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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Jie-Feng Huang, PhD, Associate Chief Physician, Associate Professor, Department of Orthopaedics and Traumatology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang Province, China. 40983285@qq.com

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Endoscopic submucosal dissection for early signet ring cell gastric cancer: A systematic review and meta-analysis

Chun-Yan Weng, Shao-Peng Sun, Chang Cai, Jing-Li Xu, Bin Lv

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Chun-Yan Weng, Shao-Peng Sun, Chang Cai, Department of Gastroenterology, The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310000, Zhejiang Province, China

Jing-Li Xu, Department of Gastrointestinal Surgery, The First Clinical Medical University of Zhejiang Chinese Medical University, Hangzhou 310000, Zhejiang Province, China

Bin Lv, Department of Gastroenterology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang Province, China

Corresponding author: Bin Lv, MD, Chief Doctor, Professor, Department of Gastroenterology, The First Affiliated Hospital of Zhejiang Chinese Medical University, No. 54 Youdian Road, Hangzhou 310006, Zhejiang Province, China. lvbin@medmail.com.cn

Abstract

BACKGROUND

The use of endoscopic submucosal dissection (ESD) for treating early signet ring cell carcinoma (SRC) is controversial due to the risk of lymph node metastasis.

AIM

To carry out a meta-analysis to evaluate ESD for therapeutic efficacy and safety in early signet ring cell gastric cancer.

METHODS

The PubMed, Web of Science, Cochrane Library, and EMBASE databases were used to search for relevant studies evaluating the therapeutic efficacy and safety of ESD in SRC. The rates of recurrence, complete resection, incomplete resection, curative resection, *en bloc* resection, and adverse events were extracted and analyzed. The methodological quality of the enrolled studies was assessed using the Newcastle-Ottawa Scale. Publication bias was evaluated by the Egger's test. Institutional review board approval and written consent were not needed for this report.

RESULTS

This meta-analysis enrolled seven studies with 653 participants undergoing ESD treatment for early SRC. The overall recurrence rate was 0.010 [95% confidence interval (CI): 0.000-0.040, $Z = 1.422$, $P = 0.155$]. The total lymph-ovascular invasion rate was 0.038 (95%CI: 0.007-0.088, $Z = 3.026$, $P = 0.002$). The total *en bloc* resection rate was estimated at 0.984 (95%CI: 0.925-1.000, $Z = 19.463$, $P = 0.000$). The total

complete and incomplete resection rates were estimated at 0.785 (95%CI: 0.596-0.928, $Z = 9.789$, $P = 0.000$) and 0.188 (95%CI: 0.016-0.468, $Z = 2.531$, $P = 0.011$), respectively. The total procedure-associated gastric hemorrhage and perforation rates were estimated at 0.026 (95%CI: 0.005-0.061, $Z = 3.006$, $P = 0.003$) and 0.004 (95%CI: 0.000-0.028, $Z = 0.938$, $P = 0.348$), respectively. The curative resection, vertical margin invasion, and lateral margin invasion rates were 72.1% (145/341), 2.3% (8/348), and 34.45% (41/119), respectively.

CONCLUSION

ESD constitutes a promising therapeutic approach for early undifferentiated SRC gastric cancer. However, further improvements are required for increasing its treatment efficacy and reducing adverse outcomes.

Key Words: Endoscopic submucosal dissection; Endoscopy; Early gastric cancer; Signet ring cell; Meta-analysis

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Core Tip: Endoscopic submucosal dissection (ESD) is widely used as a curative treatment for early gastric cancer (EGC), whereas its efficacy and safety remain unclear. Totally 653 participants were included in this meta-analysis assessing the therapeutic efficacy and safety of ESD in EGC. Based on the data collected and presented, we conclude that ESD is a promising treatment option for undifferentiated signet ring cell carcinoma EGC. Large, long-term trials are warranted to confirm the current results.

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INTRODUCTION

Endoscopic resection procedures, *e.g.*, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), are broadly utilized to cure early gastric cancer (EGC) with a dismal odds of lymph node metastasis[1]. ESD has many advantages over EMR, including accurate histopathological assessment of resection margins, a reduced recurrence rate, and the possibility of curative resection[2]. In addition, ESD results in decreased morbidity and mortality and increased quality of life in comparison with surgery in EGC with undifferentiated (UD) histology[2]. As a result, ESD is currently considered an effective and widely used treatment for EGC.

ESD is mostly indicated for differentiated gastric cancer due to elevated risk of lymph node metastasis in UD EGC. Notably, however, UD EGC has been recently treated by ESD under specific settings, with favorable results.

UD EGC is utilized for lowly differentiated adenocarcinoma or signet ring cell carcinoma (SRC), despite the lack of specific criteria in the WHO classification[3]. Multiple reports have shown that SRC has improved prognosis and decreased lymph node metastasis rate in comparison with other UD EGC types[4,5]. Additionally, SRC shows a better outcome compared with poorly differentiated tubular adenocarcinoma (an EGC) upon endoscopic therapy[6]. Consequently, SRC may be an indication for ESD. However, ESD for treating SRC EGC remains debatable. Thus, we carried out a meta-analysis for assessing the clinical outcomes of ESD in SRC EGC patients with UD lesions.

MATERIALS AND METHODS

Literature search

PubMed, EMBASE, the Web of Science, and the Cochrane Library were searched using common keywords related to ESD for SRC EGC with UD-type histology (from inception to March 2021). Medical Subject Headings (MeSH) terminology was used because all four databases allow searches using the MeSH terminology. The keywords used included “gastric cancer”, “endoscopic submucosal dissection”, “ESD”, “signet ring cell carcinoma”, or “undifferentiated” using Boolean operators. Only publications on human subjects were searched, and the bibliographies of relevant articles were also reviewed to identify additional studies. The language of publication was not restricted.

Selection criteria

Due to a lack of randomized-controlled studies relevant to this topic, we included non-randomized studies meeting the following criteria: (1) Designed to evaluate ESD for SRC EGC with UT histology in the target or control group; and (2) Included at least one outcome (complete resection rate, curative resection rate, *en bloc* resection rate, recurrence rate, or procedure-related adverse event rate) that enabled an evaluation of feasibility of ESD for SRC EGC with UD-type histology. The exclusion criteria were as follows: (1) Incomplete data; (2) Review article; and (3) Abstract only (study not published as full-text article).

Selection of relevant studies

Two of the authors independently evaluated the eligibility of all studies retrieved from the databases based on the predetermined selection criteria. The abstracts of all identified studies were reviewed to exclude irrelevant articles. Full text reviews were performed to determine whether the inclusion criteria were satisfied by the remaining studies. Disagreements between the two evaluators were resolved by discussion or consultation with a third author.

Assessment of methodological quality

The methodological quality of the enrolled studies was assessed using the Newcastle-Ottawa Scale. This tool comprises three parameters: The selection of the study population, the comparability of the groups, and the ascertainment of the exposure or outcome. Each parameter consists of subcategorized questions: Selection ($n = 4$), comparability ($n = 1$) and exposure or outcome ($n = 3$) [7,8]. The stars awarded for each item allow for a rapid visual assessment of the methodological quality of the studies. A study could be awarded a maximum of nine stars, indicating the highest quality. Two of the authors independently evaluated the methodological quality of all studies, and disagreements between the two evaluators were resolved by discussion or consultation with a third author.

Main and modifier-based analyses

Two of the authors independently extracted the outcomes of all studies, and disagreements between the two evaluators were resolved by discussion or consultation with a third author. The primary outcome was recurrence rate. The secondary outcomes were as follows: (1) *En bloc* resection rate, *i.e.*, the proportion of cancers removed as a single piece without fragmentation; (2) Complete resection rate, *i.e.*, the proportion of cancers with no neoplastic components at the lateral or vertical margins on microscopic analysis, and no lymphovascular invasion; (3) Curative resection rate, *i.e.*, the proportion of cancers with 20 mm or less intramucosal tumor without ulceration, neoplastic components at the lateral or vertical margins, or lymphovascular invasion; and (4) ESD adverse event rate, *i.e.*, the proportion of cancers whose treatment resulted in procedure-related gastric hemorrhage or perforation.

Statistical analysis

Pooled effect size with 95% confidence interval (CI) was used to describe the ratio of clinical outcomes (recurrence rate, *en bloc* resection rate, complete resection rate, *etc.*) after ESD in SRC EGC patients. Statistical heterogeneity was assessed by the I^2 statistic and Cochran's Q test. Then, pooled estimates were obtained using the fixed-effects (Mantel and Haenszel; $I^2 \leq 50\%$, $P > 0.1$) or random-effects (M-H heterogeneity; $I^2 > 50\%$, $P \leq 0.1$) model [9]. In addition, sensitivity analysis was applied to evaluate whether the meta-analysis results were stable and reliable. Publication bias was tested by the Begg's test. All analyses were carried out through the application of the commands `metan`, `metaninf`, and `metabias` in STATA 15.1 (StataCorp).

RESULTS

Study selection

Figure 1 depicts the study selection procedure. Totally 260 reports were retrieved from the four core databases, and the bibliographies of relevant studies were further screened for potential studies of interest. Totally 71 duplicate reports, 2 review articles, 26 case reports, and an additional 150 reports were excluded based on title and abstract. After full text review of the remaining 11 reports, four were further excluded for no ESD technology used ($n = 1$), no distinction between SRC and other UD-type histology ($n = 1$), and no distinction between ESD and EMR ($n = 2$). Therefore, seven non-randomized trials were meta-analyzed.

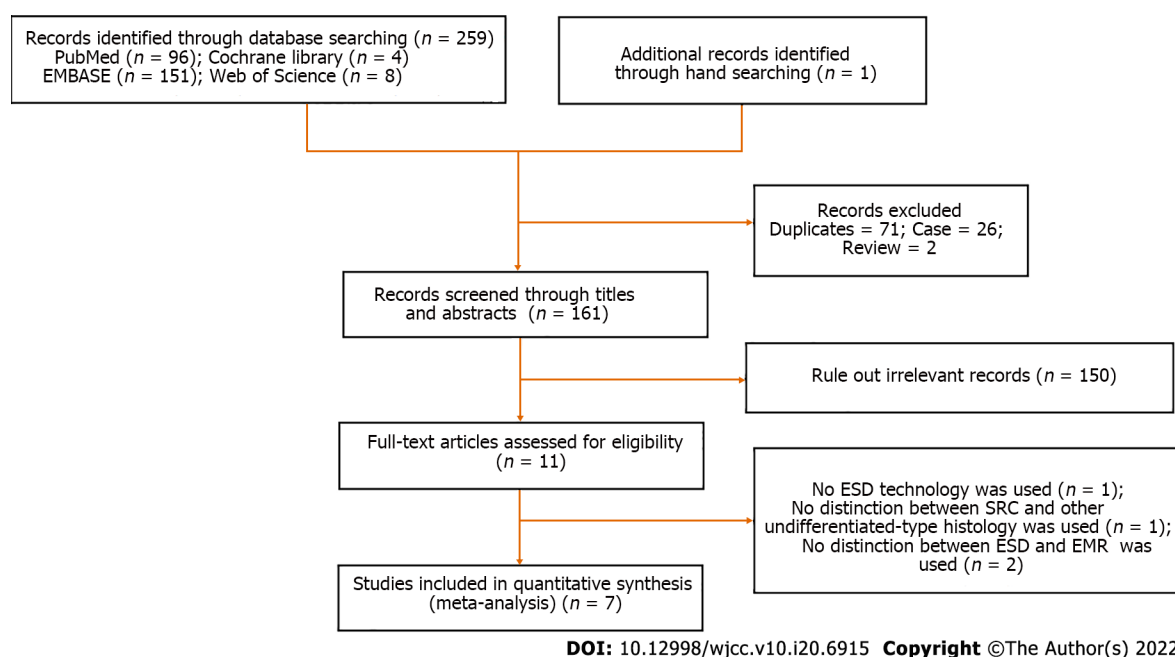
Features of the included trials

The seven included reports, involving five from South Korea [10-14] and two from Japan [15,16] investigated 653 cases of UD SRC EGC. The enrolled trials are described in detail in Tables 1 and 2. The analyzed reports were published from 2010 to 2020. The totality of trials were carried out in Asian countries, including six and one in South Korea and Japan, respectively. Six English reports and one

Table 1 Clinical characteristics of included studies

Ref.	Location (language)	Total patients	Age (yr)	Gender (male/female)	Size; mm	Tumor location	Gross type; n	Ulceration; n
Kang <i>et al</i> [10], 2010	South Korea (English)	30	55.4 ± 11.3	14/16	13.6 ± 5.4	Upper: 0; Middle: 7; Lower: 23	Elevated and flat: 8; Depressed: 19; Mixed: 3	Positive: 7
Choi <i>et al</i> [11], 2013	South Korea (Korean)	27	50.9 ± 11.2	14/13	≤ 10: 8; >10, ≤ 20: 20	Upper: 2; Middle: 13; Lower: 13	Elevated: 5; Flat: 13; Depressed: 10	NA
Kim <i>et al</i> [12], 2014	South Korea (English)	126	55 (range: 28–85)	70/56	< 10: 43; ≥ 10, < 20: 43; ≥ 20: 40	Upper: 9; Middle: 66; Lower: 55	Elevated: 10; Flat: 33; Depressed: 20; Mixed: 63	NA
Jeon <i>et al</i> [13], 2018	South Korea (English)	36	63.6 ± 11.1	14/22	≤ 20: 32; > 20: 4	Upper: 1; Middle: 14; Lower: 21	Elevated: 5; Flat: 8; Depressed: 23	Positive: 0
Horiuchi <i>et al</i> [15], 2018	Japan (English)	129	54.6 ± 11.0	73/56	> 20: 2	Upper: 2; Middle: 13; Lower: 16	Elevated and flat: 8; Depressed: 19; Mixed: 7	Positive: 0
Kwak <i>et al</i> [14], 2018	South Korea (English)	176	52.2 ± 10.8	153/178	NA	NA	Elevated: 39; Flat/Depressed: 292	Positive: 56
Ahn <i>et al</i> [16], 2020	Japan (English)	129	53.6 ± 12.1	52/77	Median (IQR): 12 (10–15)	Upper: 6; Middle: 65; Lower: 58	Elevated: 13; Flat: 13/Depressed: 116	NA

NA: Not applicable.

**Figure 1 Search strategy flowchart.** ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; SRC: Signet ring cell carcinoma.

Korean report were selected. Four studies reported *en bloc* resection rates and five reported complete resection and incomplete resection rates. Curative resection rates were reported in two studies. Resection margins were lymphovascular invasion in six studies, and lateral and vertical margin invasion in five (Table 2). Procedure-related adverse events included hemorrhage and perforation in three studies (Table 2).

As for methodological quality, there were averagely 7.86 stars awarded, including 7, 8 and 9 in two, four, and one study, respectively (Table 3). Most trials had high quality; therefore, sensitivity analysis according to methodological quality was not carried out.

Table 2 Clinical characteristics of early signet ring cell carcinoma after endoscopic submucosal dissection

Ref.	Location (language)	Total patients	Depth of invasion, n (%)	Marginal residual tumor	Resection method, n (%)	Result of resection, n (%)	Procedure-related adverse events
Kang <i>et al</i> [10], 2010	South Korea (English)	30	Mucosa: 25 (83.3); SM: 5 (16.7)	Vi(+): 1 (3.3) Li(+): 5 (16.7) Lmi(+): 9 (30) Vmi(+): 4 (13.3)	NA	Cr: 16 (53.3); Ir: 14 (46.7)	NA
Choi <i>et al</i> [11], 2013	South Korea (Korean)	27	Mucosa: 25 (89.3); SM: 3 (10.7)	Li(+): 1 (3.6) Lmi(+): 1 (3.6) Vmi(+): 1 (3.6)	Ebr: 26 (92.9); Pr: 2 (7.1)	Cr: 25 (89.3); Ir: 3 (10.7)	NA
Kim <i>et al</i> [12], 2014	South Korea (English)	126	Mucosa: 108 (85.6); SM1: ≤ 500 μm: 4 (3.2); SM2: > 500 μm: 14 (11.2)	Li(+): 6 (4.8) Lmi(+): 24 (19.0) Vmi(+): 3 (2.4) Bmi(+): 3 (2.4)	Ebr: 117 (92.9); Pr: 2 (7.1)	Cr: 81 (64.3); Ir: 45 (35.7)	Gh: 3 (2.4); Gp: 3 (2.4)
Jeon <i>et al</i> [13], 2018	South Korea (English)	36	Mucosa: 30 (83.3); SM: 6 (16.7)	Li(+): 1 (2.8) Lmi(+): 7 (19.4) Vmi(+): 0	Ebr: 36 (100.0); Cr: 24 (66.7)	Cr: 28 (77.8); Ir: 8 (22.2)	Gh: 3 (8.3); Gp: 0
Horiuchi <i>et al</i> [15], 2018	Japan (English)	129	Mucosa: 125 (96.9); SM1: ≤ 500 μm: 3 (2.3); SM2: > 500 μm: 1 (0.8)	Li(+): 0 Hmi(+): 2 (1.6) Vmi(+): 0 Vi(+): 0	Ebr: 129 (100); Cr: 121 (93.8)	NA	Gh: 2 (4.8); Gp: 0
Kwak <i>et al</i> [14], 2018	South Korea (English)	176	NA	Li(+): 10 (11.0%)	Cr: (48.3); size criterion = 1.5 cm, 54.9%; size criterion = 1.0 cm, 63.3%; size criterion = 0.6 cm, 63.6%	NA	NA
Ahn <i>et al</i> [16], 2020	Japan (English)	129	Lamina propria: 95 (73.6) Muscularis: 87 (39.9)	NA	NA	NA	NA

Bmi(+): Both margin invasion(+); Cr: Curative resection; Ebr: *En bloc* resection; ESD: Endoscopic submucosal dissection; Hmi(+): Horizontal margin invasion(+); Ir: Incomplete resection; Gp: Gastric perforation; Gh: Gastric hemorrhage; Lmi(+): Lateral margin invasion(+); Li(+): Lymphovascular invasion(+); LNM(+): Lymph node metastasis(+); Pr: Piecemeal resection; SM: Submucosa; SRC: Signet ring cell carcinoma; Vi(+): Vascular invasion(+); Vmi(+): Vertical margin invasion(+); NA: No application.

Primary outcome

Recurrence rates were available for five studies. During the 16 to 75.6 mo of median follow-up in the 441 included cases, recurrence was found in ten cases after ESD for SRC EGC. The overall recurrence rate was 0.010 (95%CI: 0.000-0.040, $Z = 1.422$, $P = 0.155$) (Figure 2).

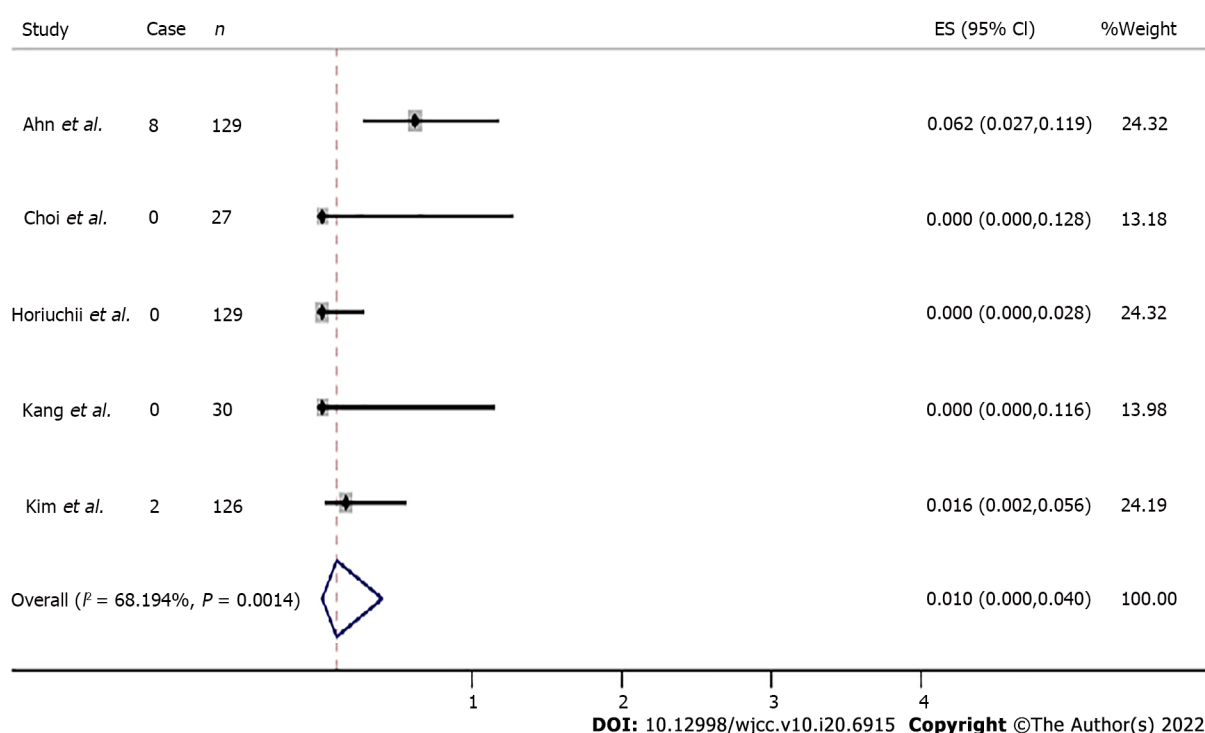
Secondary outcomes

Invasive depth: Depth of invasion post-ESD for SRC EGC was available in all six articles assessing a total of 477 patients. There were 442 patients with deep invasion into the mucosal layer, and 36 with deep invasion into the submucosal layer. The total mucosal and submucosal invasion rates ranged from 83.3% to 100% and 0% to 16.7%, respectively.

Lymphovascular invasion and resection margin invasion: Lymphovascular invasion was examined in six articles with a total of 524 patients. Four articles including 119 individuals assessed lateral margin invasion and five including 348 individuals evaluated vertical margin invasion. The total lymphovascular invasion rate was 0.038 (95%CI: 0.007-0.088, $Z = 3.026$, $P = 0.002$) (Figure 3). A total of five

Table 3 Methodological quality of included studies measured by the Newcastle-Ottawa Scale

Ref.	Selection	Comparability	Exposure or outcome	Total
Kang <i>et al</i> [10], 2010	4	1	2	7
Choi <i>et al</i> [11], 2013	4	2	3	9
Kim <i>et al</i> [12], 2014	4	1	3	8
Jeon <i>et al</i> [13], 2018	4	1	2	7
Horiuchi <i>et al</i> [15], 2018	4	1	3	8
Kwak <i>et al</i> [14], 2018	4	1	3	8
Ahn <i>et al</i> [16], 2020	4	1	3	8

**Figure 2 Total recurrence rate.**

studies involving 348 cases were meta-analyzed for vertical margin invasion and 4 articles including 119 cases for lateral margin invasion. Vertical margin invasion occurred in eight patients and lateral margin invasion was found in 41 patients.

Resection results

The overall efficacy of ESD for UD EGC was assessed by recurrence and complete, incomplete, *en bloc*, and curative resection rates. *En bloc* resection was considered for resection carried out in one piece. In case lesions were removed in many segments, the diverse samples underwent reconstruction to the fullest extent possible. Curative resection was considered in case of intramucosal UD EGC lesions ≤ 20 mm in diameter with no signs of ulceration, no horizontal or vertical margin, and no lymphovascular invasion based on the JGCA gastric cancer treatment guidelines[17].

Complete resection data were available in five articles for a total of 348 patients, as well as incomplete resection. The total complete and incomplete resection rates were estimated at 0.785 (95%CI: 0.596-0.928, $Z = 9.789$, $P = 0.000$) and 0.188 (95%CI: 0.016-0.468, $Z = 2.531$, $P = 0.011$), respectively (Figure 4A and B).

The total *en bloc* resection rate was estimated at 0.984 (95%CI: 0.925-1.000, $Z = 19.463$, $P = 0.000$) (Figure 4C). Total curative resection rates were available in three articles assessing a total of 341 patients, ranging from 46.7% to 93.8%.

Adverse events

The overall safety of ESD for UD SRC EGC was assessed for procedure-associated adverse events, with

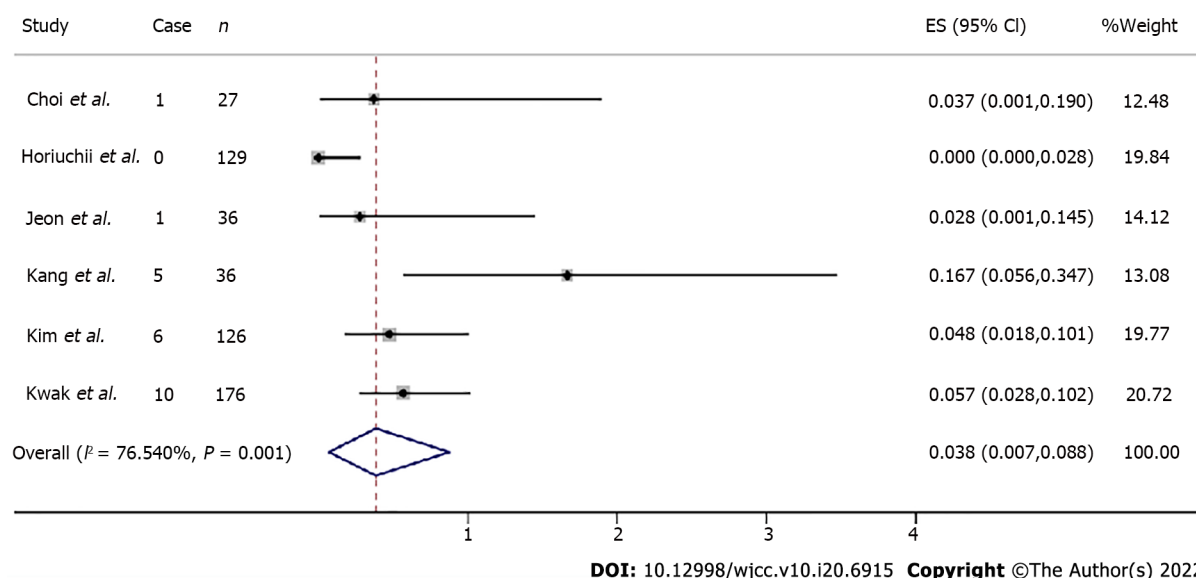


Figure 3 Total lymphovascular invasion rate.

sub-analysis based on gastric hemorrhage and perforation. The overall procedure-associated gastric hemorrhage rate was estimated at 0.026 (95%CI: 0.005-0.061, $Z = 3.006$, $P = 0.003$) (Figure 5A). Three articles including 291 individuals assessed gastric perforation and three patients showed occurrence. The total procedure-related perforation rate was estimated at 0.004 (95%CI: 0.000-0.028, $Z = 0.938$, $P = 0.348$) (Figure 5B).

Sensitivity meta-analysis

The one-study-removed meta-analysis both highlighted influential study for the lymphovascular invasion (Figure 6) and curative resection (removed before *vs* after, $I^2 = 76.54\%$ *vs* $I^2 = 16.882\%$, $I^2 = 97.745\%$ *vs* $I^2 = 0.0000\%$, respectively)[15]. As for *en bloc* resection, Horiuchi *et al*[15] also showed the biggest effect size (*en bloc* resection rate: 129/129).

Analysis of publication bias

In studies assessing recurrence rates, the Egger's regression test showed an intercept of -0.269295 (95%CI: -1.642078-1.103488, $P = 0.577$).

In studies reporting invasive depth rates, the Egger's regression test showed that the depth of invasion into the mucosal layer had an intercept of -0.8693172 (95%CI: -3.136281-1.397646, $P = 0.347$); the SM group had an intercept of 1.008564 (95%CI: -1.170687-3.187815, $P = 0.268$).

For the studies of lymphovascular invasion rate, the Egger's regression test showed that the intercept was 0.3516007 (95%CI: -0.9736407-1.676842, $P = 0.502$). For the studies of vertical margin invasion and lateral margin invasion, the Egger's regression test showed that the intercepts were 0.5103315 (95%CI: -0.8703667-1.89103, $P = 0.324$) and -0.1883809 (95%CI: -4.773827-4.397065, $P = 0.876$), respectively.

In studies reporting *en bloc*, complete, incomplete, and curative resections, the Egger's regression test revealed intercepts of 0.1672684 (95%CI: -2.680985-3.015522, $P = 0.824$), -0.5344952 (95%CI: -7.413003 to -6.344013, $P = 0.821$), 1.027296 (95%CI: -6.759482-8.814074, $P = 0.703$), and 1.635003 (95%CI: -96.74514-100.0151, $P = 0.868$), respectively.

Overall, publication bias was not detected in the analysis of total EGC lesions.

DISCUSSION

In the current meta-analysis, ESD was shown to be a promising therapeutic approach for UD SRC EGC. The total recurrence rate was estimated at 2.27%. The recurrence rate of SRC EGC after ESD should be validated by long-term follow-up. The total mucosal and SM invasion rates were estimated at 92.2% and 7.8%, respectively. The overall *en bloc*, overall complete, and incomplete resection rates were 98%, 78.5%, and 18.8%, respectively. However, treatment outcomes were not fully satisfactory. A total curative resection rate of 72.1% was obtained. As for procedure-associated adverse events, gastric hemorrhage and perforation rates for UD SRC EGC were 2.6% and 0.04%, respectively.

Gastric SRC represents a type of poorly cohesive carcinoma (WHO classification) that exhibits distinct biologic behaviors compared to other UD EGC[5]. Its particular ring appearance reflects a mucin-rich cytoplasm and crescent-shaped nucleus. On the basis of the Japanese Classification System, gastric SRC

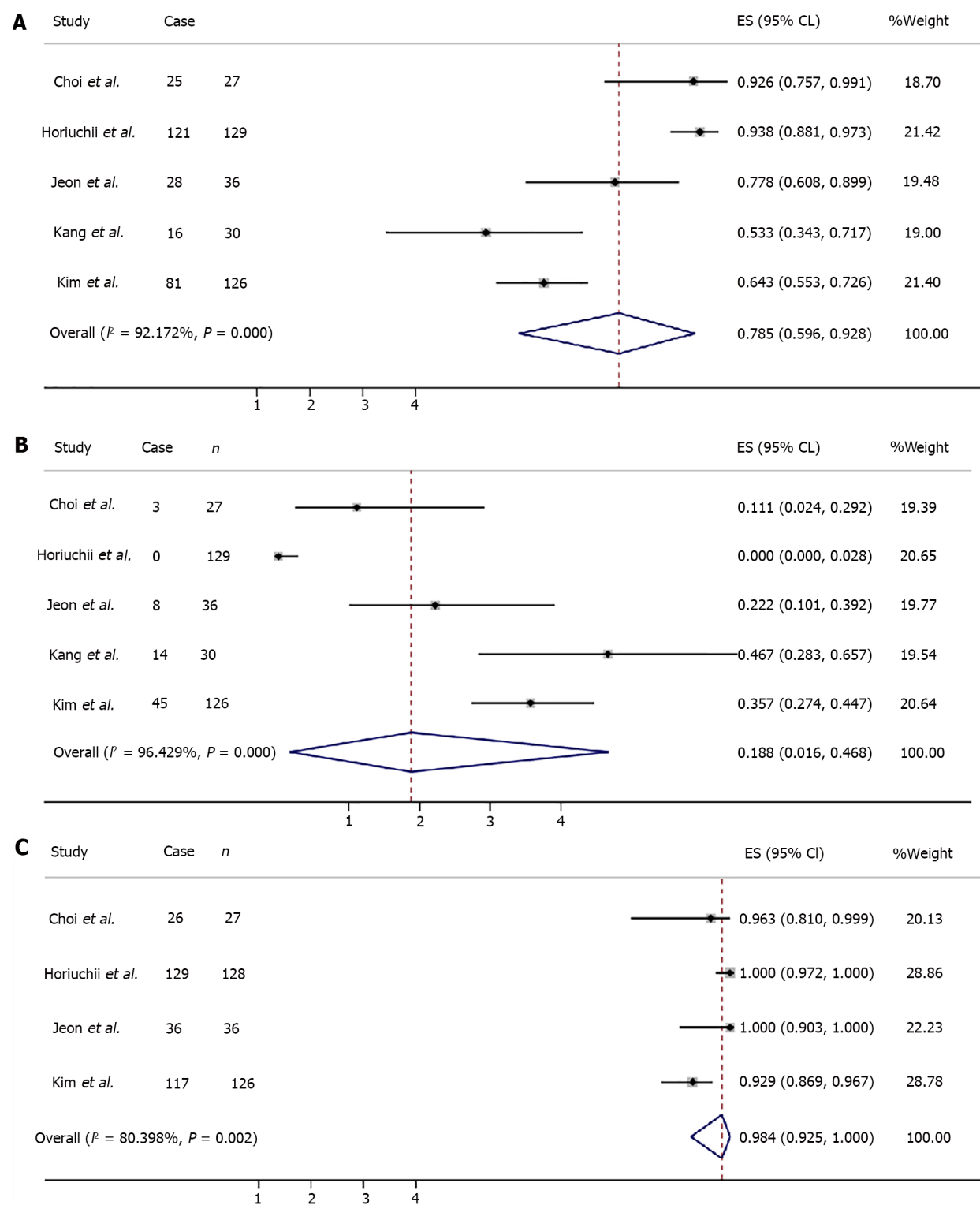


Figure 4 Enrolled studies. A: Total complete resection rate; B: Total incomplete resection rate; C: *En bloc* resection rate.

cases are considered UD[18]. Contrasting other gastric adenocarcinoma cases, signet ring cells show no intercellular adhesion because of downregulated E-cadherin, reflecting cell-to-cell adhesion[19]. E-cadherin suppression results in the migration to and invasion of surrounding tissues[20]. Thus, SRC patients have a poor prognosis, and surgery represents a treatment of choice. However, the rate of lymph node metastasis was reduced in early SRC EGC (5.3%–7.6%) compared with tumors of other UD histologies (14.7%–17.8%)[21–24] but comparable to differentiated EGC (8.2%–9.8%)[25,26], suggesting that early SRCs are possible candidates for minimally invasive surgery. Therefore, SRC EGC may be more indicated for endoscopic therapy compared with other UD EGCs.

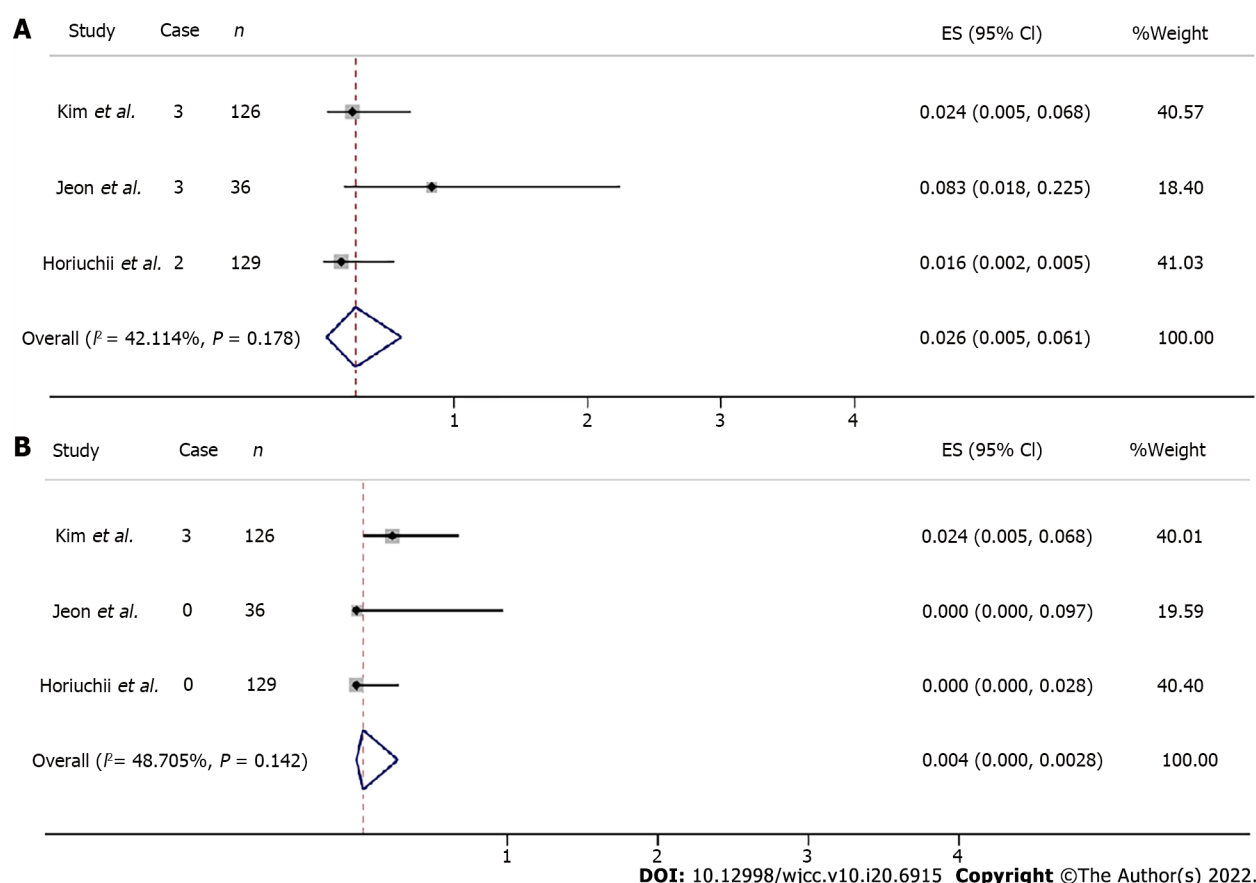


Figure 5 Enrolled studies. A: Total gastric hemorrhage rate; B: Total gastric perforation rate.

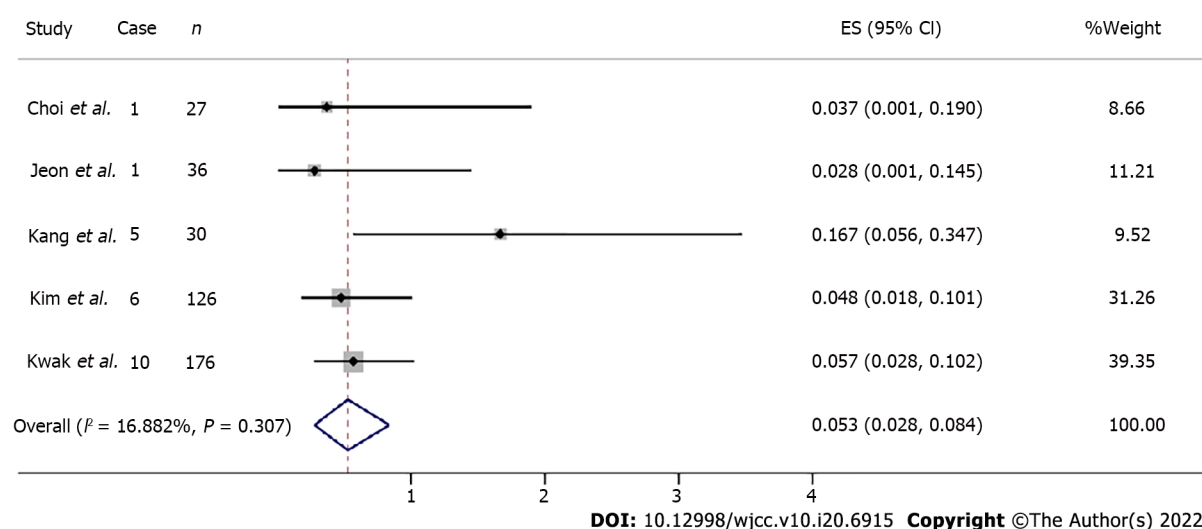


Figure 6 Total lymphovascular invasion rate.

In EGC patients, ESD yielded good long-term outcome, and this approach is increasingly utilized for many diseases[27]. The extended indications for ESD consider three discrete criteria utilized for EGC types I to III[28]. The long-term outcomes of ESD for UD EGC cases meeting these expanded indication criteria were similar to those of surgery for this malignancy.

However, multiple factors hinder ESD application for SRC EGC. For instance, lesion size and margins are not accurately determined. A report examining endoscopic therapy in SRC EGC revealed that tumor sizes are underestimated by 30.2%[12]. However, patient prognosis in SRC EGC has been evaluated on the basis of pathological results instead of endoscopic findings[29,30]. In endoscopic therapy, endoscopists should consider that the actual tumor may have a greater size than that reflected by endoscopy-obtained values, and treating EGC tumors above 2 cm endoscopically may be risky.

Therefore, the low complete resection rate is a serious problem. Curative resection rates of 36.4%-65.2% in UD tumors have been reported, and SRC commonly involves lateral margin[31-33]. Another problem is that lymph node dissection is impossible with endoscopic treatment. Reports assessing patient outcome after endoscopic therapy for EGC tumors with no or poor differentiation, *e.g.*, SRC, revealed no distant metastasis and limited lymph node recurrence[31]. In a Japanese trial, EGC recurrence upon surgery showed no association with tumor histology. However, in some cases, SRCs in EGC may spread to distant lymph nodes and organs[34,35]. Endoscopic therapy of SRCs in EGC could be increasingly applied only after overcoming the above issues.

This study is the first meta-analysis of the therapeutic outcomes of ESD for SRC EGC. A strength of the present analysis is the comprehensive literature search, with no language limitations, despite the lack of Western trials. In addition, possible modifiers were examined whenever possible, and data robustness was confirmed by sensitivity analysis.

However, this study also had multiple limitations. First, the included trials had considerable methodological heterogeneity, with potential impact on effect size estimates. The most notable modifiers were outcome heterogeneity and the inconsistent implementation of indications. The published outcomes for *en bloc*, curative, and complete resection rates varied and were not consistent among the enrolled studies. Second, only retrospective trials were included, indicating a potential effect of selection bias on treatment outcome in ESD. In addition, the histological properties were not divided according to pure SRC or mixed SRC. Furthermore, the country was another significant modifier. The one-study-removed meta-analysis showed the highlighted influential study for lymphovascular invasion and curative resection. The above limitations can result in outcome heterogeneity and publication bias. Since no related prospective/randomized trials have been performed, large, well-organized, long-term follow-up trials are warranted for elucidating ESD feasibility in UD SRC EGC.

CONCLUSION

ESD is a promising treatment modality for SRC EGC. Nevertheless, the current findings should be cautiously interpreted due to study heterogeneity. Inconsistent implementation of indications, short follow-up, and various nations cause such heterogeneity. Future reports assessing frequent primary outcomes in large and long-term trials are warranted to determine ESD feasibility in SRC EGC.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) for the treatment of early signet ring cell carcinoma (SRC) is controversial.

Research motivation

SRC may represent an indication for ESD. Nevertheless, ESD for SRC early gastric cancer (EGC) remains debatable. Therefore, a meta-analysis was carried out for assessing the clinical outcomes of ESD for undifferentiated (UD) SRC EGC cases.

Research objectives

This work aimed to meta-analyzed reports evaluating the therapeutic efficacy and safety of ESD in early SRC gastric cancer.

Research methods

The PubMed, Web of Science, Cochrane Library, and EMBASE databases were searched for relevant reports evaluating the efficacy and safety of ESD for treating SRC.

Research results

The total lymphovascular invasion and *en bloc* resection rates were 3.8% and 98.4%, respectively. The total complete and incomplete resection rates were estimated at 78.5% and 18.8%, respectively. The total procedure-associated gastric hemorrhage and perforation rates were 2.6% and 0.4%, respectively. The curative resection, vertical margin invasion, and lateral margin invasion rates were 72.1%, 2.3%, and 34.45%, respectively.

Research conclusions

ESD represents a promising therapeutic approach for UD SRC EGC. Further improvements are required to increase treatment efficacy and reduce adverse outcomes.

Research perspectives

ESD as a treatment tool constitutes a critical step in improving daily clinical practice associated with SRC EGC. Future trials with a larger sample size and longer follow-up duration are warranted to evaluate the long-term efficacy and safety of ESD treatment for SRC EGC.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Chun-Yan Weng 0000-0003-3618-9629; Shao-Peng Sun 0000-0002-2221-6545; Chang Cai 0000-0002-9872-8782; Jing-Li Xu 0000-0002-2264-8591; Bin Lv 0000-0002-6247-571X.

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