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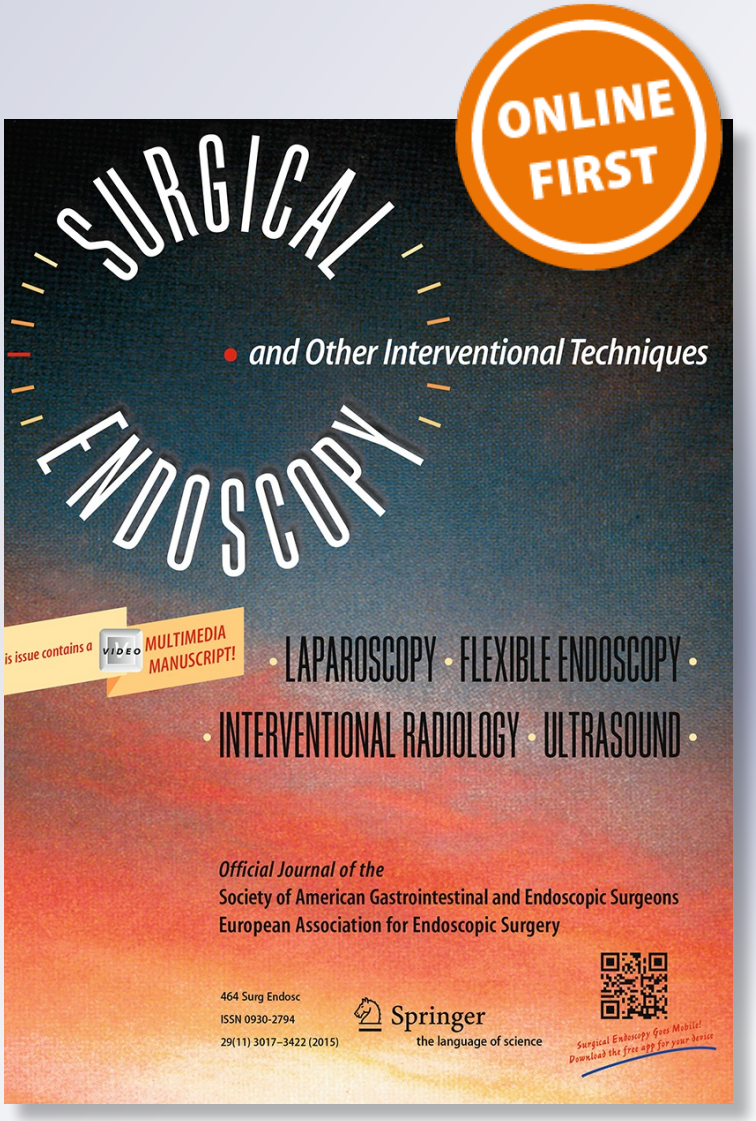


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# Prevention of esophageal stricture after endoscopic submucosal dissection: a systematic review and meta-analysis

**J. F. Oliveira[1] · E. G. H. Moura[1] · W. M. Bernardo[2,3] · E. Ide[1] · S. Cheng[1] · M. Sulbaran[1] · C. M. L. Santos[1] · P. Sakai[1]**

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**Abstract**
*Background* Endoscopic submucosal dissection (ESD) of extensive superficial cancers of the esophagus may progress with high rates of postoperative stenosis, resulting in significantly decreased quality of life. Several therapies are performed to prevent this, but have not yet been compared in a systematic review.
*Methods* A systematic review of the literature and meta-analysis were performed using the MEDLINE, Embase, Cochrane, LILACS, Scopus, and CINAHL databases. Clinical trials and observational studies were searched from March 2014 to February 2015. Search terms included: endoscopy, ESD, esophageal stenosis, and esophageal stricture. Three retrospective and four prospective (three randomized) cohort studies were selected and involved 249 patients with superficial esophageal neoplasia who underwent ESD, at least two-thirds of the circumference. We grouped trials comparing different techniques to prevent esophagus stenosis post-ESD.
*Results* We conducted different meta-analyses on randomized clinical trials (RCT), non-RCT, and global analysis. In RCT (three studies, $n = 85$), the preventive therapy decreased the risk of stenosis (risk difference $= -0.36$, 95 % CI $-0.55$ to $-0.18$, $P = 0.0001$). Two studies (one randomized and one non-randomized, $n = 55$) showed that preventative therapy lowered the average number of endoscopy dilatations (mean difference $= -8.57$, 95 % CI $-13.88$ to $-3.25$, $P < 0.002$). There were no significant differences in the three RCT studies ($n = 85$) in complication rates between patients with preventative therapy and those without (risk difference $= 0.02$, 95 % CI $-0.09$ to 0.14, $P = 0.68$).
*Conclusions* The use of preventive therapy after extensive ESD of the esophagus reduces the risk of stenosis and the number of endoscopic dilatations for resolution of stenosis without increasing the number of complications.

**Keywords** Endoscopy submucosal dissection · ESD · Esophageal stenosis · Esophageal stricture · Meta-analysis · Systematic review

## Rationale

Esophageal carcinoma is the eighth most common cancer and the sixth most common cause of cancer-related deaths worldwide [1]. Adenocarcinoma is now the most common cancer type in the western hemisphere, followed by squamous cell cancer [2].

According to the national guidelines of the Japan Esophageal Society (JES), high-grade intraepithelial neoplasms, including noninvasive squamous cell carcinomas (carcinoma in situ, m1) and intramucosal invasive carcinoma limited to the lamina propria mucosae (m2) without vessel infiltration or lymph node or distant metastases, are allocated to absolute indication of endoscopic local resection, including endoscopic submucosal dissection (ESD) [3]. Deeper lesions of 200 μm in the submucosa (m3 and sm1) are allocated to relative indication because they have a 10–15 % probability of lymph node metastasis [4, 5].

Endoscopic resection of superficial esophageal neoplasms (SENs) is widely used as an alternative to surgery

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because of its minimal invasiveness and good clinical outcome [6, 7]. Compared to esophagectomy, endoscopic resection can significantly shorten hospitalization duration, decrease the incidence of complications, and improve postoperative quality of life [8, 9].

However, because the esophagus is a narrow, hollow organ, healing of an artificial ulcer that occupies two-thirds or more of the circumference of the esophagus may result in the formation of a significant stricture [10]. Indeed, the rate of esophageal strictures after endoscopic resection for the near-circumferential or circumferential SENs has been extremely high: 88–100 % [6, 11–13].

## Objective

As larger-sized SENs became candidates for ESD, more patients begin to suffer from esophageal post-ESD strictures as a major complication, resulting in decreased quality of life [12, 14, 15].

Several prophylactic methods were used to reduce the rates of stenosis; however, whether these therapies decrease these rates is not established. We aim to systematically review and compare various existing techniques and evaluate their outcomes.

## Materials and methods

### Protocol and registration

This systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) recommendations [16].

The review was registered on the PROSPERO international database (www.crd.york.ac.uk/prospero) under number CRD42014015626.

### Eligibility criteria

(a) *Types of studies*—Clinical trials and observational studies were searched and targeted to a later selection process. No language or publication dates were initially imposed.

(b) *Types of participants*—Patients submitted to ESD of the esophagus that affected at least two-thirds of esophageal circumference.

(c) *Types of intervention*—Trials comparing different techniques to prevent or treat esophagus stenosis post-ESD. There were no restrictions regarding the different modalities of treatment in the therapeutic arm.

(d) *Types of outcome measures*—The main outcome measures were stenosis rate, number of endoscopy dilatations (EDs), and number of complications. Stenosis was defined as dysphagia to solids or impossibility to pass a standard endoscope (>9.2 mm). Complications were classified as major (which led to death or required surgical procedure to repair) or smaller (post-ESD bleeding that required hemostatic therapy or perforation and/or pneumomediastinum, resolved with medical treatment and migration of the stent).

### Information sources

Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were applied for language. MEDLINE, Embase, Cochrane, LILACS, Scopus, and CINAHL databases were reviewed. The last search was run on February 02, 2015.

### Search

The following search strategy was used for the MEDLINE database: "(Endoscopy OR endoscopic submucosal dissection OR ESD) AND ((Esophageal Stenosis OR esophageal stricture OR (Constriction, pathologic AND Esophagus) OR (Stenosis AND Esophagus)) AND (Prednisolone OR Dilatation OR Triamcinolone OR Glucocorticoids OR balloon)." As part of the process, the MEDLINE search strategy was peer-reviewed.

The Embase search was: "(Endoscopy OR endoscopic submucosal dissection OR ESD) AND ((Esophageal Stenosis OR esophageal stricture OR (Constriction, pathologic AND Esophagus) OR (Stenosis AND Esophagus)) AND (Prednisolone OR Dilatation OR Triamcinolone OR Glucocorticoids OR balloon)." For Cochrane, LILACS, Scopus, and CINAHL databases, the search was: "(esophageal, endoscopy submucosal dissection, stenosis)."

### Study selection

Eligibility assessment and the selection of screened records were performed independently in an un-blinded, standardized manner by two reviewers. Disagreements between the reviewers were resolved by consensus. To summarize the study selection processes, an adapted PRISMA flow diagram was used.

### Data collection process

The method of data extraction from each included study consisted of filling out information sheets after the paper

was read. A Scottish Intercollegiate Guidelines Network-based checklist was gathered from www.sign.ac.uk. Relevant data were then extracted from each included study using a standardized extraction form. One review author extracted data from the included studies, and a second author checked the extracted data. Disagreements were resolved by discussion between the two review authors.

### Data items

The selected articles included patients with SEN who underwent ESD for at least two-thirds of the esophageal circumference; included studies also assessed the ability of the therapeutic approach to prevent postoperative stenosis. All methods of intervention were included. The results extracted were: rate of stenosis, number of dilatations to treat the stenosis, and number of complications.

### Risk of bias in individual studies

To verify the validity of eligible studies, two reviewers, working independently and with adequate reliability, measured the risk of bias using the Newcastle-Ottawa Quality Assessment Scale for non-randomized cohort studies, the JADAD scale for randomized trials, and the Scottish Intercollegiate Guidelines Network checklist for both. Specific methodological components of the Newcastle scale were rated: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start of the study, comparability of cohorts on the basis of the design or analysis, assessment of outcome, and length and adequacy of follow-up. The critical evaluation of the included trials should reveal a score $\geq$7 out of 9, the highest possible score. The levels of evidence were obtained according to the Oxford Centre for Evidence-based Medicine. The topics evaluated by the JADAD scale are: randomization, double blinding, and description of losses. A critical evaluation of selected works must present a note $\geq$2 out of a maximum 5 points. This information was applied subsequently in the data synthesis.

### Summary measures

The analysis of risk differences of several stenosis rates after esophageal ESD was the primary outcome measure. Data on absolute risk reduction (ARR) or increase (ARI) and the number needed to treat (NNT) or harm (NNH) were analyzed. Mensuration of the secondary results was performed regarding the number of dilatations to treat stenosis and the number of complications. The values found as absolute or average number with standard deviation were meta-analyzed, but due to heterogeneity of the studies, when these data are not provided, their meta-analysis cannot be performed.

### Planned methods of analysis

The analysis was performed, using the Review Manager (RevMan) 5.3 software [17] obtained from the website of the Cochrane Informatics & Knowledge Management Department, by computing the risk differences of dichotomous variables using a fixed-effects model and providing the respective forest and funnel plots. Data on risk differences and 95 % confidence intervals for each outcome were calculated using the Mantel–Haenszel test, and inconsistency (heterogeneity) was qualified and reported by Chi-squared ($\chi^2$) and the Higgins method, termed $I^2$. The advantages of the Higgins method are that it does not depend on the number of studies and it is accompanied by an uncertainty interval. Data on ARR or ARI and NNT or NNH were obtained for validity and applicability using the Critically Appraised Topic (CAT) software.

### Risk of bias across studies

To evaluate the relation between sample size and effect size, a graphical method was used (forest plots) for each outcome. Risks of publication bias for outcomes across studies were plotted (funnel plots) and identified (outliers detection) along with $I^2$ quantitative analysis.

### Additional analyses

The categorization of values for $I^2$ would not be appropriate for all circumstances, although adjectives of low, moderate, and high were assigned to $I^2$ values of 25, 50, and 75 %, respectively [18]. As quantification of heterogeneity is only one component of a wider investigation of variability across studies, and considering the clinical implications of the observed degree of inconsistency across studies, the cutoff value of 50 % was considered adequate for this meta-analysis. To determine whether our results were adequate and reliable for medical practice (i.e., not arbitrary or based on unclear data), we performed sensitivity analysis in those studies where the heterogeneity ($I^2$) was more than 50 %. A subsequent assay excluded outliers, and other findings were compiled. When outliers were not detected, true heterogeneity was presumed.

**Table 1** Summary of included studies evaluating the prevention and treatment therapy for esophagus stenosis after ESD

| Studies | Population | Intervention | Control | Outcome |
|---|---|---|---|---|
| Takahashi et al. [19] | ESD > 3/4 | Steroid injection | No steroid injection | Stenosis number EBD complication |
| Sato et al. [20] | ESD circumferential | Oral corticoid | No oral corticoid | Stenosis number EBD complication |
| Wen et al. [21] | ESD > 3/4 | Stent | No stent | Stenosis number SGD complication |
| Uno et al. [22] | ESD > 3/4 | Scheduled EBD + tranilast | Scheduled EBD | Stenosis number EBD complication |
| Hanaoka et al. [23] | ESD > 3/4 | Steroid injection | No steroid injection | Stenosis number EBD |
| Hashimoto et al. [24] | ESD = 3/4 | Steroid injection | No steroid injection | Stenosis number EBD complication |
| Yamaguchi et al. [15] | ESD > 3/4 | Oral corticoid | No oral corticoid | Stenosis number EBD complication |

*ESD* endoscopy submucosal dissection, *EBD* endoscopy balloon dilatation, *SGD* Savary–Gilliard dilatation

## Results

### Study selection

In the MEDLINE search, 953 articles were found and 30 were selected; twelve were excluded because one evaluated only benign strictures, one was an editorial, one was a case report, one was a preliminary work, two evaluated patients that also underwent EMR, two were case series studies, one consisted of an overview, and three evaluated only prognostic factors, leaving seven studies.

In the Embase search, we found 103 articles, 34 of which were selected; all were excluded because eleven were abstracts, one was an editorial, thirteen were also found in MEDLINE, four were case reports, and five were case series.

In the CINAHL search, we found 358 articles and selected 3; all were excluded because all 3 were also found in MEDLINE.

One previously selected article was found in Cochrane and Central, and no articles were found in LILACS. In the USP Digital Library, 4 articles were found, but none were selected.

In short, 1461 articles were selected and 8 studies were eligible for our study; 7 were included in our quantitative and qualitative synthesis.

### Study characteristics

*Methods* Seven studies were selected for the review, 3 retrospective and 4 prospective (3 randomized) cohorts published in English.

*Participants* The included records involved 226 patients. The main inclusion criteria entailed patients with SENs who underwent ESD for at least two-thirds of the esophageal circumference.

*Intervention* The following therapies were analyzed: oral corticoid, steroid injection, steroid gel application, stent placement, and tranilast associated with ED.

*Comparison* Since there is still no evidence that any preventive therapy is beneficial with respect to the incidence of stenosis, we compared a group that underwent therapy versus the control group.

*Outcomes* The primary outcomes assessed were stenosis rates.

The secondary outcomes were number of dilatations and complications.

A summary of the characteristics of the included studies is shown in Table 1.

*Description of the interventions*

1. Takahashi et al. [19]: The triamcinolone acetonide was endoscopically injected immediately after the procedure. Triamcinolone was diluted with 0.9 % NaCl to a final concentration of 10 mg/ml, and then, 0.5 ml aliquots were injected at the base of the artificial ulcer using a 25-gauge, 3-mm needle. Injection commenced at the distal edge of the ulcer base and was repeated evenly at points 10 mm apart toward the proximal edge.
2. Sato et al. [20]: Oral prednisolone was started 2 days after ESD (when patients are permitted oral intake) in a dose of 30 mg/day. The dose was then gradually tapered in decrements of 5 mg/day every 2 weeks for 1 month followed by decrements of 5 mg/day every week for the next 4 weeks. Steroids were discontinued after 8 weeks.
3. Wen et al. [21]: Just after complete ESD was inserted a covered esophageal stent (Sigma) with length ranged from 25 to 180 mm and the diameter ranged from 15 to 18 mm depending of the length and range of the mucosal defect. Esophageal stents were removed 8 weeks post-ESD.
4. Uno et al. [22]: From a few days after ESD without perforation onward, was performed the scheduled EBD procedure (15- to 18-mm CRE balloon) twice per week for 4 weeks, defined as "scheduled EBD," and was administered tranilast 300 mg/d divided in 3 doses after the meal in the therapeutic group for 8 weeks.

5. Hanaoka et al. [23]: A single session of intralesional steroid injections was undertaken immediately after ESD. Triamcinolone acetonide (50 mg/5 ml) was diluted 1:1 with saline to make a 5-mg/ml solution. A 25-gauge needle was used to inject the solution evenly into the residual submucosal tissue of the ulcer bed in 0.5–1.0 ml increments (20–40 punctures). The initial injections were given at the margins of the ulcer, and these were followed by linear injections given from the distal side to proximal side of the ulcer margin totaling 100 mg in each patient regardless of the lesion size.
6. Hashimoto et al. [24]: The intralesion steroid injection was performed using triamcinolone acetonide (10 mg/ml) without further dilution beginning at 3 days after ESD. A 25-gauge, 4-mm needle was used for injections. Triamcinolone was injected in aliquots of 0.2 ml (2 mg) into the cautery ulcer base. Injections were performed equally (1 cm apart) in a semicircumferential fashion. The number of injections per session was dependent on the size of resection and ranged from 9 to 31. The total dose of triamcinolone per session ranged from 18 to 62 mg. Sessions were performed at 3, 7, and 10 days after ESD (total of three sessions).
7. Yamaguchi et al. [15]: Oral prednisolone was started at a dose of 30 mg/day on the third day post-ESD, tapered gradually (30, 30, 25, 25, 20, 15, 10, and 5 mg for 7 days each) and then discontinued 8 weeks later, except one (12 weeks later).

**Table 2** Quality measures of the analyzed studies—Scottish Intercollegiate Guidelines Network (SIGN), Newcastle-Ottawa Scale, and JADAD Scale—bias measures

| Studies | Sign | Newcastle | JADAD |
|---|---|---|---|
| Takahashi et al. [19] | High quality | – | 3 |
| Sato et al. [20] | High quality | 8 | – |
| Wen et al. [21] | Acceptable | – | 3 |
| Uno et al. [22] | Acceptable | – | 2 |
| Hanaoka et al. [23] | Acceptable | 7 | – |
| Hashimoto et al. [24] | High quality | 9 | – |
| Yamaguchi et al. [15] | High quality | 9 | – |

## Risk of bias within studies

Through a systematic approach with defined criteria, the risk of bias was assessed. The data from each selected study are shown below (Table 2).

## Results of individual studies

Table 3 shows the results regarding stenosis rate and number of dilatations (Table 4).

It was not possible to analyze the number of dilatations for the resolution of esophageal stenosis after ESD in all studies, because only Takahashi and Sato provided the means and standard deviations. All the studies show, with

**Table 4** Average dilatations in different therapies

| Studies | Number EBD | *P* value |
|---|---|---|
| Takahashi et al. [19] | *I*: 6.1 ± 6.2<br>*C*: 12.5 ± 10.1 | 0.038 |
| Sato et al. [20] | *I*: 13.8 ± 6.9<br>*C*: 33.5 ± 22.9 | <0.001 |
| Wen et al. [21] | *I*: 0.45(0–3)<br>*C*: 3.9(0–17) | < 0.05 |
| Uno et al. [22] | *I*: 8 + 0 (0–1.75)<br>*C*: 8 + 4 (0–6.5) | 0.0138 |
| Hanaoka et al. [23] | *I*: 0 (0–2)<br>*C*: 2 (0–15) | <0.0001 |
| Hashimoto et al. [24] | *I*: 1.7 (0–20)<br>*C*: 6.6 (0–22) | <0.001 |
| Yamaguchi et al. [15] | *I*: 1.7 (0–7)<br>*C*:15.6 (0–48) | <0.001 |

*ED* endoscopy dilatation, *I* intervention, *C* control

**Table 3** Risk of stenosis in different therapies

| Studies | ARI (stenosis) | ARC (stenosis) | ARR (stenosis) | NNT | CI |
|---|---|---|---|---|---|
| Takahashi et al. [19] | 0.625 | 0.875 | 25 | 4 | −53.73 to 3.727 |
| Sato et al. [20] | 1 | 1 | 0 | – | – |
| Wen et al. [21] | 0.182 | 0.727 | 54.55 | 2 | 19.73 to 89.36 |
| Uno et al. [22] | 0.3333 | 0.6875 | 35.42 | 3 | 2.48 to 68.35 |
| Hanaoka et al. [23] | 0.1 | 0.655 | 55.52 | 2 | 35.16 to 75.88 |
| Hashimoto et al. [24] | 0.19 | 0.75 | 55.95 | 2 | 30.61 to 81.29 |
| Yamaguchi et al. [15] | 0.053 | 0.318 | 26.56 | 4 | 4.656 to 48.45 |

*ARI* absolute risk in intervention, *ARC* absolute risk in control, *ARR* absolute risk reduction, *NNT* number needed to treat, *CI* 95 % confidence interval

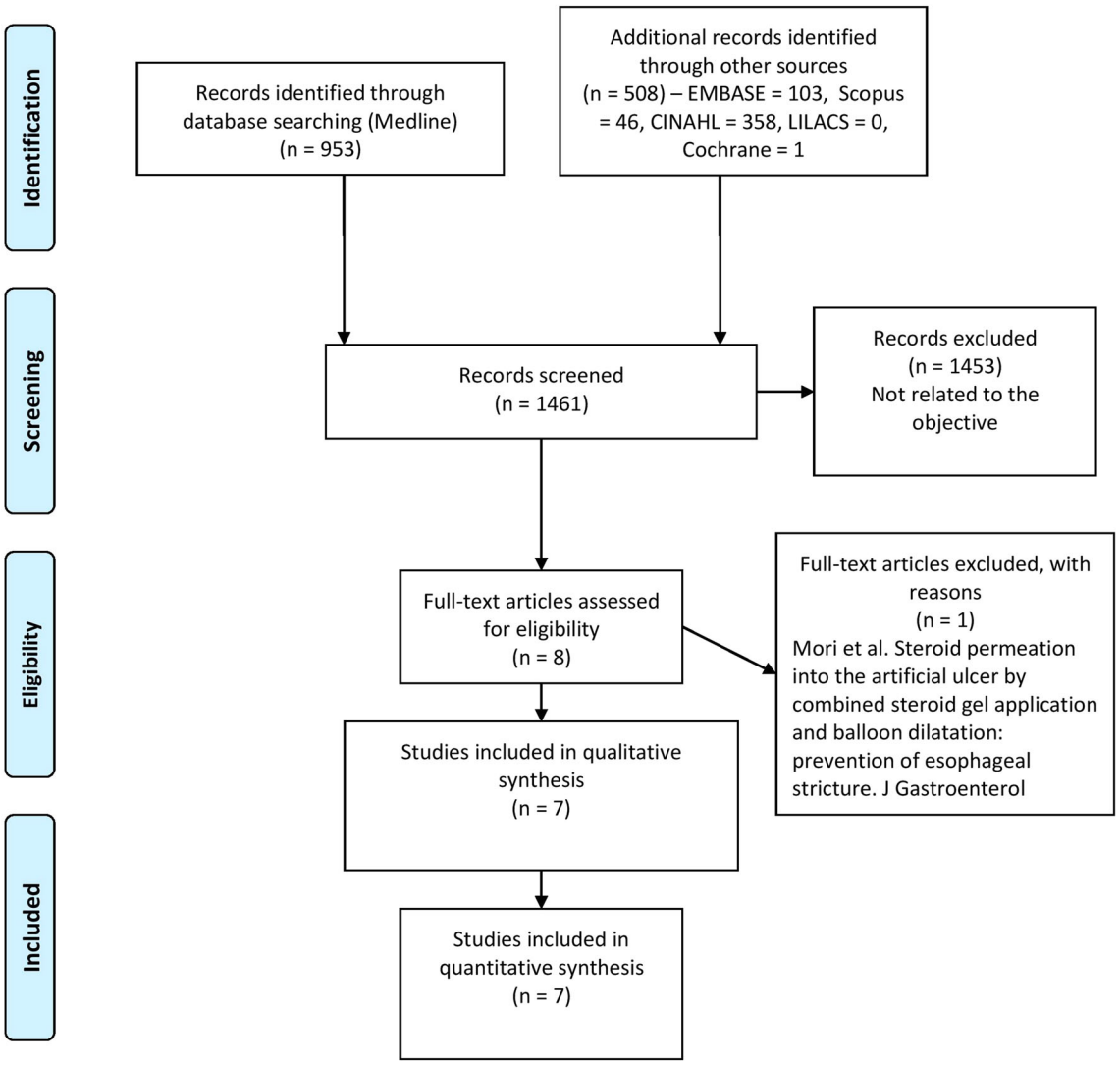


**Fig. 1** Search strategy—prevention of esophageal stricture after endoscopy submucosal dissection: systematic review and meta-analysis

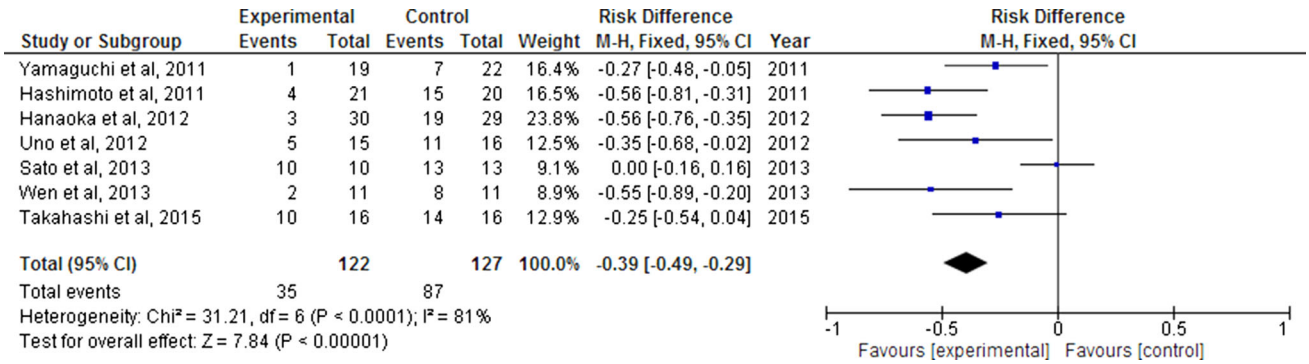


**Fig. 2** Stenosis rate after esophageal ESD for different preventive therapies

statistical significance ($P < 0.05$), that the use of preventive therapy decreases the number of dilatations to resolve dysphagia; however, when performing Student's $t$ test, we calculated a mean difference of $-8$, in favor of preventive therapy, but a $P$ value of 0.07639, which was not statistically significant.

## Synthesis of results

*Rate of stenosis*

The data on effect estimates and confidence intervals for each study are shown below. The numerical group-specific summary information, effect size, confidence interval, and percentage weight are also shown in the following tables (forest and funnel plots).

Our evaluations of the frequency of stenosis are shown in the graphs below.

Stenosis rates were available for seven studies ($n = 249$ patients), as shown in Fig. 1. In the pooled analysis, the preventive therapy decreased the risk of stenosis after ESD [risk difference (RD) = −0.39, 95 % confidence interval (CI) −0.49 to −0.29)]. The $P$ value was < 0.00001, indicating statistical significance; however, significant heterogeneity was detected within this comparison ($\chi^2 = 31.21$ and $I^2 = 81$ %; Fig. 1). Sensitivity analysis, through a funnel plot, identified that one study differed from the others [20], as shown in Fig. 2.

Exclusion of this study decreased the statistical heterogeneity to 26 % (Figs. 3, 4) and did not affect the finding of decreasing the risk of stenosis, and further improved the results in favor of the use of preventive therapy, as shown in Figs. 3 and 4.

In the new pooled analysis, the preventive therapy decreased the risk of stenosis after ESD (RD = −0.43, 95 % CI −0.54 to −0.33). The $P$ value for was <0.00001, indicating statistical significance. Clinically, the exclusion of this study does not significantly affect the overall analysis, because Sato only examined patients submitted to ESD of the entire circumference of the esophagus, which has a known stenosis rate of 100 %.

Because randomized studies present better methodological quality, we decided to conduct a meta-analysis of the risk of stenosis using only randomized studies, as shown in Fig. 5.

In the new pooled analysis, the preventive therapy showed a decreased risk of stenosis after ESD (RD = −0.36, 95 % CI −0.55 to −0.18). The $P$ value was <0.00001, statistically significant, and heterogeneity = 0 %. Although slightly different from the results of

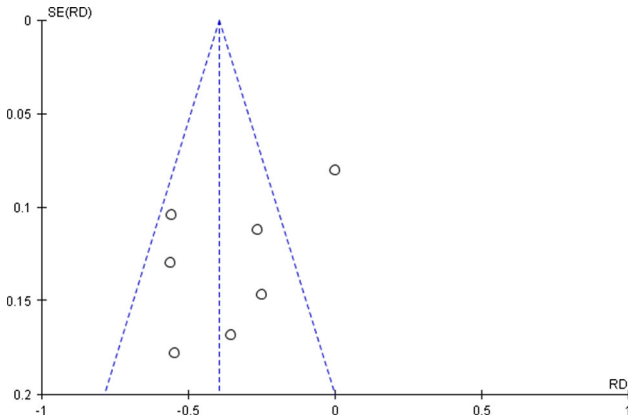


**Fig. 3** Distribution of stenosis rate in the seven studies after esophageal ESD with different preventive therapies

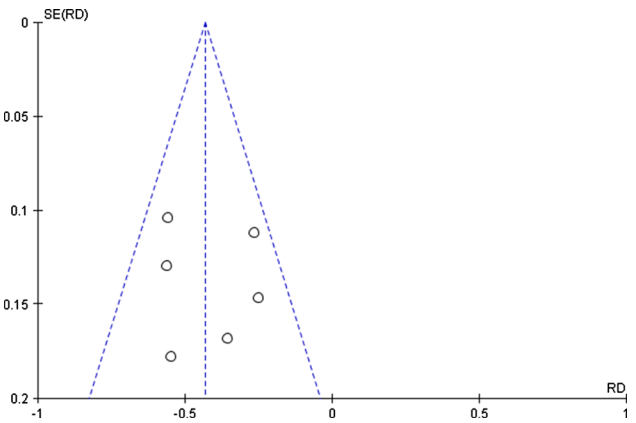


**Fig. 5** Distribution of the six studies' stenosis rates after esophageal ESD with different preventive therapies (excluded outlier)

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Difference M-H, Fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Yamaguchi et al, 2011 | 1 | 19 | 7 | 22 | 18.1% | -0.27 [-0.48, -0.05] | 2011 |
| Hashimoto et al, 2011 | 4 | 21 | 15 | 20 | 18.2% | -0.56 [-0.81, -0.31] | 2011 |
| Hanaoka et al, 2012 | 3 | 30 | 19 | 29 | 26.1% | -0.56 [-0.76, -0.35] | 2012 |
| Uno et al, 2012 | 5 | 15 | 11 | 16 | 13.7% | -0.35 [-0.68, -0.02] | 2012 |
| Wen et al, 2013 | 2 | 11 | 8 | 11 | 9.7% | -0.55 [-0.89, -0.20] | 2013 |
| Takahashi et al, 2015 | 10 | 16 | 14 | 16 | 14.2% | -0.25 [-0.54, 0.04] | 2015 |
| **Total (95% CI)** | | **112** | | **114** | **100.0%** | **-0.43 [-0.54, -0.33]** | |
| Total events | 25 | | 74 | | | | |

Heterogeneity: Chi² = 6.76, df = 5 (P = 0.24); I² = 26%
Test for overall effect: Z = 7.94 (P < 0.00001)

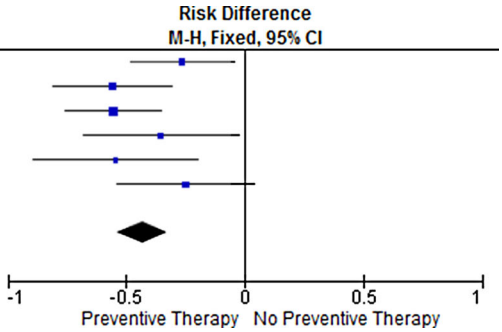


**Fig. 4** Stenosis rate after esophageal ESD with different preventive therapies (excluded outlier)

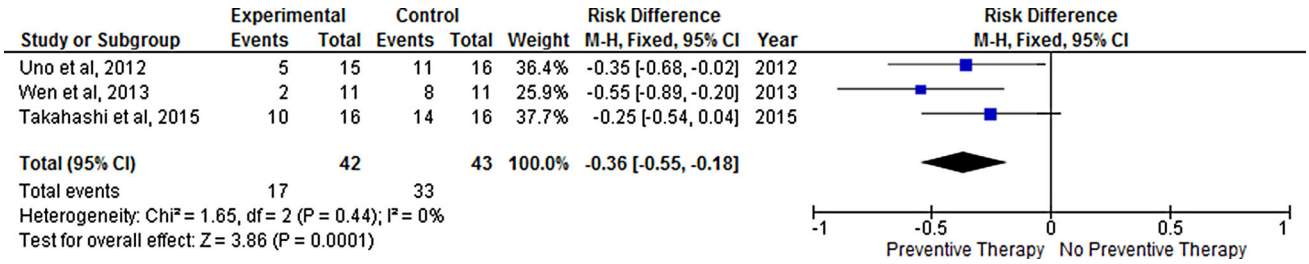


**Fig. 6** Stenosis rate after esophageal ESD with different preventive therapies in randomized trials

the previous evaluation, preventative therapy in the randomized studies still reduced the risk of post-ESD stenosis.

We performed another meta-analysis to assess whether non-randomized studies would show similar results.

Stenosis rates were available for the four non-randomized studies ($n = 72$ patients), as shown in Fig. 6. In the pooled analysis, the preventive therapy decreased the risk of stenosis after ESD (RD = −0.41, 95 % CI −0.52 to −0.29). The $P$ value was $< 0.00001$, indicating statistical significance; however, significant heterogeneity was detected within this comparison ($\chi^2 = 30.91$ and $I^2 = 90$ %, Fig. 7). Sensitivity analysis, through a funnel plot, identified that one study differed from the others [20], as shown in Fig. 8.

Exclusion of this study decreased the statistical heterogeneity to 56 % (Figs. 9, 10) and did not affect the finding of decreased stenosis risk, and further improved the results in favor of the use of preventive therapy, as shown in Figs. 9 and 10.

In the new pooled analysis, preventive therapy decreased the risk of stenosis after ESD (RD = −0.47, 95 % CI −0.60 to −0.34). The $P$ value was <0.00001, indicating statistical significance. As in the first analysis, clinically, the exclusion of this study does not significantly affect the overall analysis, because Sato only examined patients submitted to ESD with stenosis rates of 100 %.

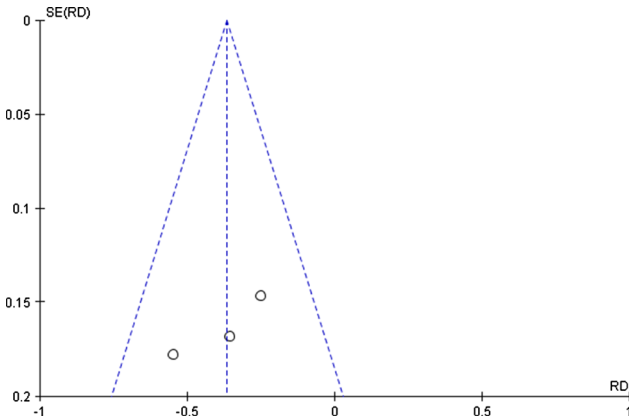


**Fig. 7** Distribution of the stenosis rate after esophageal ESD with different preventative therapies in three randomized studies

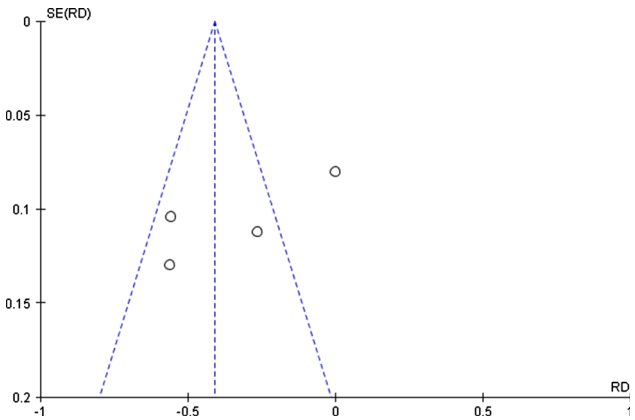


**Fig. 9** Distribution of stenosis rate after esophageal ESD with different preventive therapies in three non-randomized studies

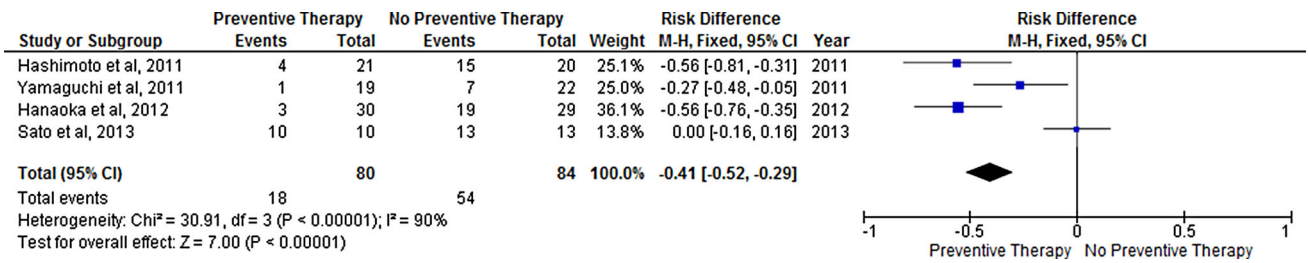


**Fig. 8** Stenosis rate after esophageal ESD with different preventive therapies in non-randomized trials

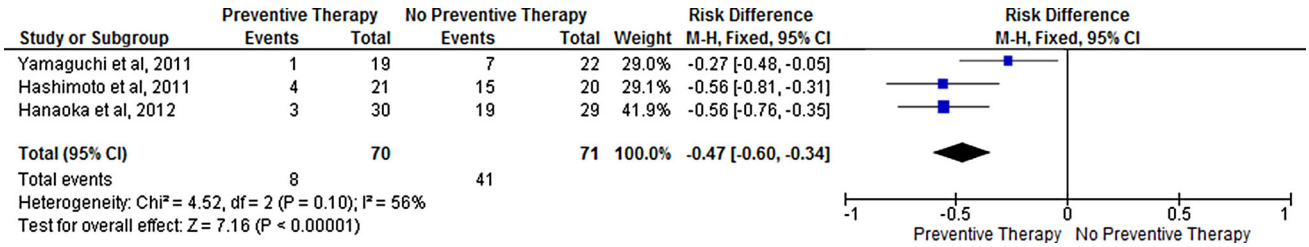


**Fig. 10** Stenosis rate after esophageal ESD with different preventive therapies in non-randomized trials (excluded outlier)

*Number of endoscopy dilatations*

Regarding the number of dilatations for resolution of stenosis, only two studies provided the data needed to perform the meta-analysis, as shown in Figs. 11 and 12.

The mean difference in the number of dilatations for resolution of the stenosis was −8.57, favorable to the use of preventive therapy, 95 % CI −13.88, −3.25, $P$ value = 0.002. Analyzing these data, a high heterogeneity was detected ($\chi^2 = 3{:}28$ and $I^2 = 70$ %); the funnel plot was drawn and no outlier was detected, so we assumed a true heterogeneity.

*Number of complications*

Complication rates were available for six studies ($n = 190$ patients), as shown in Fig. 13. In the pooled analysis, there were no significant differences in the number of complications between groups that received preventative therapy and those that did not (RD = 0.00, 95 % CI −0.06 to 0.07). The $P$ value was 0.97, which was not statistically significant. Heterogeneity $[I]^2 = 0$ %, as demonstrated in Fig. 9. No major complications were noted in any of the studies.

In the study of Hanaoka, two complications occurred in the therapy group (2/30 = 7 %), a deep laceration without drilling and a local bleeding that required hemostatic therapy; however, this study did not describe whether there were any complications in the control group, so Hanaoka's study was excluded from the meta-analysis of the complications, as shown in Figs. 13 and 14.

To assess whether these results also occurred if we selected only randomized studies, we performed another meta-analysis, as shown in Figs. 15 and 16.

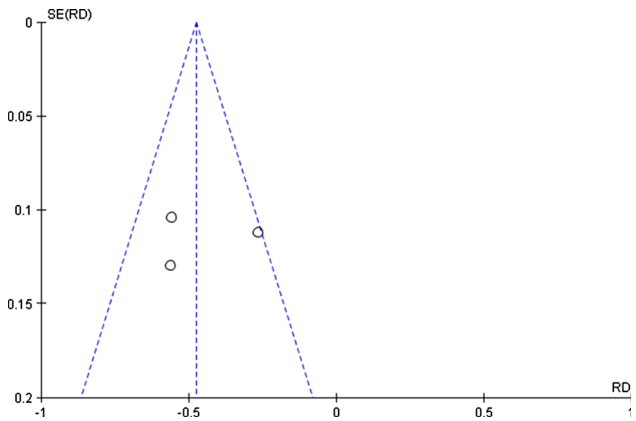


**Fig. 11** Distribution of stenosis rate after esophageal ESD with different preventative therapies in four non-randomized studies (excluded outlier)

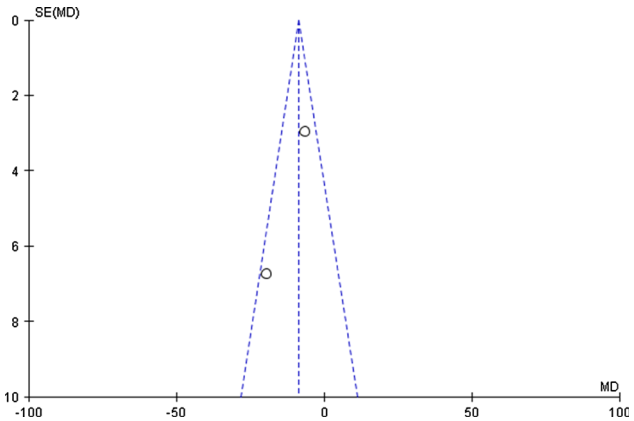


**Fig. 13** Distribution of endoscopy balloon dilatations for resolution of stenosis after esophageal ESD with different preventive therapies in two studies

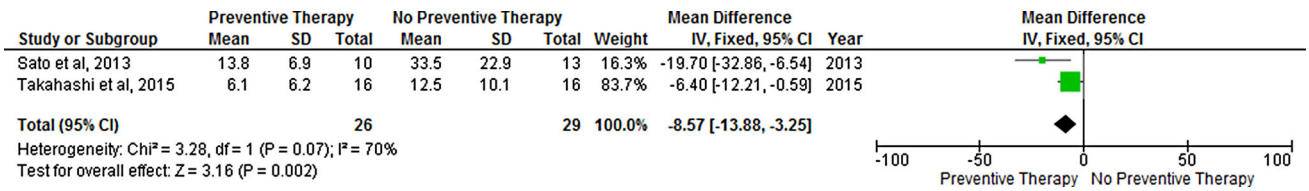


**Fig. 12** Number of endoscopy balloon dilatations for resolution of stenosis after esophageal ESD with different preventive therapies

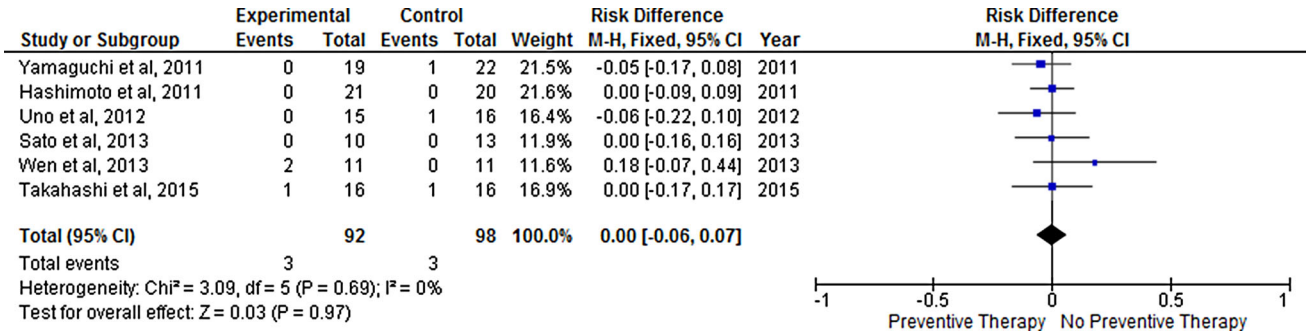


**Fig. 14** Complication rate after esophageal ESD with different preventive therapies

In the new pooled analysis, there was no significant difference in the number of complications between groups that received therapy and those that did not (RD = 0.02, 95 % CI −0.09 to 0.14). The *P* value was 0.26, and heterogeneity $[I]^2 = 25$ %.

To confirm whether these results were also true in non-randomized studies, we conducted another meta-analysis (Figs. 17, 18).

In the new pooled analysis, there was no significant difference in the number of complications between groups that received therapy and those that did not (RD = −0.02, 95 % CI −0.09 to 0.5). The *P* value was 0.63 and heterogeneity $[I]^2 = 0$ %.

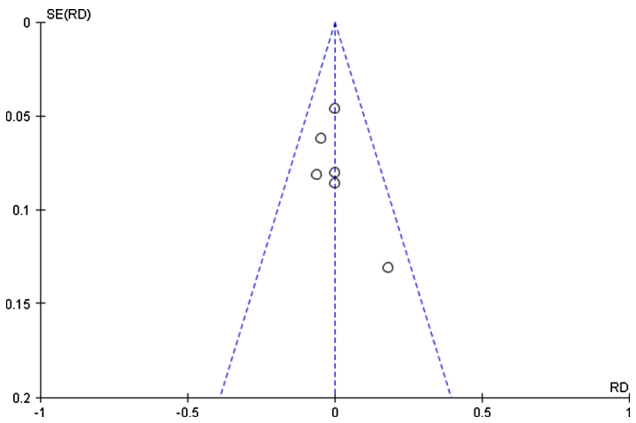


**Fig. 15** Distribution of the six studies' complication rates after esophageal ESD with different preventive therapies to prevent stenosis

### Additional analyses

Although there is no consensus in the literature about the best technique, local injection of corticosteroids after esophageal ESD has promise. In view of this, we compiled the studies that utilized this technique to evaluate the results with regard to reductions in stenosis rate, as shown in Figs. 19 and 20.

In the pooled analysis, the preventive therapy decreased the risk of stenosis after ESD (RD = −0.48, 95 % CI −0.62 to −0.34). The *P* value was <0.00001 and heterogeneity = 40 % (Fig. 21).

## Discussion

In Japan, the ESD method has become the method of choice for the resection of SENs within the esophagus [25, 26]. Although the quality of life after endoscopic treatment is much better than after extended esophagectomy with dissection of regional lymph nodes, a standard surgical procedure for the treatment of esophageal cancer, esophageal stenosis after the endoscopic treatment is a clinical problem for some patients [27]. More significantly, once a severe esophageal stricture has developed, it is difficult to reverse the condition [28].


**Fig. 16** Complication rates after esophageal ESD with different preventive therapies in randomized studies

So far, no prophylactic therapy is indicated after extensive esophageal ESD to prevent postoperative stenosis; however, these recent studies show a decreased risk of stenosis and fewer endoscopic dilatations for the treatment of stenosis without increasing the number of complications.

Theoretically, steroids are the most suitable choice, owing to their mechanism of action, modulating wound healing by preventing inflammation by reducing prolyl hydroxylase, which helps reduce collagen tissue [15, 24, 29, 30].

However, treatment with corticosteroids, especially at high oral doses, may raise concerns associated with adverse effects, including immunosuppression, diabetes, psychiatric disorders, osteoporosis, optical damage, and peptic ulcer disease [15]. Thus, the use of lower dosages with the local injection could minimize these side effects, but sometimes cannot be performed if the patients are in use of platelet anticoagulants or antiplatelet agents for the treatment of cardiovascular or cerebrovascular disease. In addition, the potential risk of esophageal perforation and mediastinitis and pleural effusion is associated with local therapy [31].

Therefore, in patients presenting prohibitive risks for the use of corticosteroids, prevention of esophageal strictures by the use of stents may be a good choice despite the risk of migration.

So in our study, the best results were observed from the use of local corticosteroid injection and placement of a fully covered stent after ESD. Therefore, a randomized clinical trial comparing the two techniques can help define the best technique.

A promising technique under development is the use of tissue-engineered cell sheets obtained through buccal mucosa cell culture. These sheets are endoscopically transplanted directly to the ulcer surfaces of patients who recently underwent ESD. This technique achieved complete re-epithelialization and no stenosis or postoperative dysphagia in patients undergoing ESD exclusively of the esophagus [32].

## Limitations

A major criticism of this review is due to large heterogeneity of the selected papers, including prospective, retrospective, randomized, and non-randomized studies. However when analyzes were performed in separate groups (total, randomized and non-randomized) the results were similar. The low number of patients, 249, can also be a bias

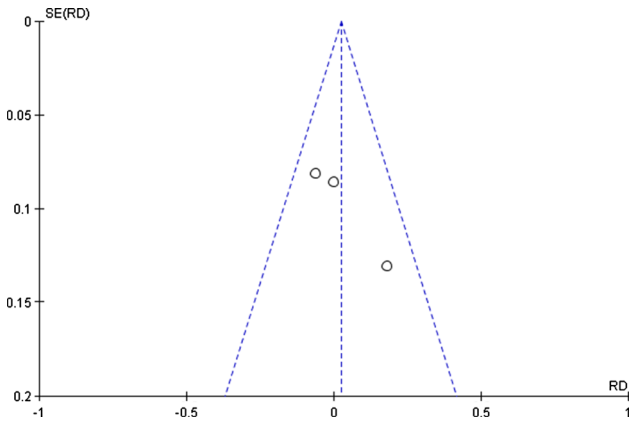


**Fig. 17** Distribution of complication rates in the three randomized studies of esophageal ESD with different preventive therapies to prevent stenosis

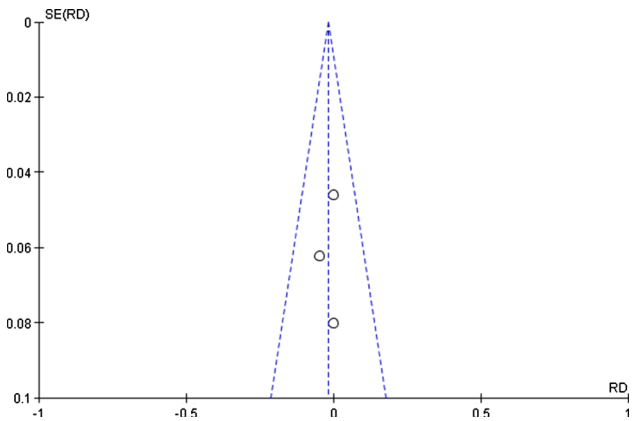


**Fig. 19** Distribution of complication rates in the three non-randomized studies of esophageal ESD with different preventive therapies to prevent stenosis

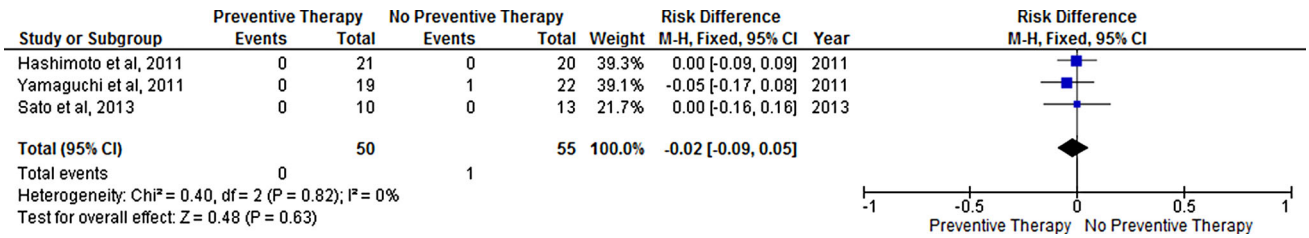


**Fig. 18** Complication rates after esophageal ESD with different preventive therapies in non-randomized studies

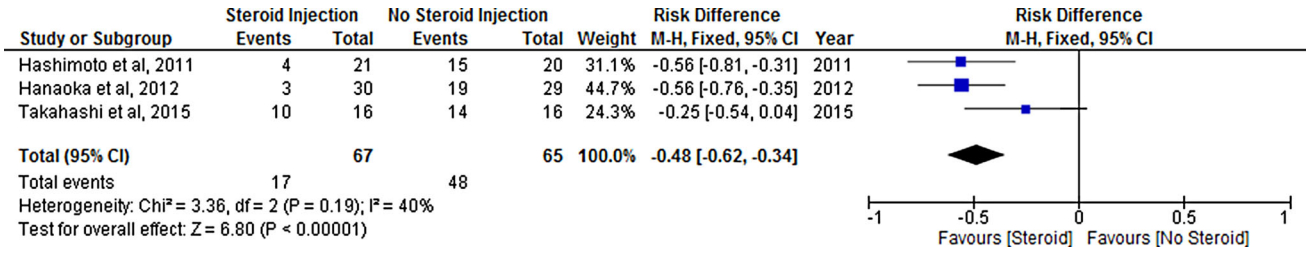


**Fig. 20** Stenosis rate after esophageal ESD using steroid injection

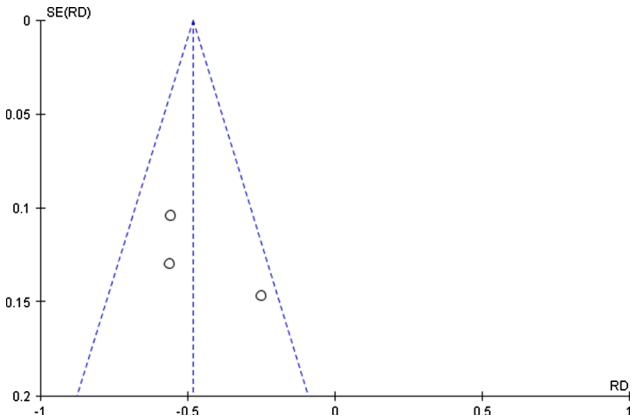


**Fig. 21** Distribution of stenosis rates in the three studies of esophageal ESD using steroid injection

in our study, but this occurs because to the limited number of studies. However, even with this small number of patients, we found in some analyses, as in Figs. 6, 14, and 18, heterogeneity of 0 % and similar weights between studies.

Another important bias across the studies is the duration of follow-up. Of the seven studies included, two [21, 23] had follow-up less than 1 year or not clear. Despite the stenosis manifest generally in 3–5 weeks (when occurs the epithelialization), these patients should have continuous monitoring, not only by the risk of stenosis but also to investigate recurrences and metachronous lesions.

Recurrence of cancer, although not the purpose of our meta-analysis, is mentioned in only three papers [15, 20, 22]. Guo et al. [33] in a review showed that recurrence rate post-ESD is 0.3 %; however, the gold standard therapy remains the esophagectomy. Despite the importance of reducing the stenosis rate, we must maintain appropriate oncologic resections.

## Conclusions

Endoscopic resection of early esophageal tumors, compared with surgical treatment, has lower morbidity and significantly improves quality of life. However, when endoscopic resection was greater than 2/3 of the total circumference, postoperative stenosis rates rose excessively, reducing quality of life.

To reduce these rates, various preventive therapies are being developed, although without being established as protocol. Our study demonstrates that such therapeutic practices reduce the risk of stenosis and the number of endoscopic dilatation for resolution of stenosis without increasing the number of complications.

Randomized clinical trials, with more patients and longer follow-up comparing different therapeutics with each other, are still necessary; however, all of these patients should receive some preventive therapeutic.

### Compliance with ethical standards

**Disclosures** J. F. Oliveira, E.G. H. Moura, W. M. Bernardo, E. Ide, S. Cheng, M. Sulbaran, C. M. L. Santos, and P. Sakai have no conflicts of interest or financial ties to disclose.

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