

# Recurrence of intestinal metaplasia and early neoplasia after endoscopic eradication therapy for Barrett's esophagus: a systematic review and meta-analysis\*




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## Bibliography

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## ABSTRACT

**Background** Conflicting data exist with regard to recurrence rates of intestinal metaplasia (IM) and dysplasia after achieving complete eradication of intestinal metaplasia (CE-IM) in Barrett's esophagus (BE) patients.

**Aim** (i) To determine the incidence of recurrent IM and dysplasia achieving CE-IM and (ii) to compare recurrence rates between treatment modalities [radiofrequency ablation (RFA) with or without endoscopic mucosal resection (EMR) vs stepwise complete EMR (SRER)].

**Methods** A systematic search was performed for studies reporting on outcomes and estimates of recurrence rates after achieving CE-IM. Pooled incidence [per 100-patient-years (PY)] and risk ratios with 95%CI were obtained. Heterogeneity was measured using the  $I^2$  statistic. Subgroup analyses, decided a priori, were performed to explore heterogeneity in results.

**Results** A total of 39 studies were identified (25-RFA, 13-SRER, and 2 combined). The pooled incidence of any recurrence was 7.5 (95%CI 6.1–9.0)/100 PY with a pooled incidence of IM recurrence rate of 4.8 (95%CI 3.8–5.9)/100 PY, and dysplasia recurrence rate of 2.0 (95%CI 1.5–2.5)/100 PY. Compared to the SRER group, the RFA group had significantly higher overall [8.6 (6.7–10.5)/100 PY vs. 5.1 (3.1–7)/100 PY,  $P=0.01$ ] and IM recurrence rates [5.8 (4.3–7.3)/100 PY vs. 3.1 (1.7–4)/100 PY,  $P<0.01$ ] with no difference in recurrence rates of dysplasia. Significant heterogeneity between studies was identified. The majority of recurrences were amenable to repeat endoscopic eradication therapy (EET).

**Conclusion** The results of this study demonstrate that the incidence rates of overall, IM, and dysplasia recurrence rates post-EET are not inconsiderable and reinforce the importance of close surveillance after achieving CE-IM.

## Introduction

Barrett's esophagus (BE) is the only identifiable premalignant condition for esophageal adenocarcinoma (EAC), a malignancy associated with a dismal 5-year survival rate of <15% and in-

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creasing annual incidence [1–7]. BE is believed to affect 1–2% of the general population and is characterized by replacement of normal squamous epithelium of the distal esophagus by a columnar lined esophagus [8–10]. Malignant transformation of BE to EAC is thought to occur in a stepwise and probabilistic fashion through the histopathologic stages of low grade dysplasia (LGD), then high grade dysplasia (HGD) which in turn gives rise to intramucosal carcinoma and eventually progresses to invasive adenocarcinoma [11–15].

This pathway of BE to invasive EAC provides an opportunity to halt the progression and decrease the incidence and prevalence of Barrett's related EAC and ultimately impact the morbidity and mortality related to this lethal cancer. To this end, various endoscopic eradication therapies (EET) have been evaluated over the years. Advances in this field have resulted in a significant decline in patients referred for esophagectomy with comparable outcomes (EAC free survival) reported in BE patients with HGD and mucosal EAC treated with esophagectomy and EET [16–19]. Two of such EETs that are widely used alone or in combination are endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA). Efficacy data from two randomized controlled trials have shown that RFA decreases the risk of neoplastic progression among patients with BE-associated HGD and LGD [20, 21]. Recently, data from the US multicenter RFA Patient Registry that included BE patients treated with RFA showed that 0.2% (0.7/1000 person-years) died from EAC [22]. Current contemporary management of BE-related neoplasia involves EMR of any visible lesion (if present) followed by ablation of the remaining Barrett's segment. The current goal of EET is not only to achieve complete eradication of dysplasia/neoplasia (CE-D; including intramucosal EAC, HGD and LGD) but also complete eradication of intestinal metaplasia (CE-IM) given the 30% risk of metachronous neoplasia [23, 24].

The effectiveness of both techniques (EMR and RFA) in achieving CE-IM and CE-D has been demonstrated in multiple studies. Reported CE-D and CE-IM rates for EMR are in the ranges 82–100% and 72–97%, respectively [25–29], and those for RFA with and without EMR are in the ranges 83–93% and 78–93%, respectively [30–33]. In addition, available data indicate that most patients maintain the status of CE-IM [30, 32, 33]. The high efficacy rate of EET in eradicating BE-related neoplasia and maintaining remission has revolutionized the management of these patients avoiding the morbidity and mortality associated with esophagectomy. However, the focus has now shifted to the durability of EET. Patients with BE-related neoplasia undergoing EET and achieving CE-IM are at persistent risk for recurrent IM and dysplasia; however, precise estimates of recurrence rates are not available. Widely variable recurrence rates have been reported after CE-IM in patients undergoing EMR alone [26–29], as well as RFA with or without EMR (dysplasia: 0–15%, IM: 7–39.5%) [30, 33–36].

The absence of a reliable estimate of recurrence rates has made it difficult to inform patients as to the expected outcomes with EET. Additionally, guidelines with regard to surveillance and the interval of surveillance for patients who have achieved CE-IM following EET currently rely on expert opinion. To this end, the aim of this systematic review and meta-analysis

was to determine the incidence of recurrence of IM and dysplasia post CE-IM for patients with BE treated with EET (EMR, RFA or a combination of both).

## Materials and methods

This systematic review and meta-analysis was performed and reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [37].

### Search strategy

Three databases (MEDLINE PubMed, EMBASE, and Web of Science) were systematically searched (by author LLFL) for relevant articles from 1996 through 31 May 2016. Keywords used in the search included a combination of "Barrett's esophagus, Barrett's oesophagus, recurrence, response, eradication, outcomes, complete, endoscopic ablation, radiofrequency ablation, endoscopic resection, endoscopic mucosal resection, subsquamous Barrett's, subsquamous intestinal metaplasia." Reference lists of pertinent articles, including the selected studies for inclusion, reviews, and practice guidelines, were also manually searched to identify any other potentially relevant articles. Relevant abstracts identified by EMBASE from the major gastroenterology conferences including Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology published within the past 5 years were also included.

### Study inclusion and exclusion criteria and definitions

Each abstract identified by the search strategy was reviewed by two independent authors (LLFL and BC) for possible inclusion in the study. Full text manuscripts were obtained and evaluated for those that were potentially relevant after abstract review. Studies were included if they met the following strict criteria: (1) study design – randomized control trial, cohort studies, case series with at least 20 patients; (2) patient population – patients who achieved CE-IM after endoscopic therapy of Barrett's esophagus with IM, dysplasia or early adenocarcinoma (EAC); (3) intervention – primary endoscopic therapy with stepwise complete endoscopic resection (SRER) or radiofrequency ablation (RFA) with or without focal endoscopic mucosal resection (EMR); (4) outcome – reported number of patients with recurrent IM, dysplasia, or EAC on histology; and (5) mean follow-up of at least 1 year after the first endoscopy confirming complete eradication. The definition of CE required both endoscopic and pathologic absence of IM and dysplasia during at least one endoscopic evaluation after EET. Recurrence was defined by the presence of IM and/or dysplasia in the esophagus and/or gastroesophageal junction/cardia after achieving CE-IM. IM obtained on biopsies of the gastric cardia alone (separate from gastroesophageal junction biopsies) was not considered a recurrence.

Studies were excluded from the final analysis if any of the following was present: (1) study design of case-control, case series with less than 20 patients, case reports, cross-sectional

studies, editorials, letters to the editor, reviews, book chapters; (2) a patient population which did not have pathologic confirmation (of the initial histologic reading before EET and recurrence) by a second or specialized pathologist, the manuscript did not specify how many patients failed endoscopic therapy (did not achieve CE-IM) or required surgical treatment; (3) other forms of primary endoscopic therapy including cryotherapy, photodynamic therapy, argon plasma coagulation; (4) studies with insufficient data to estimate an incidence of recurrence; (5) non-English reports; (6) non-human or non-clinical studies; and (7) duplicate reports. In the event where multiple manuscripts included the same cohort of patients, the study with the longest mean follow-up interval was included.

### Data abstraction

Data extraction using standardized forms was independently performed by two investigators (LLFL and BC). Any disagreement over the extracted data was resolved by consensus (LLFL, BC and SW). The following data were collected from each study: (1) study characteristics – design (cohort, randomized control trial, case series), outlook (retrospective, prospective), setting (single center or multicenter), tertiary centers vs community, location (USA vs non-USA); (2) patient characteristics – demographics (mean age, proportion of males, average maximal BE length, highest pretreatment histological grade), total number of patients who underwent EET, proportion of patients with follow-up for at least 1 year, if and how patients who were lost to follow-up were accounted for; (3) treatment characteristics – primary endoscopic treatment with SRER or RFA with or without focal EMR, definition of CE; (4) surveillance methodology – whether the neo-gastroesophageal junction/gastric cardia was biopsied separately, biopsy methods (1- or 2-cm intervals; if the study allowed biopsies every 1–2 cm, it was included in the 2-cm cohort); and (5) outcomes data including mean or median length of follow-up for the study (years) and number of events of recurrent IM, dysplasia and EAC. If a study included patients who had more than one surveillance upper endoscopy with recurrent IM or dysplasia, only the first endoscopy demonstrating recurrence was included.

### Study quality assessment

Quality assessment of each study was independently reviewed by the same two investigators using the Downs and Black quality assessment checklist [38]. This instrument was chosen as it has been validated and assesses both randomized and non-randomized (observational) studies. If recurrence after EET was a secondary objective of the manuscript and was only reported as a descriptive analysis, then the study was designated of low quality to answer the aim of this meta-analysis. As recurrence was not considered to be a main outcome in these studies, a “0” was given to the following criteria that focused on the main finding: (1) are the distributions of principal confounders in each group of subjects to be compared clearly described, (2) does the study provide estimates of the random variability in the data for the main outcome, (3) have actual probability values been reported for the main outcome, (4) were the statistical tests used to assess the main outcomes appropriate, (5)

were the main outcome measures used accurate, (6) was there adequate adjustment for confounding in the analysis from which the main findings were drawn, and (7) did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to change is <5%. Scores <15, 15–19, and >20 were considered to be low, moderate, and high quality studies, respectively. All abstracts and case series were considered to be of low quality.

### Outcomes assessed

The primary analysis focused on the pooled incidence [per 100 patient years (PY)] of IM and early neoplasia (a combination of both dysplasia and EAC for this analysis) in patients achieving CE-IM after EET. Subgroup analyses were performed for hypotheses determined a priori that may explain potential heterogeneity between the included studies. The subgroup analyses designated a priori were type of report (abstract vs full text), study outlook (prospective vs retrospective), study setting (single center vs multicenter), hospital type (solely tertiary centers vs mixed), study location (USA vs non-USA), quality (divided into high, medium and low), type of EET (SRER vs RFA with or without EMR), whether non-dysplastic BE patients were included in the treatment group, CE definition (classified as 1 vs 2 negative endoscopies), whether the neo-squamous gastroesophageal junction/gastric cardia was biopsied separately during surveillance examinations, length intervals of surveillance biopsies (1 vs 2 cm; studies that allowed biopsies every 1–2 cm were classified in the latter group), and length of Barrett’s segment ( $\leq 3$  cm vs  $> 3$  cm). A cutoff of 3 cm was used for BE length as most studies used this to differentiate between short and long segment BE. Due to the variability in reporting on continuous variables such as BE length, changing the variable to a binary variable was deemed to be the most appropriate method to include the maximum number of studies in this analysis.

### Statistical analysis

All analyses and graphs were performed using Comprehensive Meta-Analysis Version 2 or 3 (Biostat, Englewood, NJ, United States). The random effects model, as described by DerSimonian and Laird, was used for all analyses to determine incidence of recurrence (number of events per 100 PY) with the 95% confidence intervals (CI) [39]. Heterogeneity was assessed using the  $I^2$  statistic, with a value  $> 50$  considered significant for heterogeneity and was the reason we used the random effects model. Sensitivity analysis was performed to determine whether a single study had significant influence on the results, focusing on the total recurrences for both IM and dysplasia. Publication bias was assessed using a funnel plot with event rate plotted against standard error Egger’s regression intercept ( $P$  values  $\leq 0.10$  suggestive of significant publication bias). Descriptive analyses were used for the risk of recurrence given the small number of studies reporting this information and the heterogeneity of the risk factors included.

## Results

### Characteristics of included studies

From the original search, of the 3311 identified studies, 3167 were excluded based on the title and abstract alone (► Fig. 1). The full-text of the remaining 144 studies was reviewed and an additional 111 studies were excluded. We updated our search for eligible studies after the 2016 Digestive Disease Week conference and identified three more abstracts that met our study's inclusion and exclusion criteria. A total of 39 studies (33 full-text manuscripts and 6 abstracts) were included in the final analysis. The two groups in a randomized controlled trial comparing SRER to RFA with focal EMR were treated as separate patient cohorts in this analysis [34].

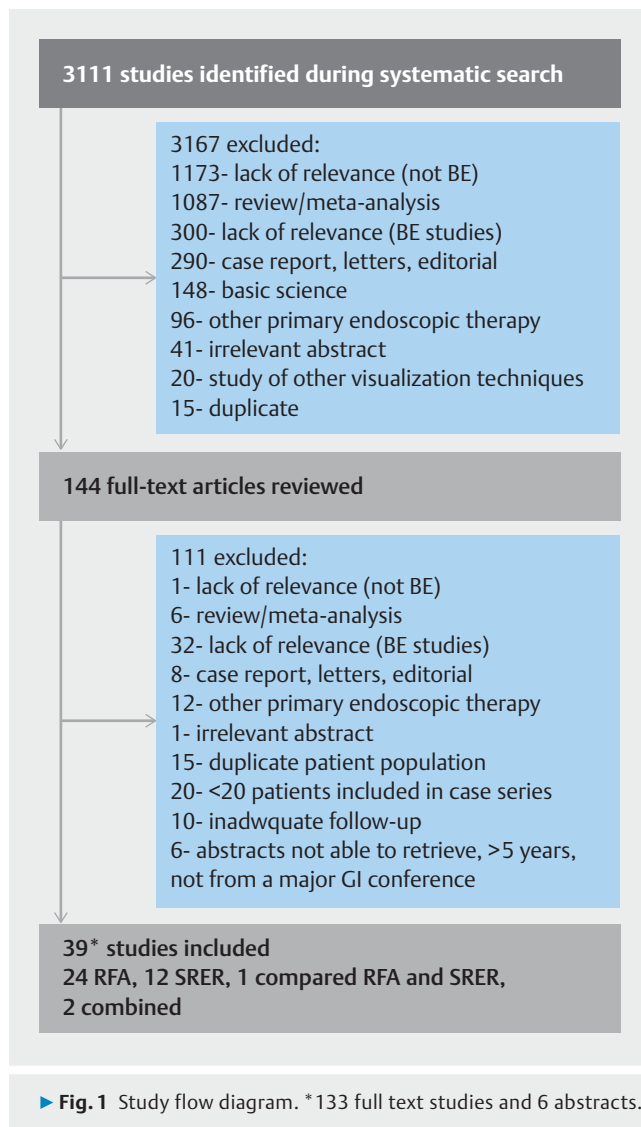
The overall study and patient characteristics are highlighted in ► Table 1 and ► Table 2, respectively. A total of 25 studies focused on RFA with or without EMR, 13 studies described outcomes in patients treated with SRER as the primary EET modality (1 study compared both RFA and SRER), and 2 abstracts combined both SRER and RFA in their analysis. Of the manuscripts focusing on RFA, 1 was a randomized controlled trial, 19 cohort observational studies, and 5 case series. Two cohort studies were included in only the recurrent dysplasia analysis as they did not report how many patients had recurrent IM [40, 41]. The distribution of studies based on geographic location was as follows: USA (23), Europe (13), Australia (2), and Canada (1). Overall, 4355 patients (3213 treated with RFA, 567 with SRER, and 575 both modalities) were included in the analysis for a total of 11 837.63 patient-years of follow-up.

### Quality of the included studies

In all of the included randomized controlled trials and cohort studies, the main objective, intervention of interest, and main findings were clearly described. Of the 18 full text randomized controlled trials or cohort studies, 4 were considered to be of high quality (3 RFA, 1 SRER), 7 moderate quality (6 RFA studies, and 1 study comparing RFA to SRER), and 7 low quality (7 RFA) as highlighted in ► Supplemental Table 1. The majority of the moderate and low quality studies reported recurrence after EET as a secondary analysis; only 7 cohort full text studies (6 RFA and 1 SRER) had recurrence as the primary outcome [27, 32, 35, 36, 42–44]. The 16 case series and 5 cohort abstracts were all considered to be low quality.

### Incidence of recurrence

Overall, a total of 1000 recurrences occurred after CE-IM, of which 722 occurred after RFA, 103 after SRER therapy, and 175 after either therapy. Overall, the pooled incidence of any recurrence was 7.5 (95%CI 6.1–9)/100 PY (► Fig. 2a), recurrence of IM was 4.8 (3.8–5.9)/100 PY (► Fig. 2b), and recurrence of dysplasia was 2.0 (1.5–2.5)/100 PY (► Fig. 2c). The total recurrence does not equal the combination of both IM and dysplasia recurrence as some studies only reported on either IM or dysplasia recurrence and these were not included in the total recurrences.



The IM and dysplasia recurrence rates for the RFA and SRER groups are highlighted in ► Table 3. Compared to the SRER group, the RFA group had significantly higher overall [8.6 (6.7–10.5)/100 PY vs 4.9 (3–6.8)/100 PY,  $P=0.007$ ] and IM recurrence rates [5.8 (4.3–7.3)/100 PY vs 3.3 (2–4.7)/100 PY,  $P=0.015$ ]. However, there was no difference in the recurrence rate of dysplasia between the two groups [1.9 (1.3–2.5)/100 PY in the RFA vs 1.2 (0.4–1.9)/100 PY in the SRER group,  $P=0.11$ ]. The majority of recurrences were amenable to repeat EET as highlighted in ► Table 4.

### Subgroup analyses on incidence of recurrence

Significant heterogeneity between studies was identified, with an overall  $I^2$  value of 86. To explore the potential causes of this heterogeneity, several subgroup analyses were performed. In the RFA group, significant factors associated with a higher IM recurrence rate included retrospective study design, inclusion of abstracts, surveillance biopsy protocol and BE length of  $\leq 3$  cm (► Table 5). Similar subgroup analyses performed in the SRER group are highlighted in ► Table 6.

► **Table 1** Study characteristics.

Study	EET type	Manuscript type	De-sign	Set-ting	Outlook	Loca-tion	Quality	Histology included	No. of EGD for CR	Cardia biop-sied	Biopsy inter-vals, cm
Fleischer et al., 2010 [52]	RFA	Full text	Co-hort	Multi	Prospect-ive	USA	Moder-ate	IM	2	No	1
Alvarez Herrero et al., 2011 [53]	RFA	Full text	CS	Multi	Prospect-ive	Europe	Low	L,H,EAC	1	Yes	2
Shaheen et al., 2011 [30]	RFA	Full text	RCT	Multi	Prospect-ive	USA	Moder-ate	L,H	1	No	1
Vaccaro et al., 2011 [36]	RFA	Full text	Co-hort	Single	Retrospec-tive	USA	Moder-ate	IM,L,H,EAC	1	Yes	NR
van Vilsteren et al., 2011 [34]	Both	Full text	RCT	Multi	Prospect-ive	Europe	Moder-ate	H,EAC	1	Yes	2
Caillol et al., 2012 [54]	RFA	Full text	Co-hort	Single	Retrospec-tive	Europe	Low	IM,L,H	NR	No	2
Gupta N 2012 [55]	RFA	Abstract	Co-hort	Multi	Retrospec-tive	USA	Low	H,EAC	NR	NR	NR
van Vilsteren et al., 2012 [56]	RFA	Full text	CS	Single	Retrospec-tive	Europe	Low	H,EAC	1	Yes	2
Akiyama et al., 2013 [45]	RFA	Abstract	Co-hort	Single	Retrospec-tive	USA	Low	IM,L,H,EAC	1	NR	NR
Dulai et al., 2013 [57]	RFA	Full text	Co-hort	Single	Retrospec-tive	USA	Low	IM,L,H,EAC	1	No	1
Ertanet al., 2013 [58]	RFA	Full text	Co-hort	Single	Retrospec-tive	USA	Low	L,H	NR	No	1
Gupta et al., 2013 [35]	RFA	Full text	Co-hort	Multi	Retrospec-tive	USA	High	IM,L,H,EAC	2	No	1–2
Haidry et al., 2013 [59]	RFA	Full text	Co-hort	Multi	Retrospec-tive	Europe	Low	L,H,EAC	1	No	NR
Korst et al., 2013 [60]	RFA	Full text	CS	Single	Retrospec-tive	USA	Low	IM,L,H,EAC	NR	Yes	1–2
Orman et al., 2013 [42]	RFA	Full text	Co-hort	Single	Retrospec-tive	USA	High	L,H,EAC	1	Yes	1
Phoa et al., 2013 [33]	RFA	Full text	CS	Single	Retrospec-tive	Europe	Low	H,EAC	NR	Yes	2
Shue et al., 2013 [47]	RFA	Abstract	Co-hort	Single	Retrospec-tive	USA	Low	IM,L,H,EAC	1	NR	2
Pasricha et al., 2014 [32]	RFA	Full text	Co-hort	Multi	Retrospec-tive	USA	Moder-ate	IM,L,H,EAC	1 or 2	No	1
Strauss et al., 2014 [61]	RFA	Full text	Co-hort	Multi	Retrospec-tive	USA	Moder-ate	EAC	NR	NR	NR
Agoston et al., 2015 [40]	RFA	Full text	Co-hort	Multi	Retrospec-tive	USA	Low	EAC	1	NR	1
Cotton et al., 2015 [43]	RFA	Full text	Co-hort	Single	Retrospec-tive	USA	Moder-ate	IM,L,H,EAC	1	Yes	1
Lada et al., 2014 [62]	RFA	Full text	Co-hort	Single	Retrospec-tive	USA	Low	H,EAC	2	NR	1
Le Page et al., 2016 [63]	RFA	Full text	Co-hort	Single	Retrospec-tive	Europe	Low	H,EAC	NR	NR	NR
Phoa et al., 2015 [64]	RFA	Full text	CS	Multi	Prospect-ive	Europe	Low	IM,L,H,EAC	1	Yes	2

► **Table 1** (Continuation)

Study	EET type	Manuscript type	Design	Setting	Outlook	Location	Quality	Histology included	No. of EGD for CR	Cardia biopsied	Biopsy intervals, cm
Small et al., 2015 [44]	RFA	Full text	Co-hort	Single	Retrospective	USA	High	H,EAC	1	NR	NR
Giovannini et al., 2004 [65]	EMR	Full text	CS	Single	Retrospective	Europe	Low	H,EAC	NR	No	NR
Larghi et al., 2007 [66]	EMR	Full text	CS	Multi	Retrospective	USA	Low	H,EAC	NR	No	1–2
Lopes et al., 2007 [67]	EMR	Full text	CS	Single	Retrospective	Europe	Low	H,EAC	NR	No	NR
Chennat et al., 2009 [68]	EMR	Full text	CS	Single	Retrospective	USA	Low	H,EAC	NR	No	1–2
Brahmania et al., 2010 [69]	EMR	Full text	CS	Single	Retrospective	Canada	Low	IM,L,H,EAC	NR	NR	NR
Moss et al., 2010 [70]	EMR	Full text	CS	Multi	Prospective	Australia	Low	H,EAC	NR	No	1
Chung et al., 2011 [26]	EMR	Full text	CS	Multi	Retrospective	Australia	Low	H,EAC	NR	No	1
Gerke et al., 2011 [25]	EMR	Full text	CS	Single	Retrospective	USA	Low	L,H,EAC	NR	Yes	NR
Anders et al., 2014 [27]	EMR	Full text	Co-hort	Multi	Retrospective	Europe	High	L,H,EAC	2	No	NR
Conio et al., 2014 [71]	EMR	Full text	CS	Single	Retrospective	Europe	Low	H,EAC	NR	Yes	NR
Konda et al., 2014 [28]	EMR	Full text	CS	Single	Retrospective	USA	Low	L,H,EAC	1	Yes	NR
Belghazi et al., 2016 [72]	EMR	Abstract	CS	Multi	Retrospective	Europe	Low	H,EAC	NR	Yes	NR
Wani et al., 2016 [51]	Both	Abstract	Co-hort	Multi	Retrospective	USA	Low	L,H,EAC	NR	NR	NR
Waxman et al., 2016 [73]	Both	Abstract	Co-hort	Multi	Retrospective	USA	Low	L,H,EAC	NR	NR	NR

EET = endoscopic eradication therapy, EGD = esophagogastroduodenoscopy, CR = complete remission, EMR = endoscopic mucosal resection, RFA = radiofrequency ablation, CS = case series, IM = intestinal metaplasia, L = low grade dysplasia, H = high grade dysplasia, EAC = early adenocarcinoma, NR = not reported, RCT = randomized control trial.

## Sensitivity analysis

A jackknife sensitivity analysis removing one study at a time did not change the incidence of total recurrence in the remaining studies within the RFA or SRER groups, indicating that no one study had a significant impact on the results (data not shown).

## Risk factors for recurrence

Risk factors for recurrence after RFA therapy were reported in 7 studies (6 manuscripts, 1 abstract) [32, 35, 40, 42, 44–46]. A single study reported that the presence of erosive esophagitis increased the risk of recurrence on multivariable regression analysis controlling for hiatal hernia length and presence of dysplasia [hazard ratio 15.41 (95%CI 1.65–144.33)] [45]. Most

studies found that age, gender, race, body mass index, baseline histology before EET, BE length, NSAID use, hiatal hernia size, and presence of a fundoplication were not associated with an increased risk of recurrence. This is in contrast to a study by Pasricha et al. that reported older age [odds ratio (OR) 1.02 per year, 95%CI 1.01–1.03], longer BE segment length (OR 1.10 per cm, 95%CI 1.06–1.15), and non-Caucasian race (OR 2.0, 95%CI 1.2–3.34) increased the risk of recurrence on multivariable regression analysis [32]. In addition, Lada et al. found that recurrent dysplasia was more common in older patients, those with longer follow-up, and those who underwent more total procedures (including initial therapeutic interventions and surveillance endoscopies) [46]. Similarly, Small et al. found that the number of treatment sessions needed to achieve CE-IM in

► **Table 2** Patient characteristics.

Study	Total no.	Mean age, years	% Male	Mean BE length, cm	Total no. of pts followed	Mean follow-up length, years	Total recurrences	IM recurrences	Dysplasia recurrences	EAC recurrences
<b>RFA group</b>										
Fleischer et al., 2010 [52]	50	54.3	74	3.1	50	5	4	4	0	0
Alvarez Herrero et al., 2011 [53]	26	66	80.8	11	20	2.4	8	8	0	0
Shaheen et al., 2011 [30]	119	66	85.7	4.9	119	3.05	19	14	3	2
Vaccaro et al., 2011 [36]	47	64.2	76.6	2	47	1.11	15	11	4	0
van Vilsteren et al., 2011 [34] <sup>1</sup>	22	69	86.4	4	21	1.8	2	2	0	0
Caillol et al., 2012 [54]	34	60	82.4	6.8	34	1	2	0	0	2
Gupta et al., 2012 [55]	128	65.7	88.3	4.4	128	1.3	34	18	16	0
van Vilsteren et al., 2012 [56]	24	68	83.3	8	20	1.2	0	0	0	0
Akiyama et al., 2013 [45]	40	62.5	80	4.1	40	2.18	7	7	0	0
Dulai et al., 2013 [57]	72	66.9	80.6	7.6	57	3.25	11	11	0	0
Ertan et al., 2013 [58]	53	65.4	73.6	5.7	47	2.75	3	3	0	0
Gupta et al., 2013 [35]	448	64	85	4.3	192	1.12	37	29	8	0
Haidry et al., 2013 [59]	335	68.1	80.9	5.8	256	1.58	37	17	16	4
Korst et al., 2013 [60]	53	59	69.8	3	53	1.5	14	14	0	0
Orman et al., 2013 [42]	112	64.1	79.5	4	107	1.1	8	3	2	3
Phoa et al., 2013 [33]	55	65	81.8	5	54	5.1	25	22	1	2
Shue et al., 2013 [47]	42	61	71.4	3.5	42	1.17	11	11	0	0
Pasricha et al., 2014 [32]	1634	61.7	74	4	NR	NR	334	269	52	13
Strauss et al., 2014 [61]	36	64	72.2	3.5	32	2	9	5	3	1
Agoston et al., 2015 [40]	78	67.1	75.6	4.1	67	2.2	–	–	–	6
Cotton et al., 2015 [43]	198	69.8	70.7	4.7	198	3	35	22	7	6
Lada et al., 2014 [62]	57	66.2	87.7	5.1	57	2.95	16	4	12	0

► **Table 2** (Continuation)

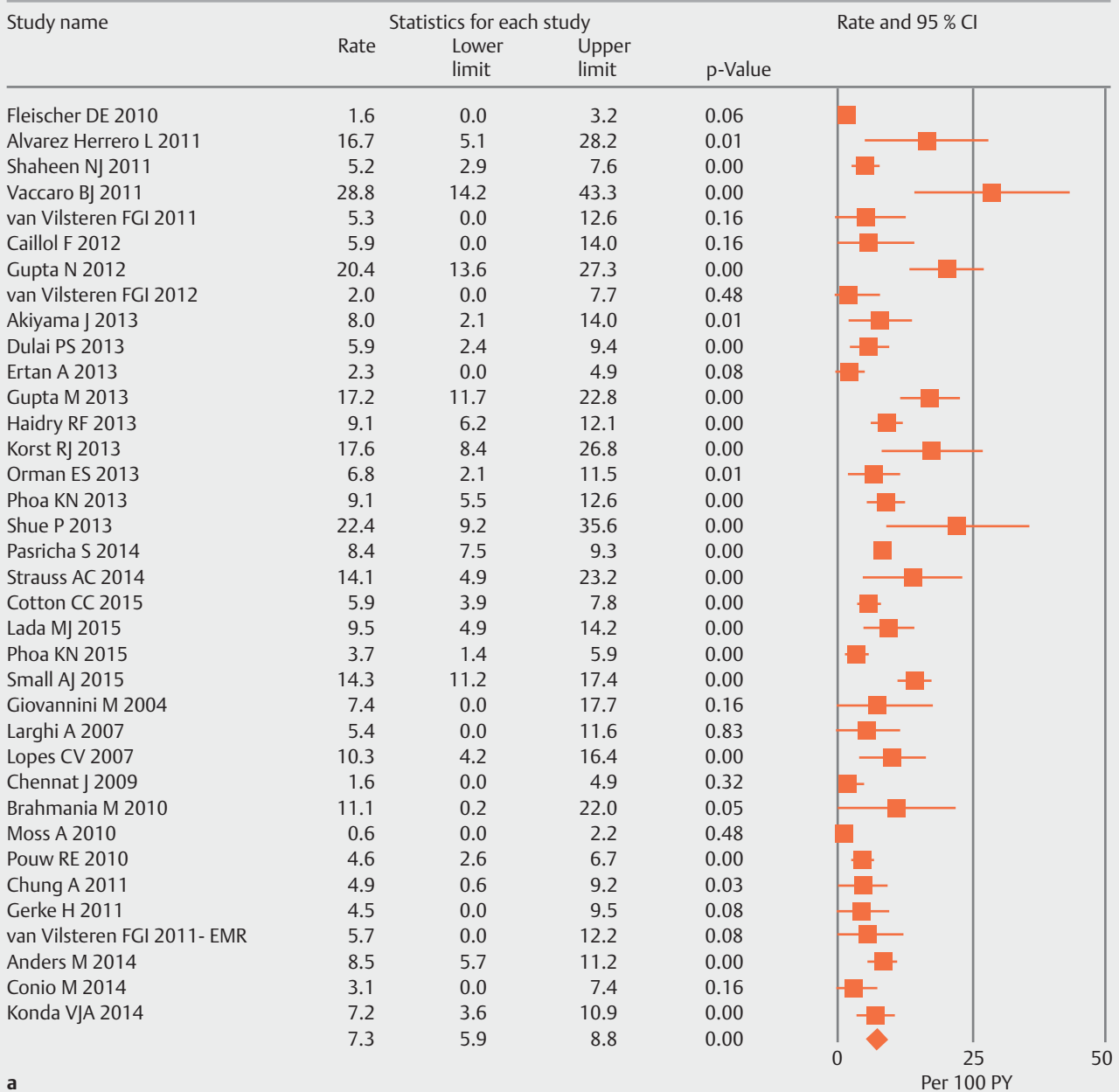
Study	Total no.	Mean age, years	% Male	Mean BE length, cm	Total no. of pts followed	Mean follow-up length, years	Total recurrences	IM recurrences	Dysplasia recurrences	EAC recurrences
Le Page et al., 2016 [63]	50	67	72	5	45	1.75	–	–	–	2
Phoa et al., 2015 [64]	132	65	81	6	121	2.25	10	5	3	2
Small et al., 2015 [44]	197	67.9	84.8	2.4	197	2.87	81	64	15	2
<b>SRER group</b>										
Giovannini et al., 2004 [65]	21	63	52.4	3.5	18	1.5	2	0	2	0
Larghi et al., 2007 [66]	24	64.1	83.3	2.5	24	2.3	3	2	0	1
Lopes et al., 2007 [67]	41	65.8	83.4	4.9	41	2.6	11	10	0	1
Chennat et al., 2009 [68]	49	67	75.5	3.2	32	1.9	1	1	0	0
Brahmania et al., 2010 [69]	22	67	100	5.5	18	2	4	0	4	0
Moss et al., 2010 [70]	75	68	78.7	3.6	33	2.6	0	0	0	0
Chung et al., 2011 [26]	77	65	83.1	2	73	1.4	5	2	3	0
Gerke et al., 2011 [25]	41	67	78	3.2	32	2.1	3	3	0	0
van Vilsteren et al., 2011 [34] <sup>1</sup>	25	68	84	4	25	2.1	3	2	0	1
Anders et al., 2014 [27]	90	63	91.1	NR	81	5.4	37	32	2	3
Conio et al., 2014 [71]	47	65	91.5	3	43	1.5	2	0	1	1
Konda et al., 2014 [28]	86	67.5	NR	3.6	74	2.8	15	7	7	1
Belghazi et al., 2016 [72]	73	64	87.6	3	73	6.33	17	16	0	1
<b>Both SRER and RFA combined</b>										
Wani et al., 2016 [51]	542	67	79.5	5.4	446	2.75	127	85	42	0
Waxman et al., 2016 [73]	152	64.9	90.1	5	129	3.53	48	34	14	

RFA = radiofrequency ablation, SRER = stepwise complete endoscopic resection, BE = Barrett's esophagus, IM = intestinal metaplasia, EAC = early adenocarcinoma, NR = not reported.

<sup>1</sup> Randomized trial of RFA vs SRER, therefore the patient data was split into the corresponding groups.



## Incidence of total recurrence across all studies



► **Fig. 2a** Overall pooled incidence of any recurrence (intestinal metaplasia or dysplasia) after achieving complete eradication of intestinal metaplasia following endoscopic eradication therapy using stepwise complete endoscopic resection or radiofrequency ablation with or without focal endoscopic mucosal resection.

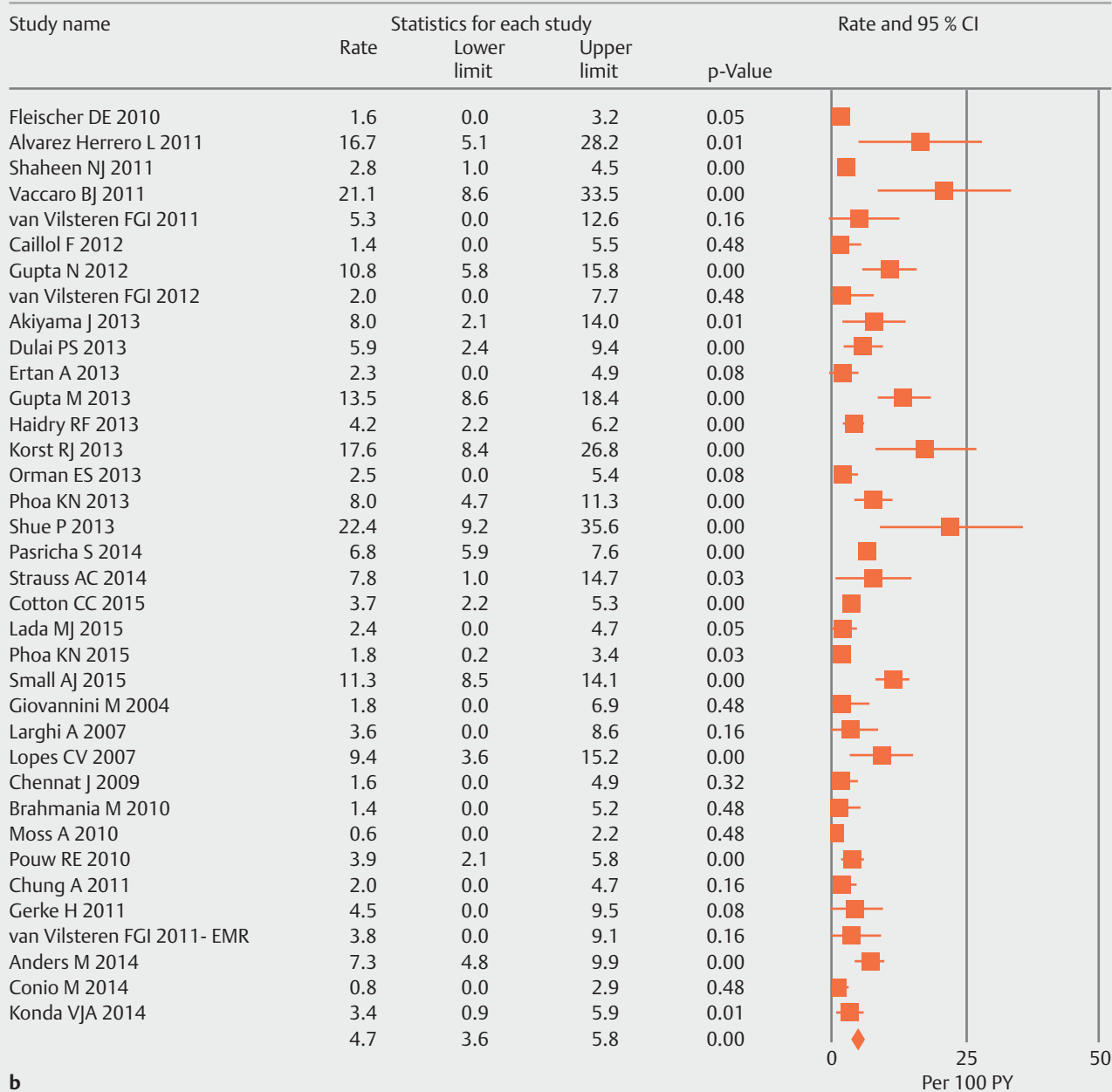
patients with HGD, but not EAC, had an increased risk of developing recurrent dysplasia, while older age and non-Caucasian race had a higher risk of recurrent dysplasia [44]. Vaccaro et al. [36] found that BE length was significantly associated with increased recurrence ( $P=0.03$ ). Other risk factors identified by Shue et al. that increased the risk of IM recurrence included smoking (39.3% vs 0% among those with and without recurrence,  $P=0.006$ ) and mean BMI (25.3 vs 29.8 among those with and without recurrence,  $P=0.002$ ) [47]. Only one study focused on recurrence post SRER and reported BE length as a pre-

dictor for IM and dysplasia on multivariable regression analysis [OR 2.73 (95%CI 1.01–7.38)] [27].

### Publication bias

Using Egger's regression intercept, the two-tailed  $P$  value of the publication bias for total recurrence and IM recurrence among all studies was 0.14 and 0.46, respectively, suggesting the lack of publication bias. The funnel plot for total recurrence is shown in ► **Fig. 3**. The  $P$  value for early neoplasia (EN) recur-

### Incidence of IM recurrence across all studies



► **Fig. 2b** Overall pooled incidence of intestinal metaplasia after achieving complete eradication of intestinal metaplasia following endoscopic eradication therapy using stepwise complete endoscopic resection or radiofrequency ablation with or without focal endoscopic mucosal resection.

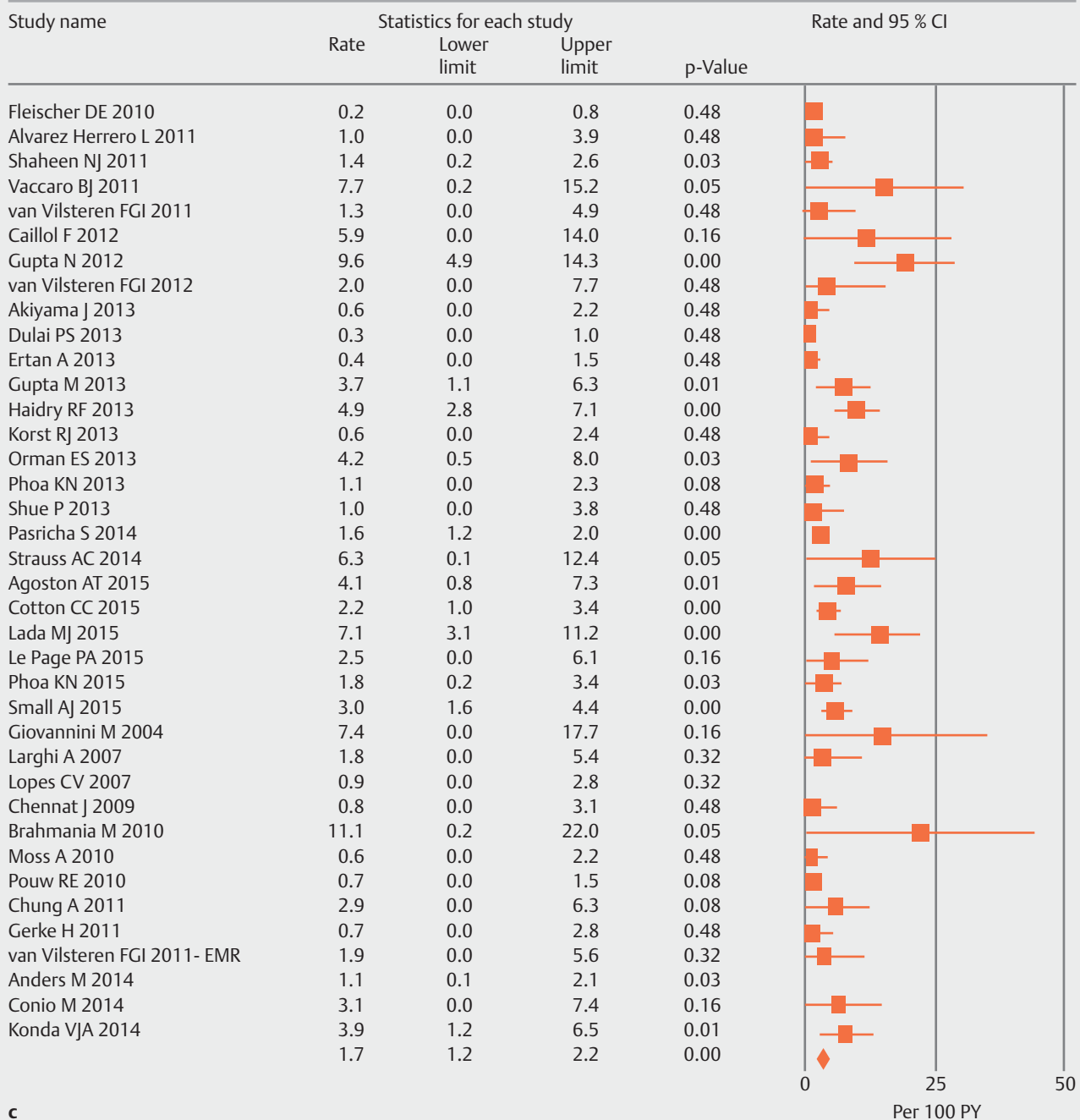
rence was  $<0.001$ , suggesting the presence of a publication bias in this subgroup.

## Discussion

EET in BE patients at highest risk for progression to invasive cancer (mucosal EAC, HGD and LGD) is a well-established and effective treatment strategy that minimizes cancer risk and reduces the morbidity and mortality associated with EAC. This practice has now been endorsed by gastrointestinal societal

guidelines and has replaced esophagectomy as the standard of care for HGD and EAC confined to the mucosa [8, 48, 49]. While the effectiveness of EET has been demonstrated in randomized controlled trials and large observational studies, variable rates of recurrence of IM and dysplasia have been reported post-EET. A reliable estimate of the risk of recurrence after achieving CE-IM is critical to establish surveillance guidelines (duration and frequency of surveillance endoscopy), determine cost-effectiveness of EET, and ultimately educate physicians and patients before embarking on EET.

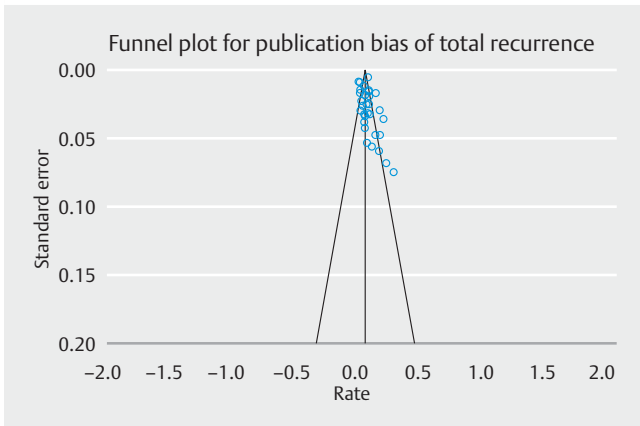
## Incidence of dysplasia recurrence across all studies



► **Fig. 2c** Overall pooled incidence of early neoplasia (EN) after achieving complete eradication of intestinal metaplasia following endoscopic eradication therapy using stepwise complete endoscopic resection or radiofrequency ablation with or without focal endoscopic mucosal resection.

The results of this systematic review and meta-analysis demonstrate a pooled incidence rate for any recurrence, IM, and dysplasia of 7.5%/100 PY (95%CI 6.1–9), 4.8%/100 PY (95%CI 3.8–5.9), and 2.0%/100 PY (95%CI 1.5–2.5), respectively using EET treatment modalities (RFA with or without focal EMR and SRER). In addition, the vast majority of recurrences were amenable to repeat EET. In a recent systematic review and

meta-analysis, Krishnamoorthi and colleagues also reported the risk of recurrence of IM, dysplasia, and HGD/EAC in patients undergoing RFA and recurrence rates after use of all endoscopic modalities [50]. While the primary results were similar, the current study focused primarily on contemporary EET therapies and also compared recurrence rates between RFA and SRER. Similar to the above study, the current study with updated



► **Fig. 3** Funnel plot for publication bias on the incidence of total recurrence among all studies.

search results noted substantial heterogeneity. Another study that provided a recurrence estimate was a study by Orman et al. that determined the efficacy and durability of RFA for patients with dysplastic and non-dysplastic BE. That study reported the proportion of patients with recurrence of IM after successful CE-IM with RFA therapy and quoted a point estimate of 13% (95%CI 9–18%) [31]. However, reporting recurrence rate per patient-year of follow-up (accounting for follow-up duration) is a more stable and meaningful outcome.

The results of this study raise the important issue with regard to the optimal EET strategy (SRER vs RFA with or without EMR) with regard to recurrence of IM and dysplasia. Patients in the RFA group had higher overall and IM recurrence rates compared to patients treated with SRER; however, there was no difference between the two groups with regard to recurrence of dysplasia. The authors acknowledge that any direct comparison between RFA and SRER is biased as only one study directly compared these two strategies in a randomized controlled trial. We emphasize that any comparison between RFA and SRER is indirect based on the rates of recurrence in each arm obtained by combining observational studies. Although several studies have confirmed the effectiveness and durability of SRER, this treatment approach is associated with a high stricture rate [27–29]. In a multicenter randomized controlled trial compar-

ing these two treatment approaches, a higher stricture rate was reported in patients treated with SRER compared to patients treated with focal EMR followed by RFA (88% vs 14%,  $P < 0.001$ ) with no difference in efficacy indicators of CE-IM and CE-D [34]. This justifies the current strategy of focal EMR for visible lesions followed by ablation of the residual Barrett's segment for optimal treatment of BE related neoplasia [8, 48, 49]. In addition, the studies evaluating SRER limited the length of BE in the included patients and, given that many studies identify BE length as a risk factor for recurrence, the lower recurrence rate (overall and IM) in the SRER group may be confounded by BE length. Whether there is a subgroup of BE-related neoplasia patients (multifocal disease, diffuse nodularity) more likely to benefit from SRER needs to be evaluated in future studies. Improvement in prevention of stricture formation post-SRER is also required before this treatment strategy can be recommended as a primary treatment modality.

This systematic review highlights the variable rates of recurrence reported in the literature, an important take-home message of this study. The purported factors for this include study design (prospective vs retrospective), participating centers (tertiary care vs community practices), sample size, variability in study inclusion criteria (histologic grades of BE), treatment and surveillance protocol, duration of follow-up, and definitions of CE-IM and recurrence (whether IM at or just below the neo-squamocolumnar junction is included in the numerator of patients with recurrences). Although some studies reported on subsquamous IM recurrence and recurrence of the cardia, the significance of these findings was unclear. With the low number of studies focusing on these outcomes, this was not a focus of the manuscript. Several factors in the subgroup analyses were associated with a significant difference in incidence rates; however, none completely account for the heterogeneity noted in this meta-analysis. For example, in the RFA group, prospective studies were associated with a lower incidence of total, IM, and dysplasia recurrence rates compared to retrospective studies and a higher dysplasia recurrence rate was reported in trials conducted at tertiary care centers. This may be related to inherent limitations associated with retrospective and multicenter studies (lack of standardized definitions, treatment and surveillance protocol). Contrary to previous studies, recurrence of dysplasia was higher in BE patients with length  $< 3$  cm. The rea-

► **Table 3** Incidence of recurrence after achieving CE-IM following EET.

	Total recurrence		IM recurrence		Dysplasia recurrence	
	No. of studies	Incidence per 100 PY (95%CI)	No. of studies	Incidence per 100 PY (95%CI)	No. of studies	Incidence per 100 PY (95%CI)
Overall	36 <sup>1</sup>	6.8 (5.4–8.1)	35 <sup>1</sup>	4.4 (3.4–5.4)	38 <sup>1</sup>	1.6 (1.1–2.1)
RFA	23	8.6 (6.7–10.5)	23	5.8 (4.3–7.3)	25	1.9 (1.3–2.5)
SRER	13	4.9 (3–6.8)	12	3.3 (2–4.7)	13	1.2 (0.4–1.9)

CE-IM = complete eradication of intestinal metaplasia, EET = endoscopic eradication therapy, RFA = radiofrequency ablation, SRER = stepwise complete endoscopic resection, IM = intestinal metaplasia, PY = patient-years; Dysplasia recurrence includes dysplasia and EAC.

<sup>1</sup> One study compared RFA to SRER. Its data is separated into each group, making the overall number of studies one less than the total RFA and SRER studies combined.

► **Table 4** Treatment of recurrent intestinal metaplasia and dysplasia.

Study	Total recurrences	IM recurrences	Dysplasia recurrences	EAC recurrences	Management of recurrence
Fleischer et al., 2010 [52]	4	4	0	0	NR
Alvarez Herrero et al., 2011 [53]	8	8	0	0	NR
Shaheen et al., 2011 [30]	19	14	3	2	RFA
Vaccaro et al., 2011 [36]	15	11	4	0	RFA, EMR
van Vilsteren et al., 2011 [34] <sup>1</sup>	2	2	0	0	NR
Caillol et al., 2012 [54]	2	0	0	2	NR
Gupta et al., 2012 [55]	34	18	16	0	APC/RFA, EMR
van Vilsteren et al., 2012 [56]	0	0	0	0	No recurrence
Akiyama et al., 2013 [45]	7	7	0	0	NR
Dulai et al., 2013 [57]	11	11	0	0	RFA
Ertan et al., 2013 [58]	3	3	0	0	All three underwent surgery
Gupta et al., 2013 [35]	37	29	8	0	NR
Haidry et al., 2013 [59]	37	17	16	4	NR
Korst et al., 2013 [60]	14	14	0	0	RFA
Orman et al., 2013 [42]	8	3	2	3	RFA
Phoa et al., 2013 [33]	25	22	1	2	NR
Shue et al., 2013 [47]	11	11	0	0	NR
Pasricha et al., 2014 [32]	334	269	52	13	NR
Strauss et al., 2014 [61]	9	5	3	1	RFA
Agoston et al., 2015 [40]	–	–	–	6	Unclear as primary failure not differentiated from recurrences
Cotton et al., 2015 [43]	35	22	7	6	NR
Lada et al., 2014 [62]	16	4	12	0	NR
Le Page PA 2016 [63]	–	–	–	2	APC/RFA, EMR
Phoa et al., 2015 [64]	10	5	3	2	APC, EMR
Small et al., 2015 [44]	81	64	15	2	Treated endoscopically but did not specify how
Giovannini et al., 2004 [65]	2	0	2	0	NR
Larghi et al., 2007 [66]	3	2	0	1	NR
Lopes et al., 2007 [67]	11	10	0	1	NR
Chennat et al., 2009 [68]	1	1	0	0	NR
Brahmania et al., 2010 [69]	4	0	4	0	All recurrences were LGD and under surveillance
Moss et al., 2010 [70]	0	0	0	0	No recurrence
Chung et al., 2011 [26]	5	2	3	0	EMR
Gerke et al., 2011 [25]	3	3	0	0	RFA, EMR
van Vilsteren et al., 2011 [34] <sup>1</sup>	3	2	0	1	NR
Anders et al., 2014 [27]	37	32	2	3	APC, EMR
Conio et al., 2014 [71]	2	0	1	1	NR
Konda et al., 2014 [28]	15	7	7	1	EMR

► **Table 4** (Continuation)

Study	Total recurrences	IM recurrences	Dysplasia recurrences	EAC recurrences	Management of recurrence
Belghazi et al., 2016 [72]	17	16	0	1	Esophagectomy for T1b cancer
Wani et al., 2016 [51]	127	85	42		NR
Waxman et al., 2016 [73]	48	34	14		NR

NR = not reported, RFA = radiofrequency ablation, EMR = endoscopic mucosal resection, APC = argon plasma coagulation, LGD = low grade dysplasia.  
<sup>1</sup> Randomized trial of RFA vs SRER, therefore the patient data was split into the corresponding groups.

son for this finding is unclear. Subgroup analyses provided no evidence that overall recurrence rates are higher in patients with BE related neoplasia compared to those with non-dysplastic BE. Consistent with the results from the US RFA Registry [32], there was no difference in recurrence rates based on the definition of CE-IM (CE-IM defined by one or two successive negative endoscopies).

There are limitations of this systematic review and meta-analysis that merit discussion. One inherent limitation of the study design is the quality of the individual studies. The majority of the studies that met the inclusion criteria were of low to moderate quality, with only three studies meeting the criteria for high quality. This is predominantly because recurrence after EET was often a secondary analysis rather than the primary end point of the study. Another major limitation is the substantial heterogeneity noted in the assessment of recurrence rates. This may be related to patient characteristics, significant variability in the baseline pathology of included patients (proportion of included patients with HGD/early EAC), endoscopic surveillance intervals, surveillance biopsy protocols, confirmation by a dedicated gastrointestinal pathologist, and variability in definition of recurrence between each study. This was addressed by using strict inclusion and exclusion criteria and a priori subgroup analyses to explore sources of heterogeneity. However, the authors acknowledge that the substantial heterogeneity tempers the confidence level associated with the estimates of recurrence reported in this study and the precision of these estimates may change as data from large prospective multicenter trials become available.

The authors acknowledge that it would be ideal to conduct a time-to-event analysis accounting for individual patient data and patients lost to follow-up. However, these data were reported in few studies thus precluding this analysis. This study also highlights the fact that only a limited number of studies report on the risk factors associated with recurrence, and they comprise only a small number of overall recurrences, limiting our ability to perform multivariable regression analysis. Hence, only a descriptive analysis of risk factors was provided in this study. The associations between the presence of erosive esophagitis, older age, non-Caucasian race, pretreatment BE length, and recurrence of IM and dysplasia need to be explored and confirmed in future studies. The generalizability of these estimates is limited by the fact that most of the included studies were conducted at tertiary care centers. Future studies need

to clarify if differences in technique and protocols, for instance, the routine performance of circumferential RFA at the gastroesophageal junction (location of most recurrences) at each RFA session, regardless of the presence of visible BE, impact the durability of EET. Similarly, differences in acid suppressive regimens need to be correlated with the likelihood of recurrence of IM and dysplasia. This study did not address the durability of other ablative techniques such as argon plasma coagulation but focused on the most widely used techniques.

Finally, temporality of recurrence after achieving CE-IM cannot be established with the available data in published reports. Although surveillance post-CE-IM is uniformly recommended, surveillance intervals suggested by current guidelines [8] are largely driven by expert opinion and low quality evidence. Future prospective studies need to provide guidance on current surveillance strategies post CE-IM. The strengths of this study include the use of strict study definitions and inclusion criteria, and provision of point estimates for incidence of recurrence for IM and dysplasia per patient-year for contemporary EET modalities.

In conclusion, this systematic review highlights the variable rates of recurrence reported in the literature. The results of this meta-analysis report the incidence rates of recurrence of IM and dysplasia after successful CE-IM in patients with BE post-EET. The vast majority of recurrences were without dysplasia and could be managed with repeat EET, adding credence to the current strategy of EET for management of BE-related neoplasia. This study emphasizes the importance of routine long-term endoscopic surveillance following EET and highlights the need to discuss these recurrence estimates with patients before embarking on EET. Future prospective studies that use standardized definitions for study end points and focus on recurrence risk as the primary outcome are required to more precisely define the annual recurrence risk and the predictors associated with recurrence. This will allow for evidence-based recommendations with regard to surveillance endoscopic and biopsy protocols after successful EET of BE-related neoplasia patients with the goal of stopping or reducing the frequency of surveillance in low risk individuals and enrolling high risk patients in an intensive surveillance protocol.

► **Table 5** Subgroup analyses on the incidence of any recurrence and recurrent IM and EN after RFA.

	No. of studies	Total recurrence [incidence per 100 PY (95%CI)]	I <sup>2</sup>	P value	IM recurrence [incidence per 100 PY (95% CI)]	I <sup>2</sup>	P value	EN recurrence [incidence per 100 PY (95% CI)]	I <sup>2</sup>	P value
Manuscript type				0.11			0.04			0.55
▪ Full text	20	7.9 (6–9.8)	77.20		5.3 (3.8–6.8)	47.01		1.9 (1.2–2.5)	70.54	
▪ Abstract	3	16.1 (6.4–25.9)	86.30		11.4 (5.8–17)	85.24		3.1 (0–7.3)	84.39	
Study outlook				0.001			<0.001			0.01
▪ Prospective	5	4.1 (1.6–6.6)	68.15		2.4 (0.9–4)	49.18		0.9 (0.1–1.7)	34.15	
▪ Retrospective	18	9.7 (7.6–11.7)	80.53		6.5 (4.8–8.2)	81.13		2.3 (1.5–3)	71.08	
Study design				0.62			0.80			0.19
▪ Case series	5	8.1 (3.3–12.9)	88.48		7.5 (2.7–12.6)	85.75		1.2 (0.4–2)	0	
▪ Cohort	17	9 (6.8–11.3)	77.75		5.7 (4–7.3)	84.18		2.2 (1.5–3)	78.29	
▪ Randomized control	1	5.3 (0–12)	0		5.3 (0–12.6)	0		1.3 (0–0.5)	0	
Setting				0.94			0.80			0.29
▪ Multicenter	10	8.8 (5.9–11.8)	90.97		5.7 (3.5–7.9)	88.68		2.3 (1.3–3.3)	79.89	
▪ Single center	13	8.7 (5.9–11.4)	79.77		6.1 (3.8–8.4)	80.76		1.6 (0.3–2.5)	61.22	
Hospital type				0.24			0.68			0.03
▪ Tertiary only	20	9.4 (7.1–11.6)	96.32		6 (4.3–7.7)	94.01		2.4 (1.6–3.1)	67.36	
▪ Included community	3	5.8 (0.3–11.3)	81.82		5.1 (0.8–9.4)	80.83		0.8 (0–2)	88.57	
Location				0.13			0.13			0.65
▪ USA	16	9.6 (7.2–12)	89.43		6.5 (4.6–7.1)	86.98		1.8 (1.1–2.6)	77.3	
▪ Non-USA	7	6.7 (3.8–9.5)	63.38		4.2 (1.8–6.5)	66.58		2.2 (1–3.3)	34.87	
Quality				0.20			0.51			0.06
▪ Low	13	8.6 (5.9–11.4)	78.19		5.5 (3.5–7.6)	75.08		2 (1–3)	69.88	
▪ Moderate	7	6.9 (3.7–10.1)	91.12		4.8 (2.3–7.2)	88.56		1.5 (0.6–2.4)	76.19	
▪ High	3	12.7 (7.2–18.3)	79.1		9 (2.2–15.7)	91.68		3.3 (2.1–4.5)	0	
Non-dysplastic BE included				0.85			0.57			0.02
▪ No	12	8.9 (6–11.8)	82.11		5.5 (3.4–7.5)	78.5		2.9 (1.7–4)	69.42	
▪ Yes	11	8.5 (5.7–11.3)	89.51		6.4 (4–8.7)	88.85		1.2 (0.5–1.9)	71.27	
Number of EGDs negative for IM and EN required to define CE				0.78			0.51			0.48
▪ 1	14	7.8 (5.9–9.7)	78.5		5.7 (3.8–7.5)	84.54		1.9 (1.2–2.5)	59.84	
▪ 2	3	9.2 (0–18.5)	95.37		5.1 (0.4–9.9)	90.24		3.3 (0–7.2)	88.57	
Cardia biopsied				0.61			0.48			0.67
▪ No	8	6.6 (3.7–9.5)	91.54		4.5 (2.4–6.6)	88.74		1.4 (0.5–2.2)	82.98	
▪ Yes	9	7.7 (4.8–10.6)	71.1		5.7 (3.1–8.3)	76.2		1.6 (1–2.3)	0	
Surveillance biopsy protocol, cm				0.08			0.04			0.99
▪ 1	8	5.5 (3.2–7.9)	89.53		3.5 (1.7–5.3)	87.51		1.4 (0.6–2.2)	80.72	
▪ >1	9	9.8 (5.6–14.1)	78.33		8.1 (4.1–12.1)	83.76		1.4 (0.7–2.1)	0	
BE length >3 cm				0.04			0.002			0.69
▪ No	3	17.4 (11–23.9)	48.66		14.5 (8.7–20.3)	45.37		2.4 (0–4.8)	68.89	
▪ Yes	20	7.6 (5.7–9.4)	84.47		4.9 (3.5–6.7)	82.16		1.9 (1.2–2.5)	72.03	

EGD = esophagogastroduodenoscopy, IM = intestinal metaplasia, EN = early neoplasia, CE = complete eradication, BE = Barrett's esophagus, PY = patient-years, RFA = radiofrequency ablation.

► **Table 6** Subgroup analyses on the incidence of recurrent IM and EN after SRER.

	No. of studies	Total recurrence [incidence per 100 PY (95%CI)]	I <sup>2</sup>	P value	IM recurrence [incidence per 100 PY (95% CI)]	I <sup>2</sup>	P value	EN recurrence [incidence per 100 PY (95% CI)]	I <sup>2</sup>	P value
Manuscript type				0.3			0.9			0.004
▪ Full text	12	5.2 (2.9–7.5)	72		3.3 (1.7–4.9)	55.85		1.3 (0.7–2)	2.23	
▪ Abstract	1	3.7 (1.9–5.4)	0		3.5 (1.8–5.2)	0		0.2 (0–0.6)	0	
Study outlook				0.22			0.45			0.95
▪ Prospective	3	2.9 (0–6.5)	61.95		1.2 (0–4.8)	0		1.1 (0–2.5)	0	
▪ Retrospective	10	5.5 (3.6–7.4)	52.96		3.5 (1.9–5)	58.81		1.2 (0.3–2)	47.09	
Study design				0.42			0.004			0.93
▪ Case series	11	4.2 (2.4–6.1)	60.3		2.6 (1.6–3.7)	19.27		1.3 (0.1–2.1)	42.83	
▪ Cohort	1	8.5 (5.7–11.2)	0		7.3 (4.8–9.9)	0		1.1 (0.1–2.1)	0	
▪ Randomized control	1	5.7 (0–12.2)	0		3.8 (0–9.1)	0		1.9 (0–5.6)	0	
Setting				0.67			0.25			0.13
▪ Multicenter	6	4.5 (1.7–7.3)	81.12		4.1 (2.1–6.1)	56.37		0.7 (0.1–1.3)	20.88	
▪ Single center	7	5.3 (2.7–8)	43.85		2.6 (0.9–4.2)	36.97		1.8 (0.4–3.2)	33.41	
Location				0.72			0.75			0.43
▪ USA	4	4.5 (1.7–7.3)	42.46		3 (1.3–4.8)	0		1.6 (0.2–3.1)	22.99	
▪ Non-USA	9	5.2 (2.7–7.7)	76.18		3.5 (1.5–5.4)	67.59		1 (0.2–1.8)	38.07	
Quality				0.042			0.004			0.93
▪ Low	11	4.2 (2.4–6.1)	60.28		2.6 (1.6–3.7)	19.27		1.3 (0.4–2.1)	42.83	
▪ Moderate	1	5.7 (0–12.2)	0		3.8 (0–4.9)	0		1.9 (0–5.6)	0	
▪ High	1	8.5 (5.7–11.2)	0		7.3 (4.8–9.9)	0		1.1 (0.1–2.1)	0	
Non-dysplastic BE included				0.26			0.31			0.07
▪ No	12	4.8 (2.8–6.7)	70.64		3.5 (2–4.9)	54.21		1.0 (0.4–1.7)	30.82	
▪ Yes	1	11.1 (0.2–22)	0		1.4 (0–5.2)	0		11.1 (0.2–22)	0	
Number of EGDs negative for IM and EN required to define CE				0.46			0.03			0.09
▪ 1	2	6.9 (3.7–11.1)	0		3.5 (1.2–5.7)	0		3.2 (1–5.4)	0	
▪ 2	1	8.5 (5.7–11.2)	0		7.3 (4.8–9.9)	0		1.1 (0.1–2.1)	0	
Cardia biopsied				0.68			0.37			0.66
▪ No	7	45 (1.7–8.3)	81.47		4.1 (1.5–6.7)	66.21		1.1 (0.4–1.8)	0	
▪ Yes	5	4.3 (2.9–5.7)	0		2.8 (1.5–4.1)	17.2		1.4 (0–2.97)	57.3	
Surveillance biopsy protocol, cm				0.76			0.75			0.98
▪ 1	2	2.3 (0–6.4)	70.66		2 (0–4.7)	0		1.3 (0–3)	36.26	
▪ >1	34	34 (0.4–5.6)	0		2.6 (0–4.7)	0		1.3 (0–3.4)	0	
BE length > 3 cm				0.51			0.46			0.87
BE length > 3 cm	4	3.9 (2.4–5.3)	0		2.3 (0.9–3.8)	26.55		1.2 (0–2.8)	38.7	
▪ No	8	5 (2–7.9)	69.98		3.1 (1.5–4.7)	10.57		1.4 (0.3–2.5)	26.09	
▪ Yes										

EGD = esophagogastroduodenoscopy, IM = intestinal metaplasia, EN = early neoplasia, CE = complete eradication, BE = Barrett's esophagus, PY = patient-years, SRER = stepwise complete endoscopic resection.

## Competing interests

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► Supplemental Table 1 Quality assessment of the full text randomized control trials and cohort studies.

	Fleischer 2010	Shah- een 2011	Vac- caro 2011	van Vij- steren 2011	Caillol 2012	Dulai 2013	Ertan 2013	Gupta 2013	Hai- dry 2013	Or- man 2013	Pasri- cha 2014	Strauss 2014	An- ders 2014	Agos- ton 2015	Cot- ton 2015	Lada 2014	Le Page 2016	Small 2015	
<b>REPORTING</b>																			
Hypothesis/aim	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Main outcomes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Characteristics of included patients	1	1	1	1	0	1	1	1	1	1	1	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
Distributions of principal confounders	0	0	2	0	0	0	0	2	0	2	2	0	2	0	1	0	0	2	2
Main findings	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Estimates of random variability	0	0	1	0	0	0	0	1	0	1	1	0	1	0	1	0	0	1	1
Important adverse effects	1	1	0	1	1	1	1	1	1	0	0	1	0	1	0	1	1	0	0
Characteristic of patients lost to follow-up	1	1	0	1	1	1	0	1	1	1	0	1	1	1	1	1	0	1	1
Actual probability values	0	0	1	0	0	0	0	1	0	1	1	0	1	0	1	0	0	1	1
<b>EXTERNAL VALIDITY</b>																			
Subjects asked to participate	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
Subjects prepared to participate	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
Staff, places, facilities	1	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
<b>INTERNAL VALIDITY – BIAS</b>																			
Blinding of subjects	0	0	0	0	0	0	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	0	0	0	0	0	0	0	0	0	0	0	0

► Supplemental Table 1 (Continuation)

	Fleischer 2010	Shah- een 2011	Vac- caro 2011	van Vil- steren 2011	Caillol 2012	Dulai 2013	Ertan 2013	Gupta 2013	Hai- dry 2013	Or- man 2013	Pasri- cha 2014	Strauss 2014	An- ders 2014	Agos- ton 2015	Cot- ton 2015	Lada 2014	Le Page 2016	Small 2015
Data dredging	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Adjustment for different follow-up time	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1
Statistical testing	0	0	1	0	0	0	0	1	0	1	1	0	1	0	1	0	0	1
Compliance to testing reliability	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Main outcomes accuracy	0	0	1	0	0	0	0	1	0	1	1	0	1	0	1	0	0	1
<b>INTERNAL VALIDITY – CONFOUNDING</b>																		
Different interventions	0	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	1
Recruitment over same time period	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0
Randomization	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Randomization concealment	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adequate adjustment for confounding	0	0	1	0	0	0	0	1	0	1	1	0	1	0	0	0	0	1
Losses to follow-up	1	1	1	1	1	0	0	0	0	1	0	0	1	1	1	1	1	1
<b>POWER</b>																		
Sufficient power	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
<b>TOTAL</b>	15	17	17	17	13	11	12	20	12	20	19	13	20	13	18	13	10	20