in the field of BE management, endoscopy, surgery, oncology and pathology defined a treatment algorithm for BE with and without dysplasia and cancer.

The major outcome of the Austrian expert panel meeting was, that RFA with and without EMR is recommended for the treatment of BE with dysplasia and early cancer. Furthermore the response is to be assessed using endoscopy data and histopathology, using the *Chandrasoma classification*. In cases with increased cancer risk, RFA may also be applied for the elimination of BE without dysplasia. However, for this indication the patients should be treated in specialized centers and within clinical studies. Therefore the conclusions of the Austrian expert panel are largely in conformity with US guidelines. In contrast to these guidelines the Austrian panel supports to examine the efficacy of RFA for NDBE and recommends to do this exclusively within clinical trials.

Of note, post RFA biopsies should accurately include the neo-squamocolumnar junction for the exclusion of buried CLE glands beneath normally appearing squamous lined esophagus. Here the panel points out the importance of expert pathology and the necessity for adequate follow-up biopsy sampling during endoscopy of the esophagus. Thus, going in line with international recommendations, the involvement of second opinion pathologists are mandatory for any dysplasia and cancer. In addition, the management of cancer should be performed within interdisciplinary tumor boards, including pathology, gastroenterology, surgery, radiology etc. LGD and HGD should be handled according to multidisciplinary institutional guidelines.

Generally, RFA is recommended for the treatment of BE with dysplasia and early cancer. BE without dysplasia may be treated by RFA in the presence of an increased cancer risk profile and solely within clinical trials. Future data will allow assessing the efficacy of RFA for cancer prevention in individuals with NDBE.

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Conflict of interest
The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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