

Systematic review and meta-analysis of the effectiveness of radiofrequency ablation in low grade dysplastic Barrett's esophagus

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Bibliography

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 Figs. e8–e13, Appendix e1

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ABSTRACT

Background Barrett's esophagus (BE) is a premalignant condition characterized by replacement of the esophageal lining with metastatic columnar epithelium, and its management when complicated by low grade dysplasia (LGD) is controversial. This systematic review and meta-analysis aimed to determine the efficacy of radiofrequency ablation (RFA) in patients with LGD.

Methods MEDLINE, EMBASE, and Web of Science were searched for studies including patients with BE-associated LGD receiving RFA (January 1990 to May 2017). The outcome measures were complete eradication of intestinal metaplasia (CE-IM) and dysplasia (CE-D), rates of progression to high grade dysplasia (HGD) or cancer, and recurrence.

Results Eight studies including 619 patients with LGD (RFA=404, surveillance=215) were analyzed. After a median follow-up of 26 months (range 12–44 months), the overall pooled rates of CE-IM and CE-D after RFA were 88.17% (95% confidence interval [CI] 88.13%–88.20%; $P < 0.001$) and 96.69% (95%CI 96.67%–96.71%; $P < 0.001$), respectively. When compared with surveillance, RFA resulted in significantly lower rates of progression to HGD or cancer (odds ratio [OR] 0.07, 95%CI 0.02–0.22). The pooled recurrence rates of IM and dysplasia were 5.6% (95%CI 5.57–5.63; $P < 0.001$) and 9.66% (95%CI 9.61–9.71; $P < 0.001$), respectively.

Conclusions RFA safely eradicates IM and dysplasia and reduces the rates of progression from LGD to HGD or cancer in the short term.

Introduction

Barrett's esophagus (BE) is a premalignant condition characterized by the replacement of the squamous lining of the esophagus by columnar epithelium resembling intestinal metaplasia (IM) [1]. The main risk factor for developing BE is gastroesophageal reflux disease (GERD), yet many patients are asymptomatic [2]. BE is also associated with obesity, smoking, and the presence of a hiatus hernia, and is commoner in men [3,4]. Endoscopic screening in patients with two or more risk factors and GERD symptoms can be considered, with a lower threshold

in patients with a family history of BE or esophageal carcinoma [3].

The incidence of BE is increasing in the Western world, being reported to occur in 2% of the adult population, and this has been associated with a concomitant increase in the incidence of esophageal adenocarcinoma (EAC) [3]. IM can progress via low grade dysplasia (LGD) and high grade dysplasia (HGD) to EAC, which has a poor prognosis [1]. The rate of progression to cancer in patients with LGD is reported to vary between 0.6% and 26.5% per year [5–7]. Dysplastic segments must be confirmed by two expert pathologists because misclassification of

LGD has been shown to contribute to lower progression rates in some studies [8–10].

The management of BE is determined by its stage. The National Institute for Health and Care Excellence (NICE) recommends that patients with IM or LGD undergo endoscopic surveillance and repeat biopsy; if HGD or cancer is detected, endoscopic treatment or esophagectomy is recommended [1]. Endoscopic treatments include endoscopic mucosal resection (EMR), photodynamic therapy (PDT), cryotherapy, and radiofrequency ablation (RFA) [1, 3]. Because the risk of cancer increases with the grade of dysplasia, it is important to treat BE when the risk is at its lowest, thereby avoiding high risk surgical treatments such as esophagectomy.

RFA consists of the delivery of controlled radiofrequency energy endoscopically, and two randomized controlled trials (RCTs) have reported it to be safe and effective, with a significant reduction in progression to esophageal cancer [8, 9]. Although RFA has been shown to decrease the progression of LGD to HGD or cancer compared with surveillance [9, 10], it is neither widely available nor routinely used. Therefore, the aim of this review was to assess the efficacy of RFA in the treatment of LGD.

Methods

Search strategy

A systematic review was completed according to the Preferred Reporting Items for Systematic review and Meta-analyses (PRISMA) guidelines [11]. Electronic database searches were performed in Ovid MEDLINE, EMBASE, and Web of Science during May 2017 using the following search terms: radiofrequency ablation, low grade, dysplasia, Barrett's esophagus, esophagitis etc. (**Appendix e1**, available online in Supplementary material). Searches were limited to articles in the English language and were then imported into EndNote to remove duplicates. Titles were screened for relevance, then abstracts, and finally full text articles were screened.

Data extraction

The following information was extracted: authors, year, study design, location, sample size, participants, intervention, control, outcomes, results, follow-up period, quality of study, and whether baseline LGD was confirmed by more than one pathologist. Some studies included participants with non-dysplastic BE and HGD, as well as LGD. Where possible the data specific to LGD was extracted.

The primary outcome measures were the rates of complete eradication of IM (CE-IM) and dysplasia (CE-D), meaning the absence of IM or dysplasia of any grade, respectively. Secondary outcomes included the rates of progression to HGD or cancer, recurrence of dysplasia post-eradication, and adverse events.

Inclusion and exclusion criteria

Eligibility criteria were formed a priori using the PICO (T) model and are listed in ► **Table 1** [12]. The model identified the population, intervention, comparison, outcomes, and type of study. Studies comparing outcomes in patients with LGD, with and without RFA therapy, were included. Where there were pilot

► **Table 1** Eligibility criteria for studies of radiofrequency ablation (RFA) in low grade dysplastic Barrett's esophagus.

Inclusion criteria	Exclusion criteria
Randomized controlled trial or observational study	Reviews, commentaries, case reports
Adults diagnosed with low grade dysplasia	Age < 18 years
Patients receiving RFA compared with control group not receiving RFA	Studies with high grade dysplasia and adenocarcinoma but no low grade dysplasia
Outcome measure: progression to high grade dysplasia or esophageal adenocarcinoma or complete eradication	Articles with full text unavailable

studies, the most recent study by the same authors was included; where there were follow-up studies, the original study was included and other studies were excluded from the analysis. Studies with less than 10 patients and data from conference abstracts were excluded.

Quality assessment

The quality of the RCTs was assessed, being guided by the Cochrane risk of bias tool and the Critical Appraisal Skills Programme (CASP) checklist [13, 14]. The quality of observational studies was assessed using the Newcastle–Ottawa scale, which assesses patient selection, comparability of intervention, control group, and outcome assessment [14].

Statistical analysis

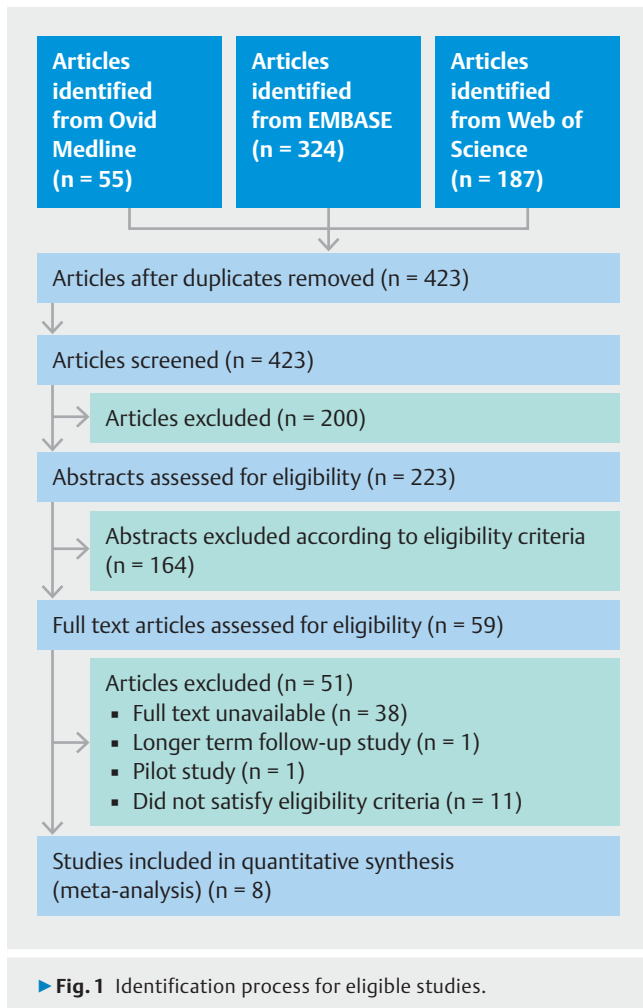
Statistical analysis was performed using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis was used to pool study estimates of the outcome measures as detailed above. The pooled estimated outcomes were calculated using generic inverse-variance random-effects meta-analysis using data from studies that reported at least one event in the outcome under investigation, with standardized mean differences and 95% confidence intervals (CI) quoted. Statistical analysis of studies comparing outcomes in patients receiving RFA and surveillance only was carried out using odds ratios.

Heterogeneity among study estimates was quantified using the I^2 value and associated test for heterogeneity which was reported for each analysis. Where heterogeneity was apparent the DerSimonian and Laird random-effects method was used to pool estimates with inverse-variance weights. The fixed-effects method of Mantel–Haenszel was applied otherwise.

Results

Characteristics of included studies

The search identified 566 articles, of which eight were suitable for inclusion (► **Fig. 1**). Two studies were RCTs [15, 16] and six were observational cohort studies [17–22]. Three of the observational studies were of prospective design [18, 20, 22].



In total, the studies included 619 patients (501 men; median age 65 [range 18–84]) with low grade dysplastic BE. The total number of patients treated with RFA was 404. Three studies compared RFA to surveillance endoscopy. Complete eradication of IM or dysplasia was assessed in all studies except for Orman et al. [19]. Progression to HGD or cancer was recorded in four studies [15, 16, 21, 22] and recurrence after eradication in five studies [17–21].

The length of the BE segment ranged from 0.5 to 13 cm. Diagnosis of LGD was confirmed by two pathologists in all of the studies. All patients with visible mucosal abnormalities underwent EMR prior to RFA therapy with either HALO360 (circumferential) or HALO90 (focal) catheters. The median follow-up was 26 months (range 12–44 months).

Quality assessment and data extraction

The studies were ranked 1 to 4 in terms of quality. The two RCTs, Phoa et al. [15] and Shaheen et al. [16], were ranked 1 (highest quality), and Guthikonda et al. [17] was ranked as the poorest quality. The study characteristics are outlined in ► **Table 2**. Only one of the six observational studies had a control cohort and was therefore ranked higher [21].

Complete eradication of intestinal metaplasia

Six out of the eight studies addressed CE-IM in the results [15–18, 21, 22]. Small et al. [21] only reported the rate of CE-IM in patients receiving ablative therapy, despite recruiting a control group. Ablative therapy was found to be very effective in eradicating IM [15, 16]. Komanduri et al. [18] recorded the highest proportion of patients achieving complete eradication, with 71/76 patients (93.4%). In contrast Small et al. [21] recorded the lowest proportion of patients receiving ablation achieving complete eradication, with 35/45 patients (77.8%). The overall pooled rate of CE-IM after RFA was 88.17% (95%CI 88.13%–88.20%; $P < 0.001$) (► **Fig. 2**).

Complete eradication of dysplasia

Six studies reported CE-D in the results [15, 16, 18, 20–22]. RFA was found to be effective in achieving CE-D (► **Table 2**) and was more effective in eradicating dysplasia than in eradicating IM. Phoa et al. [15] found that 98.4% of patients achieved CE-D in the RFA group compared with only 27.9% of patients in the endoscopic surveillance group. Although Small et al. [21] did not report outcomes on eradication of IM, the authors reported that 95.6% of patients achieved CE-D in the RFA cohort compared with 28.9% in the control cohort. Pooled results of all the studies concluded that 96.69% of patients receiving RFA achieved CE-D (95%CI 96.67%–96.71%; $P < 0.001$) (► **Fig. 3**). When compared with surveillance, patients who underwent RFA were more likely to achieve CE-D ($P < 0.001$) (► **Fig. 4**).

Progression to high grade dysplasia or cancer

Progression of LGD to HGD or cancer was reported in three studies that compared RFA with surveillance [15, 16, 21]. Patients who underwent RFA were less likely to progress to HGD or cancer (OR 0.07, 95%CI 0.02–0.22) (► **Fig. 5**).

Five patients who received RFA progressed to HGD or cancer (2.6%), of whom three progressed to cancer (1.5%). One patient receiving RFA progressed to EAC [15] and two to an intramucosal carcinoma (IMC) [21, 22]. In patients undergoing surveillance, 57 progressed to HGD or cancer (26.5%), of whom eight progressed to cancer (3.7%). Komanduri et al. [18] aimed to report the rate of progression; however, they did not include the rate of progression in patients with baseline LGD in their results.

Recurrence rates

Recurrence of IM or dysplasia after complete eradication was reported in five studies [17–21]. The rates of recurrence of IM and dysplasia ranged from 2.8% [18] to 25.3% [17] and from 0% [18, 20] to 16.3% [21], respectively. The overall pooled recurrence rates of IM and dysplasia were 5.6% (95%CI 5.57%–5.63%; $P < 0.001$) (► **Fig. 6**) and 9.66% (95%CI 9.61%–9.71%; $P < 0.001$) (► **Fig. 7**), respectively.

Adverse events

Adverse events were reported in five studies [15, 16, 18, 20, 22] (► **Table 3**). In studies reporting adverse events in patients other than those with LGD, it was not possible to identify the

► **Table 2** Characteristics of the eight included studies.

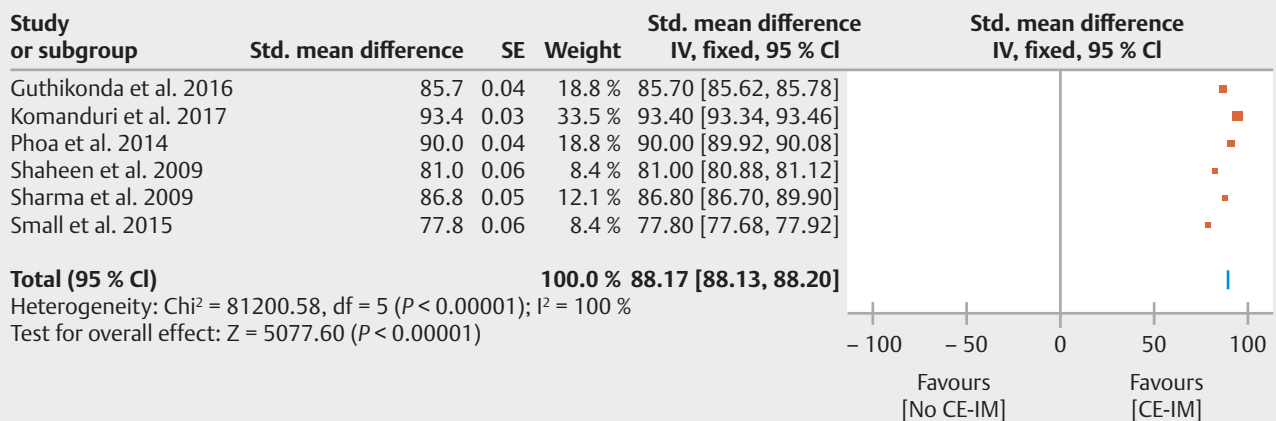
First author, year	Therapy	Number of patients	Median follow-up ¹ , months	Progression to high grade dysplasia, n (%)	Complete eradication, n (%)		Recurrence ² , n (%)	Study quality
					Intestinal metaplasia	Dysplasia		
Phoa K, 2014 [15]	RFA	68	36	0 (0); 1 EAC (1)	54/60 (90)	62/63 (98)	NR	1
	Control ³	68		18 (26)	0/68 (0)	19/68 (28)	NR	
Shaheen NJ, 2009 [10]	RFA	42	NR	2 (5)	34 (81)	38 (90)	NR	1
	Control ³	22		3 (14)	1 (5)	5 (23)	NR	
Guthikonda A, 2016 [17]	RFA	98	NR	NR	84 (86)	NR	19/75 (25); 6/75 dysplasia (8)	4
Haidry RJ, 2013 [20]	RFA	12	25	NR	NR	10 (83)	0 dysplasia (0)	3
Komanduri S, 2017 [18]	RFA	76	44 (mean)	NR	71 (93)	74 (97)	2/71 (3); 0/74 dysplasia (0)	3
Orman ES, 2013 [19]	RFA	24	13	NR	NR	NR	1 dysplasia (4)	3
Small AJ, 2015 [21]	RFA	45	29.6	0 (0); 1 IMC (2)	35 (78)	43 (96)	7/43 dysplasia (16)	2
	Control ³	125	28.3	29 (23); 5 IMC (4); 2 EAC (2)	NR	39 (31)	NR	
Sharma VK, 2009 [22]	RFA	39	23	0 (0); 1 IMC (3)	33/38	36/38 (95)	NR	3

RFA, radiofrequency ablation; EAC, esophageal adenocarcinoma; NR, not recorded; IMC, intramucosal carcinoma.

¹ Median unless otherwise indicated.

² Recurrence of intestinal metaplasia after complete eradication unless otherwise indicated.

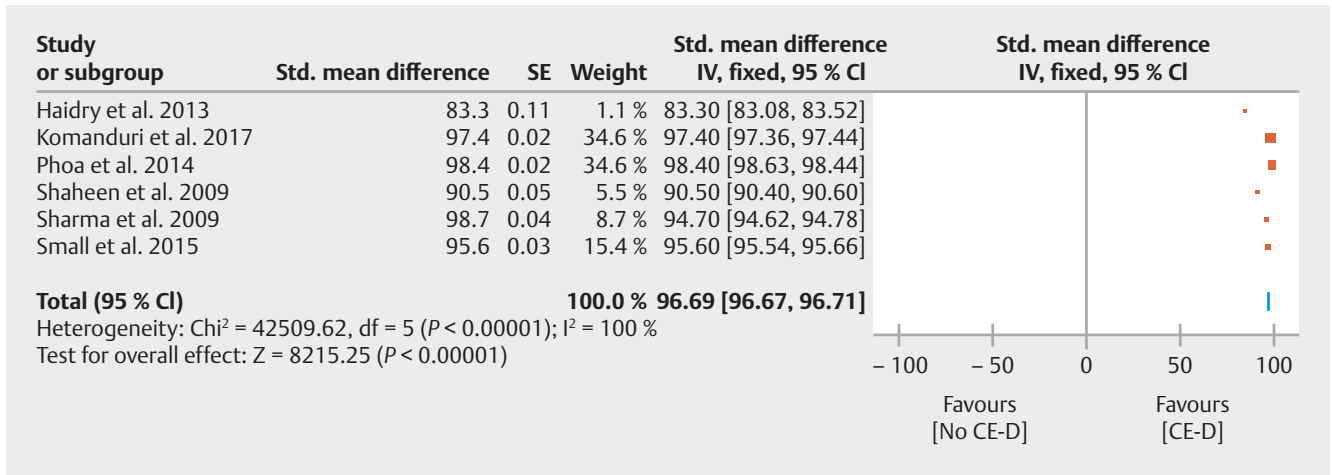
³ Surveillance endoscopy only.



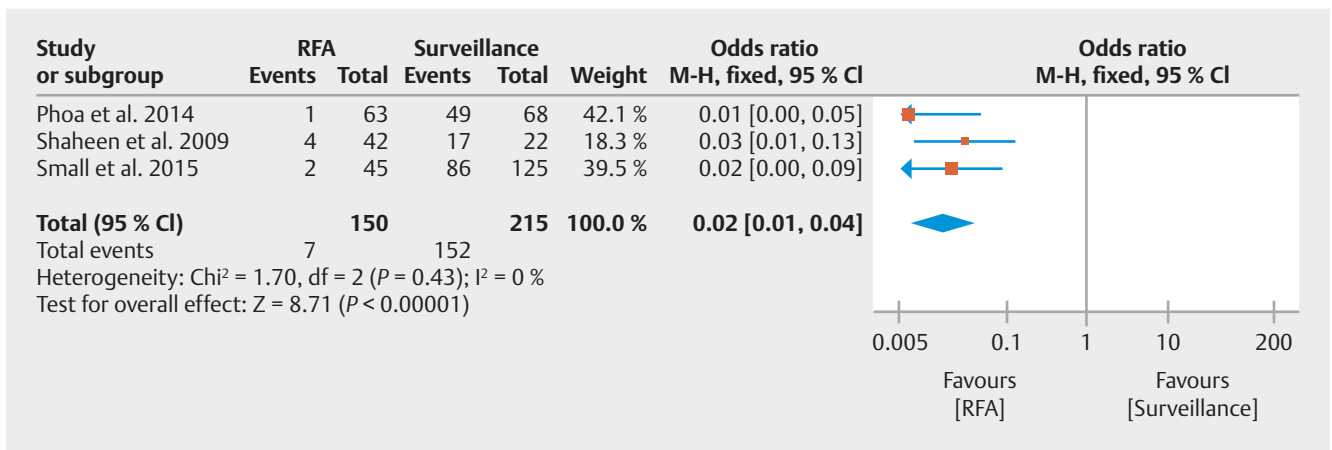
► **Fig. 2** Effect of radiofrequency ablation (RFA) on the complete eradication of intestinal metaplasia (CE-IM) in patients with low grade dysplastic Barrett's esophagus. Effect sizes are shown with 95% confidence intervals (CIs).

baseline histology. Therefore, the events reported in this study are not exclusive to patients with LGD, they are still however noteworthy as they are complications of RFA.

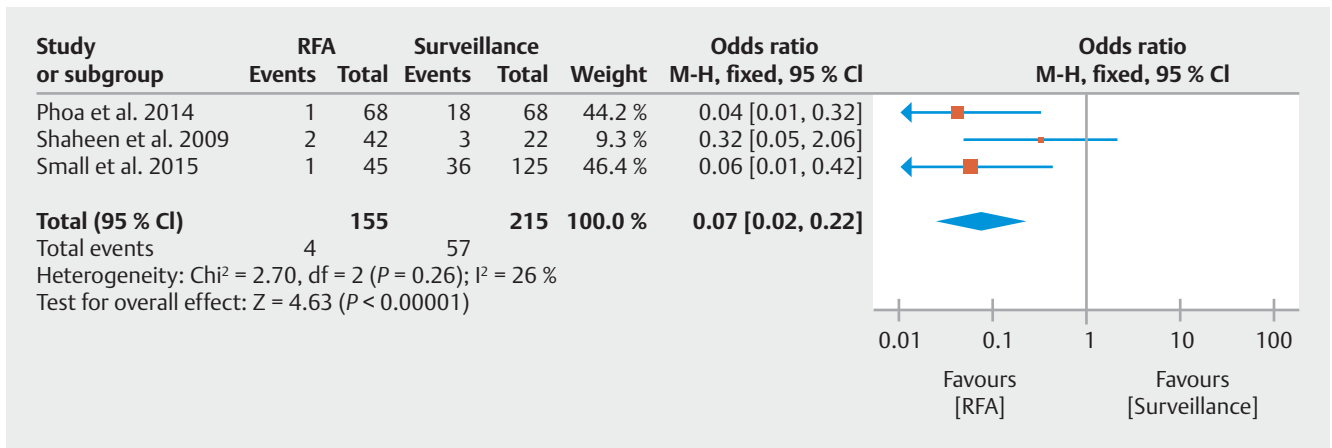
The most common adverse event reported was esophageal stricture formation [15, 18, 22], followed by bleeding [16, 18, 22]. Haidry et al. [20] reported that one patient was hospitalized a few days post-ablation with abdominal pain; another re-



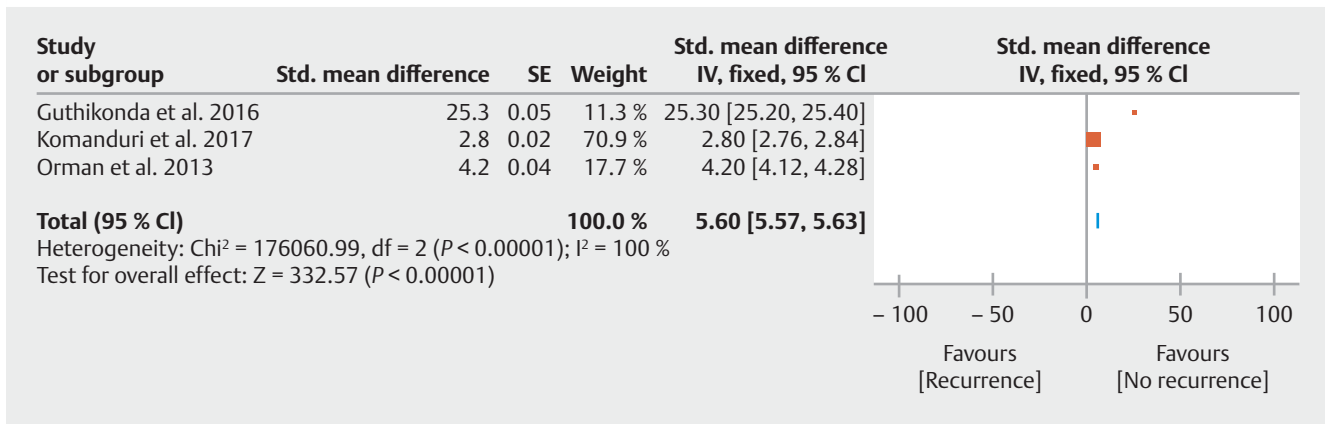
► **Fig. 3** Effect of radiofrequency ablation (RFA) on the complete eradication of dysplasia (CE-D) in patients with low grade Barrett's esophagus. Effect sizes are shown with 95 % confidence intervals (CIs).



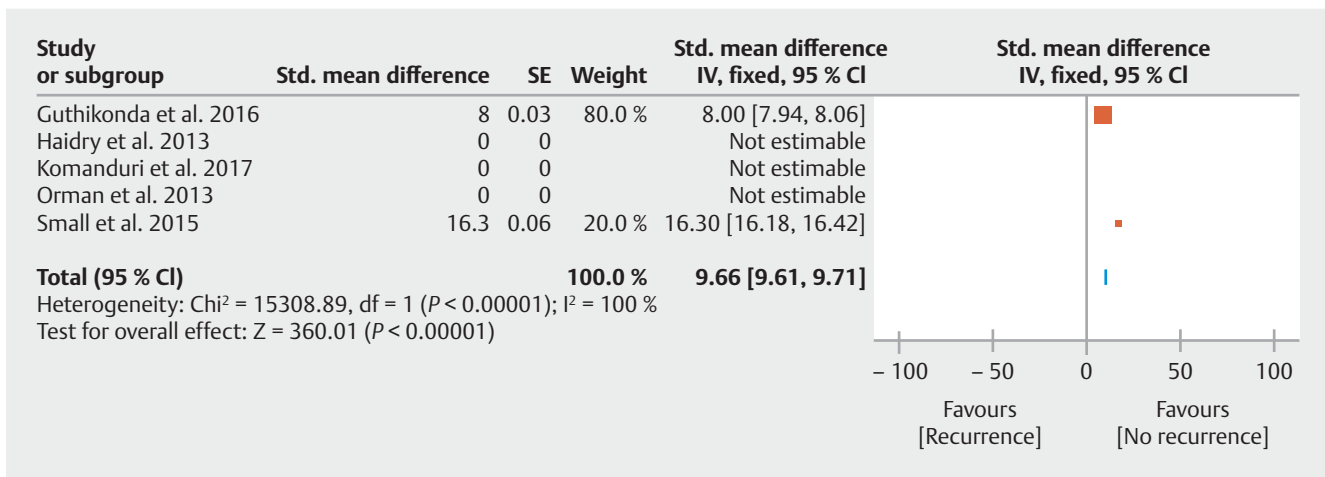
► **Fig. 4** Effect of radiofrequency ablation (RFA) compared with surveillance on the complete eradication of dysplasia in patients with low grade dysplastic Barrett's esophagus. Odds ratios are given with 95 % confidence intervals (CIs).



► **Fig. 5** Effect of radiofrequency ablation (RFA) compared with surveillance on the progression of low grade dysplasia to high grade dysplasia or cancer. Odds ratios are given with 95 % confidence intervals (CIs).



► **Fig. 6** Effect of radiofrequency ablation (RFA) on the recurrence of intestinal metaplasia post-eradication in patients with low grade Barrett's esophagus. Effect sizes are shown with 95% confidence intervals (CIs).



► **Fig. 7** Effect of radiofrequency ablation (RFA) on the recurrence of dysplasia post-eradication in patients with low grade Barrett's esophagus. Effect sizes are shown with 95% confidence intervals (CIs).

ported retrosternal chest pain weeks after the ablation, which resolved with analgesics. Chest/retrosternal chest pain was a reported adverse event [15, 16]; as well as perforation, which was reported by only one patient in one study [20]. Two studies reported subsquamous IM (buried glands) [16, 18]. Komanduri et al. reported one patient with buried glands on surveillance biopsy [18]. Shaheen et al. assessed the presence or absence of subsquamous IM before and after treatment [16]. At baseline, 25.0% of patients in the RFA group had evidence of subsquamous IM and 25.6% in the control group. At 12 months 5.1% of patients in the RFA group had subsquamous IM and 40.0% of those in the control cohort ($P < 0.001$).

Publication bias

Funnel plots for each analysis (► **Figs. e8 – e13**) are available online in Supplementary material.

Discussion

This study of over 600 patients is the only comprehensive meta-analysis of the outcomes of RFA in patients diagnosed with low grade dysplastic BE. The results have shown that RFA safely eradicates LGD in 96% of patients and significantly lowers the rate of progression to HGD and cancer when compared with surveillance endoscopy.

Until the recent publication of the amended British Society of Gastroenterology guidelines [8], the recommended management of patients diagnosed with LGD in BE consisted of surveillance endoscopy every 6 months, until unequivocal progression to a diagnosis of HGD or cancer occurred. Endoscopic ablative therapy is now recommended if persistent LGD is confirmed at follow-up surveillance endoscopy, 6 months after the initial index endoscopy and histological diagnosis [8]. Nevertheless, despite the reported benefits, surveillance endoscopy remains a viable option because RFA is not widely available and uncertainty persists regarding its long-term efficacy.

► **Table 3** Details of the adverse events reported.

First author, year	Number of patients	Perforations, n (%)	Stricture formation, n (%)	Bleeding, n (%)	Chest pain, n (%)	Abdominal pain, n (%)	Mucosal laceration, n (%)	Total adverse events, n (%)
Phoa K, 2014 [15]	68	0 (0)	8 (12)	1 (1)	1 (1)	1 (1)	3 (4)	14 (21)
Shaheen NJ, 2009 [10]	84	0 (0)	5 (6)	1 (1)	2 (2)	NR	NR	8 (6)
Haidry RJ, 2013 [20]	335	1 (<1)	30 (9)	NR	NR	NR	NR	31 (9)
Komanduri S, 2017 [18]	221	0 (0)	5 (2)	8 (4)	NR	NR	NR	14* (6)
Sharma VK, 2009 [22]	63	NR	1 (2)	1 (2)	NR	NR	NR	2 (3)
Total	771	1 (<1)	49 (6)	11 (1)	3 (<1)	1 (<1)	3 (<1)	69 (9)

NR = not recorded.

* One patient with buried glands on surveillance biopsy.

Several controversies exist in the management of patients with low grade dysplastic BE. Firstly, the natural history of LGD is not fully understood but it is thought to be a slowly progressive lesion in most cases [23]. Secondly, the reported risk of malignant progression of LGD varies widely. These controversies arise because the diagnosis of LGD by community pathologists is unreliable and LGD tends to be overdiagnosed [24]. An expert gastrointestinal (GI) pathology panel has been shown to downstage 85% of community LGD diagnoses. Moreover, even among expert GI pathologists, there is high interobserver variation for diagnosing LGD, with kappa scores ranging from 0.14 to 0.32, suggesting only poor to fair agreement [25, 26]. As such, a reliable diagnosis of LGD is questionable even in studies that included expert histopathologists [27]. It is the quality and homogeneity of the expert panel that is essential to establish a reliable baseline LGD diagnosis and reported progression risks [24]. Evidently, despite all of the studies in this meta-analysis including expert histopathological review, the reported progression risks of LGD to HGD or carcinoma ranged from 0.6%–26.5%. In addition, sampling variability could contribute to these various progression risks and could also explain apparent complete regression of dysplasia in the surveillance arm in up to 27% of patients [15, 28]. Nevertheless, true neoplastic regression may exist, although it is not proven [23].

RFA involves the delivery of radiofrequency energy to the esophageal mucosa using balloons or catheters [29]. Other endoluminal techniques are available and offer alternative vectors in the management of dysplastic and non-dysplastic BE. EMR is used to target visible abnormalities (nodular BE) [30], but there are no recommendations with regard to its use in the management of LGD, especially in the absence of nodular abnormalities [31]. EMR was used in three of the studies in this review [16, 19, 20].

Caillol et al. [32] have reported data on treatment of dysplastic BE with EMR and RFA. Patients were divided into two cohorts: cohort 1 received EMR followed by RFA; cohort 2 received RFA only. Cohort 1 consisted of 13 patients with HGD and 3 with LGD. HGD eradication was achieved in 12 patients (92%) and LGD eradication in 3 patients (100%). Cohort 2 consisted of 18 patients (1 with HGD, 14 with LGD, and 3 with IM). HGD eradication was achieved in 1 patient (100%) and LGD eradication in 9 (64%). Although the results suggest that EMR prior to RFA would be beneficial for the eradication of dysplasia, no significant differences emerged in the results when the cohorts were compared.

Kim et al. [30] reported a comparison of two treatment modalities, recruiting 50 patients to receive EMR before RFA and 98 to receive only RFA. CE-IM was achieved in 44 patients (88%) in the cohort receiving EMR+RFA, and in 76 (78%) in a RFA only cohort ($P=0.13$). CE-D was achieved in 47 (94%) of the EMR+RFA cohort, and 81 (83%) of the RFA only cohort ($P=0.06$).

This study has a number of inherent potential limitations. Both observational cohort studies and RCTs were included. Meta-analysis of retrospective cohort studies is sensitive to confounding and selection bias. Although the sample sizes of patients with LGD receiving RFA were all less than 100 patients, all supported the use of RFA. In one study, the trial was terminated because of concerns for patient safety, as RFA was found to be significantly more effective [15].

In contrast, the study has a number of strengths. The outcome measures were clearly and consistently defined in trials and observational studies. Moreover, over 90% of patients were adequately followed-up for over 2 years. In keeping with published guidance, most studies confirmed the baseline histology with more than one expert pathologist, thereby improving the accuracy of LGD diagnosis. The main concern was the

rate of stricture formation, which was found to be 6% in this study. These results are consistent with a review reporting the rate of RFA-associated adverse events, with or without EMR, to be of the order of 8.8%: strictures developed in 5.6%, bleeding occurred in 1%, and perforation in 0.6% of patients [33].

In conclusion, RFA safely eradicates IM and dysplasia and reduces the rates of progression from LGD to HGD or cancer in the short term. Long-term RFA outcomes however remain unknown and further research including detailed follow-up is warranted.

Competing interests

None.

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