

A systematic review of the evidence for radiofrequency ablation for Barrett's esophagus

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Abstract

Background Radiofrequency ablation with the HALO system is a new option for the treatment of patients with Barrett's esophagus. This systematic review summarizes the results of all relevant publications on this topic to answer patient-relevant clinical questions and to evaluate the potential benefit and harm of this new therapy.

Methods A systematic literature search of MEDLINE and CENTRAL up to May 2009 was performed. To identify the relevant literature, references were evaluated by two reviewers independently. The inclusion criteria for the review required that studies investigated patients with Barrett's esophagus, used radiofrequency ablation as the intervention, and had a minimum follow-up period of 12 months.

Results A total of nine relevant observational studies (involving 429 patients) were identified. Complete eradication of Barrett's esophagus dysplasia and metaplasia was achieved respectively for 71–100% and for 46–100% of the

patients. Only six cases of stenosis and one case of buried intestinal metaplasia were reported among all the patients. Only a few mild adverse events were reported.

Conclusions Based on the evidence of observational studies, the summary of the current data suggests that radiofrequency ablation with the HALO system could be a promising method associated with a low complication rate, low risk of stricture formations, and a minor probability of buried glands. To evaluate the potential benefit at a higher level of evidence, randomized controlled trials (RCTs) involving a direct comparison with other more established endoscopic methods such as photodynamic therapy are necessary.

Keywords Barrett's esophagus ·
Radiofrequency ablation · Systematic review

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Barrett's esophagus is an acquired condition resulting from long-lasting and severe mucosal injury to the esophagus, with a prevalence of 1.6% in the general population [1]. The major concern is the potential for progress to malignancy, mainly adenocarcinoma [2]. It is thought that adenocarcinoma in Barrett's epithelium does not arise as a single event but rather follows a stepwise process from metaplasia through low-grade dysplasia (LGD) and high-grade dysplasia (HGD) to early carcinoma and eventually to invasive cancer [3]. Therefore, depending on the grade of mucosal alterations, regular surveillance endoscopy following the Seattle protocol is warranted.

For focal irregularities, the most common recommendation is that an endoscopic mucosal resection (EMR) should be performed, with further management based on the findings of the EMR [4–6]. For multifocal lesions or infiltration in submucosa, esophagectomy is the most

common option. For the first time, updated guidelines from the American College of Gastroenterology consider endoscopic treatment such as radiofrequency ablation (RFA) as one possible option [6].

Radiofrequency ablation with the HALO system (BARRX Medical Inc., Sunnyvale, CA), a new and promising option for treating Barrett's esophagus, has top actuality and initial results from case reports and mainly small studies recently have been published extensively in endoscopic journals [7–13]. Thus, RFA may provide a more efficient mode of treatment for intraepithelial dysplasia than other endoscopic options such as photodynamic therapy or Argon plasma coagulation, which have resulted in a high stricture rate and the formation of buried glands ("buried Barrett") [14–16]. On the other hand, it is a relatively new device, and the number of patients treated to date has been limited.

At this writing, no systematic review has summarized the available literature regarding the potential benefit and harm of this therapeutic option. Therefore, we aimed to perform a systematic review to answer clinically relevant, patient-oriented questions by assessing evidence for possible advantages of RFA with the HALO system for patients with Barrett's esophagus.

Material and methods

Inclusion criteria

For our systematic review, we considered all the relevant trials that had been conducted with people of any age or sex who experienced Barrett's esophagus and metaplasia or dysplasia with or without EMR. The duration of study follow-up period had to be at least 12 months. The publication language was restricted to English and German. Studies were included if at least one of the following end points or surrogates were reported: esophagus stenosis, postinterventional symptoms, adverse events, quality of life (QoL), mortality, elimination of dysplasia and metaplasia, and buried metaplasia.

Search strategy for identification of studies

A search for all relevant studies was performed in OVID MEDLINE and CENTRAL. The Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA), and the NHS Economic Evaluation Database (NHS EED) were searched for relevant secondary literature.

All the searches were last updated 11 May 2009. The following phrases and terms were used for the search in

both full text and subject headings and adapted depending on the database: "Barrett's esophagus" (medical subject heading), "Barrett," "ablation," "catheter ablation" (medical subject heading), and "barrx." We also hand-searched reference lists from relevant secondary literature.

Study selection, data collection, and quality assessment

Two reviewers independently screened references for their potential relevance using titles and abstracts. References considered relevant by only one reviewer were reassessed by both reviewers and classified by consensus. In this way, a list of potentially relevant publications was prepared, the full texts of which were obtained for further evaluation. Data from the included studies were extracted by the two independent reviewers.

Results

The initial search using the aforementioned search strategy yielded 371 references. After exclusion of duplicates, there were 322 hits, 303 of which were classified as irrelevant by the reviewers on the basis of their titles or abstracts. Among the remaining 19 publications assessed using full text, eight did not meet the inclusion criteria. For further detailed information see Fig. 1.

Screening of the references in the 26 retrieved secondary literature publications failed to generate any further studies meeting the inclusion criteria. In the end, nine studies (11 publications) with usable information, all published between 2007 and 2009, were included in our systematic review. Five of the studies (six publications [9, 10, 12, 17–19]) included

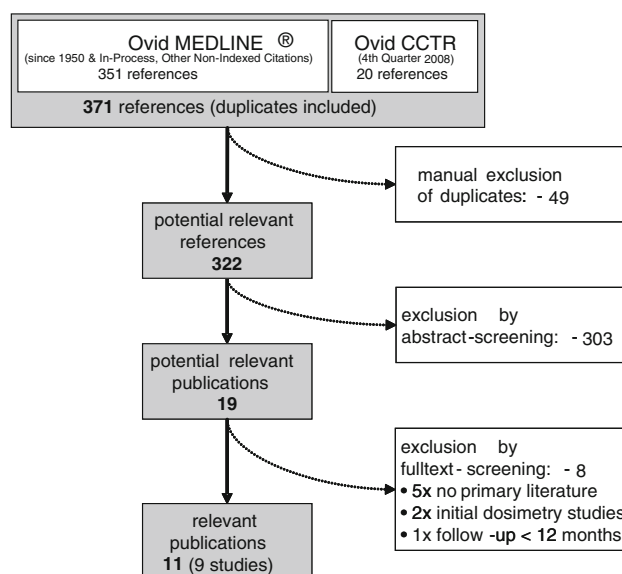


Fig. 1 Flow-chart of publications through review

patients who had Barrett's esophagus with dysplasia, whereas three trials (three publications [11, 20, 21]) examined patients who had Barrett's esophagus but without limitation, and one study (two publications [22, 23]) examined patients with Barrett's esophagus containing intestinal metaplasia but no dysplasia. In six of the included studies, EMR was conducted before ablation in case of endoscopically visible abnormalities or nodules [9–11, 17–20].

Study design and population

To date, no randomized controlled trials (RCTs) on the topic of RFA of Barrett's esophagus have been published. All included studies had an observational design without a control group. The study centers were located in the United States and the Netherlands, and most of the publications could be attributed to two author groups. A total of 429 participants took part in the nine observational studies, with sample sizes in individual studies ranging from 10 to 142. The duration of the studies ranged from a minimum of 12 months to a maximum of 30 months.

The ages of the patients ranged from 19 to 83 years. The proportion of men (73–92%) was much higher than the proportion of women. In six studies, the ethnicity of the patients was not reported, whereas in the remaining three studies the Caucasian group prevailed.

The baseline mean endoscopic Barrett's esophagus length ranged from 2.3 to 7 cm. All details of the study characteristics and the subjects' baseline characteristics are summarized in Table 1.

Treatment

All the studies used the HALO system for RFA. In seven of the studies [9–12, 17, 19, 21–23], the patients were treated with a stepwise HALO³⁶⁰ circumferential ablation followed by the HALO⁹⁰ focal ablation, whereas two studies [18, 20] used only the HALO³⁶⁰ circumferential system. For the patients with baseline intestinal metaplasia, a double 10 J/cm² and 40 W/cm² regimen was applied, whereas the patients with baseline HGD or LGD received a double 12 J/cm² and 40 W/cm² treatment within the circumferential ablation. For focal ablation, a double × double 12 J/cm² and 40 W/cm² regimen was advised in all cases.

The patients' first follow-up visit occurred a median of 3 months (range, 1–12 months) after the first circumferential ablation treatment. At this visit, a second ablation for residual Barrett's esophagus was performed. The maximum number of ablations per treatment was reported in seven studies and ranged from two [12, 18, 20] to five [9–11, 22]. The two remaining publications [19, 21] did not report the maximum number of ablations allowed in the study. In all

the trials, the patients obtained high-dose proton pump inhibitors for the whole observation period.

Outcomes

The main outcome, investigated in all the studies, was eradication of Barrett's esophagus. Information about esophageal stenosis, postinterventional symptoms, adverse events, and buried glands were given in most of the publications. None of the included studies assessed outcomes in terms of mortality or QoL. A summary of the major outcomes can be found in Table 2.

Complete responses for dysplasia

Six [9, 10, 12, 18–20] of the eight studies that included patients with dysplasia at baseline reported on the eradication of dysplasia after RFA therapy. Complete responses were achieved for 71–100% of the patients within the number of ablations allowed by the study protocols. In the two studies [18, 20], with only circumferential ablation performed, the proportion was only 71–80%, whereas in the studies with stepwise circumferential and focal ablation [9, 10, 12, 19], a complete eradication of dysplasia was described for 89–100% of the patients. A subgroup analysis of the histologic response rate, performed in one study [18], showed no significant difference between the patients with and those without baseline EMR.

Complete responses for intestinal metaplasia

Information about the complete responses for intestinal metaplasia were found in all the included studies. The two studies [18, 20] that used only the HALO³⁶⁰ circumferential system in their protocol reported a complete response rate of 46–54%. The stepwise ablation procedure with the HALO³⁶⁰ circumferential and HALO⁹⁰ focal systems, as used in all the other trials [9, 10, 12, 19, 21–23], was more successful and resulted in a complete eradication of Barrett's esophagus in 59–100% of all the subjects.

Stenosis

Because the occurrence of strictures is a common adverse event in ablative treatments, all the included studies reported on this issue. In the study of Velanovic [21], stenosis developed in four of 54 patients. Three of these strictures occurred in patients with a baseline Barrett's esophagus length exceeding 12 cm, and the fourth patient had a Barrett's esophagus length of 6 cm. Among the remaining eight trials, only two [18, 19] reported one stenosis after RFA in one patient each.

Table 1 Characteristics of the included studies and subjects

Observational study	Study characteristics		Subjects' baseline characteristics			
	Duration of study months (range)	No. of subjects	Main in/ex criteria	Mean age ^a Years (range)	Mean length of BE ^a cm (range)	Histology before intervention
Sharma et al. [19]	24 (3–46)	Included: 63 Analyzed: 62	In: BE with HGD or LGD Ex: History of prior ablative therapy for BE	Median: 71 (43–83)	Median: 5 (1–13)	24 HGD 39 LGD
Velanovich [21]	15	Included: 66 Analyzed: 27 ^b after ≥12 months follow-up	In: BE with IM, LGD or HGD Ex: Invasive adenocarcinoma; carcinoma in situ	62 (NA)	3 (1–14)	12 HGD 54 LGD
Gondrie et al. [10, 17]	14 (IQR 13–15)	12	In: BE with HGD or IMC Length of BE: 2–10 cm Ex: Esophagus stenosis; invasive cancer	Median: 70 (IQR 52–76)	Median: 7 (IQR 6.5–8)	11 HGD 1 IMC
Ganz et al. [18]	12 (IQR 8–15)	Included: 142 Analyzed: 92	In: BE with HGD Ex: History of prior esophageal surgery or radiotherapy	Median: 67 (IQR 59–75)	Median: 6 (IQR 3–8)	NA 24
Gondrie et al. [9]	19 (IQR 18–22)	11	In: BE with HGD or IMC Length of BE: 2–10 cm Ex: Esophagus stenosis; invasive cancer	Median: 60 (IQR 57–67)	Median: 5 (IQR 4–7)	2 IMC 3 LGD 1 HGD 5 NA
Hernandez et al. [11]	12	10	In: BE with IM, LGD or HGD Length of BE: >1 cm Ex: Esophagus stenosis; history of prior esophageal surgery, ablation, or radiotherapy; esophagitis; esophageal malignity	62 (19–73)	4.9 (1–11)	7 IM 2 LGD 1 HGD
Sharma et al. [12]	24	10	In: BE with LGD Ex: Esophagus stenosis; history of prior esophageal surgery, EMR, ablation, or radiotherapy; esophagitis; history of HGD or esophageal cancer	66.9 (48–79)	4.4 (3–6)	10 LGD
Roorda et al. [20]	12 (IQR 6–19)	13	In: BE with IM, LGD or HGD Ex: IM on esophagogastric junction	57 (31–75)	3 Patients: BE length <3 cm 10 Patients: BE length >3 cm	6 IM 4 LGD 3 HGD

Table 1 continued

Observational study	Study characteristics		Subjects' baseline characteristics			
	Duration of study months (range)	No. of subjects	Main in/ex criteria	Mean age ^a Years (range)	Mean length of BE ^a cm (range)	Histology before intervention
Sharma et al. [22, 23]	30	102	In: BE with IM without dysplasia Length of BE: 2–3 cm (dose-finding group) 2–6 cm (effectiveness-group) Ex: Esophagus stenosis; history of prior EMR, esophageal ablation, or radiotherapy; esophagitis; history of dysplasia or malignancy	56.8 (35–75) 55.7 (26–79) 55.5 (26–79)	2.3 3.2 (2–6) 3.1 (2–6)	102 IM
	Dose Finding: 12 Effectiveness: 12 Follow-up: 30	Doses Finding: 32 Effectiveness: 70 (62 included in follow-up ≥ 13 months)				EMR before ablation (n)

BE Barrett's esophagus; EMR endoscopic mucosal resection; HGD high-grade dysplasia; LGD low-grade dysplasia; IM intestinal metaplasia; NA not available; IQR interquartile range; IMC intramucosal cancer

^a Unless otherwise stated

^b 27 subjects analyzed for histologic results, 54 subjects analyzed for safety results

Postinterventional symptoms

Posttreatment symptoms and patient tolerability were investigated in three observational trials [9, 12, 22, 23] using a discharge survey, a 14-day symptom diary, or both. Overall, the intervention was well tolerated by the patients, with any adverse symptoms described as mild and short term (disappearing after a maximum 5 days). The remaining six studies did not provide information on this issue.

Adverse events

Safety parameters were assessed in all the included trials. No serious adverse events occurred in the studies. Overall, only a small number of mild adverse events were reported. The most common adverse events were chest and throat pain, sedation-related nausea and fever, and odynophagia.

Buried glands

Details about the presence of buried glands after intervention were given in all the studies except one [21]. The histologic results for more than 8,500 biopsies, performed during the follow-up visits, were assessed, and only one study reported one case of buried Barrett's metaplasia, which was encountered at the 3-month postablation follow-up visit.

Esophageal functions

One publication [17] focused on the function parameters of the esophagus, and no significant changes between pre- and postintervention were found in terms of the esophageal diameter, the lower esophageal sphincter (LES) pressure and length, the contraction amplitude, or the compliance of the esophagogastric junction.

Discussion

This systematic review was based on the importance of answering clinically relevant, patient-oriented questions by assessing evidence in terms of esophagus stenosis, postinterventional symptoms, adverse events, QoL, mortality, and surrogates such as eradication of dysplasia and metaplasia and buried metaplasia in patients with Barrett's esophagus. We searched for all studies on ablation therapy used for patients with Barrett's esophagus and reviewed these studies. Nine studies met the inclusion criteria.

Most of the publications were performed by two working groups around Bergman [9, 10, 17] and Sharma and Fleischer [12, 18, 19, 22, 23].

Table 2 Histologic and safety results

Study	CR-D % (months follow-up)	CR-IM % (months follow-up)	Postinterventional symptoms	Stenosis/adverse events	Buried glands (no. of biopsies)
Sharma et al. [19]	89 (24)	79 (24)	NA	1 Mild symptomatic stenosis AEs: mild bleeding (1) No SAEs	No buried glands in any biopsies (<i>n</i> > 1,500)
Velanovich [21]	NA	93 ^a (≥12)	NA	4 Stenoses ^b No AEs No SAEs	NA
Gondrie et al. [10, 17]	100 (14)	100 (14)	NA	No stenosis AEs: escape EMR (1) No SAEs	No buried glands in any biopsies (<i>n</i> = 363)
Ganz et al. [18]	80.4 (12)	54.3 (12)	NA	1 Stenosis AEs: 2 esophagectomies No SAEs	No buried glands in any biopsies (<i>n</i> = NA)
Gondrie et al. [9]	100 (19)	100 (19)	Symptom diary (until 14 days after intervention): mild symptoms: days 2–4	No stenosis AEs: escape EMR (1), fever and chest pain (1), retrosternal pain (1) No SAEs	No buried glands in any biopsies (<i>n</i> = 473)
Hernandez et al. [11]	NA	CR: 70 (12) PR: 30 (12)	NA	No stenosis AEs: mild chest and throat pain No SAEs	1 Case of buried glands in any biopsies (<i>n</i> = 247)
Sharma et al. [12]	90 (12) 100 (24)	70 (12) 90 (24)	Discharge survey (VAS 1–100): mild symptoms after CA VAS during intervention: 1. CA: 8 (2–29), 2. CA: 0 (0–29) FA: 0 (0–0) VAS 2 h after intervention: 1. CA: 0 (0–29), 2. CA: 1 (0–2) FA: 0 (0–0) Symptom diary (until 14 days after intervention): CA: mild symptoms: days 1–4 (VAS: median <10/100), FA: mild symptoms: days 1–5 (VAS: median <25/100)	No stenosis AEs: CA: vomiting (1) FA: No AEs No SAEs	No buried glands in any biopsies (<i>n</i> = 886)
Roorda et al. [20]	71 (12)	46 (12)	NA	No stenosis AEs: mild fever (1), mild dysphagia and odynophagia (3) No SAEs	No buried glands in any biopsies (<i>n</i> = NA)

Table 2 continued

Study	CR-D % (months follow-up)	CR-IM % (months follow-up)	Postinterventional symptoms	Stenosis/adverse events	Buried glands (no. of biopsies)
Sharma et al. [22, 23]	NA	Dose finding (12): CR: 59 PR: 25 NR: 16 Effectiveness (12): CR: 69 PR: 24 NR: 7 Follow-up (30): CR: 97	Exit survey (VAS 1–100): Dose finding-group: VAS during intervention: 1.CA: 3 (1–6) 2.CA: 0 (0–1) VAS 2 h after intervention: 1.CA: 3 (1–9) 2.CA: 3 (1–8) Effectiveness-group: mild symptoms for CA and FA (n.s.) VAS during intervention: 1. CA: 3 (0–7) 2. CA: 1 (0–4) VAS 2 h after intervention: 1.CA: 15 (4–23) 2.CA: 2 (0–11) Symptom diary (until 14 days after intervention): Dose finding-group: 1. CA: mild symptoms (chest pain, dysphagia) on day 1 (median <10/100), disappeared by day 4 (0/100) Effectiveness-group: mild symptoms for CA and FA (chest, throat, and abdominal pain, painful swallowing and difficulty swallowing (n.s.))	No stenosis AEs: Dose finding-group: 1. CA: 5 AEs among 5 patients: chest pain (3), superficial mucosa-lesions (1), mucosal scarring (1) 2. CA: 7 AEs among 6 patients: fever (3), mucosal scarring (1), abdominal pain (1), nausea (1), hypotension after anesthesia (1) Effectiveness-group (after 12 months): 24 AEs among 16 patients: chest/throat pain (9), nausea (8), fever (2), superficial mucosa-lesions (1), mild bleeding during ablation (1), mucosal scarring (1), dyspnea after anesthesia (1), hypotension after anesthesia (1) Effectiveness-group (after 30 months): FA: 4 AEs among 3 patients No SAEs	No buried glands in any biopsies (n = 5229)

CR-D complete responses for dysplasia; CR-IM complete responses for intestinal metaplasia; NA not available; AE adverse events; SAE serious adverse events; EMR endoscopic mucosal resection; CR complete responses; PR partial responses; VAS visual analog scale; CA circumferential ablation; FA focal ablation; NR no responses; n.s. not significant

^a 27 subjects analyzed

^b 54 subjects analyzed

In the majority of the studies, the follow-up period was only 12–24 months, and the number of subjects treated with RFA was low. Unfortunately, no RCTs met the inclusion criteria. Hence, only the results of observational studies are discussed in this report. Because study designs other than RCTs usually are not suitable for proving causality, a major limitation of this review is the lack of data from RCTs comparing RFA with other therapy options for Barrett's esophagus (e.g., surveillance following the Seattle protocol, photodynamic therapy, Argon plasma coagulation, or total ablation of the esophagus with EMR). For the interpretation of this review, it is important to state that the nonavailability of studies with the highest evidence level cannot generally be viewed as sufficient justification for a benefit assessment conducted using studies with lower evidence levels.

None of the included studies evaluated outcomes in terms of mortality and QoL. Postinterventional symptoms were rare and disappeared after a few days. No serious adverse events were reported. However, when the reported events were classified according to the International Conference of Harmonization—Good Clinical Practice (ICH-GCP) guidelines [24], some. However, some of these events should be considered as serious. Levels of complete responses for dysplasia and metaplasia were very high, and it would seem that combined treatment with stepwise HALO³⁶⁰ circumferential and the HALO⁶⁰ focal systems is superior to the HALO³⁶⁰ circumferential treatment alone.

All but one study investigated the presence of buried intestinal metaplasia after RFA therapy, and only one case of buried glands was reported. The occurrence of stenosis was reported for only six of 429 patients, with three of the six patients having a rather long Barrett's esophagus, measuring more than 12 cm at baseline. Furthermore, due to the lack of data, it remains unclear whether these strictures appeared only in patients with additional EMR. An indirect comparison between RFA and other endoscopic treatments such as photodynamic therapy, based on the data found in secondary literature [25, 26], suggests less buried intestinal metaplasia and also less stenosis after treatment with the HALO system. Similar results of such a comparison also were presented in a conference paper in 2008 [27].

The results of two new relevant studies, one RCT and one cohort study, have been published most recently. The first study, the AIM Dysplasia Trial, a U.S. multicenter, randomized, sham-controlled trial, evaluated the safety and effectiveness of RFA for 127 patients with Barrett's esophagus containing dysplasia. Shaheen et al. [28] reported a significantly higher rate ($p < 0.001$) for complete eradication of dysplasia and for intestinal metaplasia among patients in the ablation group than among the control patients. Furthermore, the patients in the ablation

group had significantly less disease progression than those in the control group ($p = 0.03$), and the prevalence of subsquamous intestinal metaplasia also was significantly lower after RFA than after sham intervention ($p < 0.001$).

According to safety parameters, three serious adverse events occurred in the intervention group compared with none in the control group, whereas esophageal strictures developed in five patients of the ablation group.

The preliminary results of this RCT concerning the patients' QoL were presented during the Digestive Disease Week Conference 2008 (www.ddw.org). A large effect was reported after 1 year of follow-up assessment, with a better QoL score for the patients with a complete response for dysplasia compared with baseline perception [29].

The second study was a European multicenter prospective cohort study of patients with Barrett's esophagus. Data concerning the histologic response rate presented for 24 patients support the results found in the studies included in this review [30]. The complication rates for 65 patients suggest that the HALO system is safe for patients without EMR before ablation. For the patients with EMR, some adverse events such as superficial mucosal lacerations or symptomatic stenosis due to an overstretching of the esophagus by the HALO³⁶⁰ balloon were reported. In this case, the authors advise limiting the extent of the EMR and making a rather conservative selection of the ablation catheter diameter [31].

Although some of the results from this comprehensive systematic review are very promising in terms of improvement in patient-relevant outcomes for patients with Barrett's esophagus care, we should still keep in mind that the benefit of RFA with the HALO system cannot be proved until well-designed comparative studies are performed.

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