資料10

SYSTEMATIC REVIEW AND META-ANALYSIS

Efficacy of endoscopic preventive procedures to reduce delayed adverse events after endoscopic resection of superficial nonampullary duodenal epithelial tumors: a meta-analysis of observational comparative trials

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Background and Aims: Although various procedures have been used to prevent serious adverse events after endoscopic resection of the duodenum, their effectiveness has not been determined. In this study, we conducted a systematic review and meta-analysis to determine whether endoscopic preventive procedures reduce delayed adverse events.

Methods: Studies on endoscopic treatment for superficial nonampullary duodenal tumors were selected. We compared the following 2 groups: the closure group, which underwent mucosal sutures and coverage of mucosal defects after resection, and the unclosed group, which did not. The primary outcome was the rate of delayed adverse events, including perforation and bleeding. The pooled risk ratios (RRs) of all outcomes investigated, the 95% confidence intervals (CIs), and *P* values were calculated.

Results: A total of 438 patients from 4 studies were included in the meta-analysis. The pooled overall adverse event rates in the closure group and unclosed group were 3.6% and 21.1%, respectively. This rate was significantly lower in the closure group (RR, 0.19; 95% CI, 0.10-0.38; $P < .01$; $I^2 = 0\%$), and the rate of delayed bleeding was significantly lower in the closure group (RR, 0.14; 95% CI, 0.06-0.33; $P < .01$; $I^2 = 0\%$). Regarding delayed perforation, the RR in the closure group was 0.39 (95% CI, 0.12-1.32; $P = .13$; $I^2 = 0\%$).

Conclusions: Preventive procedures significantly reduced the risk of delayed adverse events by more than 80%. After endoscopic resection of the duodenum, the implementation of preventive procedures, including mucosal sutures and coverage of mucosal defects, to delay adverse events is strongly recommended. (Gastrointest Endosc 2021;93:367-74.)

INTRODUCTION

Superficial nonampullary duodenal epithelial tumors (SNADETs) are relatively rare. Most lesions are found incidentally on upper GI endoscopy for screening, with a prevalence of 0.1% to 4.6%.[1-4] However, with recent advances in endoscopic technologies and in the understanding of SNADETs, the opportunity to detect during screening and then treat duodenal lesions by upper GI endoscopy has been steadily increasing.[5]

In recent years, endoscopic resection by EMR or endoscopic submucosal dissection (ESD) for SNADETs is frequently performed instead of highly invasive surgical procedures, such as the Whipple procedure. Specifically, the complete resection rate in ESD is 80% to 99%,[6-9] indicating its effectiveness as a local treatment for SNADETs. However, duodenal endoscopic resection has a high risk of intraprocedure adverse events. Even if the resection is successful, the rate of delayed adverse events (range,

Abbreviations: CI, confidence interval; ESD, endoscopic submucosal resection; OTSC, over-the-scope clip; PGA, polyglycolic acid; RCT, randomized controlled trial; RR, risk ratio; SNADET, superficial nonampullary duodenal tumor.

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6.3%-17.5%), such as perforation and bleeding, is high due to the anatomically thin wall and direct exposure to bile and pancreatic juice, sometimes resulting in near-fatal events requiring emergency surgery.[10-14]

Thus, various preventive procedures are performed after duodenal endoscopic resection to prevent delayed adverse events.[15-22] However, there is no consensus on their role. Therefore, we conducted a systematic review and meta-analysis on whether preventive procedures are recommended to preclude delayed adverse events after endoscopic resection for SNADETs.

METHODS

Search strategy and selection

A systematic search using PubMed, the Cochrane Library databases, Web of Science, and the Japan Medical Abstracts Society database was conducted up to March 2019 by 2 independent investigators. The detailed search strategy is provided in Appendix 1 (available online at www.giejournal.org). The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement was followed and is provided in Appendix 2 (available online at www.giejournal.org).[23]

Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: (1) randomized controlled trials (RCTs), non-RCTs, and case studies regarding endoscopic treatment for SNADETs, and (2) studies published in English or Japanese. On the other hand, studies were excluded if they were (1) conference abstracts, (2) case reports, (3) studies for other duodenal lesions (such as ampullary carcinoma, distal cholangiocarcinoma, lymphoma, GI stromal tumor, or neuroendocrine tumor) and polyposis syndrome, or (4) duplicated publications (the same patient data published by the same authors in different journals). We also excluded studies with missing or unclear information regarding whether any preventive procedures were performed after the endoscopic treatment. The full-text articles of potentially relevant studies were obtained. We excluded articles that did not report the incidence of delayed adverse events. Studies containing our primary endpoints were included in the noncomparative trial synthesis, including single-arm trials and 2-arm trials. In addition, we performed a comparative trial synthesis after excluding single-arm trials.

Data extraction

The following data were extracted independently by 2 investigators (K.T. and M.K.): name of first author, year of publication, country where study conducted, study design, number of patients included, patient characteristics (age, sex, treatment method, prevention method), presence or absence of comparison for preventive procedures, and outcome of the study.

Risk of bias (quality) assessment

The methodological quality and standard of outcome reporting within the studies were assessed by 2 independent researchers (K.T. and M.K.) to avoid bias. The Newcastle-Ottawa scale was used to assess the quality of the nonrandomized studies.[24] Publication bias was assessed with a funnel plot when 5 or more studies were eligible.

Outcome assessment

We compared the following 2 groups: the closure group, which underwent mucosal sutures and coverage of mucosal defects after resection, and the unclosed group, which did not. Most importantly, cases with incomplete sutures or covering were included in the unclosed group. The primary outcome was the rate of delayed adverse events (delayed bleeding and perforation) after endoscopic resection of SNADETs. We defined a delayed adverse event as any event (including bleeding and perforation) that occurred after the end of the procedure. We also carried out a systematic review to analyze what kind of preventive procedures were performed in the studies.

Statistical analysis

The meta-analysis was performed using a random-effects model. Pooled risk ratios (RRs) were used for all investigated outcomes of the comparative trials with 95% confidence intervals (CIs) and P values, and to harmonize data from the noncomparative cohorts, pooled proportions (ie, delayed perforation and bleeding rates) were used. Statistical heterogeneity was assessed using I^2 statistics. I^2 values less than 30%, 30% to 60%, 61% to 75%, and 76% to 100% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[25] Outcomes from each study were synthesized using a meta-analysis and interaction by meta-regression using the Review Manager Program (RevMan version 5.3., the Cochrane Collaboration, the Nordic Cochrane Center, Copenhagen). Two researchers (K.T. and M.K.) analyzed the data and calculated the pooled incidence independently, and discrepancies were resolved through discussion. We assessed the overall quality of evidence for the primary outcome by applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[26]

RESULTS

Study characteristics and quality

The flow diagram for the study search and selection process is shown in Figure 1. In total, 198 studies were identified through database searches and screened for

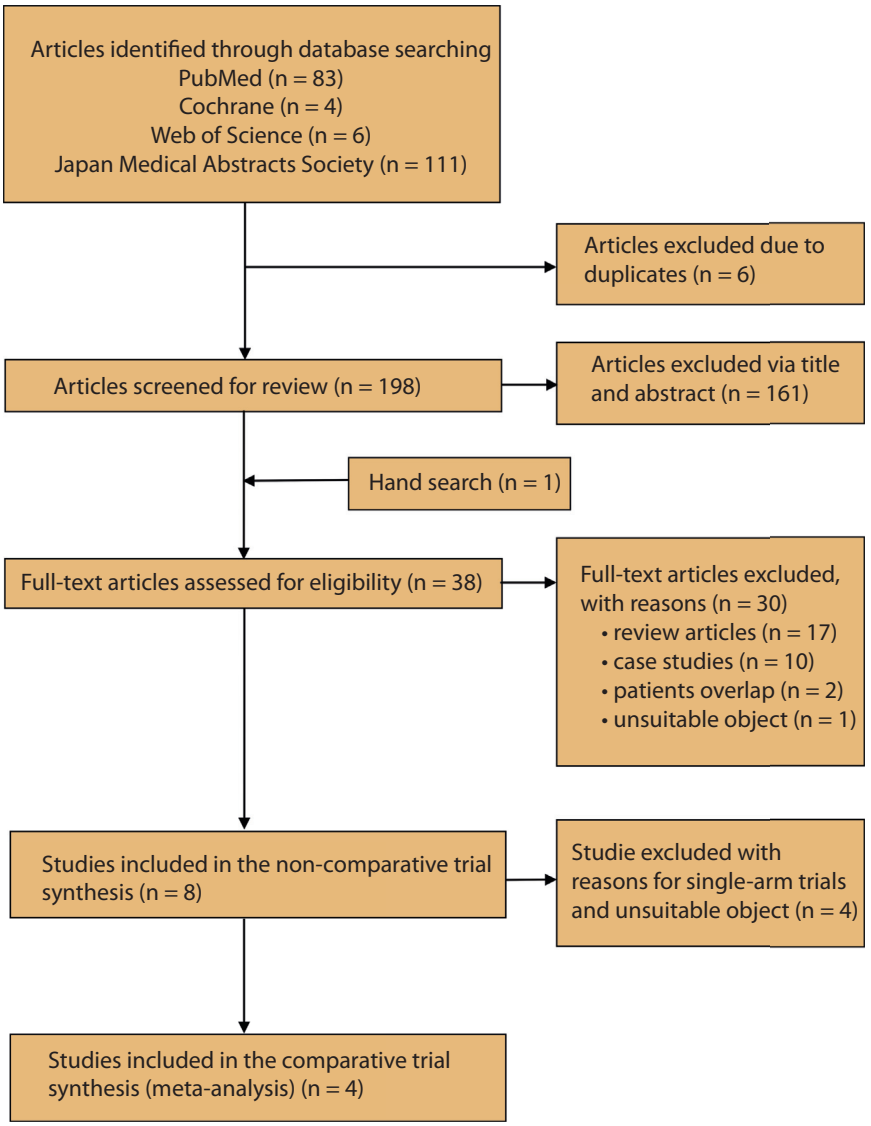

Figure 1. Flow diagram of the search and selection process.

review. One hundred sixty-one studies were excluded based on title and abstract screening. A full-text review of 38 studies, including 1 study selected by a hand search, was performed, and 30 studies were excluded. Eight studies were included in the noncomparative trial synthesis, and the detailed assessment is summarized in Supplementary Table 1 (available online at www.giejournal.org).[7,18,27-32] These 8 studies were of medium to high quality. Of the 8 studies, 3 studies were excluded because they only included single-arm trials, and 1 study in which a preventive procedure was performed only in high-risk cases as determined by each endoscopist without unified criteria was also excluded; finally, 4 studies were included in the comparative trial synthesis.[7,27-29]

Comparative trial synthesis

All 4 studies were performed in Japan. Four observational cohort studies informed the comparative meta-analysis. All 4 studies were conducted between a group that received an intervention, such as clips, clips with a string, an endoloop, or coverage with polyglycolic acid (PGA) sheets after endoscopic resection, and a group that did not receive any successful intervention.

Overall adverse events. A total of 305 patients underwent interventions for closure after endoscopic resection, and in 133 cases, mucosal defects were unclosed. The rates of the pooled overall adverse events, including delayed bleeding and perforation, in the closure group and the unclosed group were 3.6%

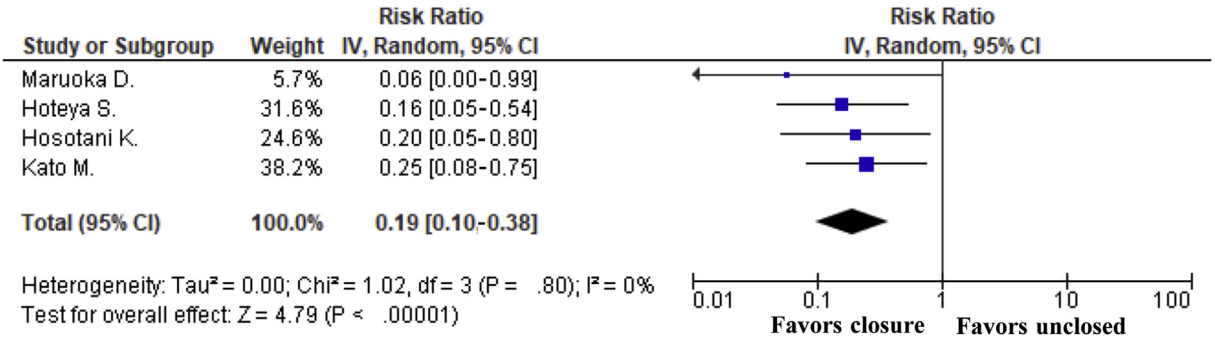

Figure 2. Forest plot indicating the rates of total adverse events. *CI*, Confidence interval; *IV*, interval variable.

and 21.1%, respectively. The RR was 0.19, and the rate of overall adverse events was significantly lower in the closure group, with a low level of heterogeneity (95% CI, 0.10-0.38; $P < .01$; $I^2 = 0\%$) (Fig. 2). In addition, a meta-analysis was performed after dividing the sample into EMR and ESD; delayed adverse events in the closure group were significantly lower in the patients who underwent EMR (RR, 0.06; 95% CI, 0.01-0.25; $P < .01$; $I^2 = 0\%$) (Fig. 3A); although there was a tendency for reduction of adverse events in the patients who underwent ESD, it was not statistically significant in the meta-analysis (RR, 0.37; 95% CI, 0.12-1.17; $P = .09$; $I^2 = 44\%$) (Fig. 3B).

Delayed bleeding. The rates of delayed bleeding in the closure group and the unclosed group were 2.0% and 17.3%, respectively. The rate of delayed bleeding was significantly lower in the closure group, and the RR was 0.14 with a low level of heterogeneity (95% CI, 0.06-0.33; $P < .01$; $I^2 = 0\%$) (Fig. 4).

Delayed perforation. The rates of delayed perforation in the closure group and the unclosed group were 1.6% and 3.8%, respectively. The RR in the closure group was 0.39 (95% CI, 0.12-1.32; $P = .13$; $I^2 = 0\%$) (Fig. 5).

Noncomparative trial synthesis

We examined the specific procedures and the effects for the prevention of adverse events in the 8 studies in the noncomparative trial synthesis (Table 1). The total number of cases in the 8 studies was 800, and the methods included clips, clips with a string, an endoloop, and an over-the-scope clip (OTSC) for suturing, and coverage with PGA sheets after endoscopic resection. The total delayed bleeding rates with intervention and without intervention were 4.3% (95% CI, 2.6-6.0) and 11.4% (95% CI, 7.4-15.4), respectively. In addition, the delayed perforation rates with intervention and without intervention were 1.6% (95% CI, 0.6-2.6) and 2.1% (95% CI, 0.3-3.9), respectively.

Quality of evidence

The overall body of evidence was rated down for serious risk of bias because all studies included in the analysis were retrospective. There was no inconsistency, imprecision, or indirectness for any of the direct comparisons. There was no obvious publication bias because only 4 studies were included. The overall body of evidence was rated as moderate quality (Table 2).

DISCUSSION

In this meta-analysis, we found that successfully applied prophylactic endoscopic methods, such as suturing or covering mucosal defects, reduces the incidence of delayed adverse events after endoscopic resection of the duodenum. This incidence was significantly lower among cases with closure than among cases without closure, with an RR of 0.16. To the best of our knowledge, this is the first meta-analysis to examine the efficacy of the prevention of delayed adverse events after endoscopic resection of lesions in the duodenum.

One of the most important strengths of our study is that in the meta-analysis, we included more than 300 cases with closure; this was a relatively large number of cases for duodenal neoplasia considering the rarity of SNADETs, and statistical heterogeneity was not observed. Although only retrospective studies were included and the risk of bias and imprecision were related to the downgrade of the level of evidence, the results of our study are valuable for further discussions of this topic. Patients with duodenal endoscopic resection are at higher risk for delayed adverse events than patients undergoing resections involving other organs in the digestive tract, such as the esophagus, stomach, or colon. In previous reports, the rates of delayed bleeding and perforation in the esophagus, stomach, and colon were 2.1% to 4.0% and 0.39% to 5.0%,[33-36] respectively, whereas these rates in the duodenum were 5.2% to 17.5% and 1.0% to 18%, respectively.[10-14] This difference

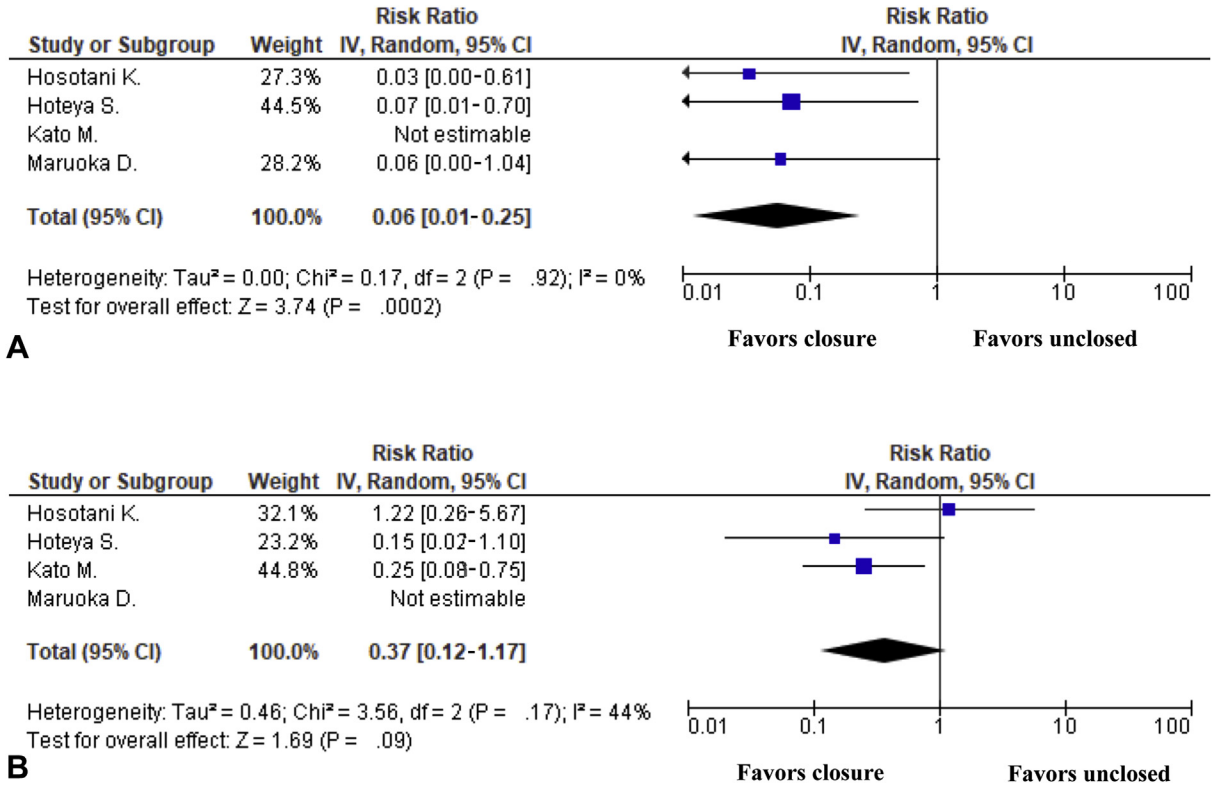

Figure 3. **A**, Forest plot indicating the rates of total adverse events of EMR. **B**, Forest plot indicating the rates of total adverse events of ESD. *CI*, Confidence interval; *IV*, interval variable.

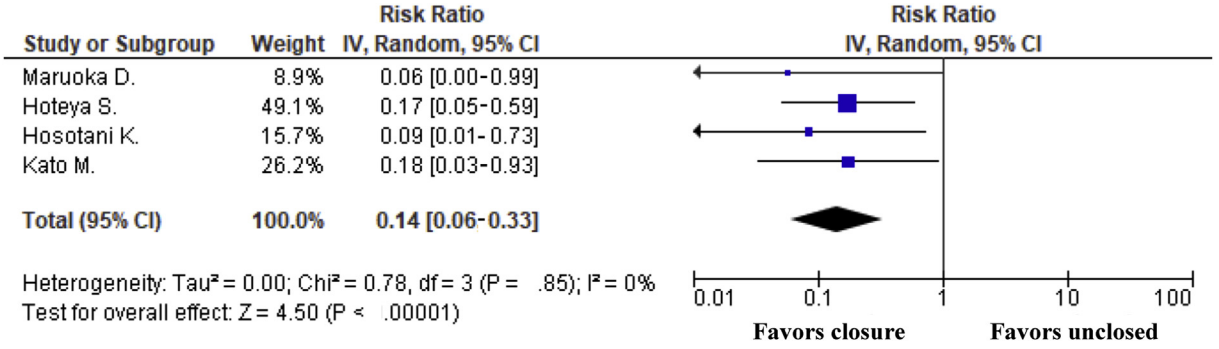

Figure 4. Forest plot indicating the rate of delayed bleeding. *CI*, Confidence interval; *IV*, interval variable.

in outcome between the duodenum and other organs may be due to the anatomic features of the duodenum: The duodenal wall is extremely thin, and the wound is exposed to bile and pancreatic juice, especially if the lesion is located in the distal duodenum. Furthermore, both the frequency and severity of delayed adverse events tend to be higher in the duodenum. A highly invasive surgery that includes emergency laparotomy is required when additional surgical treatment is considered, and even if conservative treatment is possible, a longer hospital stay is required with increased medical costs.[10,37,38] Therefore, various procedures have been performed to prevent delayed adverse events after duodenal endoscopic resection.

In this study, we found a significant decrease in delayed adverse events of more than 80% after duodenal endoscopic resection was performed with preventive procedures. Specifically, protection of the wound revealed a significant decrease in delayed bleeding of almost 90%, whereas the incidence of delayed perforation tended to be low but not significant. One reason for the absence of significance in perforation would be the limited number of delayed perforations.

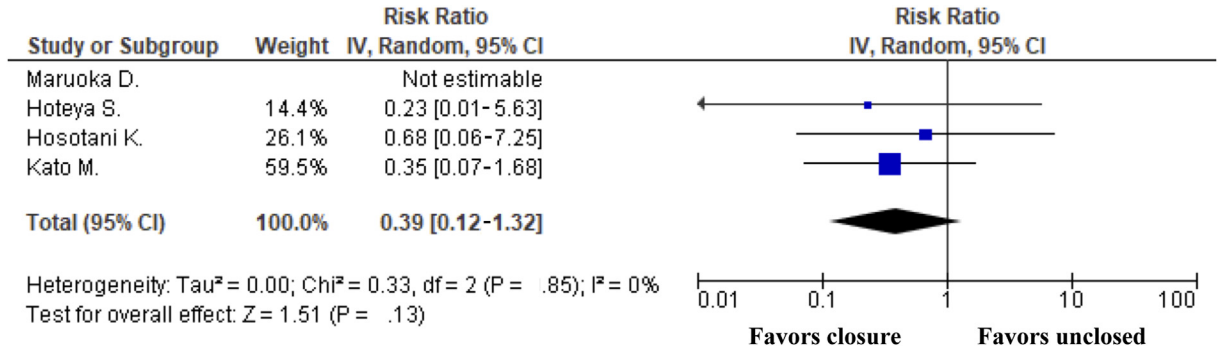

Figure 5. Forest plot indicating the rate of delayed perforation. *CI*, Confidence interval; *IV*, interval variable.

TABLE 1. Characteristics of the 8 studies included in the noncomparative trial synthesis

Study	Design	Intervention	Delayed bleeding (%)			Delayed perforation (%)			Overall (%) (95% CI)
			With intervention (n/N)	Without intervention (n/N)	Total (95% CI)	With intervention (n/N)	Without intervention (n/N)	Total (95% CI)	
Kato et al, 2019[27]	Retrospective, cohort	Clips/clips with a string endoloop, PGA sheets	1.6 (2/128)	8.9 (4/45)	3.5 (0.8-6.2)	2.3 (3/128)	6.7 (3/45)	3.5 (0.8-6.3)	6.9 (3.1-10.7)
Tomizawa and Ginsberg, 2018[32]	Retrospective, cohort	Clips	6.5 (4/62)	3.8 (4/104)	4.8 (1.5-8.1)	0 (0/62)	0 (0/104)	0	4.8 (1.5-8.1)
Muramoto et al, 2018[31]	Retrospective, cohort	OTSC	5.4 (6/112)	NA	5.4 (1.2-9.6)	0.9 (1/112)	NA	0.9 (0.8-2.6)	6.3 (1.8-10.8)
Hosotani et al, 2018[29]	Retrospective, cohort	Clips, PGA sheets	3 (3/99)	14.0 (4/28)	5.5 (1.5-9.5)	4 (4/99)	4 (1/28)	3.9 (0.5-7.3)	9.4 (4.3-14.5)
Tashima et al, 2018[18]	Retrospective, cohort	OTSC	6.3 (3/48)	NA	6.3 (0.6-13.2)	2.1 (1/48)	NA	2.1 (2.0-6.2)	8.3 (0.5-16.1)
Hoteya et al, 2017[7]	Retrospective, cohort	Clips, endoloop	3.9 (3/76)	22.6 (12/53)	11.6 (6.1-17.1)	0 (0/76)	1.9 (1/53)	0.8 (0.7-2.2)	12.4 (6.7-18.1)
Mori et al, 2015[30]	Retrospective, cohort	Clips, OTSC	15.8 (3/19)	NA	15.8 (0.6-32.2)	0 (0/19)	NA	0	15.8 (0.6-32.2)
Maruoka et al, 2013[28]	Case series	Clips	0 (0/19)	42.9 (3/7)	11.5 (0.8-23.8)	0 (0/19)	0 (0/7)	0	11.5 (0.8-23.8)
					6.4 (1.7-8.1)			1.8 (0.9-2.7)	8.1 (6.2-10.0)

CI, Confidence interval; *PGA*, polyglycolic acid; *OTSC*, over-the-scope clip; *NA*, not available.

TABLE 2. Summary of findings for quality of the evidence across systematic reviews

Outcome	Quality assessment					Summary of findings			Quality of the evidence (GRADE)
	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Closure, n/N (%)	Unclosed, n/N (%)	Risk ratio (95% confidence interval)	
Overall adverse events	Serious	Not serious	Not serious	Not serious	Not serious	11/305 (3.6)	28/133 (21.1)	0.19 (0.10-0.38)	⊕⊕⊕◯ moderate

We found that various preventive procedures were attempted, including a simple closure technique using clips, clips with a string,[15,16] an endoloop,[17] an OTSC,[18-20] and coverage with PGA sheets.[21,22] Unfortunately, we could not compare the outcomes according to preventive procedures because many of the studies were single-arm descriptive studies and not comparative studies. Each procedure has pros and cons regarding reliability, technical difficulty, cost, and other issues; therefore, future studies would be required to evaluate their advantages and disadvantages further. In addition, a treatment applying laparoscopic endoscopic cooperative surgery has been reported and is expected to be a promising approach.[39,40]

These preventive procedures also have disadvantages, including the time and cost of the procedure. In a report comparing conventional clips and the OTSC, the total cost of treatment using the OTSC was significantly higher than that using conventional clips (US$7850 vs US$1257, $P = .005$).[30] In addition, the use of PGA sheets and fibrin glue at the same time is expensive, at US$150 and US$310, respectively. In addition, because fibrin glue is a blood product, the risk of infection must be considered.

There are several limitations in this study. First, all the studies were retrospective because there were no RCTs. However, conducting an RCT to examine whether to perform preventive procedures is difficult considering the high incidence rate of delayed adverse events after endoscopic resection in the duodenum. Second, although we included comparative studies with and without a preventive procedure arm, we excluded some studies based on a priori inclusion criteria, which may have induced selection bias in the estimation of the pooled risk of delayed adverse events without preventive procedures. Furthermore, all studies included in the meta-analysis were performed at high-volume centers in Japan, and one particular institution accounted for 163 of 438 cases, which may have introduced selection bias. Third, we were unable to perform a meta-regression analysis of the predictors of delayed adverse events because of ethical issues that prevented us from obtaining data related to individual cases. Fourth, many studies were single-arm studies, and no studies performed direct comparisons of preventive procedures by method. Therefore, future studies should clarify the differences between the methods. Finally, publication bias could not be considered due to the small number of studies. Interpretation of our results should take these limitations and future advancements into consideration.

Based on the results of this study, a significant decrease in delayed adverse events of ~80% was achieved by preventive procedures. Although preventive procedures require time and are costly, it is worth considering the high incidence rate of serious adverse events. We conclude that to limit the risk of delayed adverse events, prophylactic implementation of procedures including mucosal sutures and coverage of mucosal defects after endoscopic resection by EMR or ESD of lesions in the duodenum is strongly recommended.

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APPENDIX 1: SEARCH TERMS

PubMed (N = 83)

(Search "Duodenal Neoplasms"[mh]) AND (Search duodenal cancer*[tiab] OR duodenal tumo*[tiab] OR duodenal carcinoma*[tiab] OR duodenal adenocarcinoma*[tiab] OR duodenal adenoma*[tiab] OR duodenal epithelial tumo*[tiab]) AND (Search "Endoscopy, Gastrointestinal"[mh] OR (endoscop*[tiab] AND (resection*[tiab] OR dissection*[tiab])) AND (Search "Postoperative Complications"[mh] OR "Intestinal Perforation"[mh] OR complication*[tiab] OR bleed*[tiab] OR perforation*[tiab] OR adverse[tiab] OR complications[sh] OR "adverse effects"[sh]) AND (Search "Wound Closure Techniques"[mh] OR prevent*[tiab] OR prophyla*[tiab] OR closure*[tiab] OR shield*[tiab] OR sutur*[tiab] OR "prevention and control"[sh]) AND (Publication date to 2019/03/31)

Japan Medical Abstracts Society (N = 111)

(Duodenal Tumor/MTH OR Duodenal Adenocarcinoma/TA OR Duodenal Adenoma/TA OR Duodenal Tumor/TA) AND (Gastrointestinal Endoscopy/MTH OR Endoscopy/TA AND Resectiom/TA OR Dissection/TA) AND (Postoperative Complications/MTH OR Perforation/MTH OR Complications/TA OR Bleeding/TA OR Perforation/TA OR Adverse/TA or Accidental/TA) AND (Prevention/AL OR Prophylaxis/AL OR Closure/AL OR Suture/AL OR Shield/AL OR Anastomosis/TA OR Sewing/TA) AND (PDAT=//:2019/3/31)

Cochrane (N = 4)

([mh "Duodenal Neoplasms"] OR (duodenal NEAR/3 (cancer OR carcinoma OR adenocarcinoma OR adenoma OR tumo*)):ti,ab,kw) AND ([mh "Endoscopy, Gastrointestinal"] OR (endoscop* AND (resection* OR dissection*)):ti,ab,kw) AND ([mh "Postoperative Complications"] OR [mh "Intestinal Perforation"] OR (complication* OR bleed* OR perforation* OR adverse):ti,ab,kw) AND ([mh "Wound Closure Techniques"] OR (prevent* OR prophyla* OR closure* OR shield* OR sutur*):ti,ab,kw) AND (in Trials)

Web of Science (N = 6)

("Duodenal neoplasms" AND "duodenal cancer" OR "duodenal carcinoma" OR "duodenal adenocarcinoma" OR "duodenal adenoma" OR "duodenal epithelial tumor") AND ("gastrointestinal endoscopy" OR "endoscopic resection" OR "endoscopic dissection") AND ("postoperative complication" OR "intestinal perforation" OR complication OR bleeding OR perforation OR adverse OR complication OR "adverse effects") AND ("wound closure" OR prevention OR prophylactic OR closure OR shield OR suture OR "prevention and control")

APPENDIX 2: PRISMA 2009 CHECKLIST

Section/topic	no	Checklist item	Reported on page no
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7

(*continued on the next page*)

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Section/topic	no	Checklist item	Reported on page no
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	9-10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-13

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Section/topic	no	Checklist item	Reported on page no
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-14
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.

SUPPLEMENTARY TABLE 1. Assessment of study quality

	Selection					Outcome				
Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Compar-ability	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Score	Quality
Kato et al, 2019[27]	*	*	*	*	*	*	*	*	8	High
Tomizawa and Ginsberg, 2018[32]	*	*	*	*	*	*	*	*	8	High
Muramoto et al, 2018[31]	*	*	*	*		*	*		6	Medium
Hosotani et al, 2018[29]	*	*	*	*	*	*		*	7	High
Tashima et al, 2018[18]	*	*	*	*		*	*	*	7	High
Hoteya et al, 2017[7]	*	*	*	*	*	*	*	*	8	High
Mori et al, 2015[30]	*	*	*	*		*	*	*	7	High
Maruoka et al, 2013[28]	*	*	*	*	*	*	*	*	8	High

Score >6, high quality; 4 to 6, medium quality; <4, low quality.