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# Efficacy and safety of underwater endoscopic mucosal resection for superficial non-ampullary duodenal epithelial tumors: Systematic review and meta-analysis

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**Abstract**

**Background** Superficial non-ampullary duodenal epithelial tumors (SNADET) are increasingly found during upper endoscopy. Underwater endoscopic mucosal resection (UEMR) is an emerging technique for the endoscopic resection of SNADET. We performed a systematic review and meta-analysis to evaluate the efficacy and safety of this technique.

**Methods** We conducted a comprehensive search of several databases from inception to August 2019, which included Ovid Cochrane Database of Systematic Reviews, Ovid Embase, Scopus, Ovid Cochrane Central Register of Controlled trials, Ovid MEDLINE®, and In-Process and other non-indexed citations. The primary outcome assessed was the pooled clinical success rate of UEMR. Secondary outcomes included rate of *en bloc* resection, pooled rate of high-grade dysplasia or intramucosal carcinoma (HGIC), and pooled rate of adverse events. Meta-regression analysis was performed based on tumor size.

**Results** A total of 8 study arms were included for analysis with UEMR performed in a total of 258 lesions. The pooled clinical success rate was 89.9% (95% confidence interval [CI] 83.4-94.1). *En-bloc* removal was achieved in 84.6% of treated lesions (95%CI 75.5-90.7). The pooled rate of HGIC was 24.7% (95%CI 10.3-48.3). The pooled rate of adverse events was 6.9% (95%CI 2.5-17.9). This included 10 total adverse events, with the majority being self-limited delayed bleeding. There were no duodenal perforations.

**Conclusions** UEMR for endoscopic resection of SNADET has a high efficacy. In addition, this technique has a high rate of *en bloc* resection and an acceptable adverse event profile. Given these data, UEMR should be considered as a method for endoscopic resection of SNADET.

**Keywords** Duodenum, non-ampullary adenoma, underwater endoscopic mucosal resection

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Conflict of Interest: None

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## Introduction

Superficial non-ampullary duodenal epithelial tumors (SNADET) are uncommonly encountered during upper endoscopy as opposed to ampullary tumors [1]. However, the incidence of non-ampullary adenomas and duodenal adenocarcinoma is increasing. A multicenter study conducted in Japan from 2007-2012 showed 396 SNADET resected lesions in 364 patients [2]. The incidence increased 2-fold over the study duration (from first to second half) and the incidence of duodenal adenocarcinoma increased 3-fold.

There is no standardized technique for endoscopic resection of SNADET. Endoscopic mucosal resection (EMR) with submucosal injection and endoscopic submucosal dissection (ESD) are commonly utilized. EMR has been shown to have a superior safety profile; however, this technique has

the disadvantage of lower rates of complete initial resection, requiring multiple endoscopy sessions, and a recurrence rate of up to 37% [3]. In contrast, ESD has been shown to be superior regarding the rate of complete resection. However, ESD has limited experience in western countries and is associated with higher rates of perforation [4].

Underwater EMR (UEMR) is an emerging technique for endoscopic resection. This technique was first described by Binmoeller *et al* for mucosal resection of large colonic polyps [5]. UEMR for colonic polyps has been shown to be superior to traditional EMR with submucosal injection in terms of macroscopic resection and local recurrence [6]. In addition, subsequent studies have shown that UEMR has low rates of adverse events and self-limited delayed bleeding [7]. UEMR has been more recently described for the endoscopic resection of SNADET. The purpose of our study was to perform a systematic review and meta-analysis of the available literature to evaluate the efficacy and safety of UEMR for SNADET.

## Materials and methods

### Search strategy

We conducted a comprehensive search of several databases from inception to August 2019. An experienced medical librarian assisted with the literature search. The databases searched were as follows: Ovid Cochrane Database of Systematic Reviews, Ovid Embase, Scopus, Ovid Cochrane Central Register of Controlled trials, Ovid MEDLINE®, and In-Process and other non-indexed citations. Controlled vocabulary supplemented with keywords was used to search for studies of interest. The full search strategy is available in Appendix1. The PRISMA and MOOSE checklists were followed and are provided in Appendices 2 and 3 [8,9].

### Study selection

In this meta-analysis, we included studies that evaluated the clinical outcomes of UEMR. Studies were included regardless of sample size, study setting or location, as long as the data needed for the analysis were available.

Our exclusion criteria were studies that had pediatric patients (age <18 years old) and studies not published in the English language. If there were multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

### Data abstraction and quality assessment

Outcomes data from each study were abstracted onto a standardized form by a minimum of 2 authors, and 2 authors independently completed quality scoring. The Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies [10]. The details of this scoring system can be found in Supplementary Table 1.

### Outcomes assessed

1. Pooled rate of clinical success
2. Pooled rate of *en bloc* tumor removal
3. Pooled rate of high-grade dysplasia/intramucosal carcinoma (HGIC)
4. Pooled rate of adverse events

Meta-regression analysis based on the tumor size was also performed. Clinical success was defined in 7 studies as complete endoscopic resection without local recurrence on follow-up examination. A single study defined clinical success as complete endoscopic resection and did not have follow up.

### Statistical analysis

The meta-analysis was carried out by calculating the pooled estimates following the methods suggested by DerSimonian and Laird. The random-effects model was used [11]. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [12]. Heterogeneity was assessed by using the Cochran Q statistical test for heterogeneity, 95% prediction interval (PI) [13-15], and the $I^2$ statistics [16,17]. In the latter, values of <30%, 30-60%, 61-75% and >75% were considered to be of low, moderate, substantial and considerable heterogeneity, respectively [18]. Publication bias was ascertained qualitatively, by visual inspection of a funnel plot, and quantitatively, by the Egger test [19-21]. A P value of <0.05 was used *a priori* to define significance of differences between groups, as provided by the statistical software. All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, NJ).

## Results

### Search results and population characteristics

From an initial 69 studies, 33 records were screened and 25 full-length articles were assessed. Eight studies were included in the final analysis [22-29]. A schematic diagram of the study selection is provided in Supplementary Fig. 1 and the population characteristics are described in Table 1.

### Characteristics and quality of included studies

There were no multicenter or population based studies. Two studies had sample sizes >40. The detailed assessment is

**Table 1** Study and population characteristics

| Author | Design, study period, center, country | Total number of patients | Total number of lesions | Age (mean/ median) | Male/ female | Clinical success (%) | Mean tumor size (mm) | *En bloc* removal | Procedure time (min) | HGD/ IMC | Adverse events | Follow up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yamasaki, 2018 [29] | Single-center, Prospective, Aug 2015 to Jun 2016, Japan | 30 | 31 | 61 | 21/9 | 97 (30/31) | 12 | 27/31 | 5.9 | 13 | 1 (aspiration pneumonia) | 3 |
| Binmoeller, 2013 [22] | Single-center, Prospective, Feb 2012 to Aug 2012, USA | 12 | 12 | 60 (40-70) | 1/11 | 97 (11/12) | 35 (20-150) | NR | 65 | 0 | 4 (2 delayed bleed, 1 stricture, 1 hyponatremia) | 4 |
| Shibuwaka, 2018 [25] | Single-center, Retrospective, Aug 2015 to Dec 2017, Japan | 14 | 16 | 61.9 | 5/9 | 88 (14/16) | 10.5 (6-18) | 14/16 | NR | 9 | 1 (bleed requiring APC next day) | 1-3 |
| Flynn, 2014[26] | Single-center, Prospective, USA | 3 | 3 | NR | NR | 100 (3/3) | 36 (18-50) | 0 | 18 | 0 | 0 | 3 |
| Doyama, 2018 [28] | Single-center, Prospective, 2014 to 2016, Japan | 23 | 23 | 69 | 20/3 | 100 (23/23) | 11 | 17/23 | NR | 10 | 0 | 20 |
| Cornella, 2017 [23] | Single-center, Retrospective, Jan 2007 to Mar 2015, USA | 11 | 11 | 70.6 | NR | 82 (9/11) | 34 (10-60) | NR | 99.1 | 0 | 2 (delayed bleed) | 6 |
| Kiguchi, 2019 [27] | Single-center, Prospective, Nov 2017 to Dec 2018. Japan | 89 | 104 | 62.8 | 71/33 | 87 (90/104) | 10.3 | 78/90 | NR | NR | 2 (delayed bleed) | NR |
| Takahashi, 2018 [24] | Single-center, Prospective Feb 2016 to Feb 2018 | 58 | 58 | 66 | NR | 100 (58/58) | 7 | 53/58 | NR | 0 | 0 | NR |

*HGD, high grade dysplasia; IMC, intramucosal carcinoma; APC, argon plasma coagulation; NR, not reported*

summarized in Supplementary Table 1. Overall, 7 studies were considered to be of medium-quality and one study of high-quality. There were no low-quality studies.

## Meta-analysis outcomes

### *Demographics and clinical success*

There were 258 SNADET resected using the UEMR technique in 240 patients. The median patient age was 64.5 years. The mean tumor size was 19.4 mm (6-150).

Clinical success was reported in 8 studies that evaluated 240 patients. The pooled clinical success rate was 89.9% (95%CI 83.4-94.1). The $I^2$ heterogeneity was 13% with a 95% PI of 76-96.

*En bloc* removal was reported in 6 studies that evaluated 221 patients and the achieved pooled rate was 84.6% of treated lesions (95%CI 75.5-90.7), with an $I^2$ heterogeneity of 44% and 95% PI of 55-96. HGIC lesions reported in 7 studies, evaluated 151 patients. The pooled rate of HGIC lesions was 24.7% (95%CI 10.3-48.3), with an $I^2$ heterogeneity of 70% and 95% PI of 2-87.

### *Adverse events*

Adverse events were reported in 8 studies that evaluated 240 patients. The pooled rate of adverse events was 6.9% (95%CI 2.5-17.9), with an $I^2$ heterogeneity of 60% and 95% PI 1-63. This included 10 total adverse events, of which 9 were postoperative. There were no documented duodenal perforations. There were 7 patients with delayed bleeding. Of these patients, 6 were managed conservatively and 1 patient required endoscopic therapy. Other adverse outcomes included 1 patient with aspiration, 1 patient with postprocedural hyponatremia, and 1 patient who developed a duodenal stricture.

### *Analysis based on tumor size*

A meta-regression analysis was performed based on tumor size and the result was not significant, with a 2-sided P value of 0.47. This was performed to assess if there was any difference in clinical success based on tumor size, and no significant difference was found. The pooled results are summarized in Table 2 and Supplementary Fig. 2-5.

## Validation of meta-analysis results

### *Sensitivity analysis*

We excluded each study, one at a time, and analyzed the effect on the main summary estimate. This was to assess whether any single study had a dominant effect on the meta-analysis outcome results. In this analysis, no single study significantly affected the outcome or the heterogeneity. This was performed for all outcomes.

**Table 2** Summary of pooled results

| Outcomes | Pooled rate (95%CI, $I^2$) |
|---|---|
| Clinical success (8 studies, 240 patients) | 89.9% (83.4-94.1, 13) (PI: 76-96) |
| *En bloc* removal (6 studies, 221 patients) | 84.6% (75.5-90.7, 44) (PI: 55-96) |
| HGD/Intramucosal Ca (7 studies, 151 patients) | 24.7% (10.3-48.3, 70) (PI: 2-87) |
| Adverse events (8 studies, 240 patients) | 6.9% (2.5-17.9, 60) (PI: 1-63) |
| Meta-regression based on tumor size | 2-sided P-value=0.47 |
| Publication bias, Eggers 2-tailed P-value=0.07 | |

*HGD, high-grade dysplasia; Ca, carcinoma; CI, confidence interval; PI, prediction interval*

**Table 3** Summary of findings, quality of evidence

| Outcomes | Number of studies / patients | Quality of evidence (GRADE) |
|---|---|---|
| Clinical success | 8 studies, 240 patients | Low |
| *En bloc* removal | 6 studies, 221 patients | Low |
| HGD/ Intramucusal Ca | 7 studies, 151 patients | Low |
| Adverse events | 8 studies, 240 patients | Low |

*HGD, high-grade dysplasia; Ca, carcinoma*

### Heterogeneity

We assessed the dispersion of the calculated rates using the PI and $I^2$ percentage values. The PI gives an idea of the range of the dispersion and $I^2$ tell us what proportion of the dispersion is true vs. chance [15]. The calculated PIs are reported with the pooled results in Table 2. The PI was narrow with minimal heterogeneity in the pooled clinical success rate.

### Publication bias

Publication bias assessment was carried out in relation to the primary outcomes in hand, which were the pooled rate of clinical success and pooled rate of *en bloc* removal. Based on visual inspection of the funnel plot, as well as quantitative measurement using the Egger regression test, there was no evidence of publication bias (Supplementary Fig. 6, Eggers 2-tailed P=0.07, 0.6).

### Quality of evidence

The GRADE working group approach was used to assess the quality of evidence [30]. Observational studies start with a low-quality rating. This meta-analysis would be considered low quality of evidence, based on factors such as publication bias, heterogeneity, risk of bias and indirectness. These results are summarized in Table 3.

## Discussion

In this study we present a systematic review and meta-analysis of the efficacy and safety of UEMR for SNADET. The pooled clinical success rate was 89.9% and the adverse event rate was 6.9%. The adverse events were generally self-limited, with no documented perforations. In addition, the *en bloc* resection rate was high at 84.6%. Meta-regression analysis showed no significant difference in clinical success based on tumor size. Based on these results, this technique appears to be a safe and effective method for endoscopic resection in the duodenum.

UEMR is an emerging technique for resection of superficial epithelial tumors in the gastrointestinal tract. The efficacy and safety of this technique is well described for resection of colonic polyps. In a recent systematic review and meta-analysis of UEMR for colorectal lesions, complete resection was achieved in 96.4% of lesions and the adverse event rate was low at 3.3%. As in our analysis, no cases of perforation, a feared complication of both EMR and ESD, were reported [31].

Several factors make complete endoscopic resection of mucosal lesions difficult in the duodenum. These include a relatively narrow lumen, occasional luminal angulation, glandular formation precluding adequate submucosal lifting, and a thin muscular wall, which may increase the risk of perforation [32]. The most commonly described technique is traditional EMR with submucosal injection. A recent systematic review of 10 studies showed a 93% rate of complete resection using traditional EMR. However, this technique was also associated with a pooled bleeding rate of 16%, a perforation rate of 1% and a recurrence rate of 15% [33]. There was a delayed bleeding rate of 5% requiring endoscopic therapy, with one patient requiring surgical intervention.

Although less well studied, ESD is also a commonly utilized technique for the treatment of SNADET. This procedure is associated with less procedural bleeding than EMR; however, it carries a high perforation rate of 6-50%, limiting its utility in this setting [34-36]. In addition, this technique is not frequently employed in western countries, thus limiting its generalizability.

UEMR for SNADET has thus far shown promise. The pooled clinical success rate is comparable to both EMR and ESD. In addition, the adverse event profile appears acceptable, with no documented duodenal perforations and relatively benign post-procedural bleeding in previous studies.

There are several strengths to this study. There were no low-quality studies included. In addition, there was minimal heterogeneity and no publication bias found. However, the study also has limitations. Given the novelty of UEMR for SNADET, only 8 studies were included for analysis. In addition, all of the studies were single-center observational studies, although the majority were prospective. There was also a wide range in the mean size of tumor resection (6-150 mm). Finally,

2 studies did not report on rate of *en bloc* resection, 1 study did not report on HGIC, and 1 study did not report follow-up endoscopic examinations. Regardless, there is a relative paucity of data regarding endoscopic resection of SNADET and this study supports using UEMR in this setting.

In conclusion, UEMR appears to be an effective technique for SNADET. In addition, the adverse event profile is acceptable, with no documented duodenal perforation. Based on these results, this technique should be considered as a therapeutic option for resection of SNADET.

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### Summary Box

**What is already known:**

- The incidence of superficial non-ampullary duodenal epithelial tumors (SNADET) is increasing
- Commonly used techniques for endoscopic removal including traditional endoscopic mucosal resection (EMR) and endoscopic submucosal dissection both have limitations in this setting
- Underwater EMR (UEMR) is an emerging technique for endoscopic resection; previous studies involving the colorectum have shown excellent efficacy and safety

**What the new findings are:**

- UEMR has high pooled rates of clinical success and *en bloc* removal for SNADET
- UEMR has an acceptable pooled rate of adverse events, with no documented duodenal perforations
- UEMR is an effective technique for endoscopic removal of SNADET

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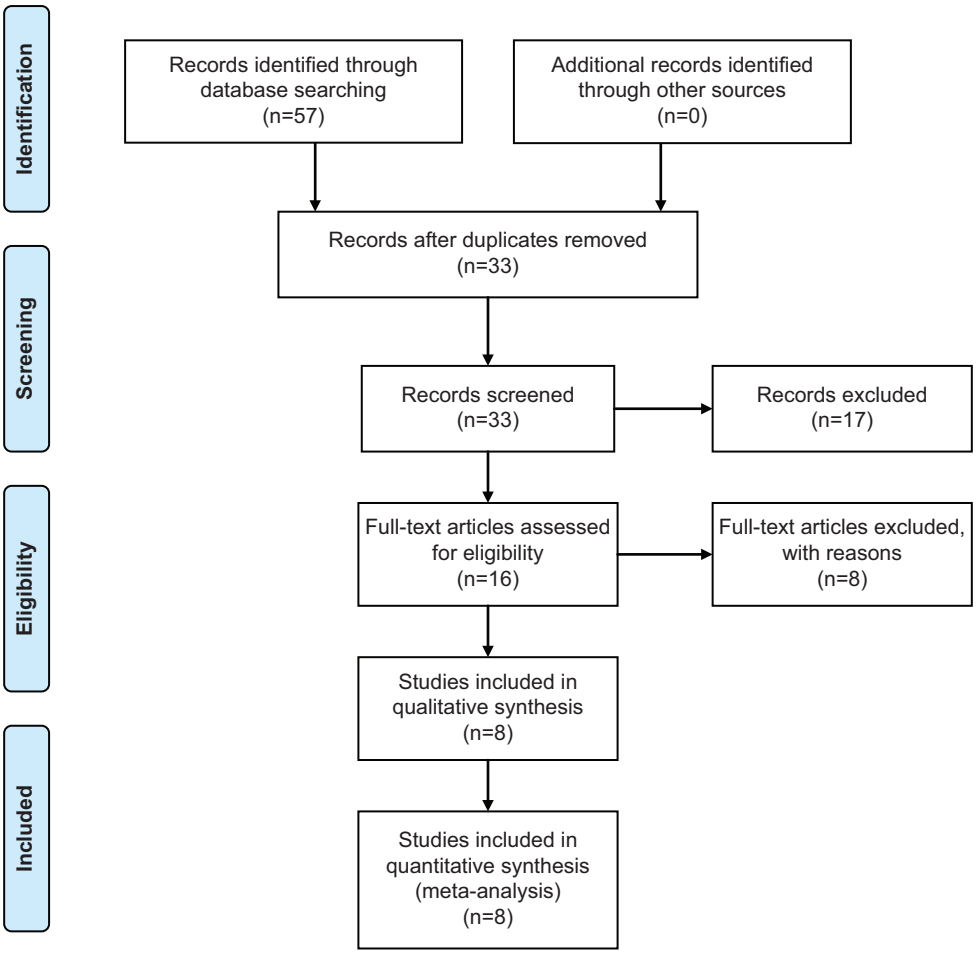
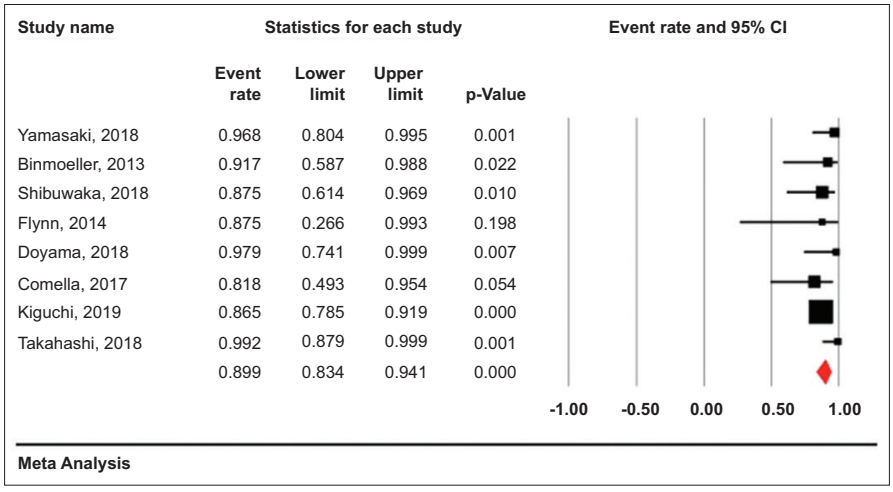
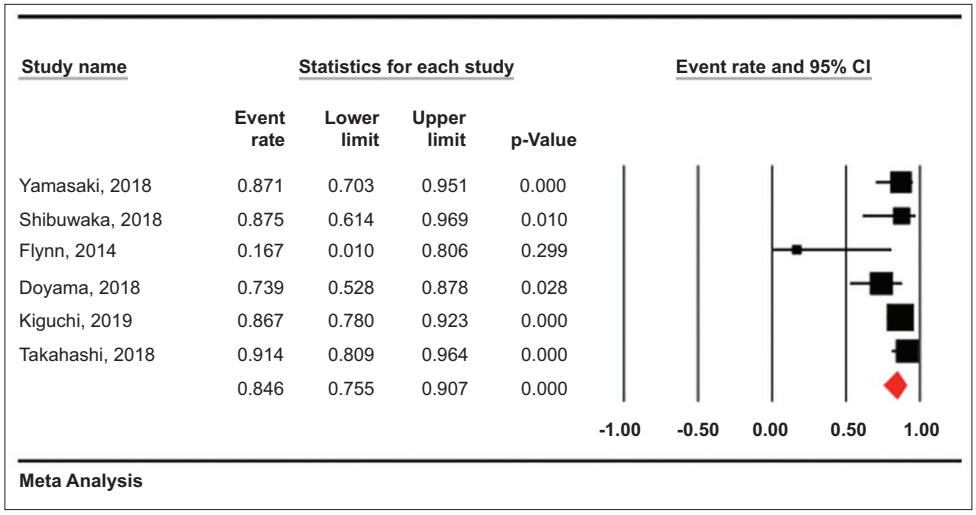
## Supplementary material



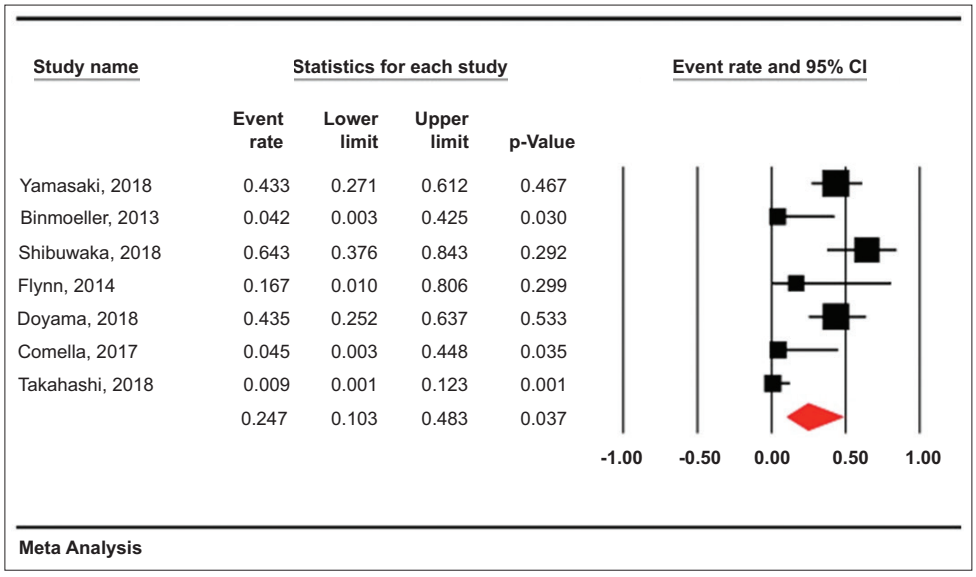

**Supplementary Figure 1** Study flow selection



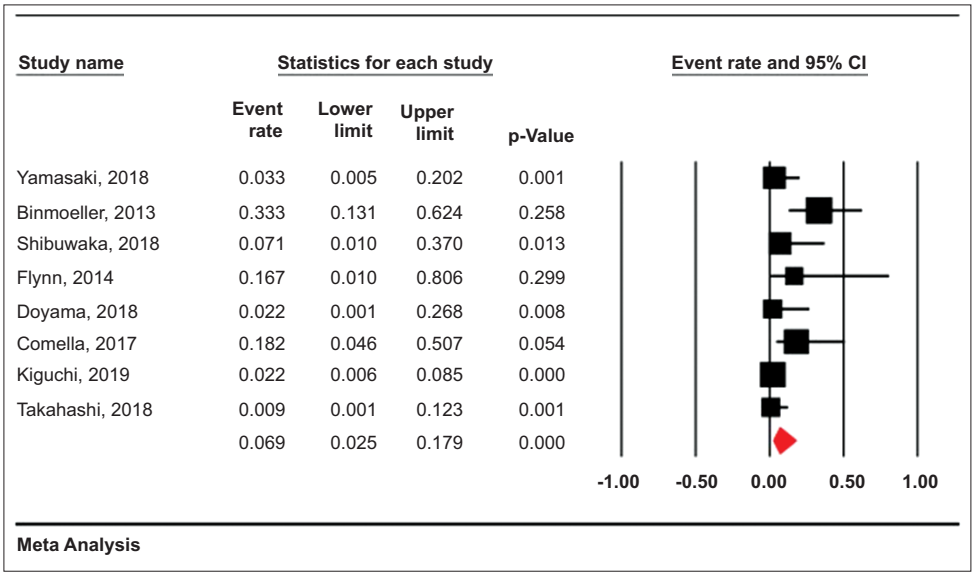

**Supplementary Figure 2** Forest plot, clinical success



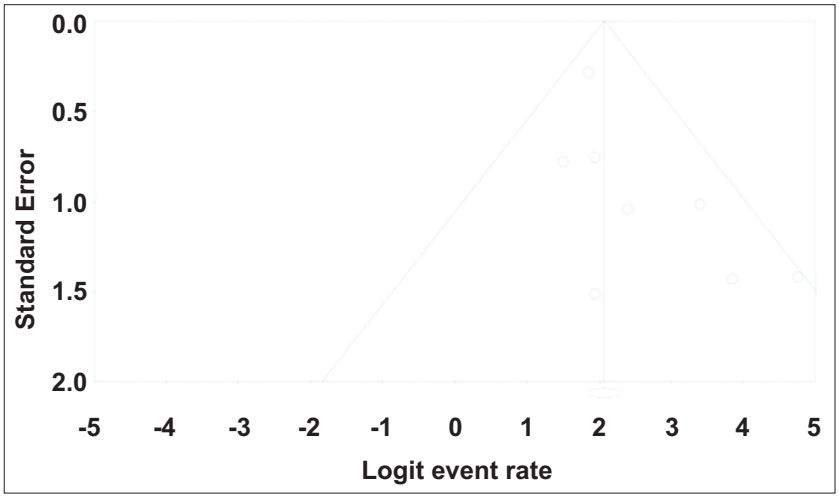

**Supplementary Figure 3** Forest plot, *en bloc* removal




**Supplementary Figure 4** Forest plot, high-grade dysplasia / intramucosal carcinoma




**Supplementary Figure 5** Forest plot, adverse events




**Supplementary Figure 6** Funnel plot

**Supplementary Table 1** Study quality assessment

| STUDY | Selection | | | | Comparability | Outcome | | | Score | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the average adult in community | Cohort size | Information on weight-loss outcomes | Outcome not present at start | Factors comparable between the groups | Adequate clinical assessment | Follow-up time of 12-months | Adequacy of follow up | MAX=8 | HIGH>6, MEDIUM 4 to 6, LOW <4 |
| | population-based: 1; multi-center: 0.5; single-center: 0 | >40 patients: 1; 39 to 20: 0.5; <20: 0 | information with clarity: 1; information derived from percentage value: 0.5; unclear: 0 | not present: 1; present: 0 | yes: 1; no: 0 | yes: 1; no: 0 | yes: 1; not mentioned: 0 | all patients followed up: 1; >50% followed up: 0.5; <50% followed up OR not mentioned: 0 | | |
| Yamasaki, 2018 | 0 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 6.5 | HIGH |
| Binmoeller, 2013 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 6 | MEDIUM |
| Shibuwaka, 2018 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 6 | MEDIUM |
| Flynn, 2014 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 6 | MEDIUM |
| Doyama, 2018 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 6 | MEDIUM |
| Cornella, 2017 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 6 | MEDIUM |
| Kiguchi, 2019 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 6 | MEDIUM |
| Takahashi, 2018 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 6 | MEDIUM |

## APPENDIX 1

Literature search strategy:

**Strategy:**

**PubMed (15)**
((Underwater AND endoscop*) OR "UW-EMR" OR UEMR) AND (duodenum OR duodenal) Limit to English

**Embase (26)**
(underwater AND endoscop* OR "UW-EMR" OR uemr) AND ('duodenum'/exp OR duodenum* OR duodena*)AND [english]/lim

**Scopus (16)**
(TITLE-ABS-KEY ((underwater AND endoscop*) OR "UW-EMR" OR uemr) AND TITLE-ABS-KEY (duoden*))

**APPENDIX 2**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **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. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3-4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3-4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | -na- |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| 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). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4-5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4-5 |
| 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. | 5 |

| | | | |
|---|---|---|---|
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5-6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5-6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5-6 |
| **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. | 6 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6 |
| 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). | 7 |
| 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. | 7 |
| Synthesis of results | 21 | Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency | 6 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 7 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 6-7 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 7-9 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 7-9 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 7-9 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;**6**:e1000097*

**APPENDIX 3** MOOSE Checklist for meta-analyses of observational studies

| Item No | Recommendation | Reported on Page No |
|---|---|---|
| Reporting of background should include | | |
| 1 | Problem definition | 3-4 |
| 2 | Hypothesis statement | - |
| 3 | Description of study outcome(s) | 4-5 |
| 4 | Type of exposure or intervention used | 4-5 |
| 5 | Type of study designs used | 4-5 |
| 6 | Study population | 4 |
| Reporting of search strategy should include | | |
| 7 | Qualifications of searchers (e.g., librarians and investigators) | 4, appendix1 |
| 8 | Search strategy, including time period included in the synthesis and key words | 4, appendix1 |
| 9 | Effort to include all available studies, including contact with authors | 4 |
| 10 | Databases and registries searched | 4, appendix 1 |
| 11 | Search software used, name and version, including special features used (e.g., explosion) | Appendix1 |
| 12 | Use of hand searching (e.g., reference lists of obtained articles) | -na- |
| 13 | List of citations located and those excluded, including justification | Appendix1 |
| 14 | Method of addressing articles published in languages other than English | -na- |
| 15 | Method of handling abstracts and unpublished studies | 4 |
| 16 | Description of any contact with authors | -na- |
| Reporting of methods should include | | |
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 4 |
| 18 | Rationale for the selection and coding of data (e.g., sound clinical principles or convenience) | 4 |
| 19 | Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability) | 4 |
| 20 | Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate) | 4 |
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 7 |
| 22 | Assessment of heterogeneity | 7 |
| 23 | Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 5 |
| 24 | Provision of appropriate tables and graphics | Table1, supplementary materials |
| Reporting of results should include | | |
| 25 | Graphic summarizing individual study estimates and overall estimate | Supplementary materials |
| 26 | Table giving descriptive information for each study included | Supplementary Table 1 |
| 27 | Results of sensitivity testing (e.g., subgroup analysis) | 6-7 |
| 28 | Indication of statistical uncertainty of findings | 5 |
| Reporting of discussion should include | | |
| 29 | Quantitative assessment of bias (e.g., publication bias) | 7 |
| 30 | Justification for exclusion (e.g., exclusion of non-English language citations) | -na- |
| 31 | Assessment of quality of included studies | 7, Supplementary Table 1 |
| Reporting of conclusions should include | | |
| 32 | Consideration of alternative explanations for observed results | 7-9 |
| 33 | Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review) | 7-9 |
| 34 | Guidelines for future research | 8-9 |
| 35 | Disclosure of funding source | 1 |

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA* 2000;**283**:2008-2012