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Risk of recurrence of Barrett's esophagus after successful endoscopic therapy

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Abstract

Background and Aims—Previous estimates of incidence of intestinal metaplasia (IM) recurrence after achieving complete remission of IM (CRIM) through endoscopic therapy of Barrett's esophagus (BE) have varied widely. We performed a systematic review and meta-analysis of studies to estimate an accurate recurrence risk after CRIM.

Methods—We performed a systematic search of multiple literature databases through June 2015 to identify studies reporting long-term follow-up after achieving CRIM through endoscopic therapy. Pooled incidence rate (IR) of recurrent IM, dysplastic BE, and high-grade dysplasia (HGD)/esophageal adenocarcinoma (EAC) per person-year of follow-up after CRIM was estimated. Factors associated with recurrence were also assessed.

Results—We identified 41 studies that reported 795 cases of recurrence in 4443 patients over 10,427 patient-years of follow-up. This included 21 radiofrequency ablation studies that reported 603 cases of IM recurrence in 3186 patients over 5741 patient-years of follow-up. Pooled IRs of recurrent IM, dysplastic BE, and HGD/EAC after radiofrequency ablation were 9.5% (95% CI, 6.7-12.3), 2.0% (95% CI, 1.3-2.7), and 1.2% (95% CI, .8-1.6) per patient-year, respectively. When all endoscopic modalities were included, pooled IRs of recurrent IM, dysplastic BE, and HGD/EAC were 7.1% (95% CI, 5.6-8.6), 1.3% (95% CI, .8-1.7), and .8% (95% CI, .5-1.1) per patient-year, respectively. Substantial heterogeneity was noted. Increasing age and BE length were predictive of recurrence; 97% of recurrences were treated endoscopically.

Conclusions—The incidence of recurrence after achieving CRIM through endoscopic therapy was substantial. A small minority of recurrences were dysplastic BE and HGD/EAC. Hence, continued surveillance after CRIM is imperative. Additional studies with long-term follow-up are needed.

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Endoscopic therapy is currently the accepted first-line treatment modality for Barrett's esophagus (BE)-related dysplasia and mucosal adenocarcinoma.[1,2] Several endoscopic modalities are used in isolation or in combination for endoscopic therapy of BE, such as EMR, radiofrequency ablation (RFA), photodynamic therapy (PDT), cryotherapy, argon plasma coagulation (APC), multipolar electrocoagulation, and laser therapy.[3] Endoscopic therapy with EMR followed by PDT or RFA has been shown to be effective in reducing the risk of progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC).[4-6]

High rates of elimination of intestinal metaplasia (IM) and dysplasia have been shown in several reports from single and multicenter studies with short- and medium-term follow-up.[7,8] As the benefits of initial ablative therapy are well described, attention is now focused on the durability of response to endoscopic therapy, specifically recurrence rates of IM, dysplasia, and carcinoma. Studies have varied considerably in estimates of recurrence of IM after achieving successful ablation defined as complete remission of IM (CRIM). Although some studies have reported low rates of recurrence,[9-11] others have reported significantly higher rates of recurrence.[12] The wide variation between studies could be because of several factors, both implicit (patient characteristics such as age, smoking status, use of potentially chemopreventive medications after CRIM) and explicit (differences in study design, follow-up duration, and surveillance protocols after CRIM). Several potential predictors of recurrence have been assessed, but only in small studies with limited power to make conclusive observations.[13-15]

It is important to reliably estimate the recurrence risk after successfully achieving CRIM for several reasons. First, recurrent dysplastic BE (DBE) or carcinoma is important to detect, because it may require further endoscopic therapy or esophagectomy. Second, currently, there are no consensus/guidelines on duration of follow-up and frequency of surveillance endoscopies after successfully achieving CRIM, and accurate estimates of recurrence would be helpful in determining this. Finally, the cost-effectiveness of endoscopic therapy for BE will depend on durability of CRIM and need for additional therapy of recurrent BE.

We performed a systematic review and meta-analysis of all studies that reported long-term results after achieving CRIM in BE patients using endoscopic eradication therapy to estimate an accurate recurrence risk (for IM and dysplasia). Although some techniques like PDT and APC are not currently in use, we believed it was important to include them in this review given their pioneering role in demonstrating success with endoscopic therapy and because other than RFA, level 1 evidence supporting endoscopic therapy for BE is only available for PDT.[6] Also, outcomes with older modalities can serve as a useful comparator for current modalities. We also identified clinical factors associated with recurrence of IM after CRIM.

Methods

This systematic review was performed according to guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions.[16] It is reported according to the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] We followed a priori established protocol.

Search strategy

We conducted a systematic literature search of several databases from each database's inception to June 1, 2015 for relevant articles on recurrence of IM, dysplasia, or adenocarcinoma after endoscopic treatment of DBE and nondysplastic BE (NDBE). The databases included MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. The search was restricted to the studies on human participants published in English. The search was conducted by an experienced librarian with input from the study authors (R.K., S.S., and P.G.I.). The details of the search strategy and data sources are reported in Appendix 1 (available online at www.giejournal.org).

Selection criteria

We included studies that met the following inclusion criteria: (1) reported recurrence of IM, dysplasia, and/or EAC in BE subjects (dysplastic and nondysplastic) who achieved CRIM using any endoscopic therapy and (2) reported follow-up period since CRIM in "patient-years" or reported mean/median follow-up period after CRIM and number of patients in surveillance, thereby permitting calculation of follow-up period since CRIM in "patient-years." Recurrence was defined as the presence of IM in the esophagus and/or gastroesophageal junction (GEJ) after achieving CRIM. CRIM was defined by individual studies as biopsy samples being negative for IM on a single or 2 successive endoscopies. [12,18-20] We included all endoscopic therapeutic modalities. We excluded studies that used >1 endoscopic ablation modality, studies with mean/median follow-up <1 year after CRIM was achieved, studies with <20 subjects who achieved CRIM, studies that reported recurrence after complete remission of dysplasia instead of CRIM, studies with subjects who had previously failed endoscopic therapy, and case-control studies, letters to the editor, editorials, and review articles. Studies using a combination of 1 endoscopic ablative modality with EMR were included. When multiple publications from the same population were identified, only data from the most recent comprehensive report were included. Two of the included studies had 2 arms, 1 comparing outcomes with different endoscopic modality[21] and 1 comparing outcomes in long- versus ultralongsegment BE.[22] For the purpose of the review, each arm was counted as a separate study.

Data abstraction and quality assessment

After identifying relevant studies, data on study characteristics, patient characteristics, treatment characteristics, study outcomes, and risk factors for recurrence were abstracted onto a standardized form by 2 authors (R.K., K.R.). Details of data abstraction are reported in Appendix 2 (available online at www.giejournal.org).

The quality of the individual studies was independently assessed by 2 authors (RK, KR) using a scale modified from the Newcastle-Ottawa scale for cohort studies.[23] This quality score consisted of 10 questions. The details of the quality scale are reported in Appendix 3

(available online at www.giejournal.org). A score of ≥7, 4 to 6.5, and <4 was considered suggestive of a high-, medium-, and low-quality study, respectively.

Outcomes assessed

The primary outcome of the review was to assess the annual incidence rate (IR) of IM recurrence after achieving CRIM using RFA given that it is the most commonly used endoscopic modality in current practice. Secondary outcomes measured included annual IR of IM recurrence after use of all endoscopic modalities and IR of recurrent DBE and HGD/EAC.

We performed preplanned subgroup analysis based on primary endoscopic modality (eg, RFA, PDT, APC), study location (eg, North America, Europe), baseline dysplasia status in pretreatment histology (NDBE vs DBE ± early neoplasia), type of publication (abstract vs full article), post-CRIM surveillance biopsy sampling protocol (inclusion vs exclusion of GEJ in surveillance biopsy specimen), and study quality (high, medium, low). In addition, we identified risk factors associated with recurrence (demographic factors such as age and sex and clinical factors such as BE length and baseline dysplasia).

Statistical analysis

For each included study we calculated the IR of recurrence based on the total number of subjects who had IM recurrence and the total follow-up duration after CRIM (either reported as person-years by study authors or estimated from mean/median follow-up of the study). Using the random-effects model described by DerSimonian and Laird,[24] we calculated the pooled IR of recurrence per person-year and 95% confidence intervals (CIs).

We assessed heterogeneity between study-specific estimates using inconsistency index (I^2 statistic), which estimates the proportion of total variances across studies because of heterogeneity rather than by chance. Values of <30%, 30% to 59%, 60% to 75%, and >75% were considered suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[25] Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics (as described earlier). In this analysis, a *P* value for differences between subgroups of <.10 was considered statistically significant, meaning that stratifying based on those subgroups can potentially explain heterogeneity observed in the overall analysis. We assessed for publication bias qualitatively by visual inspection of funnel plot and quantitatively using Egger's regression test.[26] Statistical analysis for identifying predictors of recurrence is detailed in Appendix 4 (available online at www.giejournal.org). All calculations and graphs were performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

Results

From a total 1699 studies identified by our search strategy, 41 studies were included in the meta-analysis.[7,9,12-15,18-22,27-54] Five studies[4,10,11,55,56] were excluded because they had overlapping populations with already-included studies. Two studies with post-CRIM follow-up <1 year[57,58] and 8 studies with <20 patients reaching CRIM[59-66] were excluded.

Together, the 41 studies reported a total of 795 cases of IM recurrence after CRIM in 4443 patients over 10,427 patient-years of follow-up. This included 21 RFA studies that reported 603 cases of IM recurrence in 3186 patients over 5741 patient-years of follow-up.[9,12,14,15,18,21,22,27,29,30,32,39-41,43,47,49,51,53,54] Figure 1 shows the schematic diagram of study selection.

Characteristics of included studies

Table 1 describes the characteristics of the included studies. Fourteen of the 41 included studies were multicenter studies.[12,21,29,34,39,41,44,47,49-51,53,54] Mean patient age at endoscopic therapy was 61.4 years, and 78.9% were men. The median of average follow-up after CRIM was 2.5 years, ranging from 1 year to 10.5 years in individual studies. Among the 41 included studies, the primary endoscopic treatment modality was RFA in 21 studies,[9,12,14,15,18,21,22,27,29,30,32,39-41,43,47,49,51,53,54] APC in 7 studies,[33,34,36,45,46,48,52] EMR in 7 studies,[20,21,31,37,42,44,50] PDT in 2 studies,[7,19] multipolar electrocoagulation in 2 studies,[13,28] laser in 1 study,[35] and cryotherapy in 1 study.[38] Twenty-three studies were from North America,[9,12,14,15,18-20,22,27,30,32,35,37-39,41-44,47,53,54] 15 studies were from Europe,[7,13,21,31,33,34,40,45,46,48-52] and 1 study each was from South America,[28] Africa,[36] and the Asia-Pacific.[29] Four studies included NDBE patients only,[13,28,34,52] and 16 studies included only DBE ± early neoplasia patients,[7,19-21,29,31,37,39,40,42,44,49,51,53,54] with the remainder including NDBE and DBE patients.

Quality of included studies

Table 2 summarizes the quality of the included studies. Among the RFA studies, 7 studies were deemed high quality,[9,12,18,32,39,49,54] 11 studies were deemed medium quality[14,21,22,29,40,41,43,47,51,53] and 3 studies were deemed low quality.[15,27,30] When all endoscopic modalities were included, 9 studies were deemed high quality,[9,12,18,32,37,39,42,49,54] 22 studies were deemed medium quality,[7,13,14,19-22,28,29,31,34,35,40,41,43,44,47,50,51,53] and 10 studies were deemed low quality.[15,27,30,33,36,38,45,46,48,52]

Recurrence of IM: RFA studies

On meta-analysis of 21 RFA studies (603 cases of recurrence in 3186 patients over 5741 patient-years of follow-up), the pooled incidence of IM recurrence (with or without dysplasia/EAC) was 9.5% per patient-year (95% CI, 6.7-12.3), with rates in individual studies ranging from .9% to 28.8% (Fig. 2A). Substantial heterogeneity (I^2 = 90%) was seen in the analysis. On meta-analysis of the 15 RFA studies that reported histology of recurrent IM,[9,12,14,15,18,22,29,30,32,39,43,47,49,54] the pooled incidence of DBE was 2.0% per patient-year (95% CI, 1.3-2.7) (Fig. 2B) and of HGD/EAC was 1.2% per patient-year (95% CI, . 8-1.6) (Fig. 2C). Only 4.6% of patients with recurrence needed surgical treatment in 11 studies where data were available, whereas the rest were treated endoscopically.[9,12,14,18,22,29,30,39,49,53]

Subgroup analysis: RFA studies

Several subgroup analyses were performed to explore reasons for heterogeneity (Table 3). Recurrence rates in the RFA + EMR studies (19 studies, IR, 9.2% per patient-year) were numerically lower than RFA alone studies (2 studies, IR, 14.3% per patient-year) without statistical significance ($P = .46$). Recurrence rates in European RFA studies (4 studies, IR, 7.5% per patient-year) and North American RFA studies (16 studies, IR, 10.0% per patient-year) were statistically similar ($P = .67$).

Recurrence rates were statistically similar between subgroups based on type of publication (abstract vs full article), post-CRIM surveillance biopsy sampling protocol (inclusion vs exclusion of GEJ in surveillance biopsy sample), and study quality (high, medium, low). Subgroup analysis based on baseline dysplasia status was not performed in RFA studies because none of the included RFA studies had a study population of only NDBE subjects. However, on restricting analysis to the 7 RFA studies [21,29,39,40,51,53,54] that had an exclusive study population of DBE ± early neoplasia subjects, pooled IRs of recurrent IM, DBE, and HGD/EAC recurrence rates were 10.3% (95% CI, 5.7-15.0), 6.0% (95% CI, .5-11.6), and 4.1% (95% CI, .0-8.5) per patient-year, respectively. These recurrence rates were statistically similar to the overall recurrence rates in RFA studies.

Recurrence of IM: all endoscopic modalities

On meta-analysis of 41 studies (795 cases of IM recurrence over 10,427 patient-years of follow-up), the pooled incidence of IM recurrence (with or without dysplasia/EAC) was 7.1% per patient-year (95% CI, 5.6-8.6), with rates in individual studies ranging from .07% to 28.8% (Fig. 3A). Substantial heterogeneity ($I^2 = 93\%$) was seen in the analysis. On meta-analysis of the 28 studies that reported histology of recurrence,[7,9,12-15,18,22,28-32,34,35,37,39,42-50,54] the pooled incidence of DBE was 1.3% per patient-year (95% CI, .8-1.7) (Fig. 3B) and of HGD/EAC was .8% per patient-year (95% CI, .5-1.1) (Fig. 3C). Only 3.4% of recurrences needed surgical treatment in 20 studies where data were available, whereas the rest were treated endoscopically.[7,9,12-14,18,22,28-31,33,35,37,39,46,48,49,53] In the 17 studies that reported if recurrences where endoscopically visible,[9,13,21,28,31-35,37,43-45,49-51] only 58% of recurrences were endoscopically visible. The remaining 42% of recurrences were noted in biopsy specimens from normal-appearing mucosa. In the 17 studies that reported location of recurrence,[12-14,18,21,22,31-34,37,38,43,44,50,51] 43% of recurrences occurred in tubular esophagus, 55% of recurrences occurred in the GEJ, and 2% occurred in tubular esophagus and GEJ.

Subgroup analysis: all endoscopic modalities

Table 4 describes the subgroup analysis of studies including all endoscopic modalities. Considerable differences were observed in the risk of recurrence based on primary endoscopic eradication modality, with RFA studies reporting higher rates of recurrence than APC studies. The IM recurrence rates associated with 2 commonly used modalities, RFA (21 studies, IR, 9.5% per patient-year) and EMR (7 studies, IR, 6.3% per patient-year), were statistically similar ($P = .16$). The recurrence rate in studies using current modalities (ie, RFA, EMR, and cryotherapy) was significantly higher than studies using historical

modalities (ie, PDT, APC, multipolar electrocoagulation, and laser): 9.2%, 29 studies vs 3.8%, 12 studies ($P < .01$).

Recurrence rates in European studies (15 studies, IR, 4.6% per patient-year) were lower than North American studies (23 studies, IR, 9.5% per patient-year) ($P < .01$). Recurrence rates in studies with NDBE patients (4 studies; IR, 2.2% per patient-year) were lower than studies with DBE patients (16 studies, IR, 8.8% per patient-year) ($P < .01$).

The recurrence rates observed in high-quality studies (9 studies, IR 7.5% per patient-year) were statistically similar to recurrence rates in medium-quality studies (22 studies, IR 9.1% per patient-year) ($P = .66$) but were higher than recurrence rates in low-quality studies (10 studies, IR 2.5% per patient-year) ($P < .01$). Recurrence rates were statistically similar between subgroups based on type of publication (abstract vs full article) and post-CRIM surveillance biopsy sampling protocol (inclusion vs exclusion of GEJ in surveillance biopsy).

Additional subgroup analysis based on definition of CRIM (negative biopsy samples from single endoscopy versus 2 successive endoscopies), inclusion of cardia in surveillance biopsy samples (inclusion vs exclusion of cardia), and the biopsy sampling protocol (4-quadrant biopsy samples every 1 to 2 cm vs biopsy samples from GEJ and visible lesions) did not reveal a statistically significant difference in recurrence rates. However, the analysis was limited by the fact that only 4 studies used the latter definition of CRIM,[12,18-20] 2 studies reported biopsy sampling cardia,[32,42] and 3 studies used the latter biopsy sampling protocol.[13,14,37]

Publication bias

Based on visual inspection of the funnel plot (Fig. 4) as well as quantitative measurement using Egger's test, there was evidence of publication bias ($P < .01$). Given considerable heterogeneity observed in the analysis, the assessment of publication bias should be interpreted with caution.

Predictors of recurrence

Only 10 studies reported predictors of recurrence.[9,12-15,27,34,39,47,54] Increasing age (4 studies, odds ratio, 1.02; 95% CI, 1.01-1.03) and BE length (4 studies, odds ratio, 1.10; 95% CI, 1.05-1.15) were predictive of recurrence (Table 5). Male sex (5 studies, odds ratio, 1.12; 95% CI, .85-1.47) and baseline dysplasia grade (4 studies, odds ratio, 1.03, 95% CI, .63-1.70) were not statistically significant predictors. However, these estimates are limited by the small number of studies providing relevant data.

Discussion

Endoscopic therapy is an established treatment for BE-related dysplasia and mucosal adenocarcinoma. Systematic reviews have reported a high efficacy and low adverse event rate with endoscopic therapy.[8,67] However, currently, there is no reliable estimate of recurrence risk after successfully achieving CRIM. In this systematic review and meta-analysis of 21 RFA studies, the estimated annual incidence of IM recurrence after CRIM

was considerable at 9.5%. Annual recurrence rates of DBE and HGD/EAC (in the 15 RFA studies that reported histology of recurrence) were 2.0 % and 1.2%, respectively. When “all” endoscopic modalities were included in the meta-analysis (41 studies), the estimated annual incidence of recurrent IM was also considerable at 7.1%. Annual recurrence rates of DBE and HGD/EAC (in the 28 studies that reported histology of recurrence) were 1.3% and 0.8%, respectively. Most recurrences (97%) were amenable to endoscopic therapy without the need for esophagectomy.

Several GI society guidelines recommend endoscopic therapy as a treatment for BE with HGD and early EAC. Two recent studies supported consideration of endoscopic therapy for BE with low-grade dysplasia as well.[5,68] Hence, the use of endoscopic therapy for treatment of BE is expected to increase in the near future. This makes the type of data in the current study attempting to reliably assess the long-term durability of CRIM essential for physicians and patients in weighing the benefits and risks of ablative therapy. To our knowledge, Orman et al's[8] systematic review on durability of CRIM is the only other study that addressed this question. This review was restricted to RFA studies, and the meta-analysis included a total of 5 studies on durability. The current review was not restricted to a single endoscopic modality and included a total of 41 studies with 21 detailing results after RFA. Although the value of including historical modalities is questioned, we believed it to be important because level 1 evidence supporting endoscopic therapy for BE is available only for PDT other than RFA.[6] Additionally, older modalities such as PDT provided crucial information on the comparability of outcomes in subjects treated endoscopically and surgically. The inclusion of multiple endoscopic modalities also allowed us to compare the relative long-term durability of CRIM across different endoscopic modalities. The previously published systematic review estimated the proportion of patients with recurrent IM after successful RFA therapy and did not calculate the incidence of recurrence per patient-year of follow-up. In the current review we chose “incidence of recurrence per patient-year” over “proportion of patients who recurred” because the latter is more susceptible to variation depending of follow-up duration.

Another highlight of the review is the use of strict inclusion and exclusion criteria that we developed a priori. To be included, the studies had to report details that allowed calculation of follow-up patient-years with CRIM as the starting point. Studies with follow-up duration < 1 year were excluded because our objective was to assess long-term durability. We also developed a detailed quality scoring scale with 10 different variables to identify high-quality studies.

Recurrence risk after endoscopic therapy

Focusing on the currently used modalities, the recurrence rate with RFA + EMR (9.2%) was numerically lower than RFA alone (14.3%) but without statistical significance. The recurrence rates in RFA studies (9.5%) were numerically higher but statistically similar to studies using EMR only (6.3%). The recurrence rates were higher in RFA studies (9.5%) compared with APC studies (2.9%). Both RFA and APC are thermal ablation techniques. No randomized control trials have directly compared the treatment outcomes with RFA and

APC. In current practice, RFA is preferred over APC for BE treatment for the ease of ablating longer segments and stronger level 1 evidence of efficacy and safety.

In subgroup analyses of RFA studies, there were no differences in recurrence rates based on study location or study quality. Unlike the RFA studies, the subgroup analysis of “all” modalities revealed significant differences in recurrence rates based on study location and study quality. The lower recurrence rates in European studies compared with North American studies (4.6% vs 9.5%, $P < .01$) may be explained by the fact that 6 of the 7 APC studies included in the review were from Europe and none was from North America. Similarly, the lower recurrence rates in low-quality studies compared with high-quality studies (2.5% vs 7.5%, $P < .01$) and historical modalities' studies compared with current modalities' studies (3.8% vs 9.2%, $P < .01$) may be explained by the fact that 6 of the 10 low-quality and 7 of the 12 historical modalities' studies were APC studies.

None of the RFA studies included in the review had an exclusive study population of NDBE patients, which limited our ability to analyze the impact of baseline dysplasia status on recurrence after successful RFA therapy. However, subgroup analysis of “all” modalities revealed lower recurrence rates in studies with NDBE patients than studies with DBE patients (1.7% vs 7.6%, $P < .01$). Currently, there is debate on whether the presence of dysplasia in pretreatment histology influences recurrence risk after achieving CRIM. Several studies have investigated the association between baseline dysplasia and recurrence risk without conclusive results.[9,12,27,47,54] Our results provide indirect evidence to support the hypothesis that recurrence rates may be higher in those with DBE at baseline.

Predictors of recurrence

Increasing age and BE length were found to predict recurrence. A longer preablation BE segment likely reflects a higher biologic propensity to redevelop BE, likely through more severe gastroesophageal reflux and other mechanisms such as genetic predisposition or risk factors such as obesity. Our estimates of association need to be interpreted with caution, because several studies that reported nonsignificant associations did not report the actual hazard/odds ratio, leading to their exclusion. It is interesting to note that in our analysis of predictors of recurrence, baseline dysplasia status was not significantly associated with risk of recurrence of IM, but this was reported only in 4 studies[12,27,47,54] and is likely related to reporting bias in individual studies.

Limitations

The current systematic review has several potential limitations. Substantial heterogeneity was noted in assessment of recurrence risk with all endoscopic modalities. At a conceptual level, heterogeneity could be because of various factors, both implicit (patient characteristics such as age, smoking status, use of potentially chemopreventive medications after CRIM, etc) and explicit (differences in study design, follow-up duration, and biopsy sampling protocols after CRIM). We tried to minimize conceptual heterogeneity by using strict inclusion and exclusion criteria in study design. We also performed preplanned subgroup analyses to assess stability of association and explore sources of heterogeneity and observed that heterogeneity could be partially explained based on modality of endoscopic therapy,

study location, baseline dysplasia status, and study quality. Regardless, the presence of considerable heterogeneity for most of the analyses does decrease the confidence in a single summary estimate of recurrence risk and decreases the rating of overall quality of evidence. Second, we found evidence of publication bias, but it should be interpreted with caution given the high heterogeneity. Third, most of the included studies did not directly report follow-up periods as patient-years, and hence it was imputed. However, there was no statistically significant difference in recurrence rates between RFA studies that reported follow-up in patient-years and studies in which it was imputed (7.2% [4 studies] vs 10.2% [17 studies], $P = .39$) (Appendix 5, available online at www.giejournal.org). The same was true for studies of "all" endoscopic modalities (6.9% [5 studies] vs 6.7% [36 studies], $P = .89$). Finally, in our attempt to quantify risk factors associated with recurrence of IM, there was significant concern for selective reporting bias with only a few studies consistently reporting on plausible factors.

Conclusions

The incidence of recurrence after achieving CRIM through endoscopic therapy was substantial. Although only a small proportion of recurrences were dysplastic, HGD, or EAC, the risk was not negligible. Increasing age and BE length might have a role in predicting recurrence. Based on current results, it is imperative that patients who successfully achieved CRIM should continue to stay on lifelong surveillance. Reassuringly, most recurrences could be treated endoscopically without need for esophagectomy. Further prospective studies with standardized protocols and long-term follow-up are needed to accurately estimate the recurrence risk after BE endotherapy.

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Appendix 1. Summary of search strategy

A systematic literature search of several databases from each database's inception to June 1, 2015 for relevant articles on recurrence of IM, dysplasia, or adenocarcinoma after endoscopic treatment of DBE and NDBE was conducted. The databases included MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. The search was restricted to the studies on human participants published in English. The search was conducted by an experienced librarian with input from the study authors (RK, SS, PGI). The search was performed using a combination of keywords and medical subject heading terms, including "Barrett's (o)esophagus," "dysplasia,""low-grade dysplasia," "high-grade dysplasia," "intramucosal carcinoma," AND "endoscopic therapy," "endoscopic resection," "endoscopic mucosal resection," "ablation," "photodynamic therapy," "radiofrequency ablation," "cryotherapy," "laser," "Nd-YAG," "KTP," "multipolar electrocoagulation," and "argon plasma coagulation." Two authors (RK, KR) independently reviewed the title and abstract of the identified studies to exclude studies that were not pertinent to the research question, based on prespecified inclusion and exclusion criteria (see below). The full text of the

remaining articles was examined to determine if they were relevant to the research question. Any discrepancy in article selection was resolved by consensus and in discussion with an additional coauthor (PGI). Next, a manual search of bibliographies of the selected articles and review articles on the topic was performed for additional articles. Finally, we manually searched conference proceedings from major gastroenterology meetings for additional abstracts on the topic. In case of missing information, we attempted to contact the study authors with specific questions regarding their studies.

Appendix 2. Summary of data abstraction

After identifying relevant studies, data on study characteristics (design, location, number of centers, enrollment time, number of patients undergoing endoscopic therapy, reaching CRIM, and in surveillance after CRIM), patient characteristics (age, sex, race, smoking status, body mass index, proton pump inhibitor use, presence of baseline dysplasia, and BE segment length), treatment characteristics (type of endoscopic modality, number of endoscopic modalities [endoscopic ablation alone vs endoscopic ablation + EMR], and definition of CRIM), outcome assessment (number of patients who recurred after achieving CRIM, post-CRIM follow-up duration, histologic grade of recurrent BE, and treatment [endoscopic vs surgical] of recurrence), covariates (post-CRIM surveillance intervals, inclusion of gastric cardia in surveillance biopsy sampling protocol, and availability of expert GI pathologist), and risk factors for recurrence (all reported associations from univariate/multivariate analysis, regardless of statistical significance) were abstracted onto a standardized form by 2 authors (RK, KR).

Appendix 3. Study Quality Assessment Scale

1. Representative of the average BE subject in the community	
1 point	Multicenter study
0 points	Single center
2. Large cohort size	
1 point	Cohort size > 100 patients
.5 points	Cohort size between 50 and 100 patients
0 points	Cohort size < 50 patients
3. Definite histologic confirmation of recurrent BE	
1 point	Histology reviewed by GI pathologist
0 points	Histology reviewed only by community pathologist/not reported
4. Adequate follow-up of cohort after CRIM for the outcome to occur	
1 point	Mean follow-up of entire cohort > 5 years
.5 points	Mean follow-up 3-5 years
0 points	Mean follow-up of cohort 1-3 years
5. Reporting of duration of follow-up of patients after CRIM	

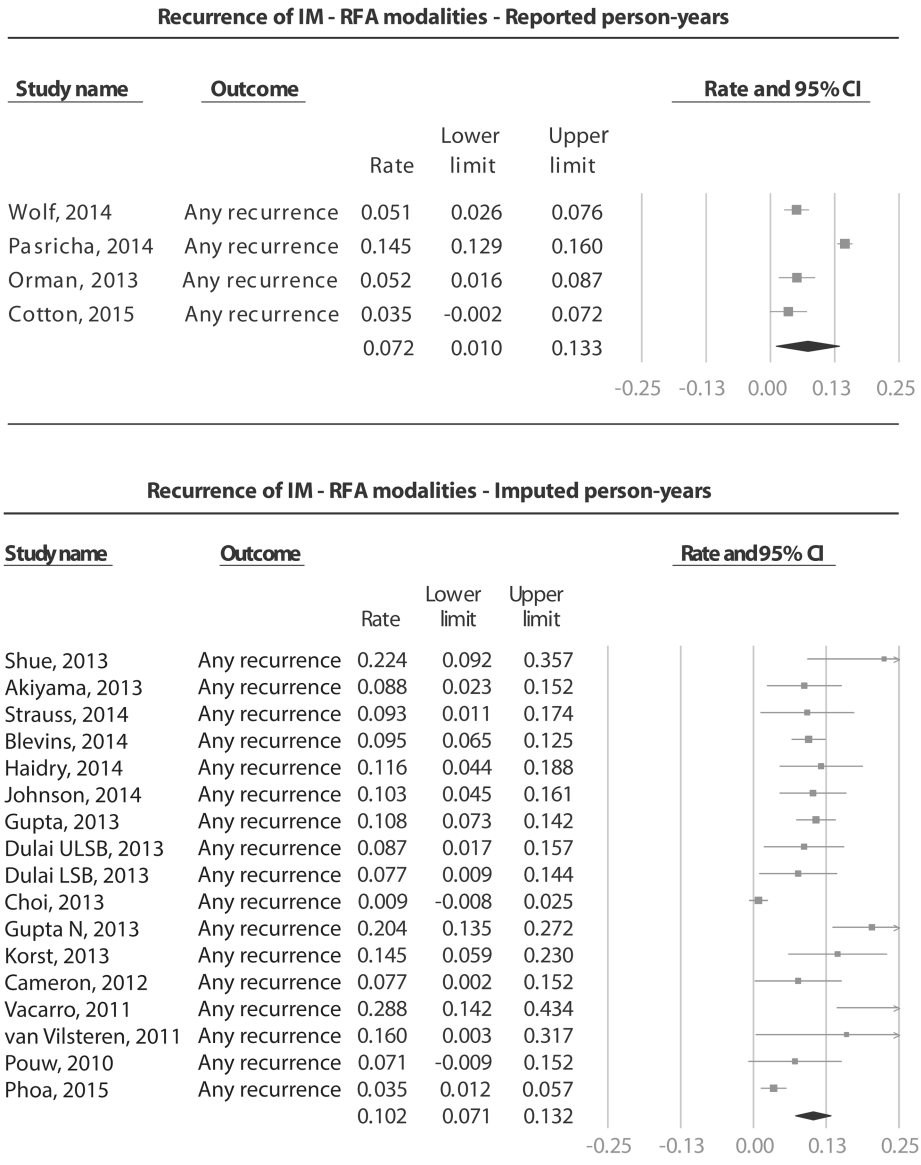
1 point	Reported in study in total person-years after CRIM
.5 points	Reported as mean follow-up years after CRIM
0 points	Reported as median follow-up years after CRIM
6. Attrition rate in follow-up after CRIM	
1 point	80% of cohort followed-up
.5 points	60%-80% of cohort followed-up
0 points	60% of cohort followed-up
7. Definition of CRIM	
1 point	≥2 endoscopies with biopsy specimen showing CRIM
.5 points	1 endoscopy with biopsy specimen showing CRIM
0 points	Not reported
8. Inclusion of biopsy sample from GEJ as part of surveillance protocol	
1 point	Biopsy specimens were obtained from GEJ and esophagus
.5 points	Biopsy specimens were obtained from esophagus only
0 points	Not reported
9. EMR done before ablation in dysplastic subjects	
1 point	EMR was done before ablation
0 points	EMR was not done before ablation
10. Reporting histology of recurrent BE	
1 point	Histology of recurrent BE was reported
0 points	Histology recurrent BE was not reported

BE, Barrett's esophagus; *CRIM*, complete remission of intestinal metaplasia; *GEJ*, gastroesophageal junction; *EMR*, endoscopic mucosal resection.

Appendix 4. Statistical analysis: meta-analysis of predictors of recurrence

To identify risk factors associated with recurrence of IM, we performed a meta-analysis of reported demographic and clinical factors associated with recurrent IM, if reported in ≥2 studies. We preferentially used adjusted estimates for the pooled analysis; however, if adjusted estimates were not reported, we used results from univariate analysis pooling. When studies reported exposure grouped into categories (such as for body mass, BE length, etc.) to provide a dose-specific odds ratio (using the lowest category as referent category), we transformed this into a risk estimate per unit exposure (for example, per unit body massindex, per cm of BE length, etc.), using linear trend meta-analytic statistical methodology. Briefly, we assigned the midpoint of the cut-points of the class as the dose value. For studies with open-ended categories, we used the lowest and highest reported exposure category from the study to calculate the midpoint. We then calculated the odds ratio for that range of exposure category (subtracting the midpoints from the highest risk category with the lowest-risk category) to estimate a per-unit odds ratio, after log-transformation. This methodology assumes a linear relationship between exposure and logarithm of the odds ratio.

Appendix 5



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Abbreviations

APC	argon plasma coagulation
BE	Barrett's esophagus
CRIM	complete remission of intestinal metaplasia
DBE	dysplastic Barrett's esophagus
EAC	esophageal adenocarcinoma
GEJ	gastroesophageal junction
HGD	high-grade dysplasia
IM	intestinal metaplasia
IR	incidence rate
NDBE	nondysplastic Barrett's esophagus
PDT	photodynamic therapy
RFA	radiofrequency ablation

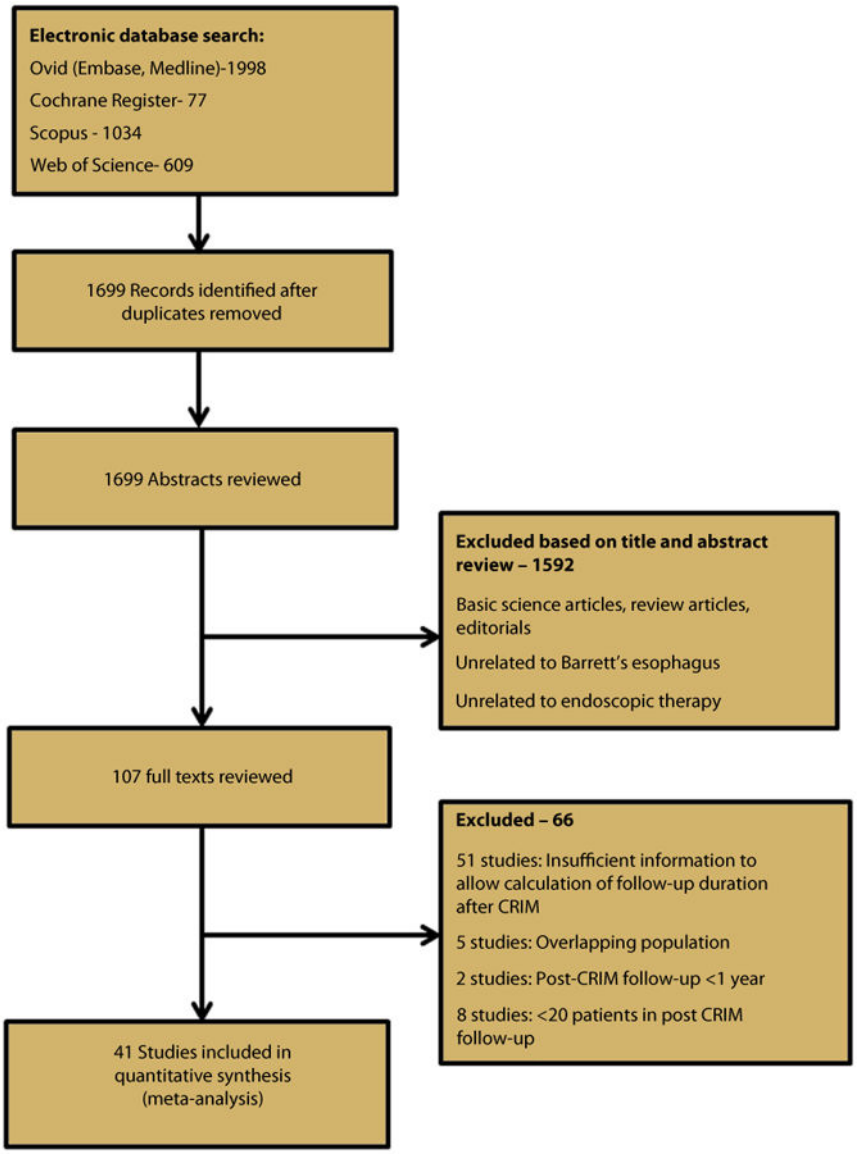

Figure 1.
Flow sheet summarizing study identification and selection.

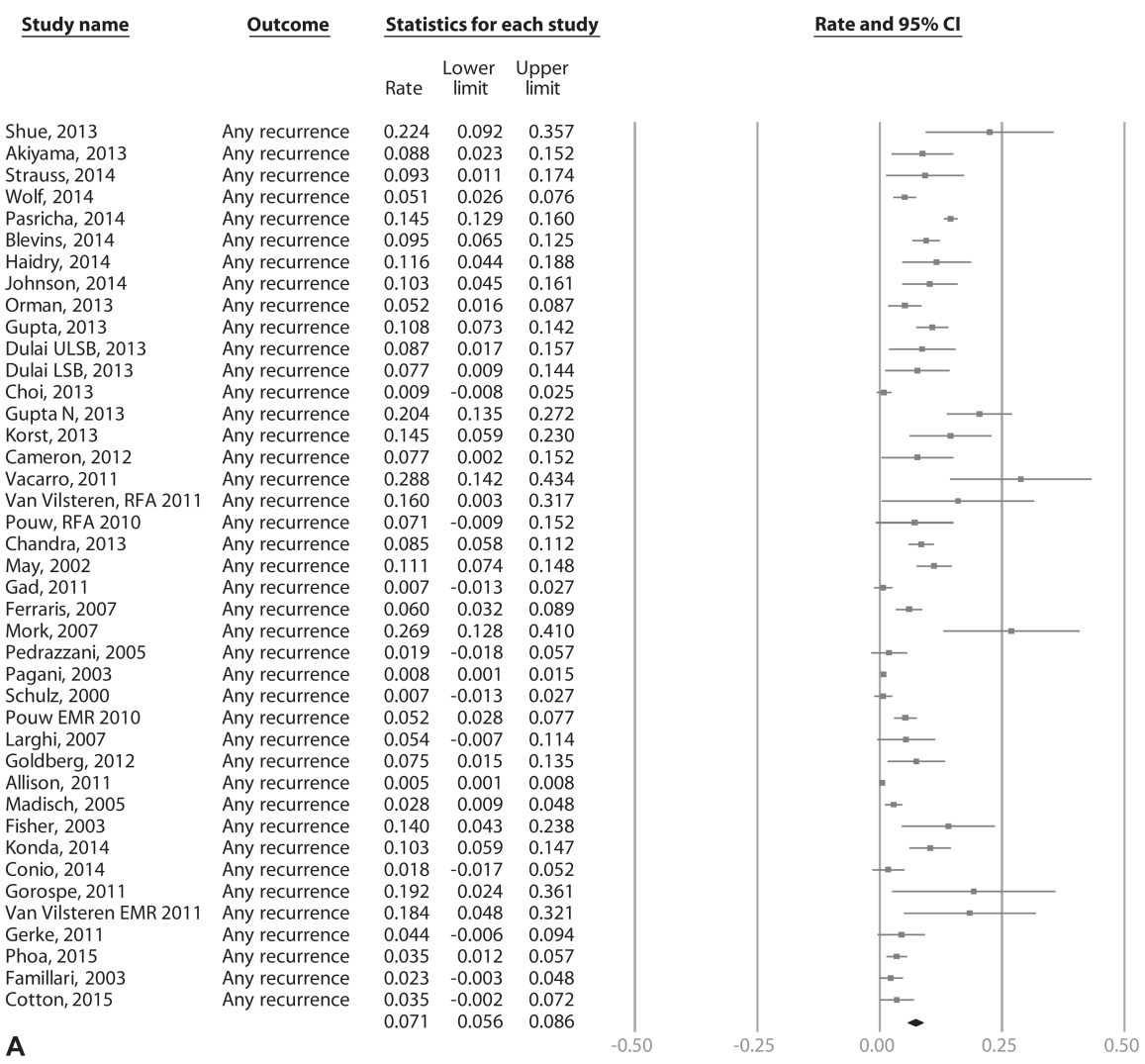

Figure 3a

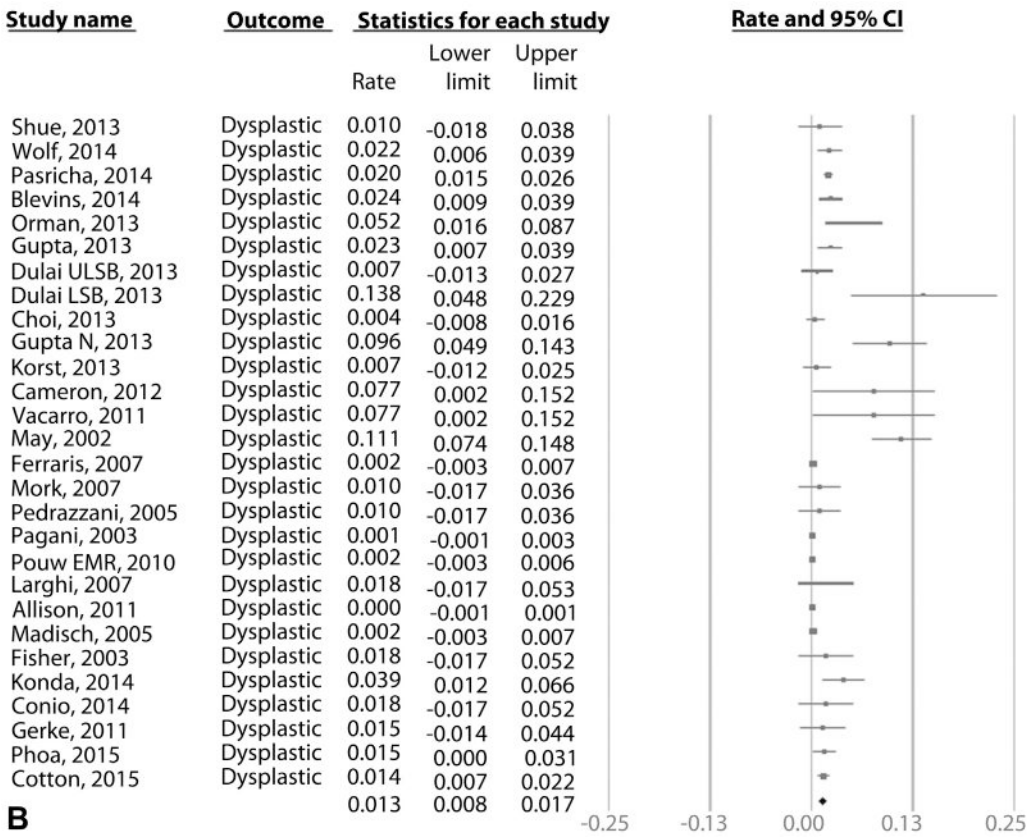

Figure 3b

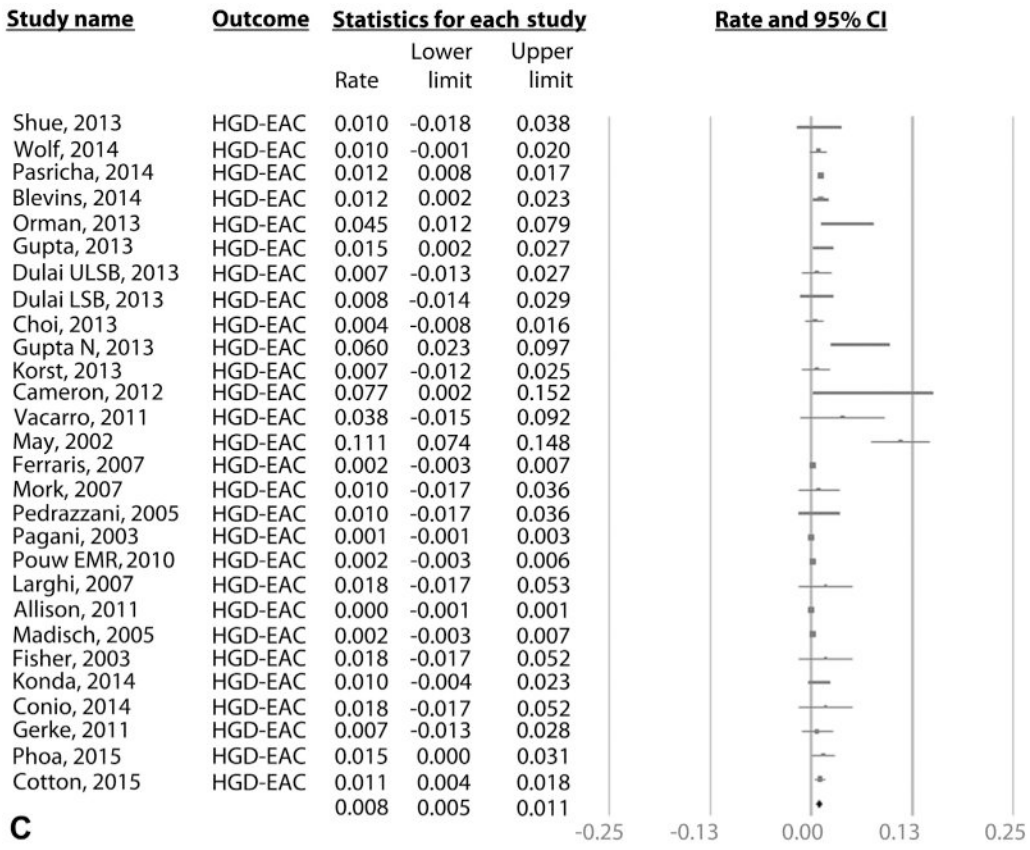

Figure 3c

Figure 2.

A, Incidence of recurrent IM after achieving CRIM using any endoscopic modality in patients with BE. **B**, Incidence of recurrent DBE after achieving CRIM using any endoscopic modality in patients with BE. **C**, Incidence of recurrent HGD/EAC after achieving CRIM using any endoscopic modality in patients with BE. *IM*, intestinal metaplasia; *CRIM*, complete remission of intestinal metaplasia; *BE*, Barrett's esophagus; *HGD/EAC*, high-grade dysplasia/esophageal adenocarcinoma.

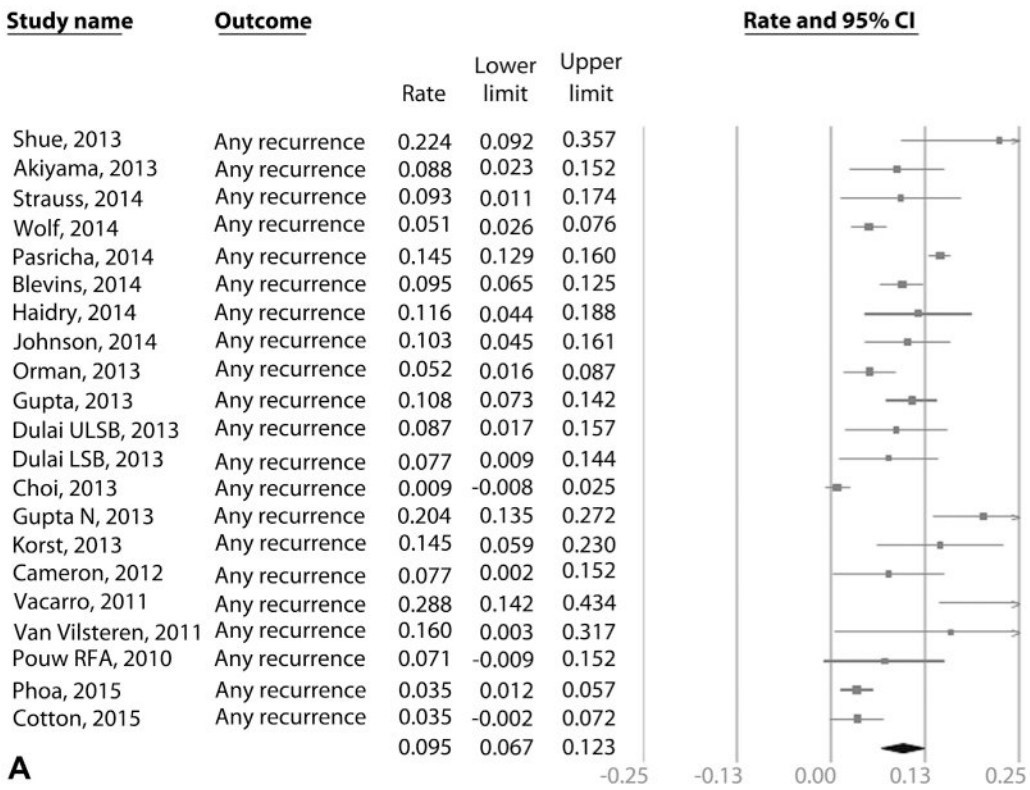

Figure 4a

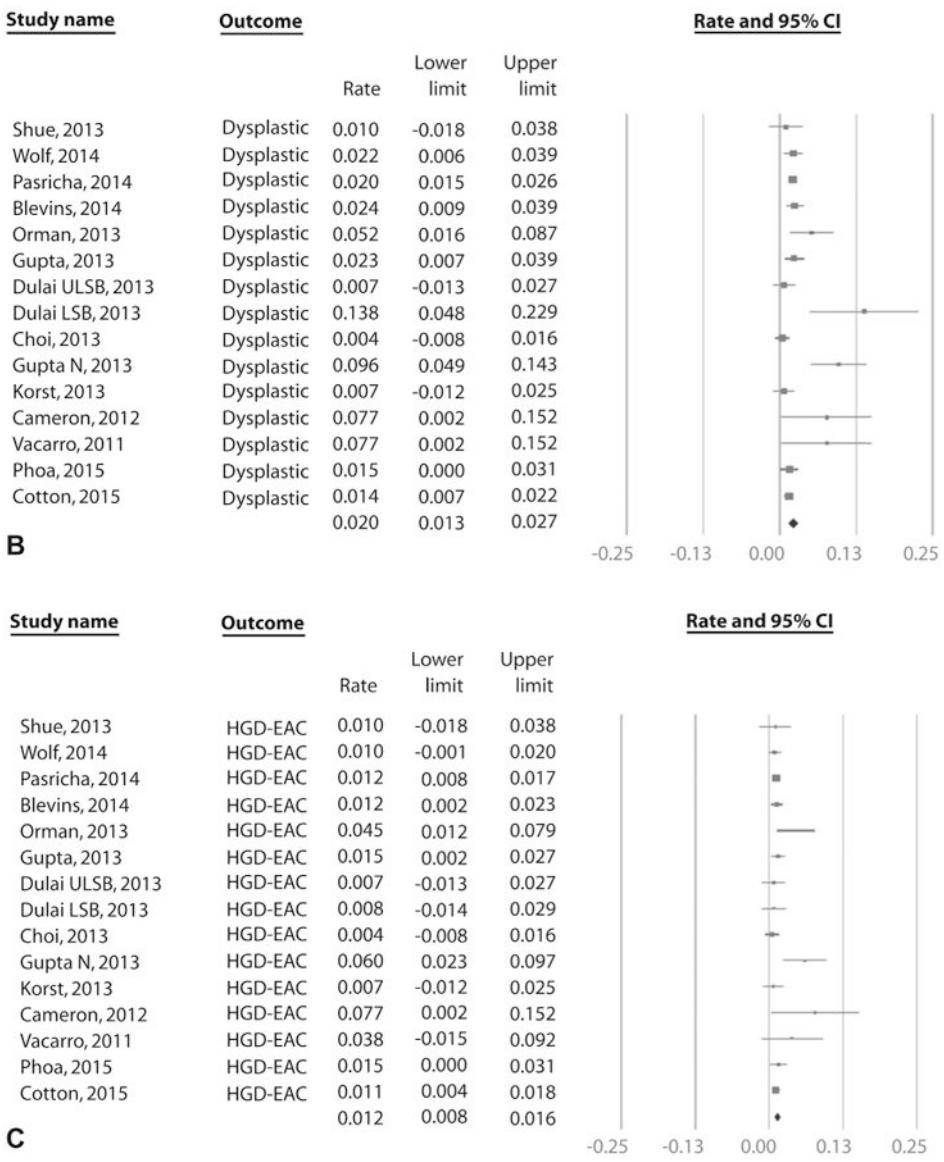

Figure 4b

Figure 3.

A, Incidence of recurrent IM after achieving CRIM using RFA in patients with BE. **B**, Incidence of recurrent DBE after achieving CRIM using RFA in patients with BE. **C**, Incidence of recurrent HGD/EAC after achieving CRIM using RFA in patients with BE. *IM*, intestinal metaplasia; *CRIM*, complete remission of intestinal metaplasia; *RFA*, radiofrequency ablation; Barrett's esophagus; *DBE*, dysplastic Barrett's esophagus; *HGD/EAC*, high-grade dysplasia/esophageal adenocarcinoma.

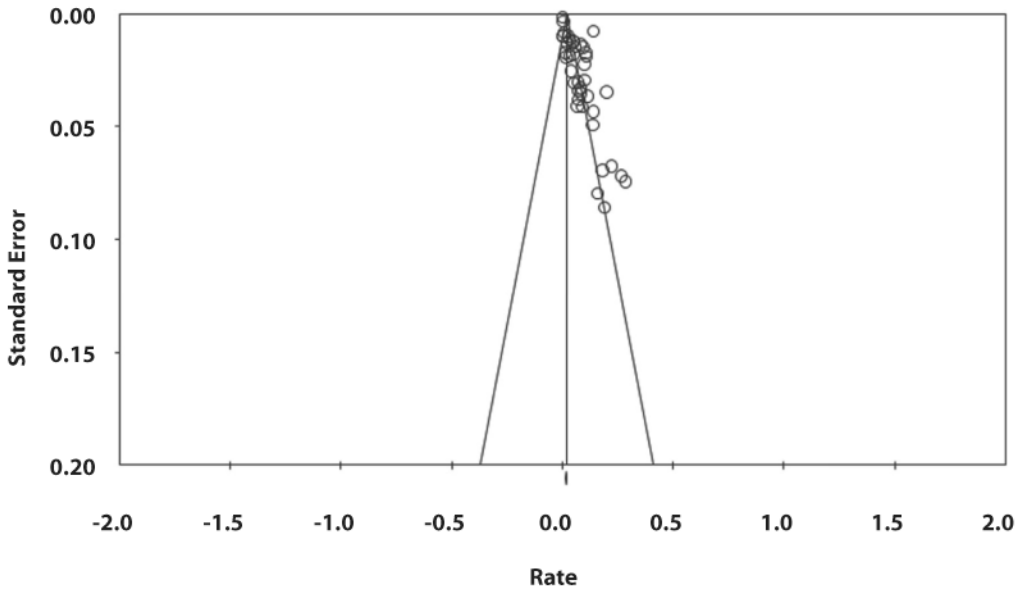

Figure 4.
Funnel plot assessing publication bias in primary analysis.

Table 1

Characteristics of included studies

First author, year of publication, country	Study type, no. of center	Total no. of patients, histology included	No. reaching CRIM	No. in surveillance after CRIM	Surveillance protocol	GEJ biopsy sample in surveillance, expert GI pathologist	Follow-up after CRIM (person-years)	No. of recurrent IM and recurrent HGD/EAC	Endoscopic treatment of recurrence	Quality score
RFA										
Shue et al 2013 USA[15]	Retrospective NR	42; NDBE, DBE, IMC	42	42	NR	GEJ, no GI pathologist, no	49	Total: 11 HGD/EAC: 0	NR	2
Akiyama et al 2013 USA[27]	Retrospective single center	86; NDBE, DBE, IMC	40	40	NR	GEJ, no GI pathologist, no	80	Total: 7 HGD/EAC: NR	NR	2
Phoa et al 2016 Netherlands[49]	Retrospective multicenter	132; NDBE, DBE, IMC	115	115	6 months, then yearly	GEJ, yes GI pathologist, yes	259	Total: 9 HGD/EAC: 4	100	8
Cotton et al 2015 USA[32]	Retrospective single center	198 NDBE, DBE	198	198	NR	GEJ, yes GI pathologist, yes	NR	Total: 32 HGD/EAC: 10	NR	7
Strauss et al 2014 USA[53]	Retrospective multicenter	36 IMC	27	27	NR	GEJ, no GI pathologist, yes	54	Total: 5 HGD/EAC: NR	66	4
Wolf et al 2014 USA[54]	Prospective multicenter	127 DBE	108	72	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, yes	288	Total: 18 HGD/EAC: 3	64.2	7.5
Pasricha et al 2014 USA[47]	Retrospective multicenter	5521 NDBE, DBE, IMC, EAC	3764	1634	<6 months first 2 years, then yearly	GEJ, no GI pathologist, yes	2494	Total: 334 HGD/EAC: 28	NR	6.5
Blevins et al 2014 USA[18]	Retrospective single center	338 NDBE, DBE, IMC	158	158	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	411	Total: 39 HGD/EAC: 5	100	8.5
Haidry et al (2) 2014 UK[40]	Prospective single center	145 DBE, IMC	94	94	NR	GEJ, no GI pathologist, no	470	Total: 22 HGD/EAC: NR	NR	5

First author, year of publication, country	Study type, no. of center	Total no. of patients, histology included	No. reaching CRIM	No. in surveillance after CRIM	Surveillance protocol	GEJ biopsy sample in surveillance, expert GI pathologist	Follow-up after CRIM (person-years)	No. of recurrent IM and recurrent HGD/EAC	Endoscopic treatment of recurrence	Quality score
Johnson et al 2014 USA[41]	Retrospective multicenter	49 NDBE, DBE, IMC	44	44	NR	GEJ, no GI pathologist, no	117	Total: 12 HGD/EAC: NR	NR	4
Orman et al 2013 USA[8]	Retrospective single center	262 NDBE, DBE, EAC	168	112	<6 months 1st year, 6 months 2nd year, then yearly l	GEJ, yes GI pathologist, yes	123	Total: 8 HGD/EAC: 7	80	7
Gupta M et al 2013 USA[12]	Retrospective multicenter	448 NDBE, DBE, EAC	229	229	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	344	Total: 37 HGD/EAC: 5	96	8.5
Dulai et al (ULSB) 2013 USA[22]	Retrospective single center	34 NDBE, DBE, IMC	26	26	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, no GI pathologist, no	69	Total: 6 HGD/EAC: 0	100	4
Dulai et al (LSB) 2013 USA[22]	Retrospective single center	38 NDBE, DBE, IMC	31	31	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, no GI pathologist, no	65	Total: 5 HGD/EAC: 0	NR	4
Choi et al 2013 USA[30]	Retrospective single center	58 NDBE, DBE, IMC	56	56	NR	GEJ, no GI pathologist, no	117	Total: 1 HGD/EAC: 0	100	3.5
Gupta N et al 2013 USA[12]	Retrospective multicenter	128 DBE, IMC, EAC	128	128	NR	GEJ, no GI pathologist, yes	167	Total: 34 HGD/EAC: 10	100	7
Korst et al 2013 USA[43]	Prospective single center	53 NDBE, DBE, EAC	53	51	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, no	76	Total: 11 HGD/EAC: 0	NR	5
Cameron et al 2012 Australia[29]	Retrospective multicenter	114 DBE, IMC	39	39	NR	GEJ, no GI pathologist, no	52	Total: 4 HGD/EAC: 4	NR	4
Vacarro et al 2011 USA[14]	Retrospective single center	47 NDBE, DBE, EAC	47	47	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, no	52	Total: 15 HGD/EAC: 2	100	4.5
van Vilsteren et al 2011 Netherlands[21]	Prospective multicenter	22 DBE	20	20	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, yes	25	Total: 4 HGD/EAC: NR	NR	5.5

First author, year of publication, country	Study type, no. of center	Total no. of patients, histology included	No. reaching CRIM	No. in surveillance after CRIM	Surveillance protocol	GEJ biopsy sample in surveillance, expert GI pathologist	Follow-up after CRIM (person-years)	No. of recurrent IM and recurrent HGD/EAC	Endoscopic treatment of recurrence	Quality score
Pouw et al 2010 Netherlands[50]	Prospective multicenter	24 DBE	23	23	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, yes	42	Total: 3 HGD/EAC: NR	NR	5.5
PDT										
Chandra et al 2013 USA[19]	Retrospective single center	255; DBE, IMC	194	194	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	436	Total: 37 HGD/EAC: NR	NR	5
May et al 2002 Germany[7]	Prospective single center	115; DBE, IMC	108	108	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, no	306	Total: 34 HGD/EAC: 34	100	5
APC										
Gad et al 2011 Egypt[36]	Prospective single center	73; NDBE, DBE	69	69	<6 months 1st year	GEJ, yes GI pathologist, no	69	Total: 0 HGD/EAC: 0	NA	2
Ferraris et al 2007 Italy[34]	Prospective multicenter	96; NDBE	94	94	Yearly	GEJ, yes GI pathologist, no	282	Total: 17 HGD/EAC: 0	NR	4.5
Mork et al 2007 Germany[45]	Prospective single center	25; NDBE, DBE	21	21	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, no GI pathologist, no	52	Total: 14 HGD/EAC: 0	NR	2.5
Pedrazzani et al 2005 Italy[48]	Prospective single center	25; NDBE, DBE	24	24	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, no	52	Total: 1 HGD/EAC: 0	100	3.5
Pagani et al 2003 Italy[46]	Prospective single center	94; NDBE, DBE	68	43	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, no GI pathologist, no	638	Total: 5 HGD/EAC:0	100	2.5
Familiari et al 2003 Italy[33]	NR single center	35; NDBE, DBE	32	32	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, no	132	Total: 3 HGD/EAC: NR	100	2
Schulz et al 2000 Germany[52]	Prospective single center	73; NDBE	69	69	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, no	69	Total: 0 HGD/EAC: 0	NA	1.5

First author, year of publication, country	Study type, no. of center	Total no. of patients, histology included	No. reaching CRIM	No. in surveillance after CRIM	Surveillance protocol	GEJ biopsy sample in surveillance, expert GI pathologist	Follow-up after CRIM (person-years)	No. of recurrent IM and recurrent HGD/EAC	Endoscopic treatment of recurrence	Quality score
Cryotherapy										
Goldberg et al 2012 USA[38]	Prospective single center	31; NDBE, DBE, IMC	20	20	NR	GEJ, yes GI pathologist, no	80	Total: 6 HGD/EAC: NR	NR	3
Multipolar electrocoagulation										
Allison et al 2011 Venezuela[28]	Prospective single center	139; NDBE	139	139	Yearly	GEJ, yes GI pathologist, no	1459	Total: 7 HGD/EAC: 0	100	4.5
Madisch et al 2005 Germany[13]	Prospective single center	73; NDBE	69	66	NR	GEJ, yes GI pathologist, no	281	Total: 8 HGD/EAC: 0	100	5.5
Laser therapy										
Fisher et al 2003 USA[35]	Prospective single center	31; NDBE, DBE	21	21	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	57	Total: 8 HGD/EAC: 1	87.5	4.0
EMR										
Konda et al 2014 USA[42]	Retrospective single center	107; DBE, IMC	86	74	Yearly	GEJ, yes GI pathologist, yes	204	Total: 21 HGD/EAC: 2	NR	8
Conio et al 2014 Italy[31]	Retrospective single center	47; DBE, IMC	37	37	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	57	Total: 1 HGD/EAC: 1	100	6.5
Gorospe et al 2011 USA[20]	Retrospective single center	47; DBE, IMC	23	23	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	26	Total: 0 HGD/EAC: 0	NA	5.5
van Vilsteren et al 2011 Netherlands[21]	Prospective multicenter	25; DBE, IMC	23	23	<6 months first 2 years, then yearly	GEJ, yes GI pathologist, yes	38	Total: 7 HGD/EAC: NR	NR	5.5

First author, year of publication, country	Study type, no. of center	Total no. of patients, histology included	No. reaching CRIM	No. in surveillance after CRIM	Surveillance protocol	GEJ biopsy sample in surveillance, expert GI pathologist	Follow-up after CRIM (person-years)	No. of recurrent IM and recurrent HGD/EAC	Endoscopic treatment of recurrence	Quality score
Gerke et al 2011 USA[37]	Retrospective single center	41; DBE, IMC	32	32	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	68	Total: 3 HGD/EAC: 0	100	7
Pouw et al 2010 Netherlands[50]	Prospective multicenter	169; NDBE, DBE, EAC Z	144	144	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	324	Total: 17 HGD/EAC: 0	NR	6.5
Larghi et al 2007 USA[44]	Prospective Multicenter	24; DBE, IMC	24	24	<6 months 1st year, 6 months 2nd year, then yearly	GEJ, yes GI pathologist, yes	56	Total: 3 HGD/EAC: 1	NR	5.5

NA, Not applicable; *NR*, not reported; *IMC*, intramucosal carcinoma; *RFA*, radiofrequency ablation; *NDBE*, nondysplastic Barrett's esophagus; *DBE*, dysplastic Barrett's esophagus; *HGD*, high-grade dysplasia; *EAC*, esophageal adenocarcinoma; *GEJ*, gastroesophageal junction; *IM*, intestinal metaplasia; *PDT*, photodynamic therapy; *APC*, argon plasma coagulation; *EMR*, endoscopic mucosal resection; *CRIM*, complete remission of intestinal metaplasia.

Table 2

Quality of included studies

Author	Primary endotherapy modality	Multi center vs single center	Sample size	GI pathologist	Total follow-up	Follow-up person-years vs mean years	Attrition rate	Definition of CRIM	GEJ biopsy sample	EMR before ablation	Histology of recurrent BE	Total quality score
Shue et al[15]	RFA	0	0	0	0	0	1	0	0	0	1	2
Akiyama J et al[27]	RFA	0	.5	0	0	.5	1	0	0	0	0	2
Phoa et al[49]	RFA	1	1	1	0	.5	1	.5	1	1	1	8
Cotton et al[32]	RFA	0	1	1	0	.5	1	.5	1	1	1	7
Strauss et al[53]	RFA	0	0	1	0	.5	1	.5	0	1	0	4
Wolf et al[54]	RFA	1	1	1	.5	1	.5	.5	0	1	1	7.5
Pasricha et al[47]	RFA	1	1	1	0	1	0	.5	0	1	1	6.5
Blevins et al[18]	RFA	1	1	1	0	.5	1	1	1	1	1	8.5
Haidry et al[40]	RFA	0	1	0	1	.5	1	.5	0	1	0	5
Johnson et al[41]	RFA	1	0	0	0	.5	1	.5	0	1	0	4
Orman et al[8]	RFA	0	1	1	0	1	.5	.5	1	1	1	7
Gupta M et al[12]	RFA	1	1	1	0	.5	1	1	1	1	1	8.5
Dulai et al (ULSB)[22]	RFA	0	0	0	0	.5	1	.5	0	1	1	4
Dulai et al (LSB)[22]	RFA	0	0	0	0	.5	1	.5	0	1	1	4
Choi et al[30]	RFA	0	.5	0	0	.5	0	.5	0	1	1	3.5
Gupta N et al[12]	RFA	1	1	1	0	.5	1	.5	0	1	1	7
Korst et al[43]	RFA	0	.5	0	0	0	1	.5	1	1	1	5

Author	Primary endotherapy modality	Multi center vs single center	Sample size	GI pathologist	Total follow-up	Follow-up person-years vs mean years	Attrition rate	Definition of CRIM	GEJ biopsy sample	EMR before ablation	Histology of recurrent BE	Total quality score
Cameron et al[29]	RFA	0	1	0	0	0	1	0	0	1	1	4
Vacarro et al[14]	RFA	0	0	0	0	0	1	.5	1	1	1	4.5
van Vilsteren et al[21]	RFA	1	0	1	0	0	1	.5	1	1	0	5.5
Pouw et al[50]	RFA	1	0	1	0	0	1	.5	1	1	0	5.5
Chandra et al[19]	PDT	0	1	1	0	0	1	1	0	1	0	5
May et al[7]	PDT	0	1	0	0	.5	1	.5	0	1	1	5
Gad et al[36]	APC	0	.5	0	0	.5	1	0	0	0	0	2
Ferraris et al[34]	APC	1	.5	0	.5	0	1	.5	0	0	1	4.5
Mork et al[45]	APC	0	0	0	0	.5	1	0	0	0	1	2.5
Pedrazzani et al[48]	APC	0	0	0	0	.5	1	0	1	0	1	3.5
Pagani et al[46]	APC	0	.5	0	0	.5	.5	0	0	0	1	2.5
Familiari et al[33]	APC	0	0	0	.5	0	1	.5	0	0	0	2
Schulz et al[52]	APC	0	.5	0	0	0	1	0	0	0	0	1.5
Goldberg et al[38]	Cryotherapy	0	0	0	.5	.5	1	0	1	0	0	3
Allison et al[39]	MPEC	0	1	0	1	.5	1	0	0	0	1	4.5
Madisch et al[13]	MPEC	0	.5	0	.5	1	1	.5	1	0	1	5.5
Fisher et al[35]	YAG	0	0	1	0	.5	1	.5	0	0	1	4.0
Konda et al[42]	EMR	1	1	1	0	.5	1	.5	1	1	1	8
Conio et al[31]	EMR	1	0	1	0	0	1	.5	1	1	1	6.5

Author	Primary endotherapy modality	Multi center vs single center	Sample size	GI pathologist	Total follow-up	Follow-up person-years vs mean years	Attrition rate	Definition of CRIM	GEJ biopsy sample	EMR before ablation	Histology of recurrent BE	Total quality score
Gorospe et al[20]	EMR	0	0	1	0	.5	1	1	1	1	0	5.5
van Vilsteren et al[21]	EMR	1	0	1	0	0	1	.5	1	1	0	5.5
Gerke et al[37]	EMR	1	0	1	0	.5	1	.5	1	1	1	7
Pouw et al[50]	EMR	0	1	1	0	.5	1	0	1	1	1	6.5
Larghi et al[44]	EMR	0	0	1	0	0	1	.5	1	1	1	5.5

MPEC, Multipolar electrocoagulation; *RFA*, radiofrequency ablation; *CRIM*, complete remission of intestinal metaplasia; *GEJ*, gastroesophageal junction; *EMR*, endoscopic mucosal resection; *BE*, Barrett's esophagus; *PDT*, photodynamic therapy; *APC*, argon plasma; coagulation.

Table 3
Incidence of IM recurrence after CRIM with RFA

Subgroup	Number of studies	Recurrence rate % per patient-year (95% CI)
Endoscopic modality (P = .46)		
RFA[15,27]	2	14.3 (11.4-27.5)
RFA + EMR[9,12,14,18,21,22,29,30,32,39-41,43,47,49,51,53,54]	19	9.2 (6.3-12.1)
Location of study (P = .67)		
North America[9,12,14,15,18,22,27,30,32,39,41,43,47,53,54]	16	10.0 (6.7-13.4)
Europe[21,40,49,51]	4	7.5 (2.2-12.8)
Asia-Pacific	1	7.7 (.2-15.2)
Publication type (P = .97)		
Full text[9,12,14,21,22,32,43,47,49,51,53]	12	9.4 (5.8-13.1)
Abstract[15,18,27,29,30,39-41,54]	9	9.6 (5.5-13.6)
Inclusion of GEJ biopsy sample in post-CRIM surveillance (P = .52)		
Yes[9,12,14,18,21,32,43,49,51]	9	8.3% (5.1-11.5)
No[15,22,27,29,30,39-41,47,53,54]	12	10.1% (5.7-14.4)
Study quality (P = .16)		
High[9,12,18,32,39,49,54]	7	7.5% (4.5-10.6)
Medium[14,21,22,29,40,41,43,47,51,53]	11	11.5% (8.8-14.1)
Low[15,27,30]	3	8.8% (0-18.6)

IM, intestinal metaplasia; *CRIM*, complete remission of intestinal metaplasia; *RFA*, radiofrequency ablation; *EMR*, endoscopic mucosal resection; *GEJ*, gastroesophageal junction.

Table 4
Incidence of IM recurrence after CRIM with all endoscopic modalities

Subgroup	Number of studies	Recurrence rate % per patient-year (95% CI)
Endoscopic modality ($P < .01$)		
RFA[9,12,14,15,18,21,22,27,29,30,32,39-41,43,47,49,51,53,54]	21	9.5 (6.7-12.3)
APC[33,34,36,45,46,48,52]	7	2.3 (.5-4.1)
PDT[7,19]	2	9.5 (7.0-12.0)
EMR[20,21,31,37,42,44,50]	7	6.3 (3.2-9.4)
MPEC[13,28]	2	1.5 (0-3.7)
Cryotherapy[38]	1	7.5 (1.5-13.5)
Laser[35]	1	14 (4.3-23.8)
Age of modality		
Current modalities (RFA, EMR, and cryotherapy)	29	9.2 (6.8-11.6)
Historical modalities (PDT, APC, MPEC, and laser)	12	3.8 (2.4-5.2)
Location of study ($P < .01$)		
North America[9,12,14,15,18-20,22,27,30,32,35,37-39,41-44,47,53,54]	23	9.5 (7.0-12.1)
Europe[7,13,21,31,33,34,40,45,46,48-52]	15	4.6 (2.8-6.5)
Asia-Pacific[29]	1	7.7 (.2-15.2)
Africa[36]	1	.7 (.0-2.7)
South America[28]	1	.5 (.1-.8)
Baseline dysplasia status ($P < .01$)		
NDBE[13,28,34,52]	4	2.2 (.1-4.3)
DBE ± early neoplasia[7,19-21,29,31,37,39,40,42,44,49,51,53,54]	16	8.8 (6.3-11.4)
Publication type ($P = .29$)		
Full text[7,9,12-14,21,22,28,31-35,37,42-53]	28	6.6 (4.8-8.4)
Abstract[15,18-20,27,29,30,36,38-41,54]	13	8.5 (5.4-11.5)
Inclusion of GEJ biopsy samples in post-CRIM surveillance ($P = .64$)		
Yes[9,12-14,18,20,21,31,32,37,38,42-44,48-51]	19	6.6 (4.7-8.4)
No[7,15,19,22,27-30,33-36,39-41,45-47,52-54]	22	7.2 (5.2-9.3)

Subgroup	Number of studies	Recurrence rate % per patient-year (95% CI)
Study quality ($P < .01$)		
High[9,12,18,32,37,39,42,49,54]	9	7.5 (4.9-10.1)
Medium[7,13,14,19-22,28,29,31,34,35,40,41,43,44,47,50,51,53]	22	9.1 (6.0-12.2)
Low[15,27,30,33,36,38,45,46,48,52]	10	2.5 (0.8-4.1)

IM, intestinal metaplasia; *CRIM*, complete remission of intestinal metaplasia; *RFA*, radiofrequency ablation; *APC*, argon plasma coagulation; *PDT*, photodynamic therapy; *EMR*, endoscopic mucosal resection; *NDBE*, nondysplastic Barrett's esophagus; *DBE*, dysplastic Barrett's esophagus; *GEJ*, gastroesophageal junction.

Table 5

Predictors of IM recurrence after CRIM

Predictors	Number of studies	Odds ratio (95% CI)
Age[12,27,34,47]	4	1.02 (1.01-1.03)
Sex[12,27,34,47,54]	5	1.12 (.85-1.47)
BE length (per cm)[12,27,34,47]	4	1.10 (1.05-1.15)
Baseline dysplasia[12,27,47,54]	4	1.03 (.63-1.70)

IM, intestinal metaplasia; *CRIM*, complete remission of intestinal metaplasia; *BE*, Barrett's dysplasia.