Original Article

Prophylactic eradication of non-dysplastic Barrett's esophagus to prevent progression to esophageal adenocarcinoma —a systematic review and meta-analysis

Jasmijn Sijben^, Yonne Peters^, Peter D. Siersema^

Department of Gastroenterology and Hepatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

Contributions: (I) Conception and design: All authors; (II) Administrative support: J Sijben; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: J Sijben, Y Peters; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jasmijn Sijben. Department of Gastroenterology and Hepatology (route 455), Radboud University Medical Center, Geert Grooteplein-Zuid 8, 6500 HB, Nijmegen, The Netherlands. Email: jasmijn.sijben@radboudumc.nl.

Background: Eradication of non-dysplastic Barrett's esophagus (NDBE) to prevent the development of esophageal adenocarcinoma (EAC) is controversial. Our aim was to complete a systematic review on the efficacy, durability and safety of endoscopic eradication therapy (EET) for NDBE and its effect on reducing EAC incidence compared with surveillance-only.

Methods: We systematically searched Ovid Medline/PubMed, EMBASE, and Cochrane Central (up to November 26, 2020) for prospective studies including NDBE patients managed with EET. The outcome measures were complete eradication of intestinal metaplasia (CE-IM), recurrence of intestinal metaplasia (IM), progression to high-grade dysplasia (HGD) or EAC, presence of sub-squamous glands and adverse events.

Results: Twenty-one studies including 1,050 patients with 4,026 patient-years of follow-up were identified. EET was performed with argon plasma coagulation (APC) in 13 studies, radiofrequency ablation (RFA) in 3 studies, multipolar electrocoagulation in 3 studies, photodynamic therapy (PDT) in 1 study and laser ablation in 1 study. Median follow-up ranged from 12 to 127 months. The pooled proportion of patients achieving CE-IM was 81.3% [95% confidence interval (CI) 73.6–88.1%]. IM recurred in 3.2% per patient-year (95% CI: 0.9–6.4%). Progression to EAC occurred in 0.14% per patient-year (95% CI: 0.00–0.55%) after eradication and in 0.30% per patient-year (95% CI: 0.21–0.39%) after surveillance-only. Two of 4 post-eradication EACs developed in sub-squamous glands in neo-squamous epithelium. The combined adverse event rate related to EET was 6.7% (95% CI: 1.7–14.1%), with 15 (1.5%; 95% CI: 0.6–2.6%) patients developing an esophageal stricture, 5 (0.8%; 95% CI: 0.1–1.9%) a bleeding and 1 (0.5%; CI: 0.06–1.42%) a perforation.

Conclusions: We recommend against prophylactic EET for all patients with NDBE due to the unknown long-term efficacy, unclear cost-efficacy and occurrence of adverse events related to EET. Targeted EET for high-risk NDBE patients identified through risk-stratification may however be a feasible future approach.

Keywords: Barrett's esophagus (BE); esophageal neoplasms; ablation techniques; treatment outcome; disease progression

Received: 04 May 2021; Accepted: 24 June 2021; Published online: 11 July 2021.

doi: 10.21037/aoe-21-43

View this article at: https://dx.doi.org/10.21037/aoe-21-43

^ ORCID: Jasmijn Sijben, 0000-0003-0722-0586; Yonne Peters, 0000-0002-0789-097X; Peter D. Siersema, 0000-0002-6940-8499.

Introduction

Although Barrett's esophagus (BE) is a precursor of esophageal adenocarcinoma (EAC), optimal management for non-dysplastic Barrett's esophagus (NDBE) remains unclear. BE usually develops as a complication of gastro-esophageal reflux disease (GERD) (1). In some patients with GERD, repair of the esophageal lining occurs through formation of metaplastic columnar epithelium (Barrett's metaplasia) instead of squamous epithelium. BE is associated with a 0.1–0.5% annual risk of malignant progression to EAC (2-4). Progression from columnar metaplasia to EAC usually occurs through a series of premalignant changes histologically characterized as low-grade dysplasia (LGD) and high-grade dysplasia (HGD), which may lead to intramucosal carcinoma and eventually progression to invasive adenocarcinoma (5,6). Endoscopic eradication therapy (EET), including the currently most common used technique radiofrequency ablation (RFA) but also other modalities such as argon plasma coagulation (APC) photodynamic therapy (PDT) or cryotherapy, has been suggested to prevent EAC development by eradication of the BE mucosa, allowing the formation of neo-squamous epithelium. While EET of dysplastic BE is widely accepted (7-9), its use in NDBE to prevent progression to HGD and EAC is controversial.

Reported strategies for the management of NDBE include: (I) prophylactic eradication of intestinal metaplasia (IM) to reduce the incidence of EAC; (II) surveillance to detect incident dysplasia and EAC at an early stage followed by endoscopic treatment; or (III) no action. Societal guidelines advise against eradicating NDBE because of its low risk of progression to EAC, resulting in a high number-needed-to-treat to prevent one case of EAC, and complications associated with EET (7-9). Some clinicians however prefer treating NDBE with EET (10), but this can be questioned because it is associated with high costs with unclear benefit to the patient (11). Previous meta-analyses reporting on treatment outcomes after EET mostly included both NDBE and dysplastic BE patients (12-15). A better quantification of treatment outcomes, specifically for NDBE, could help both clinicians and patients to adequately weigh the benefits and risks of prophylactic EET.

In this systematic review and meta-analysis, we aimed to determine: (I) the incidence of EAC in patients with NDBE that have undergone prophylactic EET, compared with patients undergoing surveillance-only; (II) the efficacy, durability and safety of prophylactic EET and (III) whether subgroups of NDBE patients could benefit from EET. We present this article in accordance with the PRISMA reporting checklist (available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-43/rc) (16).

Methods

The protocol for this systematic review has been registered on PROSPERO (CRD42021225405).

Search strategy and study selection

Three databases (Ovid Medline/PubMed, Ovid EMBASE and the Cochrane Controlled Trials Register) were systematically searched for relevant articles from January 1990 to November 2020. Keywords used in the search included a combination of Barrett's esophagus or oesophagus, ablation, APC, multipolar electrocoagulation, laser, RFA, PDT, cryoablation, esophageal bleeding, esophageal stricture, esophageal perforation, buried glands, sub-squamous glands, reduction, recurrence, progression, survival. The search strategy is available as Appendix 1. Reference lists of suitable articles, including studies selected for inclusion, (systematic) reviews and practice guidelines were additionally evaluated for missed but potentially relevant articles.

Each abstract identified by the search strategy was reviewed by two independent authors (JS and YP, who had no conflicts of interest) for inclusion in the study. After abstract review, full text manuscripts were obtained and reviewed according to strict eligibility criteria. A study was included if it: (I) was a prospective (randomized controlled) trial, cohort study, or case series written in English; (II) included NDBE patients who were treated using any form of EET to eradicate NDBE; (III) monitored and reported the number of patients with complete eradication of intestinal metaplasia (CE-IM), recurrent IM, progression to HGD/EAC, adverse events and/or buried glands; (IV) documented follow-up data either in person-years or mean/median follow-up period and with a mean or median follow-up of at least 12 months. A study was excluded if it: (I) was a case report, cross-sectional study, editorial, letter to the editor, (systematic) review or book chapter; (II) had a retrospective study design, because adverse events and EAC incidence might have been underestimated; (III) included patients with any histologic grade of dysplasia at baseline and outcome measures were not stratified by histological grade; (VI) contained fewer than 15 NDBE patients, because studies with minimal weight will unlikely impact

pooled effect sizes in meta-analyses; (V) was available as (conference) abstract only. In the event when more than one manuscript included the same cohort of patients, the study with the longest follow-up interval was included.

Data collection

For each selected study, key study characteristics were extracted, including publication year, country, study design, gender, age, BE length, chronic GERD symptoms, body mass index (BMI), ethnicity, smoking status, familial history of BE or EAC, type of endoscopic treatment and number of patients with CE-IM, recurrent IM, progression to HGD/EAC, buried glands and adverse events. The total follow-up time in person-years was extracted from the studies, if reported, or was estimated by multiplying the number of enrolled patients in the study by the mean or median period of follow-up in years.

The quality of each study was assessed using the Downs and Black instrument (17), which is validated for the assessment of both randomized and nonrandomized studies. This tool assesses the quality of reporting, external validity, bias, confounding, and power using a checklist of 27 items. Scores <15, 15–19, and >20 were considered as low, moderate, and high-quality studies, respectively. For criterium 5 (i.e., is the distribution of principal confounders in each group to be compared clearly described), confounders evaluated were gender, age, BE length, chronic GERD symptoms, BMI, ethnicity, smoking status and familial history of BE or EAC.

Definitions and outcomes

Primary outcomes were: (I) CE-IM, defined as both endoscopic and histologic eradication of IM and dysplasia during at least one endoscopic follow-up after EET; (II) recurrence of IM, defined as the presence of IM in the esophagus after achieving CE-IM, with IM in biopsies of the gastric cardia alone not considered as recurrence; and (III) progression to EAC and/or HGD combined, defined as incident cases of HGD/EAC that were diagnosed at least 12 months after starting surveillance.

Secondary outcomes were: (I) adverse events, including esophageal stricture, bleeding (reported as significant bleeding by the study authors), perforation and chest pain (defined as significant pain requiring evaluation in an emergency department or administration of analgesics, including paracetamol); and (II) buried glands, defined as presence of IM underneath the (neo)squamous layer in histological biopsies.

Statistical analysis

The number of patients achieving CE-IM was divided by the number of patients initially enrolled (intention-to-treat analysis) to calculate CE-IM proportions for each study. This method was also used to calculate the proportion of patients experiencing adverse events. Recurrence and progression rates were adjusted for follow-up time. The denominator for the IM recurrence outcome comprised only patients who had achieved CE-IM after ablation. Pooled annual cumulative incidence rates of EAC in BE were calculated by dividing the number of EACs by the total number of person-years. The 95% confidence intervals (CI) were calculated using the Wilson score method.

The pooled effect sizes for each of the outcome measures were calculated using a random-effects model with restricted maximum-likelihood estimator. We used the double-arcsine transformation for variance stabilization for meta-analysis of proportions (18). When the counts of EAC/adverse events were zero, a correction of 0.5 was added to the number of incident cases of EAC/adverse events and the number of person-years of follow-up, to allow for statistical analysis (19). Heterogeneity was quantified using I^2 statistic and associated tests, with values <25% indicating low and >75% indicating high heterogeneity (20).

We intended to calculate relative risk ratios for EAC incidence post-eradication versus surveillance-only, but only a limited number of studies directly compared these two management strategies. To allow for an indirect comparison, we analyzed progression rates reported in a previous systematic review on EAC incidence in NDBE after surveillance-only (3) using the statistical methods described above (Figure S1).

Possible moderators, including study quality and treatment modality, were investigated to further explore heterogeneity using subgroup analysis. Meta-regression analysis (BE-length and waist circumference) and subgroup analyses (active reflux, and smoking status) were intended to specify treatment outcomes for subgroups at higher risk for EAC. Sensitivity analysis was performed using the leave-one-out approach to ensure no major study effects were present. We assessed publication bias by visual inspection of funnel plots and by using Egger's test. R version 3.5.3. was used for all statistical analyses, in which a 2-tailed P value <0.05 was considered significant.

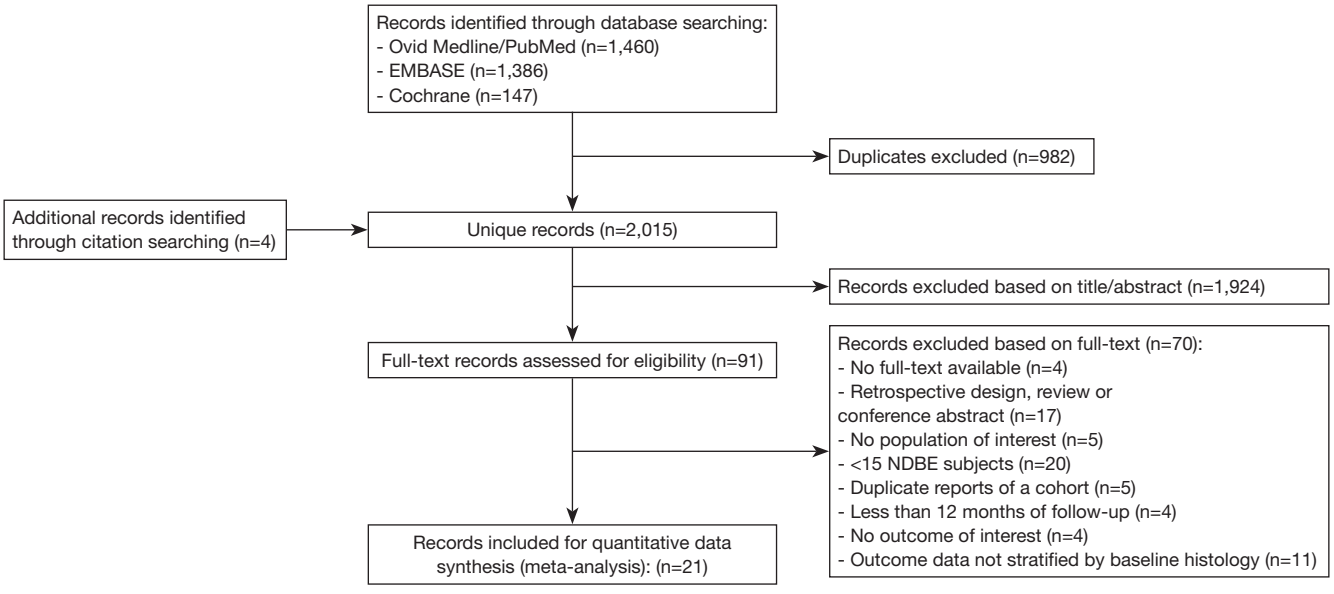

Figure 1 Flow chart summarizing study identification and selection.

Results

Literature search

Of 2,015 unique identified articles reporting on treatment outcome after EET, 1,920 were excluded based on title and abstract review (*Figure 1*). Ninety-one unique articles were fully reviewed of which 21 were included in this meta-analysis with a total of 1,050 patients and 4,026 person-years of follow-up.

Study and population characteristics are summarized in *Table 1*. Most studies were performed in Europe (11 studies), followed by the United States (4 studies), South America (2 studies), Australia (2 studies) and China (1 study). Fourteen studies were prospective case series (21-29,32,33,36,39,41), and 6 were randomized controlled trials (RCTs) (31,34,35,37,38,40). EET modalities included APC (12 studies), RFA (3 studies), multipolar electrocoagulation (MPEC) (3 studies), PDT (1 study) and laser therapy (1 study). Thirteen studies included patients treated for NDBE only, 6 studies included a combination of NDBE and LGD and 1 study included a combination of NDBE, LGD, HGD and intramucosal cancer patients. Outcome data was stratified for NDBE and dysplasia patients in all included studies.

Study quality

Study quality of EET studies ranged from 9 to 25 on the Downs and Black instrument (maximum possible score 28) (17) (Table S1). Of the 6 RCTs, only Dulai *et al.* (38) and Saligram *et al.* (40) were considered to be of high quality (both comparing APC to MPEC). The 3 RCTs comparing APC to surveillance were considered of moderate quality, as these studies scored poorly on adjustment for confounding and losses to follow-up. None of the 14 observational studies had a control cohort, which resulted in low (n=8) to moderate (n=6) quality scores.

CE-IM

All included studies reported on the proportion of patients achieving CE-IM after EET, ranging from 48.6% (37) to 100% (24,28,40). The overall pooled proportion of CE-IM after EET was 81.3% (95% CI: 73.6–88.1%; I^2=87%) (*Figure 2*). Stratified by treatment modality, the pooled proportion of CE-IM after RFA was 83.9% (95% CI: 65.6–96.4%; I^2=86%), after APC 81.9% (95% CI: 72.0–90.3%; I^2=88%) and after MPEC/Laser/PDT 77.4% (95% CI: 55.5–93.8%; I^2=87%).

Recurrence of IM

Recurrence of IM after CE-IM ranged from 0% (30,35) to 15.4% (41) (n=8 studies) (23,24,27,28,30,35,40,41). The combined IM recurrence rate was 3.2% per patient-year (95% CI: 0.87–6.41%; I^2=44%) (*Figure 3*).

Table 1 Study and population characteristics of the 21 included EET studies.

Reference	Country	Design /setting	No. of patients	Follow -up (mo), mean or median	Person -years of follow-up	No. of sessions, mean or median	Age (y), mean or median	Male gender (%)	BE length (cm), mean or median	CE-IM, n [%]	Recurrence[†], n [%]	Progression to HGD /EAC combined, n	Progression to EAC[‡], n	Buried glands, n [%]	Study quality
RFA															
Fleisher *et al.*, 2010 (21)	US	Prospective, MC	70 NDBE	60	350	NR	55.7 (SD, 11.2)	74	3.2 (IQR, 2-6)	48 [69]	NR	0	0	0	18
Skrobić *et al.*, 2016 (22)	Serbia	Prospective, SC	38 NDBE 18 LGD	24	76	NR	47.3 (SD, 10.8)	70	4.3 (SD, 2.1)	32 [84]	NS	NS	NS	NR	17
Komanduri *et al.*, 2017 (23)	US	Prospective SC	44 NDBE 76 LGD 101 HGD/ IMC	27 (SD, 9)	115	2.0 (SD, 0.9)	64.4 (SD, 14.3)	73	6.1 (SD, 3.2)	42 [95]	1 [2]	NS	NS	NS	19
APC															
Tigges *et al.*, 2001 (24)	Germany	Prospective SC	30 NDBE	12	30	2 (range, 1–7)	54 (IQR, 31–77)	77	LSBE: 5 (IQR, 3–10); SSBE: 2 (IQR, 1–2)	30 [100]	2 [7]	0	0	NR	13
Kahaleh *et al.*, 2002 (25)	Belgium	Prospective SC	32 NDBE 7 LGD	36 (range, 12–46)	96	3 (range, 1–4)	63.7 (SD, 8.7)	77	4.7 (SD, 2.2)	18 [56]	NR	NR	2 EAC; 12, 18 mo	1	12
Basu *et al.*, 2002 (26)	UK	Prospective SC	50 NDBE	14	58	4 (range, 1–8)	61.4 (SD, 11.5)	NR	5.9 (SD, 3.1)	30 [60]	NR	0	0	24 [48]	14
Pagani *et al.*, 2003 (27)	Italy	Prospective SC	94 NDBE	12.5	98	3 (range, 1–5)	51.4 (range, 17–82)	72	2.5 (range, 0.5–9.0)	68 [72]	5 (5)	0	0	NR	12
Pinotti *et al.*, 2004 (28)	Brazil	Prospective SC	19 NDBE	17 (range, 6–27)	27	2 (range, 1–6)	52.3 (range, 32–72)	58	3.6 (range, (1–9)	19 [100]	1 [5]	0	0	0 (0)	10
Madisch *et al.*, 2005 (29)	Germany	Prospective SC	73 NDBE	51 (range, 9–85)	280.5	2	55 (SD, 12)	62	4.0 (range, 1-12)	69 [95]	NR	0	0	NR	17
Manner *et al.*, 2006 (30)	Germany	Prospective MC	60 NDBE	14 (range, 12-32)	70	2.6 (range, 1–5)	57 (SD, 13)	68	3.6 (SD, 1.7)	37 [62]	0 (0)	NR	0	4 [7]	14

Table 1 (*continued*)

Table 1 (*continued*)

Reference	Country	Design /setting	No. of patients	Follow -up (mo), mean or median	Person -years of follow-up	No. of sessions, mean or median	Age (y), mean or median	Male gender (%)	BE length (cm), mean or median	CE-IM, n [%]	Recurrence†, n [%]	Progression to HGD /EAC combined, n	Progression to EAC‡, n	Buried glands, n [%]	Study quality
Bright *et al.*, 2007 (31)	Australia	RCT, SC	20 NDBE	68 (range, 43–76)	113	2.5 (range, 1–6)	56.5 (range, 43–76)	75	4.0 (range, 2–13)	12 [60]	NR	0	0	NR	15
		(Surveillance)	20 NDBE	71 (range, 42–79)	118	NR	58.3 (range, 42–79)	85	4.0 (range, 2–15)	NR	NR	2 HGD	0	NR	
Ferraris *et al.*, 2007 (32)	Italy	Prospective, MC	96 NDBE	36 (range, 12–98)	288	3.2 (range, 1–8)	75.1 (range, 21–79)	73	4 (range, 2.5–11)	94 [98]	NR	0	0	1 [1]	16
Mörk *et al.*, 2007 (33)	Germany	Prospective SC	23 NDBE 2 LGD	30	58	4 (range, 1–12)	55 (range, 37–73)	78	3.8 (range, 2–10)	19 [83]	NS	0	0	NR	9
Bright *et al.*, 2009 (34)	Australia	RCT, SC	26 NDBE 1 LGD	12	26	2 (range, 1–6)	57	NR	3.0 (range, 2–13)	18 [69]	NR	0	0	NR	15
		(Surveillance)	29 NDBE 1 LGD	12	27	NR	62	NR	4.0 (range, 1–12)	NR	NA	0	0	NR	
Zhang *et al.*, 2009 (35)	China	RCT, SC	18 NDBE	12 (range, 4–15)	18	1.3 (range, 1–3)	55 (range, 31–75)	67	2.1 (range, 1–4)	14 [78]	0 (0)	NR	NR	NR	18
		(Surveillance)	17 NDBE	12 (range, 4–16)	17	NR	53 (range, 34–67)	59	2.5 (range, 1.5–5.0)	0 (0)	X	NR	NR	NR	
Milashka *et al.*, 2014 (36)	Belgium	Prospective SC	27 NDBE 5 LGD	192	432	NR	64 (range, 46–67)	81	4.5 (range, 3–11)	25 [93]	NR	NR	2 EAC; 18, 192 mo	6 [19]	14
PDT															
Kelty *et al.*, 2004 (37) A	UK	RCT, SC	35 NDBE	12 (range, 6–24)	35	2 (range, 1–4)	61 (range, 33–83)	80	4 (range, 2–15)	17 [49]	NR	0	0	17 [24]	18
B		(APC)	37 NDBE	12 (range, 6–24)	37	3 (range, 1–5)	59 (range, 28–79)	81	4 (range, 2–8)	33 [89]	NR	0	0	33 [21]	

Table 1 (*continued*)

Table 1 (*continued*)

Reference	Country	Design /setting	No. of patients	Follow -up (mo), mean or median	Person -years of follow-up	No. of sessions, mean or median	Age (y), mean or median	Male gender (%)	BE length (cm), mean or median	CE-IM, n [%]	Recurrence†, n [%]	Progression to HGD /EAC combined, n	Progression to EAC‡, n	Buried glands, n [%]	Study quality
MPEC															
Dulai *et al.*, 2005 (38) A	US	RCT, SC	26 NDBE	36	78	2.9 (SD, 1.5)	56 (SD, 11)	88	NR	21 [81]	NR	0	0	NR	25
B		(APC)	26 NDBE	36	78	3.8 (SD, 1.7)	58 (SD, 11)	81	NR	17 [65]	NR	0	0	NR	
Allison *et al.*, 2011 (39)	Venezuela	Prospective, SC	166 NDBE	127.2 (range, 120–156)	1757	1.7 (range, 1–5)	53.0 (SD, 11.1)	75	2.6 (range, 1–15)	132 [80]	NR	0	0	2 [2]	19
Saligram *et al.*, 2015 (40)	US	Prospective, SC	22 NDBE 6 LGD	90 (range, 11–141)	165	3.3 (mean)	NR	NR	NR	22 [100]	10 [45]	NR	0	NR	21
Laser therapy															
Bonavina *et al.*, 1999 (41)	Italy	Prospective SC	18 NDBE	14 (range, 4–32)	21	3 (range, 1–5)	55 (range, 32–70)	78	4 (IQR, 1–7)	11 [61]	2 [11]	NR	1 EAC; 6 mo	NR	10

†, recurrence of intestinal metaplasia after complete eradication unless otherwise indicated; ‡, esophageal adenocarcinoma developing in patients with dysplasia at baseline are not shown. NR, not reported; NS, not stratified by baseline histology; EET, endoscopic eradication therapy; RFA, radiofrequency ablation; APC, argon plasma coagulation; PDT, photodynamic therapy; MPEC, multipolar electrocoagulation; NDBE, non-dysplastic Barrett's esophagus; LGD, low-grade dysplasia; HGD, high-grade dysplasia; IMC, intramucosal carcinoma; CE-IM, complete eradication of intestinal metaplasia; EAC, esophageal adenocarcinoma.

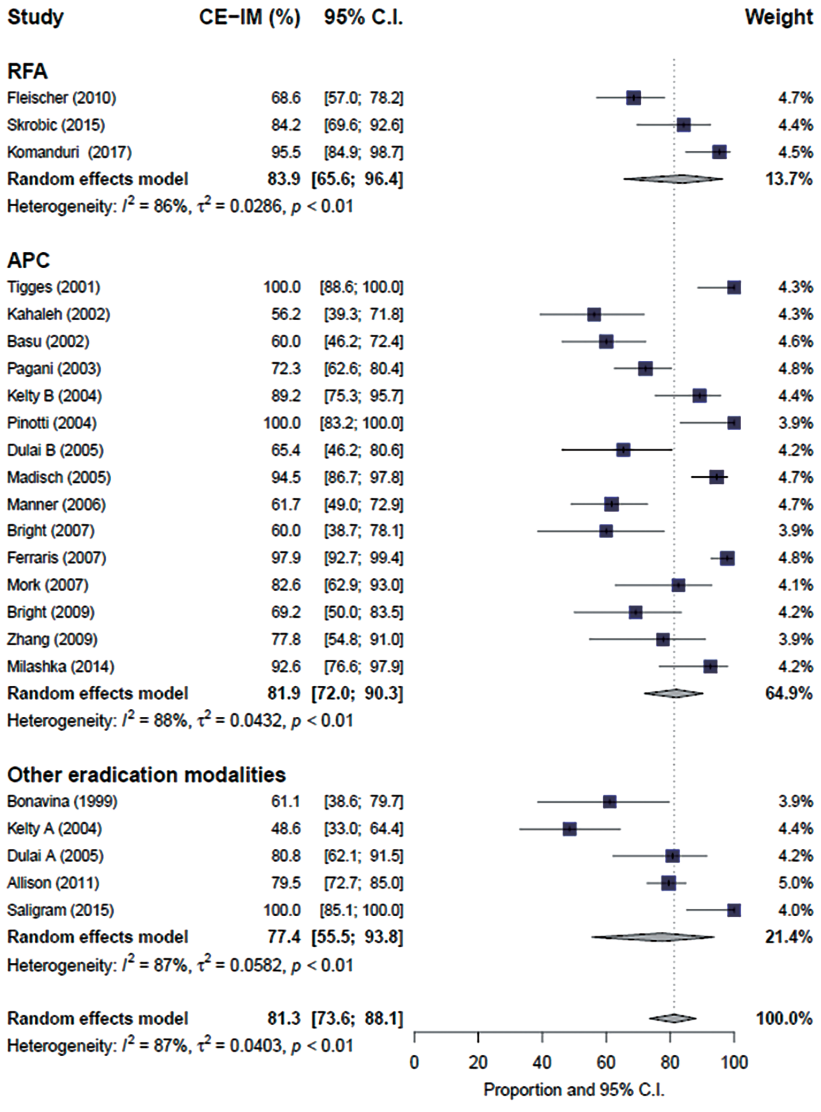

Figure 2 Effect of endoscopic eradication therapy on the CE-IM in patients with non-dysplastic Barrett's esophagus. Proportions are shown with 95% CIs. CE-IM, complete eradication of intestinal metaplasia; CIs, confidence intervals; RFA, radiofrequency ablation; APC, argon plasma coagulation.

Progression to high grade dysplasia or EAC

Two studies that directly compared EET (using APC) with surveillance-only reported progression from NDBE to HGD/EAC, i.e., 2 patients in the surveillance group progressed to HGD versus 0 in the APC group, while no cases of EAC were reported in these studies (31,34).

When including single-arm studies, 17 studies reported progression to EAC after EET (21,24-34,36-39,41). EAC was found in 4 of 928 NDBE patients treated with EET (during 3,652 patient-years of follow-up). Median time to EAC diagnosis was 18 months (IQR, 16.5–61.5 months). EET was performed with APC in all four cases. Of these, two were found in IM underneath neo-squamous epithelium. An additional case of EAC following APC treatment was reported in the study by Saligram *et al.* (40); however, it was unclear whether baseline histology was NDBE or LGD. Bonavina *et al.* reported also a case of progression to EAC in buried IM, which was not included in our analysis because it occurred within 6 months after EET (41). The pooled annual cumulative incidence of EAC post-eradication was 0.14% (95% CI: 0.00–0.55%; I^2=38%) (*Figure 4*).

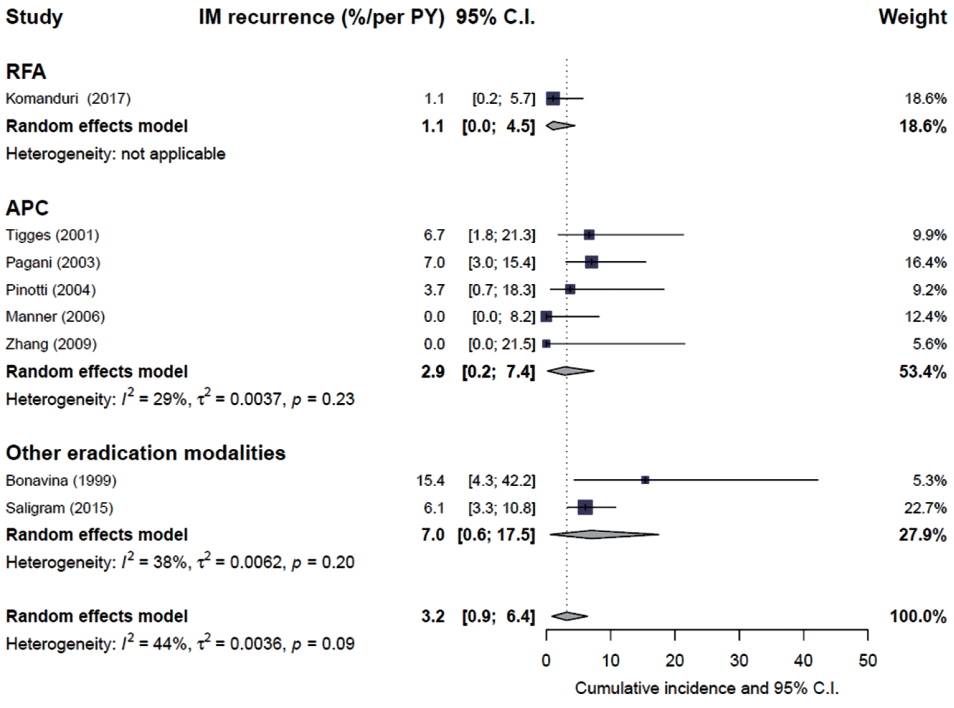

Figure 3 Effect of endoscopic eradication therapy on the recurrence of intestinal metaplasia post-eradication in patients with non-dysplastic Barrett's esophagus. Annual cumulative incidences are shown with 95% CIs. IM, intestinal metaplasia; PY, patient-year; CIs, confidence intervals; RFA, radiofrequency ablation; APC, argon plasma coagulation.

In both single-arm studies reporting EAC cases after EET, HGD incidence was not an outcome measure (25,36). Thirteen other studies reported on a combined HGD/EAC incidence (21,24,26-29,31-34,37-39), but no cases of HGD were reported after EET (*Table 1*).

Adverse events

Adverse events were reported in 16 studies (21,24,26-32, 34-39,41). The study by Komanduri *et al.* (23) also reported adverse events but it was not possible to identify baseline histology in the patients with adverse events.

A total of 15 strictures, 5 significant bleedings, 1 perforation and 44 transient (retrosternal) pain episodes were reported (*Table 2*). The pooled rate of overall adverse events was 6.7% (95% CI: 1.7–14.1%; I^2=90%). Pain accounted for the majority of reported adverse events with a pooled rate of 7.3% (95% CI: 0.1–21.5%; I^2=94%), followed by stricture formation 1.5% (95% CI: 0.6–2.6%; I^2=0%) and bleeding 0.8% (95% CI: 0.1–1.9%; I^2=0%) (Figure S2). Strictures occurred most frequently after APC with a pooled rate of 1.8% (95% CI: 0.7–3.3%; I^2=0%), followed by MPEC/Laser/PDT 1.5% (95% CI: 0.0–4.8%; I^2=29%) (Figure S2B). Bleeding occurred most frequently after APC with a pooled rate of 1.2% (95% CI: 0.2–2.8%; I^2=0%), followed by RFA 0.7% (95% CI: 0.0–4.6%; I^2= NA) (Figure S2C). The esophageal perforation occurred after APC therapy.

Sensitivity and subgroup analysis

Significant heterogeneity between studies was identified for all outcomes. Sensitivity analysis identified one outlier study for adverse events. This study reported pain requiring analgesics in 86.5% of patients (37). Leaving out the latter study reduced heterogeneity and resulted in a pooled overall adverse event rate of 3.5% (95% CI: 1.63–5.91; I^2=46%) (*Figure 5*) and a pooled rate of pain requiring analgesics of 2.1% (95% CI: 0.64–4.22; I^2=12%). Sensitivity analysis by excluding 1 study at a time revealed that none of the studies had an excessive effect on CE-IM, IM recurrence and EAC incidence outcomes.

We performed predefined subgroup analysis to explore possible causes of heterogeneity, of which the results are

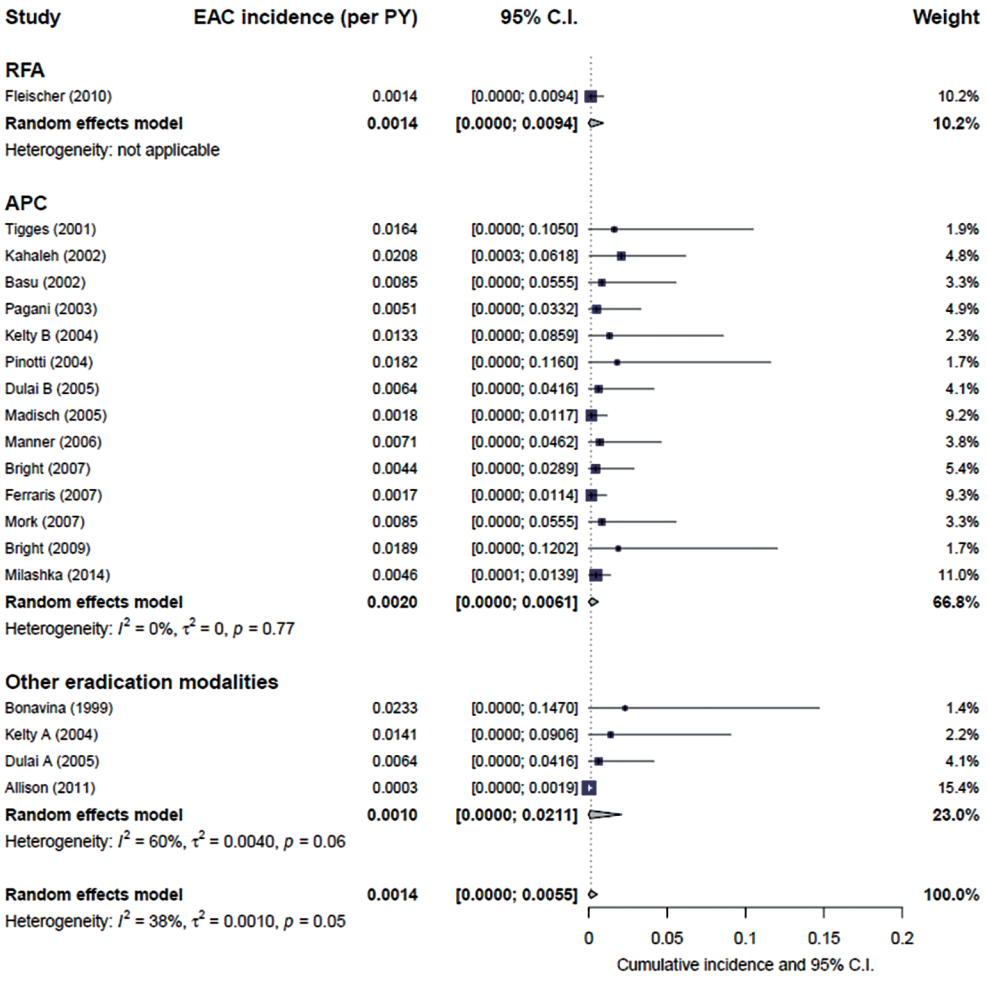

Figure 4 Effect of endoscopic eradication therapy on the progression to EAC in patients with non-dysplastic Barrett's esophagus. Annual cumulative incidences are shown with 95% CIs. EAC, esophageal adenocarcinoma; CIs, confidence intervals; RFA, radiofrequency ablation; APC, argon plasma coagulation.

highlighted in *Table 3*. However, data on BMI, ethnicity, smoking status and familial history of BE or EAC were only rarely reported. A history of chronic GERD symptoms was reported more frequently but was differently defined in the studies (e.g., symptom duration >5 years, symptom frequency >2 times/week, symptoms requiring (anti-reflux) surgery or medication). Data on presence of chronic GERD symptoms was therefore considered too heterogenous for subgroup analysis. Stratification by treatment modality, BE length and study quality as moderator variables resulted in reduced heterogeneity in some subgroups for the outcomes total adverse events and EAC progression, indicating that these moderator variables might have been causes of heterogeneity. However, none of the moderator variables were significantly associated with any of the outcomes.

The influence of mean/median BE length as a continuous variable was assessed using meta-regression analysis, which showed that mean/median BE length was positively correlated with recurrence of IM and progression to EAC, but results were not significant (Table S2).

Publication bias

Funnel plots for each analysis are shown in Figure S3. Some asymmetry was noted in the funnel plots, which indicates the possibility of publication bias. The funnel plot Egger's test indicated a significant small-study effect on the outcome EAC incidence (P=0.001). No small-study effects were seen on the outcomes CE-IM (P=0.95), recurrence of IM (P=0.62) and adverse events (P=0.08).

Table 2 Adverse events after EET for NDBE

Reference	No. of patients	Perforations, n	Stricture formation, n	Bleeding, n	Pain, n	Total adverse events, n
Bonavina *et al.*, 1999 (41)	18	0	2	NR	NR	2
Tigges *et al.*, 2001 (24)	30	0	1	0	0	1
Basu *et al.*, 2002 (26)	50	0	0	0	NR	0
Kahaleh *et al.*, 2002 (25)	32	NR	NR	NR	NR	NR
Pagani *et al.*, 2003 (27)	94	0	1	NR	0	1
Kelty *et al.*, 2004 (37)	72	0	0	NR	34	34
Pinotti *et al.*, 2004 (28)	19	0	0	0	NR	0
Dulai *et al.*, 2005 (38)	52	0	0	0	1	1
Madisch *et al.*, 2005 (29)	73	0	3	0	NR	3
Manner *et al.*, 2006 (30)	60	1	2	2	5	10
Bright *et al.*, 2007 (31)	20	0	2	0	NR	2
Ferraris *et al.*, 2007 (32)	96	0	0	0	NR	0
Mörk *et al.*, 2007 (33)	23	NR	NR	NR	NR	NR
Bright *et al.*, 2009 (34)	26	0	0	0	NR	0
Zhang *et al.*, 2009 (35)	18	0	0	1	0	1
Fleisher *et al.*, 2010 (21)	70	0	0	0	0	0
Allison *et al.*, 2011 (39)	166	0	2	1	4	7
Milashka *et al.*, 2014 (36)	27	0	2	1	NR	3
Saligram *et al.*, 2015 (40)	22	NR	NR	NR	NR	NR
Skrobić *et al.*, 2016 (22)	38	NR	NR	NR	NR	NR
Komanduri *et al.*, 2017 (23)	44	NS	NS	NS	NS	NS
Total	1,050	1	15	5	44	65

EET, endoscopic eradication therapy; NDBE, non-dysplastic Barrett's esophagus; NR, not reported; NS, not stratified by baseline histology.

Discussion

In this systematic review and meta-analysis, CE-IM was found in 81.3% of patients with NDBE, with IM recurring in 3% of patients after initial successful CE-IM. Furthermore, EET for NDBE was not able to completely prevent progression to EAC, as it was still seen in 4 of 928 patients. This resulted in a post-eradication EAC risk of 0.14% per patient-year of follow-up. Although the overall adverse events rate was low, EET resulted in strictures in 1.5% of patients, bleeding in 0.8% and perforation in 0.5%.

EAC progression risk after EET was 0.14% in the current meta-analyses. A previous meta-analysis performed in 2009 by Wani *et al.* was consistent with our findings and showed an EAC incidence rate of 0.16% per patient-year after EET for NDBE (15). EET had not been shown to convincingly reduce the incidence of developing EAC more efficiently than surveillance-only in the data that are available. Compared with patients receiving surveillance-only, the reduction in progression risk after EET was absolutely approximately 50% [based on an indirect comparison with the 0.3% per patient-year EAC progression risk after surveillance-only published (3)]. Another population-based study not included in the aforementioned meta-analysis yielded an even lower EAC risk for surveillance-only in NDBE patients of 0.12% per patient-year (2), which makes a long-term benefit of EET highly questionable. It is doubtful whether the unclear long-term benefit of EET outweighs the risks in the case of NDBE. The risk of adverse events we reported is

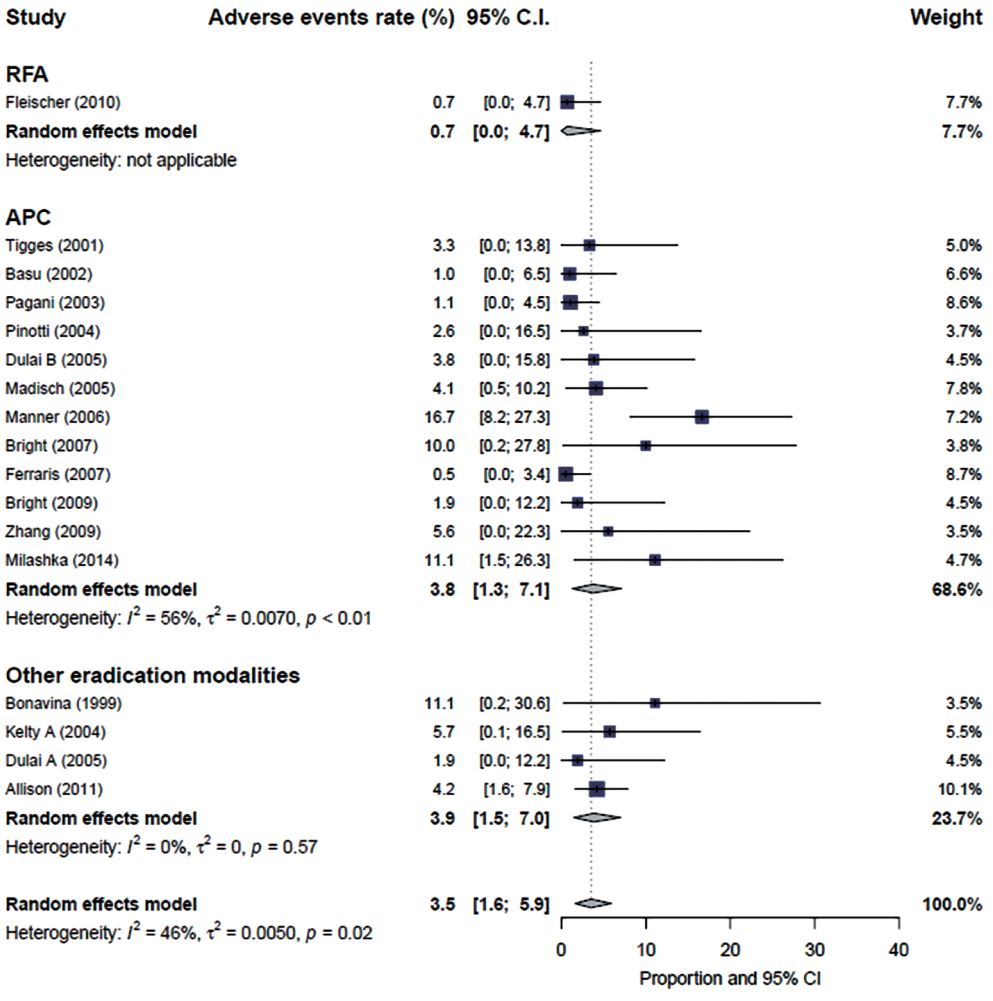

Figure 5 Overall adverse events after endoscopic eradication therapy in patients with non-dysplastic Barrett's esophagus. Proportions are shown with 95% CIs. CIs, confidence intervals; RFA, radiofrequency ablation; APC, argon plasma coagulation.

comparable with a meta-analysis of adverse events after RFA that included both NDBE and BE-related neoplasia (14). Although the overall risk of adverse events is low and the majority can be managed with analgesics in case of pain, or by endoscopic means in case of an esophageal stricture, bleeding or even perforation, their occurrence negatively affects quality of life of patients. The latter is even more important for a non-neoplastic disorder such as NDBE, with a very low (<0.5%) a priori risk of ever developing EAC (2,3).

The fact that progression to EAC can still occur after EET is likely explained by two important factors. First, persistent IM after incomplete EET in approximately 1 of 5 patients may at least partially account for this EAC risk. Our pooled CE-IM estimate is comparable with a previous meta-analysis that included also dysplasia patients and reported CE-IM in 78% (12). Second, recurrent IM in patients that had achieved CE-IM was seen in 3.2% (per patient-year) after CE-IM in our meta-analysis which could be another reason for the EAC risk. Presence of IM in follow-up biopsies could represent either remaining IM that was not detected during initial post-EET endoscopy or could be de novo IM caused by persistent gastroesophageal reflux in physiologically and genetically predisposed patients (42,43). Studies have also reported EAC originating in buried glands after EET for NDBE (36,41). However, these reports likely reflect false-positive histological diagnosis of buried BE due to accidental sampling of small islands with remaining or recurrent IM (44). Ultimately, the malignant potential in remaining and recurrent IM is likely responsible

Table 3 Subgroup analyses on the proportion CE-IM and total adverse events and EAC incidence after EET

Subgroup	CE-IM				Total adverse events				EAC incidence			
	No. of studies	Pooled proportion, % (95% CI)	I^2 (%)	P value	No. of studies	Pooled proportion, % (95% CI)	I^2 (%)	P value	No. of studies	Pooled cumulative incidence, %/PY (95% CI)	I^2 (%)	P value
Barrett's length[†]				0.62				0.35				0.66
Long segment	19	80.5 (71.5–88.2)	87.7		13	4.00 (1.52–7.29)	54.7		16	0.12 (0.00–0.44)	0	
Short segment	4	84.9 (67.1–96.9)	85.3		4	2.47 (0.63–5.13)	0		3	0.02 (0.00–1.45)	57.1	
Treatment modality				0.86				0.21				0.41
RFA	3	83.9 (65.6–96.4)	86.1		1	–	–		1	–	–	
APC	15	81.9 (72.0–90.3)	88.3		12	3.76 (1.30–7.11)	55.7		14	0.20 (0.00–0.61)	0	
Other	5	77.4 (55.5–93.8)	86.6		4	3.86 (1.48–7.02)	0		4	0.10 (0.00–2.11)	59.7	
Study quality				0.92				0.95				0.0132
Low	8	81.8 (65.8–93.9)	87.0		6	3.01 (0.34–7.29)	37.3		9	0.75 (0.30–1.40)	0	
Moderate	12	80.0 (69.7–88.7)	88.6		9	4.06 (1.31–7.88)	62.5		7	0.10 (0.01–0.27)	0	
High	3	85.8 (57.9–100.0)	85.8		2	2.82 (0.00–10.06)	0		2	0.64 (0.00–2.48)	–	

[†], Barrett's length ≥3 cm, based on the mean or median. CE-IM, complete eradication of intestinal metaplasia; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapy; CI, confidence interval; PY, patient-year; APC, radiofrequency ablation; RFA, radiofrequency ablation.

for the insufficient elimination of EAC risk following EET. Continued surveillance after EET might detect neoplasia in remaining and recurrent IM in time but is costly and burdensome for patients (11).

As we included studies with different treatment modalities, generalization of our findings as being true for all EET methods currently available may be questionable. Severe adverse events occurred most frequently in APC studies. Occurrence of EAC after EET for NDBE was only reported in studies using APC and laser therapy. Long-term treatment outcome after RFA, the currently most commonly used technique, was only measured by a single included study that reported no cases of EAC (21). However, an international registry study reported a relatively high annual incidence of HGD/EAC of 0.7% after RFA (among 83 patients with NDBE or BE with indefinite for dysplasia) (10). RFA and APC are both well-known eradication techniques for EET (45-47), but efficacy and safety have never been compared in a randomized trial. Thus, whether RFA is more effective and safe in treating NDBE than delineated in this meta-analysis of all methods combined remains undetermined. Furthermore, cryotherapy has been suggested to be a safe and effective alternative EET technique for treatment of BE-related neoplasia (48). The application of cryotherapy for removal of NDBE has not been studied, leaving its potential in this setting an open issue.

Current guidelines recommend for good reason against EET for NDBE (7-9). Arguments for a physician to still treat NDBE might include the feeling of reassurance after eradicating metaplastic esophageal mucosa (49) and avoiding the obvious shortcomings of a surveillance-only strategy (e.g., sampling error and inability to predict which patient will progress to HGD/EAC and when). However, the results of this meta-analysis show serious limitations with regard to efficacy and durability of EET for NDBE, prevention of EAC development can therefore not be guaranteed. A positive benefit-risk ratio is questionable due to occurrence of adverse events. Furthermore, superiority of EET over surveillance has never been demonstrated in a well-designed and adequately powered study. Additionally, an economic analysis by Hur *et al.* reported that EET for patients with NDBE costs between $118,000 and $205,000 per QALY gained compared with surveillance-only (11). This is likely too high for society to be willing to pay for, given that 1 QALY is valued at $50,000 to $150,000 in the US (50). In our opinion, EET should therefore not be recommended to all patients with NDBE.

Then, how should we manage NDBE? Performing routine surveillance in all NDBE patients might be leading to escalated use of financial and medical resources potentially without substantial benefit. A personalized approach through risk stratification of NDBE may lead to a more rational application of endoscopic surveillance and the use of EET for those most likely to progress to EAC. Identifying NDBE subgroups with an increased risk of neoplastic progression, such as long-segment BE, active reflux, and/or smoking (51), may be arguments to perform EET in these subgroups. Studies included in the current meta-analysis only provided data on BE length. Despite EET, increasing mean BE-length was still positively correlated with progression to EAC (although not significant, Table S2). Reduced effectivity to EET for long-segment BE has been reported previously (12), which may be contributable to the greater surface area that must be treated and the risk of insufficient eradication of BE. Targeted EET of NDBE merely based on segment-length therefore seems undesirable. Accurate prediction models to stratify risk in NDBE are crucial to efficiently select and potentially treat NDBE patients with high susceptibility for neoplastic progression (52). Current risk models might be supplemented with biomarker components and should be externally validated in population-based studies. Thereafter, studies investigating whether NDBE patients with high-risk scores truly benefit from EET are required. Additionally, we suggest that patients with NDBE with intermediate or low risk might be managed with surveillance or even discontinuation of surveillance based on a previous study that we performed (4). Another approach might be to utilize improved endoscopic and histologic surveillance techniques to increase detection of dysplasia in BE mucosa. Wide area tissue sampling (improved sampling using brushes combined with computer-assisted neural network analysis) (53), (computer-assisted) volumetric laser endomicroscopy (54), and p53 staining in biopsies from BE (55) show promise in detecting dysplasia and stratifying risk of progression in BE.

This meta-analysis has a number of strengths. We provided a quantification of treatment outcome after EET specifically for NDBE, including more than 1,000 patients. This may well help in understanding the benefits and risks of EET. Only prospective studies were included. The outcome measures were clearly and consistently defined in included trials and observational studies, which allowed us to perform this meta-analysis. Furthermore, exclusion of individual studies did not change the pooled estimates of CE-IM, IM recurrence and EAC progression substantially,

and the estimates appear therefore robust to the effects of individual studies despite heterogeneity among studies.

This systematic review also has some limitations. First, the quality of the majority of included studies was suboptimal, which was partly contributable to the lack of randomization in studies and to the absence of a control group in the majority of included case series. This also precluded a direct comparison of the results between patients that underwent EET and those that were undergoing surveillance-only. An accurate calculation of relative risk reduction following EET was therefore not possible. This was also the case for performing a survival analysis as patient-level censoring events were not available in most included studies. On the other hand, the likelihood that an RCT with sufficient follow-up time (>5 years) and comparing EET with surveillance will ever be performed is unlikely, given the yet unclear benefit of eradicating NDBE and associated risks. Instead, we obtained and analyzed follow-up data of patients undergoing surveillance-only using a previous systematic review (3), which allowed to indirectly compare the outcomes of interest. It should be noted that this indirect comparison between the two strategies is limited by potential variation in patient populations, follow-up periods and surveillance protocols. Furthermore, the included studies provided limited data on risk factors for neoplastic progression of NDBE (other than segment length). This precluded comparing treatment-outcome between low- and high-risk NDBE subgroups. Finally, there was significant heterogeneity in all pooled effect sizes. We performed multiple subgroup analyses to explore the source of heterogeneity. Although the heterogeneity decreased in the subgroup analysis, it continued to remain significantly present for the pooled proportions of CE-IM and total adverse events.

This systematic review and meta-analysis endorses that providing prophylactic EET uniformly for all NDBE patients should be discouraged due to continued risk of EAC. Based on the scarceness of evidence for a long-term benefit and the considerable risk of serious adverse events, we recommend against EET of all patients with NDBE.

Acknowledgments

The authors thank Ms Alice Tillema, senior medical librarian at Medical Library Radboud University Nijmegen, for her assistance in deriving the search strategy. *Funding:* None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Madhav Desai) for the series "Endoscopic Therapy for Barrett's Esophagus" published in *Annals of Esophagus*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-43/rc

Peer Review File: Available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-43/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-43/coif). The series "Endoscopic Therapy for Barrett's Esophagus" was commissioned by the editorial office without any funding or sponsorship. P.D.S. receives unrestricted grants from Pentax (Japan), Norgine (UK), Motus GI (USA), MicroTech (China) and The eNose Company (Netherlands) and is in the advisory board of Motus GI (USA) and Boston Scientific (USA). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Peters Y, Al-Kaabi A, Shaheen NJ, et al. Barrett oesophagus. Nat Rev Dis Primers 2019;5:35.
2. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of

adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011;365:1375-83.
3. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut 2012;61:970-6.
4. Peters Y, Honing J, Kievit W, et al. Incidence of Progression of Persistent Nondysplastic Barrett's Esophagus to Malignancy. Clin Gastroenterol Hepatol 2019;17:869-877.e5.
5. Wani S, Falk GW, Post J, et al. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. Gastroenterology 2011;141:1179-1186.e1.
6. Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc 2008;67:394-8.
7. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2017;49:191-8.
8. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016;111:30-50; quiz 51.
9. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014;63:7-42.
10. Sami SS, Ravindran A, Kahn A, et al. Timeline and location of recurrence following successful ablation in Barrett's oesophagus: an international multicentre study. Gut 2019;68:1379-85.
11. Hur C, Choi SE, Rubenstein JH, et al. The cost effectiveness of radiofrequency ablation for Barrett's esophagus. Gastroenterology 2012;143:567-75.
12. Orman ES, Li N, Shaheen NJ. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:1245-55.
13. Krishnamoorthi R, Singh S, Ragunathan K, et al. Risk of recurrence of Barrett's esophagus after successful endoscopic therapy. Gastrointest Endosc 2016;83:1090-1106.e3.
14. Qumseya BJ, Wani S, Desai M, et al. Adverse Events After Radiofrequency Ablation in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2016;14:1086-1095.e6.
15. Wani S, Puli SR, Shaheen NJ, et al. Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. Am J Gastroenterol 2009;104:502-13.
16. d meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
17. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377-84.
18. Freeman M, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950;21:607-11.
19. Methods for meta-analysis in medical research. Wiley series in probability and mathematical statistics. Chichester: John Wiley & Sons, Inc., 2000.
20. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
21. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy 2010;42:781-9.
22. Skrobić O, Simić A, Radovanović N, et al. Significance of Nissen fundoplication after endoscopic radiofrequency ablation of Barrett's esophagus. Surg Endosc 2016;30:3802-7.
23. Komanduri S, Kahrilas PJ, Krishnan K, et al. Recurrence of Barrett's Esophagus is Rare Following Endoscopic Eradication Therapy Coupled With Effective Reflux Control. Am J Gastroenterol 2017;112:556-66.
24. Tigges H, Fuchs KH, Maroske J, et al. Combination of endoscopic argon plasma coagulation and antireflux surgery for treatment of Barrett's esophagus. J Gastrointest Surg 2001;5:251-9.
25. Kahaleh M, Van Laethem JL, Nagy N, et al. Long-term follow-up and factors predictive of recurrence in Barrett's esophagus treated by argon plasma coagulation and acid suppression. Endoscopy 2002;34:950-5.
26. Basu KK, Pick B, Bale R, et al. Efficacy and one year follow up of argon plasma coagulation therapy for ablation of Barrett's oesophagus: factors determining persistence and recurrence of Barrett's epithelium. Gut 2002;51:776-80.
27. Pagani M, Granelli P, Chella B, et al. Barrett's esophagus: combined treatment using argon plasma coagulation and laparoscopic antireflux surgery. Dis Esophagus 2003;16:279-83.
28. Pinotti AC, Cecconello I, Filho FM, et al. Endoscopic ablation of Barrett's esophagus using argon plasma

coagulation: a prospective study after fundoplication. Dis Esophagus 2004;17:243-6.
29. Madisch A, Miehlke S, Bayerdorffer E, et al. Long-term follow-up after complete ablation of Barrett's esophagus with argon plasma coagulation. World J Gastroenterol 2005;11:1182-6.
30. Manner H, May A, Miehlke S, et al. Ablation of nonneoplastic Barrett's mucosa using argon plasma coagulation with concomitant esomeprazole therapy (APBANEX): a prospective multicenter evaluation. Am J Gastroenterol 2006;101:1762-9.
31. Bright T, Watson DI, Tam W, et al. Randomized trial of argon plasma coagulation versus endoscopic surveillance for barrett esophagus after antireflux surgery: late results. Ann Surg 2007;246:1016-20.
32. Ferraris R, Fracchia M, Foti M, et al. Barrett's oesophagus: long-term follow-up after complete ablation with argon plasma coagulation and the factors that determine its recurrence. Aliment Pharmacol Ther 2007;25:835-40.
33. Mörk H, Al-Taie O, Berlin F, et al. High recurrence rate of Barrett's epithelium during long-term follow-up after argon plasma coagulation. Scand J Gastroenterol 2007;42:23-7.
34. Bright T, Watson DI, Tam W, et al. Prospective randomized trial of argon plasma coagulation ablation versus endoscopic surveillance of Barrett's esophagus in patients treated with antisecretory medication. Dig Dis Sci 2009;54:2606-11.
35. Zhang L, Dong L, Liu J, et al. Endoscopic ablation of Barrett's esophagus using the second generation argon plasma coagulation: a prospective randomized controlled trail. Journal of Nanjing Medical University 2009;23:183-8.
36. Milashka M, Calomme A, Van Laethem JL, et al. Sixteen-year follow-up of Barrett's esophagus, endoscopically treated with argon plasma coagulation. United European Gastroenterol J 2014;2:367-73.
37. Kelty CJ, Ackroyd R, Brown NJ, et al. Endoscopic ablation of Barrett's oesophagus: a randomized-controlled trial of photodynamic therapy vs. argon plasma coagulation. Aliment Pharmacol Ther 2004;20:1289-96.
38. Dulai GS, Jensen DM, Cortina G, et al. Randomized trial of argon plasma coagulation vs. multipolar electrocoagulation for ablation of Barrett's esophagus. Gastrointest Endosc 2005;61:232-40.
39. Allison H, Banchs MA, Bonis PA, et al. Long-term remission of nondysplastic Barrett's esophagus after multipolar electrocoagulation ablation: report of 139 patients with 10 years of follow-up. Gastrointest Endosc 2011;73:651-8.
40. Saligram S, Tofteland N, Wani S, et al. Long-term results of the mucosal ablation of Barrett's esophagus: efficacy and recurrence. Endosc Int Open 2015;3:E189-94.
41. Bonavina L, Ceriani C, Carazzone A, et al. Endoscopic laser ablation of nondysplastic Barrett's epithelium: is it worthwhile? J Gastrointest Surg 1999;3:194-9.
42. Hemmink GJ, Alvarez Herrero L, Bogte A, et al. Esophageal motility and impedance characteristics in patients with Barrett's esophagus before and after radiofrequency ablation. Eur J Gastroenterol Hepatol 2013;25:1024-32.
43. Orlando RC. How good is the neosquamous epithelium? Dig Dis 2014;32:164-70.
44. Pouw RE, Visser M, Odze RD, et al. Pseudo-buried Barrett's post radiofrequency ablation for Barrett's esophagus, with or without prior endoscopic resection. Endoscopy 2014;46:105-9.
45. Manner H, Rabenstein T, Pech O, et al. Ablation of residual Barrett's epithelium after endoscopic resection: a randomized long-term follow-up study of argon plasma coagulation vs. surveillance (APE study). Endoscopy 2014;46:6-12.
46. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277-88.
47. Phoa KN, Pouw RE, van Vilsteren FGI, et al. Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: a Netherlands cohort study. Gastroenterology 2013;145:96-104.
48. Westerveld DR, Nguyen K, Banerjee D, et al. Safety and effectiveness of balloon cryoablation for treatment of Barrett's associated neoplasia: systematic review and meta-analysis. Endosc Int Open 2020;8:E172-8.
49. Shaheen NJ, Palmer LB. Improving screening practices for Barrett's esophagus. Surg Oncol Clin N Am 2009;18:423-37.
50. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796-7.
51. Krishnamoorthi R, Singh S, Ragunathan K, et al. Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018;16:1046-1055.e8.
52. Parasa S, Vennalaganti S, Gaddam S, et al. Development and Validation of a Model to Determine Risk of

Progression of Barrett's Esophagus to Neoplasia. Gastroenterology 2018;154:1282-1289.e2.
53. Vennalaganti PR, Kaul V, Wang KK, et al. Increased detection of Barrett's esophagus-associated neoplasia using wide-area trans-epithelial sampling: a multicenter, prospective, randomized trial. Gastrointest Endosc 2018;87:348-55.
54. Struyvenberg MR, de Groof AJ, Fonollà R, et al. Prospective development and validation of a volumetric laser endomicroscopy computer algorithm for detection of Barrett's neoplasia. Gastrointest Endosc 2021;93:871-9.
55. Snyder P, Dunbar K, Cipher DJ, et al. Aberrant p53 Immunostaining in Barrett's Esophagus Predicts Neoplastic Progression: Systematic Review and Meta-Analyses. Dig Dis Sci 2019;64:1089-97.

doi: 10.21037/aoe-21-43
Cite this article as: Sijben J, Peters Y, Siersema PD. Prophylactic eradication of non-dysplastic Barrett's esophagus to prevent progression to esophageal adenocarcinoma—a systematic review and meta-analysis. Ann Esophagus 2023;6:42.

Supplementary

Appendix 1 Search strategies

Ovid Medline/Pubmed 1990 – Current. Run 26-11-2020

1. Barrett Esophagus/
2. (Barret$ adj1 (esophag$ or oesophag$ or epitheli$ or metaplasi$ or syndrome?)).tw,kw.
3. (((no or non or without) adj1 (dysplasia or dysplastic$)) or non-dysplastic or nondysplastic).tw,kw.
4. 1 or 2
5. 3 and 4
6. 1 or 2 or 5
7. Catheter Ablation/
8. Laser coagulation/
9. photochemotherapy/
10. Cryoablation/
11. Esophagoscopy/
12. (eradicat$ adj3 (endoscopi$ or strateg$)).tw,kw.
13. (ablati$ or coagulate$ or radiofrequen$ or photodynamic$ or cryo$).tw,kw.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 6 and 14
16. postoperative complications/ or pain, postoperative/ or postoperative hemorrhage/
17. Treatment outcome/
18. Recurrence/
19. Disease progression/
20. Disease free survival/
21. Cost-Benefit Analyses/
22. Cost savings/
23. (stricture$ or bleed$ or hemorrhage$ or haemorrhage$ or pain or perforat$).tw,kw.
24. (respon$ or recurren$ or reduction or durability).tw,kw.
25. ((bury or buried or subsquamous or sub-squamous) adj2 (metaplas$ or gland?)).tw,kw.
26. (survival or mortality).tw,kw.
27. ((cost adj1 effect$) or cost-effect$ or cost-utility or economi$).tw,kw.
28. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 15 and 28
30. limit 29 to yr="1990 -Current"

Hits: 1460

EMBASE 1990-current. Run 26-11-2020

1. Barrett Esophagus/
2. (Barret$ adj1 (esophag$ or oesophag$ or epitheli$ or metaplasi$ or syndrome?)).tw,kw.
3. (((no or non or without) adj1 (dysplasia or dysplastic$)) or non-dysplastic or nondysplastic).tw,kw.
4. 1 or 2
5. 3 and 4
6. 1 or 2 or 5
7. Catheter Ablation/
8. Laser coagulation/
9. photochemotherapy/
10. Cryoablation/
11. Esophagoscopy/
12. (eradicat$ adj3 (endoscopi$ or strateg$)).tw,kw.
13. (ablati$ or coagulate$ or radiofrequen$ or photodynamic$ or cryo$).tw,kw.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 6 and 14
16. postoperative complications/ or pain, postoperative/ or postoperative hemorrhage/
17. Treatment outcome/
18. Recurrence/
19. Disease progression/
20. Disease free survival/
21. "cost benefit analysis"/
22. Cost savings/
23. (stricture$ or bleed$ or hemorrhage$ or haemorrhage$ or pain or perforat$).tw,kw.
24. (respon$ or recurren$ or reduction or durability).tw,kw.
25. ((bury or buried or subsquamous or sub-squamous) adj2 (metaplas$ or gland?)).tw,kw.
26. (survival or mortality).tw,kw.
27. ((cost adj1 effect$) or cost-effect$ or cost-utility or economi$).tw,kw.
28. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 15 and 28
30. limit 29 to yr="1990 -Current"
31. limit 30 to conference abstract
32. 30 not 31

Hits: 1386

https://dx.doi.org/10.21037/aoe-21-43

Cochrane central 1990-current. Run 26-11-2020

1. Barrett Esophagus/
2. (Barret* NEAR/1 (esophag* or oesophag* or epitheli* or metaplasi* or syndrome?)):ti,ab,kw
7. Catheter Ablation/
8. Laser coagulation/
9. photochemotherapy/
10. Cryoablation/
11. Esophagoscopy/
12. (eradicat* NEAR/3 (endoscopi* or strateg*)):ti,ab,kw
13. (ablati* or coagulate* or radiofrequen* or photodynamic* or cryo*):ti,ab,kw
16. postoperative complications/ or pain, postoperative/ or
17. Treatment outcome/
18. Recurrence/
19. Disease progression/
20. Disease free survival/
21. "cost benefit analysis"/
22. Cost savings/
23. (stricture* or bleed* or hemorrhage* or haemorrhage* or pain or perforat*):ti,ab,kw
24. (respon* or recurren* or reduction or durability):ti,ab,kw
25. ((bury or buried or subsquamous or sub-squamous) adj2 (metaplas* or gland?)):ti,ab,kw
26. (survival or mortality):ti,ab,kw
27. ((cost adj1 effect*) or cost-effect* or cost-utility or economi*):ti,ab,kw

Hits: 147

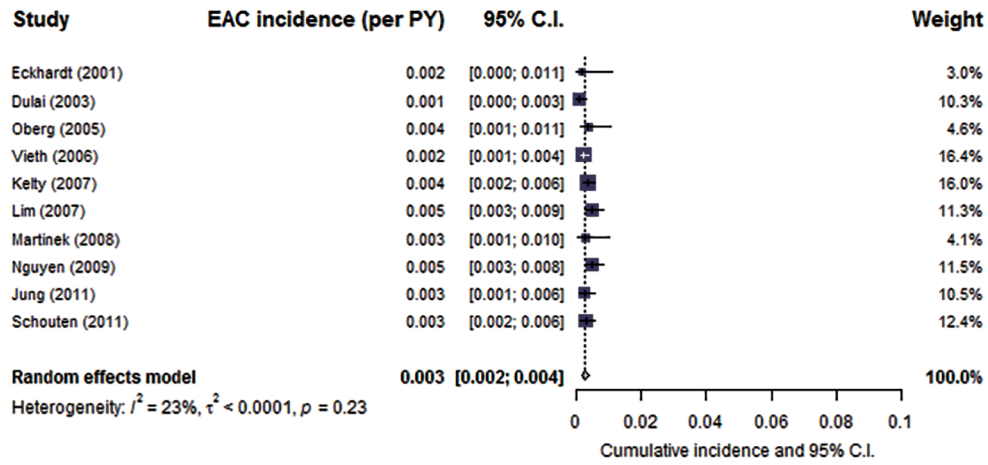

Figure S1 Effect of surveillance on the progression to esophageal adenocarcinoma (EAC) in patients with non-dysplastic Barrett's esophagus. Annual cumulative incidences are shown with 95% confidence intervals (CIs).

https://dx.doi.org/10.21037/aoe-21-43

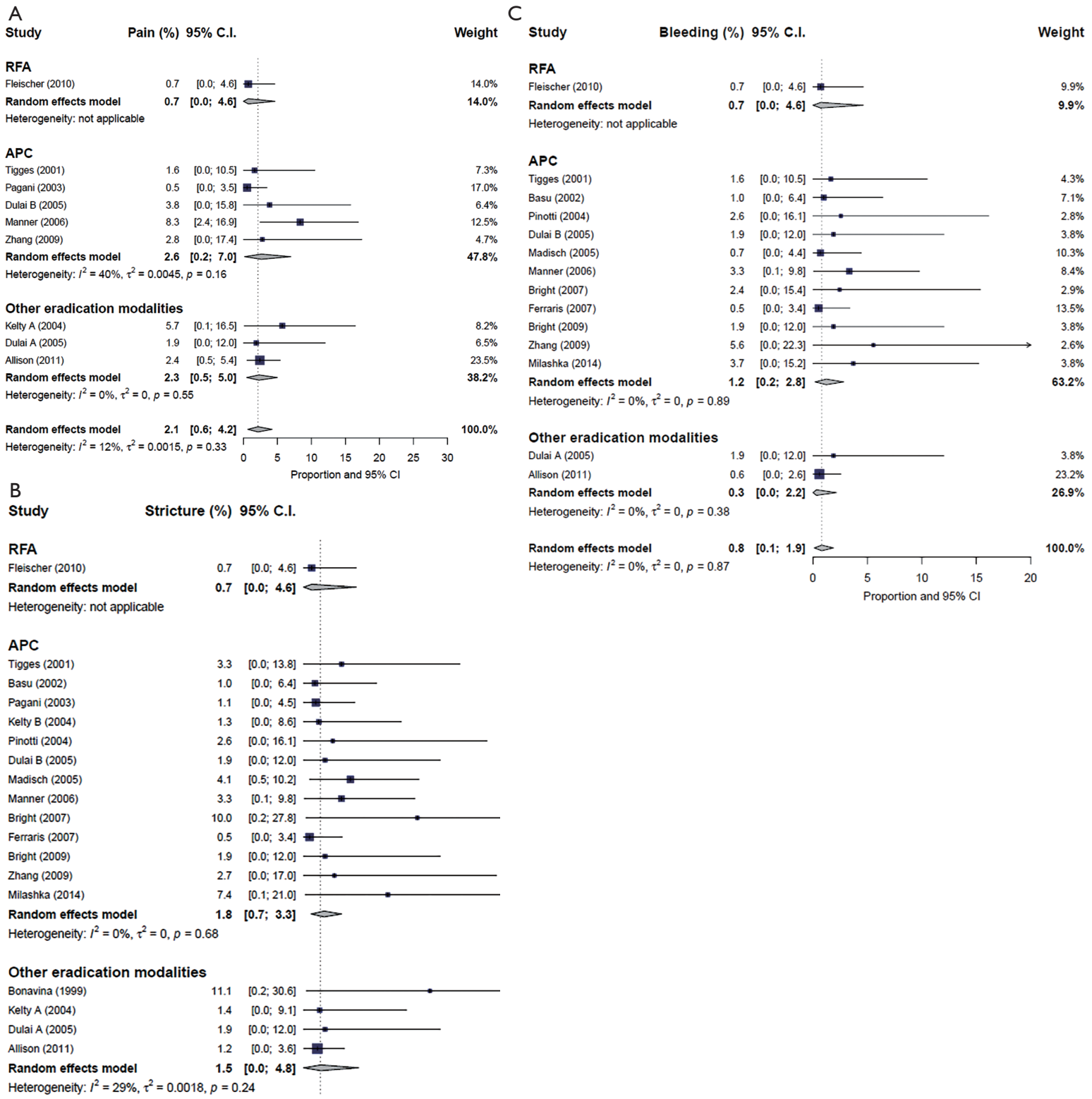

Figure S2 Forest plots for secondary outcomes of adverse events after endoscopic therapy in patients with non-dysplastic Barrett's esophagus. (A) Pain requiring analgesics. (B) Formation of strictures. (C) Bleeding.

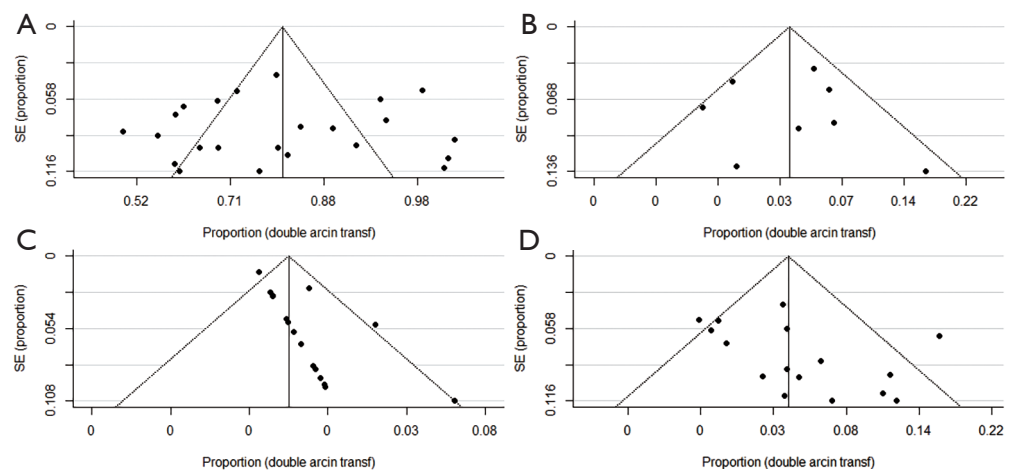

Figure S3 Funnel plots of the main study outcomes. (A) Funnel plot of the effect of endoscopic eradication therapy on the complete eradication of intestinal metaplasia (CE-IM). (B) Funnel plot of the effect of endoscopic eradication therapy on the recurrence of intestinal metaplasia post-eradication. (C) Funnel plot of the effect of endoscopic eradication therapy on the progression to esophageal adenocarcinoma (EAC). (D) Funnel plot of overall adverse events after endoscopic eradication therapy. SE, standard error.

https://dx.doi.org/10.21037/aoe-21-43

Table S1 Quality assessment of the full text randomized control trials and cohort studies

	Bonavina 1999	Tigges 2001	Basu 2002	Kahaleh 2002	Pagani 2003	Kelty 2004	Pinotti 2004	Dulai 2005	Manner 2006	Bright 2007	Ferraris 2007	Bright 2009	Mörk 2007	Zhang 2009	Fleisher 2010	Allison 2011	Madisch 2005	Milashka 2014	Saligram 2015	Skrobić 2016	Komanduri 2017
Reporting																					
Hypothesis/aim	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Main outcomes	0	1	1	1	0	1	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1
Characteristics of included patients	1	1	1	1	0	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1
Interventions	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Distributions of principal confounders	0	0	0	0	0	0	0	2	0	1	0	1	0	1	0	0	0	0	1	0	0
Main findings	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Estimates of random variability	0	0	1	0	1	1	0	1	1	0	1	0	0	1	1	1	0	0	1	1	1
Important adverse events	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1
Characteristics of patients lost to follow-up	1	0	0	0	0	1	0	1	1	0	0	1	1	0	1	1	1	1	1	1	1
Actual probability values	0	0	1	1	1	0	0	1	0	0	1	0	0	1	0	1	1	0	1	1	1
External validity																					
Subjects asked to participate	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	1	0	0	0	1
Subjects prepared to participate	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
Staff, places, and facilities	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
Internal validity—bias																					
Blinding of subjects	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Blinding of those measuring outcomes	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	1	0	0	0	0	0
Data dredging	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Adjustment for different follow-up time	0	1	1	1	0	1	0	1	0	1	1	1	0	0	1	0	1	1	1	1	1
Statistical testing	0	0	1	0	1	1	0	1	0	0	1	0	0	1	1	0	0	0	1	1	1
Compliance to testing reliability	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Main outcomes accuracy	0	1	1	1	0	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1
Internal validity—confounding																					
Different interventions	0	1	0	0	1	1	1	1	0	1	1	0	1	1	0	1	1	0	1	1	1
Recruitment over same time period	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Randomization	0	0	0	0	0	1	0	1	0	1	0	1	0	1	0	0	0	0	1	0	0
Randomization concealment	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Adequate adjustment for confounding	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Losses to follow-up	0	0	0	0	0	1	0	1	1	0	0	0	1	0	1	1	0	1	1	1	1
Power																					
Sufficient power	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	1	0	0	1	0
Total	10	13	14	12	12	19	10	25	14	15	16	15	9	18	18	19	17	14	21	17	19

Table S2 Meta-regression analysis of moderators affecting the proportion of CE-IM, recurrence, total adverse events and EAC incidence after EET

Variable	CE-IM			IM recurrence			Total adverse events			EAC incidence		
	Coefficient	I^2 (%)†	P value	Coefficient	I^2 (%)†	P value	Coefficient	I^2 (%)†	P value	Coefficient	I^2 (%)†	P value
BE segment length‡	0.08	88.2	0.78	3.03	11.2	0.08	0.05	51.7	0.81	3.59	17.6	0.058

†, I^2 = residual heterogeneity; ‡, based on the study mean or median. CE-IM, complete eradication of intestinal metaplasia; EAC, esophageal adenocarcinoma; EET, endoscopic eradication therapy; CI, confidence interval; BE, Barrett's esophagus.

https://dx.doi.org/10.21037/aoe-21-43