



Meta-Analysis

Efficacy and safety of endoscopic submucosal dissection for non-ampullary duodenal polyps: A systematic review and meta-analysis

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ABSTRACT

Background and aims: Endoscopic submucosal dissection (ESD) is commonly used to treat early-stage digestive cancer because it results in a higher frequency of en-bloc resection and a lower frequency of local recurrence. However, the efficacy and safety of duodenal ESD remain unclear. Therefore, present study is aimed at evaluating clinical outcomes of duodenal ESD.

Methods: To evaluate the efficacy and safety of duodenal ESD, electronic databases (MEDLINE, CENTRAL and EMBASE) were searched by two independent reviewers. The authors were contacted for additional information. A meta-analysis was performed to evaluate the efficacy and safety of duodenal ESD.

Results: A total of 7 studies (203 patients) were included in the quantitative synthesis analysis. The pooled proportions of the frequencies of en-bloc resection, need for surgical intervention, bleeding, intraoperative perforation and delayed perforation were 87%, 4%, 2%, 15% and 2%, respectively. The quality of evidence regarding on surgical intervention outcomes was rated as moderate, whereas that of en-bloc resection was rated as low because of its marked inconsistency.

Conclusions: Duodenal ESD produced acceptable outcomes in terms of the en-bloc R0 resection, but the incidence of procedure-related adverse events is high (PROSPERO register, CRD42017057110).

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1. Introduction

Recent advances in endoscopic imaging has increased the detection of duodenal tumors [1]. Among duodenal tumors, duodenal adenomas should be resected because they carry a high risk of malignant transformation, with the frequency of malignant transformation ranging from 35 to 85% [2–5]. However, they are relatively rare tumors with a reported prevalence of 0.4% [6], and only a few small case series have been published about their management. Thus, the optimal management strategy of these lesions is yet to be determined.

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At present, surgeries involving pancreaticoduodenectomy (PD) and local excision are commonly used two alternative strategies for the removal of duodenal tumors. PD is a highly invasive procedure (although it is also the most radical treatment), and it was reported to be associated with significant morbidity (41–52.2%) and mortality (1–2.1%) [7,8]. On the other hand, local excision is characterized by high frequencies of recurrence [9]. Considering the drawbacks associated with surgery, endoscopic resection could represent a valid alternative treatment for duodenal tumors [10,11].

Endoscopic submucosal dissection (ESD) is an advanced technique, which was originally developed as a resection procedure for gastric neoplasms [12,13]. Compared with traditional surgery, endoscopic resection is now widely accepted to be superior, as it is less invasive and results in better patient quality of life [14]. In addition, as ESD produces higher frequencies of en-bloc resection and lower frequencies of local recurrence, irrespective of lesion size, it has become a standard treatment for esophageal squamous cell

neoplasms [15–17], gastric tumors [18–20], and colorectal lesions [21,22]. In some institutions, the therapeutic indications for ESD have been gradually expanded to include duodenal neoplasms, but the efficacy and safety of duodenal ESD remains unclear.

Outcome data about the efficacy and safety of duodenal ESD are limited and restricted to small case series. In this study, we performed a systematic review on clinical outcomes of duodenal ESD for treatment for non-ampullary duodenal tumors.

2. Materials and methods

We performed a systematic review to evaluate the efficacy and safety of ESD for non-ampullary duodenal polyps. This review was conducted in accordance with the Cochrane Collaboration Handbook [23] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Supplementary Table 1) [24]. In addition, it was registered in the international prospective register of systematic reviews (PROSPERO, registration No. CRD42017057110).

2.1. Search strategy and data sources

The MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE databases were searched for relevant literature. The search term combinations used in this study consisted of the following words: Duodenal neoplasms, Polyp*, Tumor*, Adenoma*, Adenocarcinoma*, Carcinoma*, Duodenum, Duodenal, Duodenoscopy, Submuco*, Endoscop*, Endoscopic mucosal resection, and ESD. The detailed search strategy is presented in Supplementary Table 2. In addition, we searched trial registers via the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) to identify ongoing studies.

2.2. Study selection and extraction

Two reviewers (D.W. and H.H.) independently selected relevant studies according to the following criteria: whether they enrolled >10 patients and whether they reported the efficacy or safety of ESD for non-ampullary duodenal polyps, irrespective of the study's country of origin. The studies were limited to those that were written in the English language, published as articles, involved patients aged >18 years old, and involved tumors that were histologically diagnosed as adenoma/cancer without muscle invasion. After the removal of duplicates, all of the studies were initially screened based on their titles and abstracts. Then, the remaining articles had their full text carefully assessed to determine whether they were eligible for inclusion in this review. When the same data from a single research group were reported in multiple publications, only the study involving the largest cohort was included. Any discrepancies between the 2 reviewers were resolved by consensus, with another author (Y.K.) acting as an arbiter.

2.3. Data collection

The following data were extracted from the eligible studies: the first author's name, the year of publication, the number of patients, the country of origin, the cutting device that was used for the ESD, the frequency of surgical intervention for the management of adverse events, the frequency of complete endoscopic resection (the frequency of en-bloc R0 resection), the frequency of local recurrence during the follow-up period, the frequencies of adverse events (bleeding and perforation), and the mortality rate. Where necessary, we contacted the authors of the included studies to obtain any missing data or clarify unclear information.

Table 1
Risk of Bias of the Studies Reported the Efficacy and Safety of Duodenal ESD procedure.

First author	Publication year	No.	Country	Equipment of ESD procedure	Issue of indirectness					Issue of risk of bias					Refs.		
					1	2	3	4	5	6	7	8	9	10		Overall	
Inoue et al.	2014	12	Japan	Flush knife	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	[29]
Mittra et al.	2017	45	Japan	Mainly HK	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	[30]
Hoteva et al.	2017	74	Japan	DK or flex knife and/or HK	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	[31]
Jung et al.	2013	14	Korea	NK or HK or IT-K	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	[32]
Kakushima et al.	2014	12	Japan	Not mentioned	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	[33]
Ishi et al.	2015	16	Japan	Flex knife and/or HK	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	[34]
Yamamoto et al.	2014	30	Japan	IT-K or Muc2	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	[35]

- 1 Was the target population representative for the general population?
- 2 Was the sampling frame a close representation of the target population?
- 3 Was some form of random selection used to select the sample?
- 4 Was the likelihood of nonresponse bias minimal (participation >75% or non-responder analysis)?
- 5 Were data collected directly from the subjects (as opposed to a proxy)?
- 6 Was an acceptable case definition used in the study?
- 7 Was the study instrument reliable and valid?
- 8 Was the same mode of data collection used for all subjects?
- 9 Was the length of the shortest prevalence period for the parameter of interest appropriate?
- 10 Were the numerator and denominator for the parameter of interest appropriate?

Table 2
GRADE assessment.

No. of studies	Certainty assessment				Effect				Rate (95% CI)	Certainty
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	No. of events	No. of individuals		
6	Surgical intervention rate Case series (single arm uncontrolled studies)	Not serious	Not serious	Serious ^a	Not serious	None	7	129	Event rate 40 per 1000 (0–70)	⊕⊕○○ MODERATE
7	Enbloc resection rate Case series (single arm uncontrolled studies)	Not serious	Serious ^b	Serious ^a	Not serious	None	180	203	Event rate 870 per 1000 (790–960)	⊕⊕○○ LOW
7	Bleeding rate Case series (single arm uncontrolled studies)	Not serious	not serious	Serious ^a	Not serious	None	7	203	Event rate 20 per 1000 (0–50)	⊕⊕⊕○○ MODERATE
7	Intra-procedure perforation rate Case series (single arm uncontrolled studies)	Not serious	Not serious	Serious ^a	Not serious	None	37	203	Event rate 150 per 1000 (80–220)	⊕⊕⊕○○ MODERATE
7	Delayed perforation rate Case series (single arm uncontrolled studies)	Not serious	Not serious	Serious ^a	Not serious	None	8	203	Event rate 20 per 1000 (0–40)	⊕⊕⊕○○ MODERATE

Question: is the endoscopic submucosal dissection (ESD) an efficient and safe treatment for non-ampullary duodenal polyps?

Setting: patients with superficial non-ampullary duodenal tumor.

GRADE Working group grades of evidence.

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a Patients were not selected randomly.

^b There was significant unexplained heterogeneity for this outcome as defined by an I² score >50%.

2.4. Risk of bias

The risk of bias in each included study was assessed using an existing tool for evaluating prevalence studies [25]. The tool consists of 10 items relating to measurement bias, selection bias, and bias related to the analysis (all items were rated as either high or low risk). These items address both the issue of indirectness and the risk of bias. Each study was classified as having a low risk of bias when ≥ 8 of the 10 items were classified as low risk, a moderate risk of bias when 6–7 of the items were classified as low risk, and a high risk of bias when ≤ 5 items were classified as low risk.

2.5. Study outcomes of prognosis

Study outcomes of prognosis was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [26]. This system can be used to assess the overall quality of the evidence for specific study outcomes of non-randomized trials. The quality of the evidence for each outcome is assessed, and its rating may be 'downgraded' based on the following factors: the risk of bias, inconsistency, imprecision, indirectness, and publication bias. Regarding prognosis, observational evidence was regarded as high-quality evidence before the downgrading process was started. Based on the overall assessment made by the GRADE system, the quality of the evidence for each outcome was rated as high, moderate, low, or very low [25,26].

2.6. Statistical analysis

We conducted meta-analyses of the frequencies of surgical intervention, complete endoscopic resection, local recurrence, adverse events (bleeding and perforation), and mortality. Estimates were pooled across the relevant studies using random-effects models and are reported together with 95% confidence intervals (CI). The percentage of variation attributable to heterogeneity was quantified by calculating the inverse variance index (I²), and a value of >50% was considered to represent heterogeneity. The meta-analyses were performed using the metaprop Stata command in Stata/SE 13.2 (Stata Corp LP, College Station, TX). When a table contained cells with a value of zero, we added 0.5 to each of the cells in the table to allow variance to be calculated [27]. Where appropriate, sensitivity analysis was performed to investigate the effects of each statistical method or the addition of 0.5 to each value in a table by comparing fixed-effects and random-effects estimates or by comparing the estimates obtained by adding 0.5 to each value in a table with those produced by excluding the equivalent subjects.

3. Results

Literature search and extracted studies

The PRISMA [28] flow diagram for systematic reviews is presented in Fig. 1. An electronic literature search identified a total of 1566 studies (MEDLINE via PubMed: n = 711, EMBASE: n = 845, CENTRAL: n = 10, ICTRP: n = 175) that were potentially eligible for our study. After the removal of 310 duplicates, 1241 studies were excluded based on title and abstract scanning. The eligibility of the remaining 16 studies was assessed by carefully examining the relevant full-text articles, and 8 studies were identified as being eligible. Finally, after excluding an ongoing trial, a total of 7 studies [29–35] were included in the quantitative synthesis analysis.

3.1. Study characteristics

The characteristics of the 7 included studies (203 patients) are summarized in Table 1 and Supplementary Table 3. Two patients were excluded from the final diagnosis for benign histology (hyper-

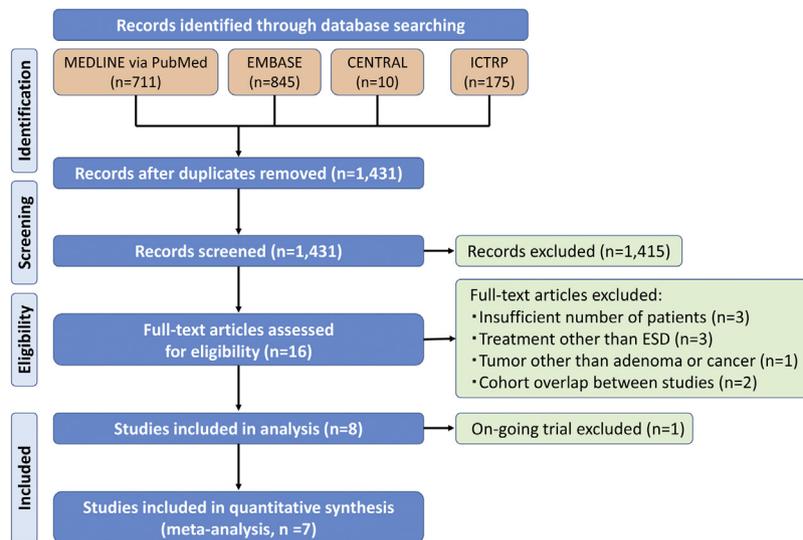


Fig. 1. The PRISMA flow diagram for systematic reviews.

plasia [33] and brunneroma [34]). These studies were published as full-text articles between 2013 and 2017. Of the 7 studies, all but one were carried out in Japan, whereas the remaining study was conducted in Korea. All of the studies were retrospective, and the numbers of patients enrolled in these studies ranged from 12 to 73. ESD was performed using the following knives: the HookKnife (KD-620LR, Olympus, Japan; $n=3$), the ITknife (KD-611L or KD-612L, Olympus, Japan; $n=2$), the FlexKnife (KD-630L, Olympus, Japan; $n=2$), the FlushKnife (DK2618JN, Fujinon, Japan; $n=1$), the DualKnife (KD-650L, Olympus, Japan; $n=1$), a needle knife (KD-1L-1, Olympus, Japan; $n=1$), the Mucosectom 2 (DP-D2518, Pentax, Japan; $n=1$), and not mentioned ($n=1$). We confirmed that all of the patients included in this analysis were older than 18 years by questioning the relevant authors.

3.2. Risk of bias in individual studies

The risk of bias in each included study is summarized in Table 1. The risk of bias associated with item 3 (random selection) was high in all studies, whereas those associated with all of the other examined items were low in all studies. Therefore, the overall risk of bias for all studies (7/7, 100%) was rated as low.

3.3. Frequency of en-bloc R0 resection

The frequency of en-bloc R0 resection was clearly documented in 3 of the 7 studies. In addition, data for the 4 remaining studies were acquired by contacting the relevant authors. The frequency of en-bloc R0 resection was 83.3% (10/12) and 78.6% (11/14), respectively, in the studies by Inoue et al. and Jung et al. After excluding cases of hyperplasia and brunneroma, the frequency of en-bloc R0 resection was 91.7% (11/12) and 80.0% (12/15) in the studies by Kakushima et al. and Ishii et al., respectively. Therefore, a total of 203 patients in 7 studies were available for the meta-analysis of the frequency of en-bloc resection. The frequency of en-bloc resection in the examined studies varied from 78.6 to 98.6%, and the pooled proportion of the frequency of en-bloc resection was 87% according to a random-effects model (Fig. 2, 95%CI: 79–96%). Heterogeneity was detected in this analysis ($I^2=70.16\%$, $p=0.00$). Sensitivity analysis conducted by comparing the estimates obtained using the random-effects model with those obtained using a fixed-effects model showed that the statistical method did not have a marked influence on the pooled estimate (87% vs. 96%).

3.4. Frequency of surgical intervention

The frequency of surgical intervention was clearly documented in 4 of the 7 studies. In addition, data for 2 of the other studies were acquired by contacting the authors. After excluding cases of hyperplasia and brunneroma, the frequencies of surgical intervention in the study by Kakushima et al. and Ishi et al. were 9.1% (1/11), and 6.7% (1/15), respectively. Therefore, a total of 129 patients in 6 studies were available for the meta-analysis of the frequency of surgical intervention. Reason for surgical intervention in this analysis was only due to perforation. The frequency of surgical intervention in the examined studies varied from 2 to 14%, and the pooled proportion of the frequency of surgical intervention was 4% according to a random-effects model (Supplementary Fig. 1, 95%CI: 0–7%). No heterogeneity was detected in this analysis ($I^2=0.0\%$, $p=0.76$).

3.5. Frequency of recurrence

The frequency of recurrence was clearly documented in all but one of the 7 studies, while the data for the remaining study were obtained by contacting the relevant author. No recurrence was observed after ESD for duodenal tumors in any of the 7 studies.

3.6. Frequency of bleeding

The frequency of bleeding was clearly documented in all but one of the 7 studies, while the data for the remaining study were obtained by contacting the author. The frequency of bleeding was 8.3% (1/12) in the study by Inoue et al. Therefore, a total of 203 patients in 7 studies were available for the meta-analysis of the frequency of bleeding. In addition, all bleeding in extracted studies occurred after ESD procedure. The frequency of bleeding in the examined studies varied from 0 to 8.9%, and the pooled proportion of the frequency of bleeding was 2% according to a random-effects model (a continuity correction of 0.5 was applied to each cell with a value of zero) (Supplementary Fig. 2, 95%CI: 0–4%). No heterogeneity was detected in this analysis ($I^2=0.0\%$, $p=0.65$). A sensitivity analysis conducted by comparing the estimates obtained after adding 0.5 to each value with those obtained after excluding the equivalent subjects showed that these methods did not have a marked influence on the pooled estimate (2% vs. 4%).

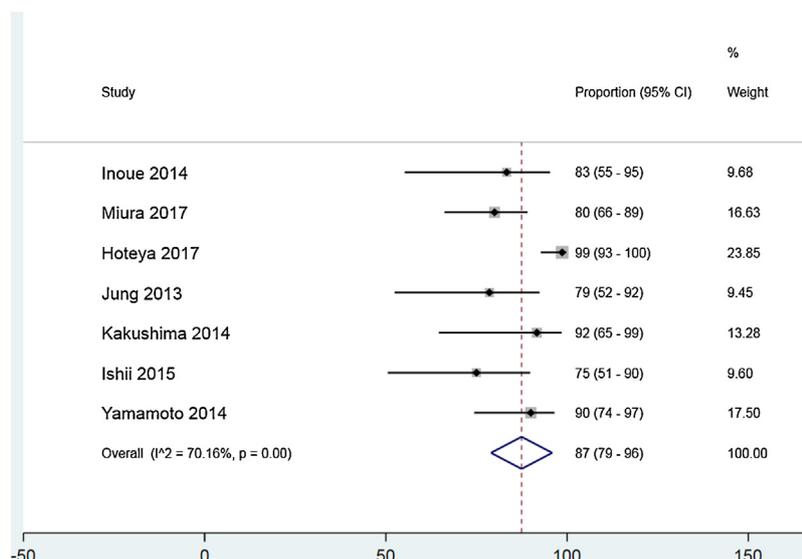


Fig. 2. Forrest plot of studies reporting the frequency of en-bloc resection. The pooled proportion of the frequency of en-bloc resection was 87% (95%CI:79–96%).

3.7. Frequency of intraoperative perforation

The frequency of intraoperative perforation was clearly documented in 4 of the 7 studies. In addition, the data for all of the remaining studies were obtained by contacting the relevant authors. The frequency of intraoperative perforation was 25.0% (3/12) in the study by Inoue et al., while after excluding cases of hyperplasia and brunneroma the frequency of intraoperative perforation was 16.7% (2/12) and 6.7% (1/15) in the studies by Kakushima et al. and Ishi et al., respectively. Therefore, a total of 203 patients in 7 studies were available for the meta-analysis of the frequency of intraoperative perforation. The frequency of intraoperative perforation varied from 6.7 to 27.0% in the examined studies, and the pooled proportion of the frequency of intraoperative perforation was 15% according to a random-effects model (Fig. 3, 95%CI: 8–22%). No heterogeneity was detected in this analysis ($I^2 = 49.56\%$, $p = 0.06$).

3.8. Frequency of delayed perforation

The frequency of delayed perforation was clearly documented in all but one of the 7 studies, while the data for the remaining study were obtained by contacting the author. After excluding cases of hyperplasia, the frequency of delayed perforation was 8.3% (1/12) in the study by Inoue et al. Therefore, a total of 203 patients in 7 studies were available for the meta-analysis of the frequency of delayed perforation. The frequency of delayed perforation in the examined studies varied from 0 to 16.7%, and the pooled proportion of the frequency of delayed perforation was 2% according to a random-effects model (a continuity correction of 0.5 was applied to each cell with a value of zero) (Fig. 4, 95%CI: 0–4%). No heterogeneity was detected in this analysis ($I^2 = 0.0\%$, $p = 0.59$). Sensitivity analysis conducted by comparing the estimates obtained after adding 0.5 to each cell with a value of zero with those obtained after excluding the equivalent subjects showed that these methods did not have a marked influence on the pooled estimate (2% vs. 2%).

3.9. Mortality rate

Mortality rates were documented in all 7 studies, and no mortality was observed after ESD for duodenal tumors in any study.

3.10. Assessment of quality

The results of the quality assessment based on the GRADE system are summarized in Table 2. In all studies, patients were not selected randomly. Moreover, one outcome (the frequency of en-bloc resection) was downgraded because of heterogeneity. Overall, the quality of the evidence regarding the frequencies of surgical intervention, bleeding, intraoperative perforation, and delayed perforation was rated as moderate, and the quality of the evidence regarding the frequency of en-bloc resection was classified as low because of its marked inconsistency.

4. Discussion

In the present study, we systematically reviewed and synthesized the published evidence regarding the efficacy and safety of duodenal ESD. Then, the following outcomes were assessed: the frequencies of surgical intervention, en-bloc R0 resection, local recurrence, bleeding, intraoperative perforation, and delayed perforation. ESD procedures for tumors that arise in other digestive organs exhibit higher frequencies of complete resection and lower risks of local recurrence during the follow-up period. Overall, the pooled proportion of the frequency of en-bloc R0 resection obtained using a random-effects model was relatively high at 87%, but the pooled proportion of the frequency of intraoperative perforation obtained using a random-effects model was also unacceptably high at 15%. Although the quality of the supporting evidence was not high, this suggests that there is substantial room for improvement in ESD procedures for duodenal tumors in order to make them more reliable.

Our systematic review indicated that ESD is useful for treating duodenal tumors, providing that appropriate prophylactic measurements are employed. To the best of our knowledge, this is the first analysis to confirm that ESD for duodenal tumors enables curative resection to be achieved although its safety cannot be guaranteed. Moreover, we evaluated the quality of the analyzed evidence using the GRADE approach.

The reported frequencies of en-bloc R0 resection in ESD procedures performed for superficial squamous cell carcinoma, early gastric adenocarcinoma, and colorectal superficial lesions ranged from 78 to 100% [36], from 88 to 93% [37], and from 53 to 91% [36], respectively. Our systematic review of 7 studies showed that duodenal ESD achieved excellent outcomes in terms of the pooled

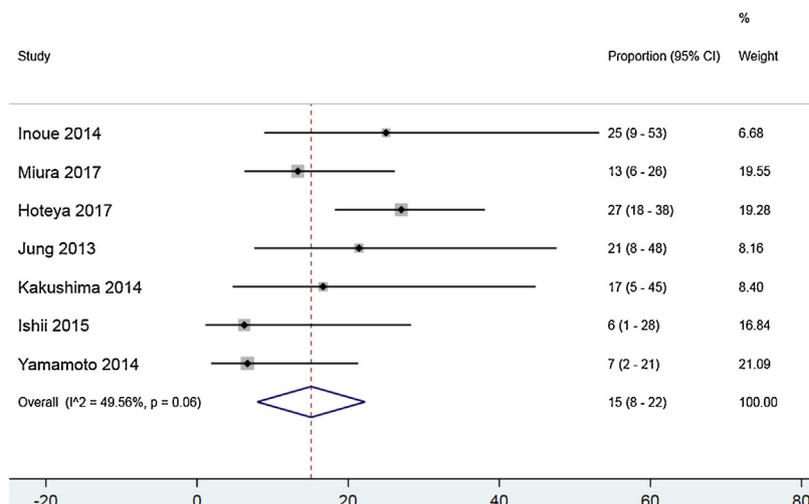


Fig. 3. Forrest plot of studies reporting the frequency of intraoperative perforation. The pooled proportion of the frequency of intraoperative perforation was 15% (95%CI: 8–22%).

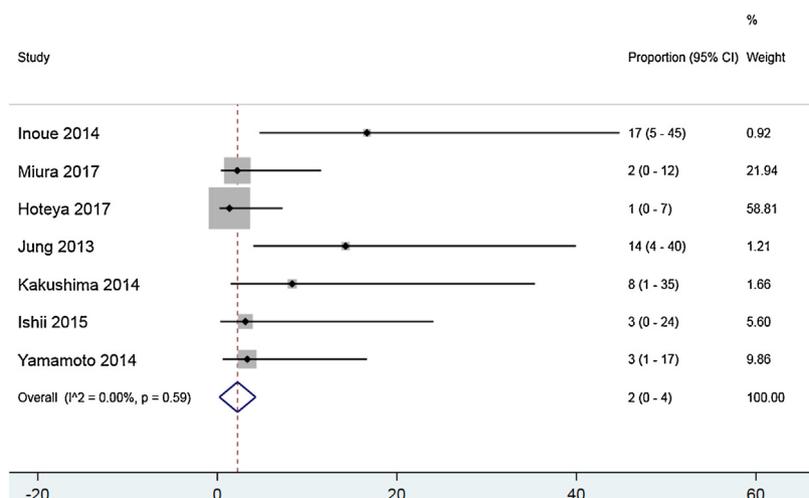


Fig. 4. Forrest plot of studies reporting the frequency of delayed perforation. The pooled proportion of the frequency of delayed perforation was 2% (95%CI: 0–4%).

frequency of R0 resection, which was 87% (95%CI: 79–96%). In addition, as the majority of duodenal tumors that can be treated by endoscopic resection are adenomas, rather than malignant tumors, most locally recurrent lesions that develop from residual primary tumors can be managed using additional endoscopic treatment alone. Therefore, in terms of the frequency of en-bloc R0 resection, duodenal ESD produces clinically acceptable results. However, our analysis showed significant heterogeneity in the estimate of the frequency of en-bloc R0 resection. In this analysis, lower frequencies of en-bloc resection were reported in smaller cohort studies than in larger ones (Ishii et al. reported a frequency of en-bloc resection of 75% (n = 16), whereas Hoteya et al. reported an en-bloc resection frequency of 99% (n = 74)). Given that the number of operations is correlated with the surgeon's level of expertise, we presume that this finding was due to differences in the surgeons' skill levels.

As the frequency of procedure-related adverse events is an important parameter for evaluating treatment safety, we assessed the frequencies of the following 3 adverse events: bleeding, intraoperative perforation, and delayed perforation. In our meta-analysis, the incidence rates of bleeding and delayed perforation

were not very high, whereas the pooled frequency of intraoperative perforation was unacceptably high (15%). Procedure-related perforation is one of the most common and critical drawbacks of ESD, and ESD for squamous cell carcinoma, gastric lesions, and colorectal superficial lesions were reported to result in procedure-related perforation frequencies of 0–4%, 1–4%, and 1.6–18%, respectively [36]. Albeit ESD usually confers advantages over EMR in terms of the en bloc resection rate, the complication rate of perforation was reported to be higher in ESD than in EMR [38,39].

There have only been a few case reports that summarized patients' clinical courses after ESD-related duodenal perforation [29,40]. In the clinical setting, most cases of ESD-related perforation involving the esophagus, stomach, colon, or rectum can be managed using a short period of conservative therapy alone. On the other hand, endoscopic procedure-related duodenal perforation can sometimes cause severe peritonitis due to the leakage of pancreatic and bile juice [41]. Therefore, when conservative therapy is chosen, the patient will sometimes require long-term hospital treatment. Inoue et al. reported that a patient who developed a retroperitoneal abscess after the endoscopic resection of a duo-

denal tumor recovered after conservative therapy, involving the endoscopically guided placement of a nasogastric tube into the duodenum in conjunction with broad-spectrum antibiotic therapy, although they took more than 2 months to recover [29]. In addition, Ohara et al. reported that a patient who suffered duodenal perforation after undergoing ESD for an ulcer, which resulted in a hole connecting the duodenum to the retroperitoneal space, developed a retroperitoneal abscess [40]. Although the patient's condition could be managed with polyglycolic-acid (PGA) sheets and fibrin glue in conjunction with a computed tomography-guided abscess puncture, they were not discharged from hospital until 87 days after the ESD procedure. In the latter report, the author mentioned that if the patient had undergone surgery to treat the perforation they might have recovered more quickly. Therefore, we consider that it is important to evaluate the indications for emergency surgery more carefully, but we should also consider that emergent pancreaticoduodenectomy is a highly invasive and challenging procedure with a cumulative mortality rate of 29% [42].

Our results confirmed that duodenal ESD is an effective procedure for duodenal tumors, although its safety cannot be guaranteed. As ESD for duodenal lesions is not recommended by the American Society for Gastrointestinal Endoscopy (ASGE) [37,43] or the European Society of Gastrointestinal Endoscopy (ESGE) [36], surgery remains the standard treatment for large non-ampullary duodenal tumors at present. To this end, the current systematic review highlights the need for a prophylactic strategy to prevent adverse events, especially procedure-related perforation. Recently, the following techniques for preventing perforation or delayed bleeding have been reported: (i) endoscopic closure of mucosal defects using conventional clips (OTSC) [44] or over-the-scope-clips [45,46], (ii) an endoscopic tissue-shielding method involving PGA sheets and fibrin glue [47,48], (iii) laparoscopy and endoscopy cooperative surgery [49,50], and (iv) laparoscopy-assisted endoscopic full-thickness resection [51,52], etc. Based on the above evidence, we recommend complete endoscopic closure for mucosal defect after endoscopic resection such as using OTSC [44], while devising the method for endoscopic resection like using the pocket-creation method with an ST hood [30] and so on. However, there are limited data regarding the safety of these prophylactic approaches; therefore, further studies are needed to establish novel resection methods involving duodenal ESD for duodenal tumors.

Several limitations of the present study need to be considered. First, all of the studies included in this analysis were retrospective non-randomized studies, which might have introduced patient selection biases, which could in turn have contributed to the high frequency of complete resection observed in our analysis. Second, since all but one of the studies included in this analysis were conducted in Japan, where many patients with early-stage digestive tumors undergo ESD procedures that are carried out by highly experienced endoscopists [20,22,53], the conclusions of this study might not be generalized to other parts of the world.

In conclusion, duodenal ESD produced acceptable clinical outcomes in terms of the frequencies of surgical intervention, en-bloc R0 resection, recurrence, and mortality. However, considering the unfavorable clinical courses of the adverse events of the procedure, particularly perforation, the unacceptably high frequency of adverse events must be improved. In order to establish duodenal ESD as a safe therapeutic strategy for duodenal tumors, reliable prophylactic countermeasures against the associated adverse events must be developed.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dld.2019.03.021>.

References

- [1] Ma MX, Bourke MJ. Management of duodenal polyps. *Best Pract Res Clin Gastroenterol* 2017;31:389–99.
- [2] Schulten MF, Oyasu R, Beal JM. Villous adenoma of the duodenum. A case report and review of the literature. *Am J Surg* 1976;132:90–6.
- [3] Miller JH, Gisvold JJ, Weiland LH, McIlrath DC. Upper gastrointestinal tract: villous tumors. *AJR Am J Roentgenol* 1980;134:933–6.
- [4] Perzin KH, Bridge MF. Adenomas of the small intestine: a clinicopathologic review of 51 cases and a study of their relationship to carcinoma. *Cancer* 1981;48:799–819.
- [5] Galandiuk S, Hermann RE, Jagelman DG, Fazio VW, Sivak MV. Villous tumors of the duodenum. *Ann Surg* 1988;207:234–9.
- [6] Jepsen JM, Persson M, Jakobsen NO, et al. Prospective study of prevalence and endoscopic and histopathologic characteristics of duodenal polyps in patients submitted to upper endoscopy. *Scand J Gastroenterol* 1994;29:483–7.
- [7] Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006;244:10–5.
- [8] Winter JM, Cameron JL, Olin K, et al. Clinicopathologic analysis of ampullary neoplasms in 450 patients: implications for surgical strategy and long-term prognosis. *J Gastrointest Surg* 2010;14:379–87.
- [9] Farnell MB, Sakorafas GH, Sarr MG, et al. Villous tumors of the duodenum: reappraisal of local vs. extended resection. *J Gastrointest Surg* 2000;4:13–21, discussion 2–3.
- [10] Alexander S, Bourke MJ, Williams SJ, Bailey A, Co J. EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). *Gastrointest Endosc* 2009;69:66–73.
- [11] Hoteya S, Yahagi N, Iizuka T, et al. Endoscopic submucosal dissection for nonampullary large superficial adenocarcinoma/adenoma of the duodenum: feasibility and long-term outcomes. *Endosc Int Open* 2013;1:2–7.
- [12] Yamamoto H, Yube T, Isoda N, et al. A novel method of endoscopic mucosal resection using sodium hyaluronate. *Gastrointest Endosc* 1999;50:251–6.
- [13] Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001;48:225–9.
- [14] Conio M, Ponchon T, Blanchi S, Filiberti R. Endoscopic mucosal resection. *Am J Gastroenterol* 2006;101:653–63.
- [15] Fujishiro M, Kodashima S, Goto O, et al. Endoscopic submucosal dissection for esophageal squamous cell neoplasms. *Digest Endosc* 2009;21:109–15.
- [16] Ishihara R, Iishi H, Uedo N, et al. Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. *Gastrointest Endosc* 2008;68:1066–72.
- [17] Guo HM, Zhang XQ, Chen M, Huang SL, Zou XP. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. *World J Gastroenterol* 2014;20:5540–7.
- [18] Park YM, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and meta-analysis. *Surg Endosc* 2011;25:2666–77.
- [19] Lian J, Chen S, Zhang Y, Qiu F. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. *Gastrointest Endosc* 2012;76:763–70.
- [20] Akintoye E, Obaitan I, Muthusamy A, Akanbi O, Olusunmade M, Levine D. Endoscopic submucosal dissection of gastric tumors: a systematic review and meta-analysis. *World J Gastrointest Endosc* 2016;8:517–32.
- [21] Akintoye E, Kumar N, Aihara H, Nas H, Thompson CC. Colorectal endoscopic submucosal dissection: a systematic review and meta-analysis. *Endosc Int Open* 2016;4:E1030–44.
- [22] Fuccio L, Hassan C, Ponchon T, et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 2017;86:74–86.e17.
- [23] Higgins J, Green SP, Cochrane C. *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons; 2008.
- [24] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
- [25] Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65:934–9.

- [26] Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.
- [27] Cai T, Parast L, Ryan L. Meta-analysis for rare events. *Stat Med* 2010;29:2078–89.
- [28] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [29] Inoue T, Uedo N, Yamashina T, et al. Delayed perforation: a hazardous complication of endoscopic resection for non-ampullary duodenal neoplasm. *Digest Endosc* 2014;26:220–7.
- [30] Miura Y, Shinozaki S, Hayashi Y, Sakamoto H, Lefor AK, Yamamoto H. Duodenal endoscopic submucosal dissection is feasible using the pocket-creation method. *Endoscopy* 2017;49:8–14.
- [31] Hoteya S, Furuhashi T, Takahito T, et al. Endoscopic submucosal dissection and endoscopic mucosal resection for non-ampullary superficial duodenal tumor. *Digestion* 2017;95:36–42.
- [32] Jung JH, Choi KD, Ahn JY, et al. Endoscopic submucosal dissection for sessile, nonampullary duodenal adenomas. *Endoscopy* 2013;45:133–5.
- [33] Kakushima N, Ono H, Takao T, Kanemoto H, Sasaki K. Method and timing of resection of superficial non-ampullary duodenal epithelial tumors. *Digest Endosc* 2014;26(Suppl. 2):35–40.
- [34] Ishii N, Akiyama H, Suzuki K, Fujita Y. Safety and efficacy of endoscopic submucosal dissection for non-ampullary duodenal neoplasms: a case series. *ACC Case Rep J* 2015;2:146–9.
- [35] Yamamoto Y, Yoshizawa N, Tomida H, Fujisaki J, Igarashi M. Therapeutic outcomes of endoscopic resection for superficial non-ampullary duodenal tumor. *Digest Endosc* 2014;26(Suppl. 2):50–6.
- [36] Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2015;47:829–54.
- [37] Committee AT, Maple JT, Abu Dayyeh BK, et al. Endoscopic submucosal dissection. *Gastrointest Endosc* 2015;81:1311–25.
- [38] Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009;41:751–7.
- [39] Arezzo A, Passera R, Marchese N, Galloro G, Manta R, Cirocchi R. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. *United Eur Gastroenterol J* 2016;4:18–29.
- [40] Ohara Y, Takimoto K, Toyonaga T, et al. Enormous postoperative perforation after endoscopic submucosal dissection for duodenal cancer successfully treated with filling and shielding by polyglycolic acid sheets with fibrin glue and computed tomography-guided abscess puncture. *Clin J Gastroenterol* 2017;10:524–9.
- [41] Cho KB. The management of endoscopic retrograde cholangiopancreatography-related duodenal perforation. *Clin Endosc* 2014;47:341–5.
- [42] Gulla A, Tan WP, Pucci MJ, et al. Emergent pancreaticoduodenectomy: a dual institution experience and review of the literature. *J Surg Res* 2014;186:1–6.
- [43] Committee ASoP, Chathadi KV, Khashab MA, et al. The role of endoscopy in ampullary and duodenal adenomas. *Gastrointest Endosc* 2015;82:773–81.
- [44] Yilmaz B, Unlu O, Roach EC, et al. Endoscopic clips for the closure of acute iatrogenic perforations: where do we stand? *Digest Endosc* 2015;27:641–8.
- [45] Mori H, Shintaro F, Kobara H, et al. Successful closing of duodenal ulcer after endoscopic submucosal dissection with over-the-scope clip to prevent delayed perforation. *Digest Endosc* 2013;25:459–61.
- [46] Mori H, Ayaki M, Kobara H, et al. Suitable closure for post-duodenal endoscopic resection taking medical costs into consideration. *World J Gastroenterol* 2015;21:5281–6.
- [47] Takimoto K, Toyonaga T, Matsuyama K. Endoscopic tissue shielding to prevent delayed perforation associated with endoscopic submucosal dissection for duodenal neoplasms. *Endoscopy* 2012;44(Suppl. 2 UCTN):E414–5.
- [48] Doyama H, Tominaga K, Yoshida N, Takemura K, Yamada S. Endoscopic tissue shielding with polyglycolic acid sheets, fibrin glue and clips to prevent delayed perforation after duodenal endoscopic resection. *Digest Endosc* 2014;26(Suppl. 2):41–5.
- [49] Hiki N, Yamamoto Y, Fukunaga T, et al. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. *Surg Endosc* 2008;22:1729–35.
- [50] Tsujimoto H, Ichikura T, Nagao S, et al. Minimally invasive surgery for resection of duodenal carcinoid tumors: endoscopic full-thickness resection under laparoscopic observation. *Surg Endosc* 2010;24:471–5.
- [51] Abe N, Takeuchi H, Shibuya M, et al. Successful treatment of duodenal carcinoid tumor by laparoscopy-assisted endoscopic full-thickness resection with lymphadenectomy. *Asian J Endosc Surg* 2012;5:81–5.
- [52] Ohata K, Murakami M, Yamazaki K, et al. Feasibility of endoscopy-assisted laparoscopic full-thickness resection for superficial duodenal neoplasms. *Sci World J* 2014;2014:239627.
- [53] Marin-Gabriel JC, Fernandez-Esparrach G, Diaz-Tasende J, Herreros de Tejada A. Colorectal endoscopic submucosal dissection from a Western perspective: today's promises and future challenges. *World J Gastrointest Endosc* 2016;8:40–55.