review

Efficacy of endoscopic mucosal resection versus endoscopic submucosal dissection for rectal neuroendocrine tumors ≤10mm: a systematic review and meta-analysis

Ce Zhou,[a] Furong Zhang,[b] Yinghua Wu[c]

From the [a]Department of Proctology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China; [b]College of Health Preservation and Rehabilitation, Chengdu University of Traditional Chinese Medicine, Chengdu, China;[c]Department of Radiology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China

Correspondence: Yinghua Wu, · Department of Radiology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China · wyh@cdutcm.edu.cn · ORCID: https://orcid.org/0000-0001-9116-1624

Citation: Zhou C, Zhang F, Wu Y. Efficacy of endoscopic mucosal resection versus endoscopic submucosal dissection for rectal neuroendocrine tumors ≤ 10mm: a systematic review and meta-analysis. Ann Saudi Med 2023; 43(3): 179-195. DOI: 10.5144/0256-4947.2023.179

Received: January 23, 2023

Accepted: March 11, 2023

Published: June 1, 2023

Funding: Natural Science Foundation of the Sichuan Province x 2022NSFSC1418

The fund from the Hospital of Chengdu University of Traditional Chinese Medicine x 20-H15

BACKGROUND: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are surgical methods used for rectal neuroendocrine tumors (NETs) with diameters of ≤ 10 mm. However, which method has a higher performance remains uncertain.

OBJECTIVES: Evaluate which of the two methods shows a higher performance.

DESIGN: Systematic review and meta-analysis

METHODS: Data from PubMed, Embase, Cochrane Library, and Web of Science were searched from inception to 12 April 2022. Outcomes, including complete resection, en bloc resection, recurrence, perforation, bleeding, and procedure time, were pooled by 95% confidence intervals (95% CI) using a fixed- or random-effects model.

MAIN OUTCOME MEASURES: Complete resection, en bloc resection, and recurrence.

SAMPLE SIZE: 18 studies, including 1168 patients were included in the study.

RESULTS: Eighteen retrospective cohort studies were included in this meta-analysis. There were no statistical differences in the rates of complete resection, en bloc resection, recurrence, perforation, and bleeding rates between EMR and ESD. However, a statistical difference was detected in the procedure time; EMR had a significantly shorter time (MD=-17.47, 95% CI=-22.31- -12.62, P<.00001).

CONCLUSIONS: EMR and ESD had similar efficacies and safety profiles in resectioning rectal NETs ≤ 10 mm. Even so, the advantages of EMR included a shorter operation time and expenditure. Thus, with respect to health economics, EMR outperformed ESD.

LIMITATION: Most of these studies are retrospective cohort studies instead of RCTs.

CONFLICT OF INTEREST: None.

Even though early detection and treatment of gastrointestinal tumors is advocated, gastrointestinal cancers remain a major public health concern worldwide.[1] Timely, effective, and safe treatment of gastrointestinal tumors reduces the incidence of cancer, national public health expenditures, and individual health care costs. With the popularization of endoscopic examinations, the detection of neuroendocrine tumors (NETs) has been increasing. NETs begin in neuroendocrine cells in the endocrine system. They include a broad family of tumors.[2] NETs commonly occur in the gastrointestinal tract, lungs, bronchi, thymus, and pancreas.[3] NETs in the G1 and G2 stages were previously called carcinoids. The incidence of NETs increases by 3%-10% yearly. This yearly increase is based on different subtypes. For example, rectal NETs account for approximately 27% of all cases.[4-6] In the United States, NETs have an incidence rate of 6.98 cases per 100 000 people; and are increasing.[7]

Rectal NETs are manifested as smooth, round polypoid lesions which are covered by normal mucosa. They are mostly asymptomatic and seldom complexed with carcinoid syndrome.[8] Rectal NETs are usually found inadvertently during physical examinations or surgeries. There is a higher incidence of NETs in men than in women. The age of onset is predominantly 50-60 years. The optimal choice for rectal NETs treatment currently includes endoscopic resection and surgical excision. These surgical methods are selected based on the size and surface characteristics of the tumors.[9]

According to the clinical practice guidelines for managing colorectal polyps released by the Japanese Society of Gastroenterology in 2020, surgical resection with lymph node dissection is recommended for NETs >10 mm in diameter.[10] NETs smaller than 10 mm in diameter rarely metastasize; therefore, they are managed with endoscopic treatment. This endoscopic treatment includes endoscopic mucosal resection (EMR). EMR includes a ligation band device (EMR-L), EMR using a fitted cap (EMR-C), and an endoscopic submucosal dissection (ESD).[11] In clinical practice, EMR outperforms ESD in terms of surgeon requirements, procedural time, technical complexity, and expenditure (day surgery for EMR and inpatient surgery for ESD). ESD is an emerging technique with advantages such as higher en bloc rates, complete resections (R0), and lower local recurrence rates.[12,13] From the perspective of evidence-based medicine, the question of whether EMR outperforms ESD in procedural time, completeness of resections, en bloc resections, bleeding, perforation, and recurrence remains unanswered. The answer to this question is important for clinicians, patients, and the nation's public health insurance.

Rectal NETs are rare and only account for 1.1%–1.3% of all rectal tumors.[14,15] Moreover, they are more common in African Americans and Asian populations than in Caucasians.[3] For this reason, studies on rectal NETs are usually reported by Asian researchers. Most of these studies are retrospective cohort studies instead of randomized controlled trials (RCTs). Our study aimed to evaluate the efficacy and safety of EMR and ESD for rectal NETs ≤10 mm by conducting a systematic review and meta-analysis of observational studies.

METHODS

This systematic review and meta-analysis conformed to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist.[16] The study protocol was previously submitted to the Prospective Register of Systematic Reviews (PROSPERO) under the registered number CRD42021266414. Since this study was a secondary literature review, approval and informed consent were not required from the IRB committee.

The initial search was conducted without restrictions on the language or publication year. The inclusion criteria were: (1) patients diagnosed with rectal NETs ≤10 mm; (2) endoscopic mucosal resections, including conventional endoscopic mucosal resection (cEMR), EMR using a fitted cap (EMR-C), EMR with a ligation band device (EMR-L), and pre-cutting EMR (EMR-P), with at least one of these applied; (3) EMR with endoscopic submucosal dissection (ESD); (4) complete resections, en bloc resections, recurrences, procedure times, perforations, bleeding, hospital stays, and treatment costs; and (5) observational design. The exclusion criteria were as follows: (1) essential data could not be extracted from published articles; (2) studies that included only one type of endoscopic resection; (3) reviews, editorials, case reports, commentaries, position papers, and book chapters; and (4) studies with less than ten cases. In addition, only studies with larger sample sizes were considered for cohort studies published in duplicate.

Electronic databases (PubMed, Web of Science, Embase, and Cochrane Library) were searched from their inception to 12 April 2022. The search strategy was (((rectum [Title/Abstract]) OR (rectal [Title/Abstract])) AND ((((carcinoid tumor*[Title/Abstract]) OR (carcinoid*[Title/Abstract])) OR (neuroendocrine tumor*[Title/Abstract])) OR (neuroendocrine [Title/Abstract]))) AND ((endoscopic [Title/Abstract]) OR (endoscopic submucosal dissection [Title/Abstract]) OR (endoscopic mucosal resection [Title/Abstract]) OR (excision [Title/Abstract])). For studies with incomplete data, the authors were contacted by email for detailed data. Citations were retrieved and managed using EndNote X9. After removing duplicates, two reviewers separately screened the studies by their titles and abstracts. Any disagreements were discussed with the third reviewer.

After study selection, complete manuscripts for the eligible articles were acquired. Two reviewers extracted the required information using a predesigned table in

Excel. The latest version was preferentially included for repeated publications. The primary outcomes included complete resections (R0), en bloc resections, and local recurrences. Secondary outcomes were bleeding, perforation, procedure time, length of hospital stay, and treatment costs. Data were collected on the study country, patient age, sex ratio, follow-up time, application of endoscopic ultrasonography, CT, MRI, quality assessment and risk of bias.The methodological quality of included studies was evaluated with the Newcastle–Ottawa quality scale (NOS).[17] This scale assigned each single study with a maximum of nine points; a study with a score higher than 6 was considered "high quality." In addition, the quality of the included studies was evaluated by patient selection, comparability, and outcome assessments.

The Review Manager software (version 5.3; RevMan 5.3; Cochrane Collaboration, Oxford, UK) was used for the statistical analysis. The odds ratios (OR) and the 95% confidence intervals (95% CI) of binary variables were calculated for each study. For studies that failed to report the mean and variance values, we converted the medians and ranges of continuous variables conforming to a normal distribution to means and standard deviations. A 95% CI and a *P* value <.05 was consideredstatistically significant.

We conducted a heterogeneity level (I^2) analysis to identify the variation percentage across studies.[18] Based on the Cochrane Handbook for Systematic Reviews of Interventions, I^2 values <30%, >50% and >75% were considered with low, substantial and considerable heterogeneity, respectively. A fixed-effects model was performed for studies with low heterogeneity (I2<50% statistics or Cochran's Q-test, *P*>.05); otherwise, a random-effects model was performed. In addition, we conducted a subgroup analysis to identify potential heterogeneities. Data from each modified EMR (m-EMR) subgroup were merged into an EMR group to enable a comparison with ESD. In addition, we conducted a subgroup analysis based on the study country and aimed to identify the characteristics of endoscopic resection in different countries. Sensitivity analysis enables an assessment of the robustness of the meta-analysis findings. We made a sensitivity analysis on procedure time, and used funnel plots, Begg's and Egger's tests to determine the publication bias.

RESULTS

A total of 1026 citations were retrieved. After duplicate removal, we screened the titles and abstracts of the remaining 681 articles (**Figure 1**). Sixty-five articles were included for full-text screening; 18 articles were included in the qualitative analysis.[19-36] Among the 18 studies included in the study, 17 were retrospective observational studies, and 1 was a prospective study conducted by Bang et al (2016).[28] This review included 1168 patients in the 18 studies, with 734 patients (62.84%) who underwent EMR, while 434 (37.16%) underwent ESD (**Table 1**). **Table 2** shows the clinical characteristics of patients in each study. Only 17 retrospective studies were included in the meta-analysis to minimize heterogeneity due to different study types.

Complete resection

The meta-analysis of R0 included 17 studies[19,27,29-36] containing 1091 patients, with 681 (62.42%) and 410 (37.58%) in the EMR and ESD group, respectively. No difference with statistical significance was detected between the groups (*P*=.45) (**Figure 2A**). Country/region-based subgroup analysis showed no statistically significant differences in the complete removal rate between Japan (*P*=.10), Korea (*P*=.15), and China (*P*=.20) (**Figure 2B**). In addition, analysis and comparison of the EMR subgroups showed statistically significant differences between cEMR and ESD (*P*=.01) (**Figure 3A**), as well as between EMR-C and EMR-L (*P*=.02) (**Figure 3B**). However, there were no statistically significant differences between EMR-C and ESD (*P*=.12), EMR-L and ESD (*P*=.12) , and EMR-P and ESD (*P*=.17) (**Supplementary Figure S1**).

En bloc resection

En bloc resection was reported in 12 studies that reported a total of 768 cases (including 491 EMR and 277 ESD). There was no statistically significant difference between the two groups (*P*=.11). Furthermore, subgroup analysis showed that there was no statistically significant difference between cEMR and ESD (*P*=.42) (**Supplementary Figure S2**). In addition, EMR-L and ESD showed 100% en bloc rates.

Recurrence

Seventeen studies reported local recurrence rates.[19-27,29-36] Of the 1091 observers, only 4 in the EMR group showed local recurrences. No statistical difference was detected between EMR and ESD (*P*=.27) (**Figure 4**).

Perforation and bleeding

Seventeen studies evaluated the perforation and bleeding rates. Perforation was reported in 12 participants, with 6 in the EMR and 6 in the ESD group. Bleeding was reported in only 16 patients, including 7 in the EMR group and 9 in the ESD group. No sta-

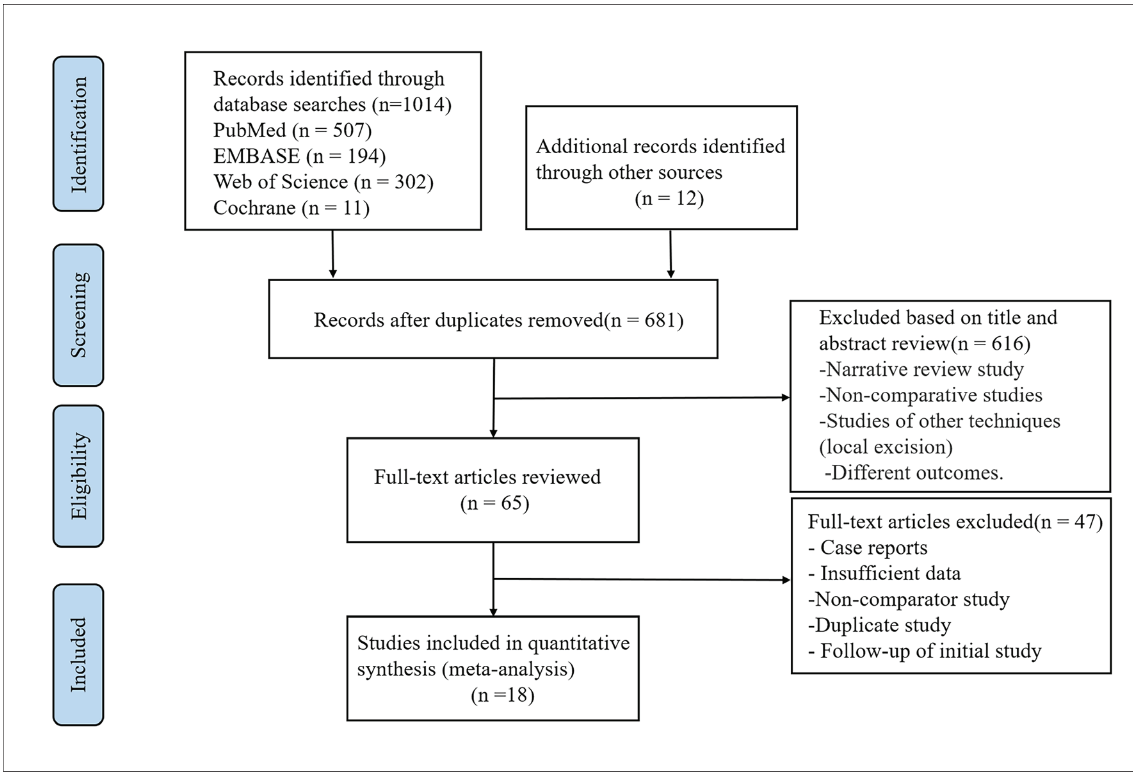


Figure 1. Flow chart of search results for EMR versus ESD for treatment of rectal neuroendocrine tumors ≤10 mm.

Table 1. Baseline characteristics of included studies (n=1168; total number of patients).

Study	Country	Treatment	Patients (n)	Age (years)	Gender (M/F)
Baek, 2010	Korea	c-EMR	9	44.00 (16.97)	7/2
		ESD	2	48.33 (9.94)	1/1
Onozato et al, 2010	Japan	c-EMR	26	NA	18/6
		ESD	9	NA	7/2
Zhou et al, 2010	China	c-EMR	23	50.30 (13.60)	14/9
		ESD	20	47.60 (18.50)	12/8
Niimi et al, 2012	Japan	EMR-L	11	45.50 (10.60)	8/3
		ESD	13	55.30 (8.60)	9/4
Zhao et al, 2012	China	c-EMR	10	54.04 (11.58)	21/9
		EMR-C	10		
		ESD	10		
Choi et al, 2013	Korea	EMR-L	29	47.75 (11.73)	15/14
		ESD	31	48.29 (14.44)	20/11
Kim et al, 2013	Korea	c-EMR	31	47.74 (11.52)	20/11
		EMR-L	40	48.15 (8.87)	23/17
		ESD	44	47.18 (10.22)	32/12

tistically significant differences were found in perforation (P=.45) (**Figure 5A**) and bleeding (P=.20) between these groups (**Figure 5B**).

Procedure time

Fifteen studies reported the procedure time, with a total of 1020 cases, with 643 (63.04%) in the EMR group and 377 (36.96%) in the ESD group. In a preliminary analysis, statistically significant differences were found between groups, confirming the existence of high heterogeneity (P<.001) (**Figure 6A**). Subgroup analysis by country showed that the comparison of procedure time was statistically significant, with significant heterogeneity: Japan (P<.00001), Korea (P<.00001), and China (P=.00001) (**Figure 6B**). Furthermore, the analysis and comparison of EMR subgroups, showed statistically significant differences between cEMR and ESD (P<.00001), as well as between EMR-C and ESD (P<.02) (**Supplementary Figure S3**), EMR-L and ESD (P<.0001), EMR-P and ESD (P=.001), and cEMR and EMR-L (P<.07) (**Supplementary Figure S4**). Significant differences in procedure time suggest that EMR is the superior surgical method; however, the combined results are highly heterogeneous.

Studies determined to be of a "high-quality" (score ≥6) on the Newcastle–Ottawa quality scale results accounted for 83.3% of all studies included (**Supplementary Figure S5**). The distributions on the funnel plots for complete resection (P=.587, **Figure 7A**) and procedure time (P=.839, **Figure 7B**) were roughly symmetrical, indicating publication bias which may hinder the reliability of the results.

DISCUSSION

Several systematic reviews and meta-analyses comparing EMR and ESD for rectal NETs have been published, but conclusions have been inconsistent. For instance, the meta-analyses by Zhong et al and He et al concluded that ESD was superior to EMR for rectal NETs[37,38] while Pan et al found that EMR was superior to ESD.[39] Furthermore, researchers found that the results for these comparative analyses varied with tumor size. Yong et al found that ESD was more effective for rectal carcinoid tumors larger than 10 mm, had a higher complete resection rate, and shared a similar efficacy with EMR for rectal carcinoid tumors smaller than 10 mm.[40] Therefore, we hypothesized that tumor size affects the selection of the surgical procedure. The consensus among surgeons is to perform surgical resection with lymph node dissection as the treatment for rectal NETs larger than 10 mm.

Table 1 (cont). Baseline characteristics of included studies (n=1168; total number of patients).

Study	Follow-up (months)	Endoscopic Ultrasonography Reported	CT/MRI Reported	Treatment Costs	Hospital Stay (day)	NOS Score
Baek, 2010	28 (15-45)	Yes	Yes	NA	NA	8
Onozato et al, 2010	70.1 (30.7)	Yes	Yes	NA	NA	7
Zhou et al, 2010	42.6 (26.1) 18.7 (10.6)	Yes	Yes	NA	NA	6
Niimi et al, 2012	24.0 (32.5) 65.1 (57.0)	Yes	Yes	NA	1.8 (3.1) 6.2 (2.1)	7
Zhao et al, 2012	18.43 (9.76)	Yes	No	NA^b	NA	5
Choi et al, 2013	6	Yes	Yes	NA[b]	NA	6
Kim et al, 2013	13.1 (6-59)	No	Yes	NA	NA	8

Table 1 (cont). Baseline characteristics of included studies (n=1168; total number of patients).

Study	Country	Treatment	Patients (n)	Age (years)	Gender (M/F)
Cheung et al, 2015	Korea	EMR-P	16	51.50 (8.76)	15/1
		ESD	17	46.29 (8.62)	11/6
Lee et al, 2015	Korea	EMR-L	68	NA	38/30
		ESD	16	NA	8/8
Bang et al, 2016[a]	Korea	EMR-L	53	53.60 (12.70)	32/21
		ESD	24	50.80 (12.40)	18/6
Choi et al, 2017	Korea	EMR-C	65	50.80 (11.30)	44/21
		EMR-L	16		11/5
		ESD	53		32/21
Ebi et al, 2018	Japan	c-EMR	14	59.83 (34.96)	12/2
		EMR-L	19	63.25 (5.75)	10/9
		ESD	19	55.50 (5.00)	8/11
Lim et al, 2019	Korea	EMR-L	66	51.61 (9.81)	37/29
		ESD	16	52.69 (9.83)	8/8
Zhang et al, 2019	China	EMR-L	22	48.18 (12.31)	17/5
		ESD	12	46.17 (12.57)	7/5
Park et al, 2020	Korea	c-EMR	36	45.70 (12.20)	22/14
		ESD	79	47.00 (10.30)	50/29
Inada et al, 2021	Japan	c-EMR	12	60.10 (13.80)	75/57
		EMR-L	58		
		EMR-P	29		
		ESD	33		
Pattarajierapan et al, 2021	Thailand	c-EMR	13	57.00 (8.00)	6/7
		EMR-P	21	60.00 (9.00)	13/8
		ESD	12	61.00 (12.00)	10/2
Toriyama et al, 2021	Japan	c-EMR	10	63.50 (37.48)	7/3
		EMR-C	27	56.00 (13.25)	22/5
		ESD	24	57.75 (12.25)	15/9

Table 1 (cont). Baseline characteristics of included studies (n=1168; total number of patients).

Study	Follow-up (months)	Endoscopic Ultrasonography Reported	CT/MRI Reported	Treatment costs	Hospital stay (day)	NOS Score
Cheung et al, 2015	12 (3-37)	Yes	Yes	300 USD	NA	6
	17 (3-35)			1,500 USD		
Lee et al, 2015	12 (1-39)	Yes	Yes	NA	NA	3
Bang et al, 2016[a]	7.8 (11.2)	Yes	Yes	NA	NA	5
	22.3 (16.8)					
Choi et al, 2017	835 (501) days	Yes	Yes	NA	NA	7
Ebi et al, 2018	75.0 (27-133)	Yes	No	NA	NA	7
	17.0 (1-58)					
	13.5 (1-99)					
Lim et al, 2019	41.9 (18-66)	Yes	Yes	NA	NA	8
Zhang et al, 2019	6-30	Yes	Yes	NA	NA	6
Park et al, 2020	19 (0-53)	No	Yes	NA	NA	7
Inada et al, 2021	57 (39-82.3)	Yes	Yes	NA[b]	NA	6
Pattarajierapan et al, 2021	55 (42-84)	No	Yes	NA	NA	8
	27 (18-42)					
	39 (21-50)					
Toriyama et al, 2021	34.8 (14.2-113.2)	Yes	Yes	NA	NA	7
	24.9 (0.07-195.0)					
	31.3 (0.4-177.9)					

[a]Only prospective study. [b]ESD incurred higher costs than EMR, but specific costs not available.

Table 2. Clinical characteristics of patients in the included studies.

Study	Treatment	Patients (n)	Complete resection (n)	En Bloc Resection (n)	Procedure Time (min)	Bleeding (n)	Perforation (n)	Local Recurrence (n)
Baek, 2010	c-EMR	9	9/9	NA	NA	0/9	0/9	0/9
	ESD	2	2/2	NA	NA	0/2	0/2	0/2
Onozato et al, 2010	c-EMR	26	22/26	NA	9.30 (2.20)	0/26	0/26	0/26
	ESD	9	7/9	NA	25.60 (8.80)	0/9	0/9	0/9
Zhou et al, 2010	c-EMR	23	12/23	20/23	12.30 (15.40)	0/23	0/23	3/23
	ESD	20	20/20	20/20	28.40 (17.20)	0/20	1/20	0/20
Niimi et al, 2012	EMR-L	11	11/11	11/11	17.40 (4.40)	1/11	0/11	0/11
	ESD	13	12/13	13/13	28.60 (16.20)	0/13	0/13	0/13
Zhao et al, 2012	c-EMR	10	8/10	NA	13.40 (17.13)	0/10	0/10	0/10
	EMR-C	10	10/10	NA	5.20 (0.78)	0/10	0/10	0/10
	ESD	10	10/10	NA	24.90 (5.78)	0/10	0/10	0/10
Choi et al, 2013	EMR-L	29	24/29	29/29	6.37 (3.52)	0/29	0/29	0/29
	ESD	31	25/31	31/31	15.09 (5.73)	1/31	0/31	0/31
Kim et al, 2013	c-EMR	31	24/31	31/31	3.50 (2.06)	0/31	0/31	0/31
	EMR-L	40	40/40	40/40	11.75 (4.58)	0/40	1/40	0/40
	ESD	44	39/44	44/44	9.38 (4.09)	0/44	0/44	0/44
Cheung et al, 2015	EMR-P	16	13/16	14/16	9.69 (3.61)	0/16	1/16	0/16
	ESD	17	15/17	17/17	20.20 (12.60)	0/17	1/17	0/17
Lee et al, 2015	EMR-L	68	64/68	68/68	7.30 (5.80)	0/68	0/68	0/68
	ESD	16	11/16	16/16	21.70 (13.00)	0/16	0/16	0/16
Bang et al, 2016	EMR-L	53	53/53	53/53	5.30 (2.80)	2/53	0/53	0/53
	ESD	24	13/24	24/24	17.90 (9.10)	0/24	0/24	0/24
Choi et al, 2017	EMR-C	65	59/65	65/65	NA	0/65	0/65	0/65
	EMR-L	16	13/16	16/16	NA	0/16	0/16	0/16
	ESD	53	43/53	53/53	NA	2/53	0/53	0/53

Table 2 (cont). Clinical characteristics of patients in the included studies.

Study	Treatment	Patients (n)	Complete resection (n)	En Bloc Resection (n)	Procedure Time (min)	Bleeding (n)	Perforation (n)	Local Recurrence (n)
Ebi et al, 2018	c-EMR	14	7/14	14/14	6.90 (4.60)	1/14	0/14	0/14
	EMR-L	19	17/19	19/19	5.63 (0.63)	0/19	0/19	0/19
	ESD	19	18/19	19/19	44.50 (8.50)	4/19	0/19	0/19
Lim et al, 2019	EMR-L	66	63/66	66/66	7.05 (4.53)	0/66	0/66	0/66
	ESD	16	12/16	16/16	24.21 (12.18)	0/16	0/16	0/16
Zhang et al, 2019	EMR-L	22	19/22	22/22	5.91 (0.87)	0/22	0/22	0/22
	ESD	12	11/12	12/12	15.67 (2.15)	0/12	0/12	0/12
Park et al, 2020	c-EMR	36	31/36	NA	5.80 (2.90)	0/36	0/36	0/36
	ESD	79	68/79	NA	26.60 (13.40)	1/79	1/79	0/79
Inada et al, 2021	c-EMR	12	5/12	NA	2.50 (1.40)	0/12	0/12	1/12
	EMR-L	58	50/58	NA	7.90 (4.10)	3/58	3/58	0/58
	EMR-P	29	25/29	NA	18.30 (8.30)	0/29	0/29	0/29
	ESD	33	32/33	NA	41.30 (22.70)	1/33	2/33	0/33
Pattarajierapan et al, 2021	c-EMR	13	12/13	13/13	3.75 (2.18)	0/13	0/13	0/13
	EMR-P	21	21/21	21/21	11.25 (1.75)	0/21	0/21	0/21
	ESD	12	12/12	12/12	19.25 (6.80)	0/12	0/12	0/12
Toriyama et al, 2021	c-EMR	10	6/10	7/10	13.20 (18.95)	0/10	0/10	0/10
	EMR-C	27	26/27	27/27	8.40 (3.58)	2/27	1/27	0/27
	ESD	24	22/24	24/24	58.55 (27.50)	0/24	1/24	0/24

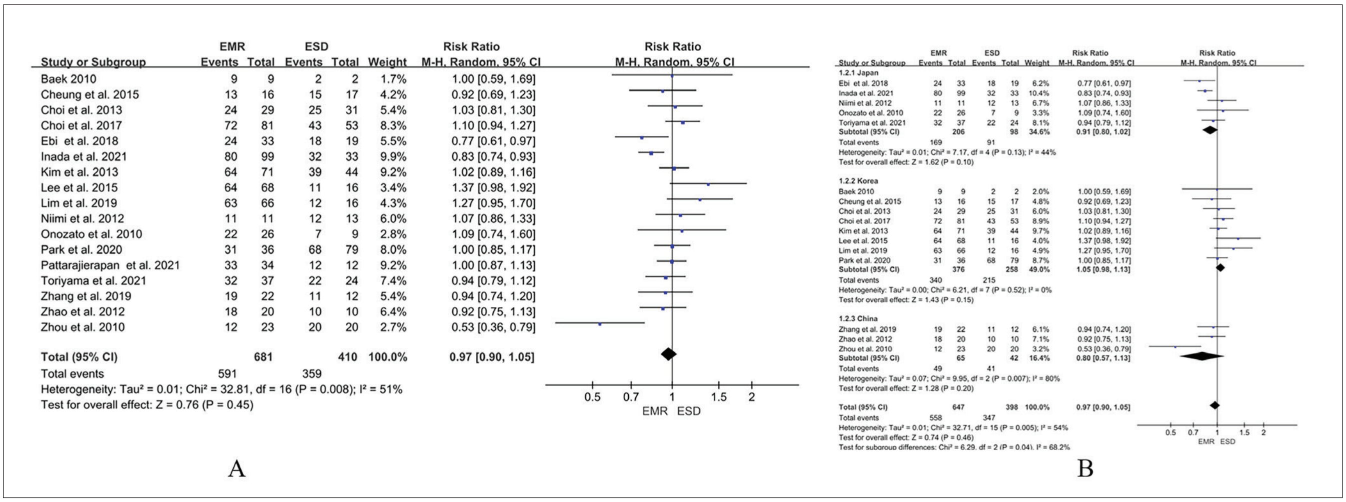


Figure 2. Complete resection (R0) rate comparison. A: EMR group versus ESD group; B: Subgroup analysis by country (Japan, Korea, and China).

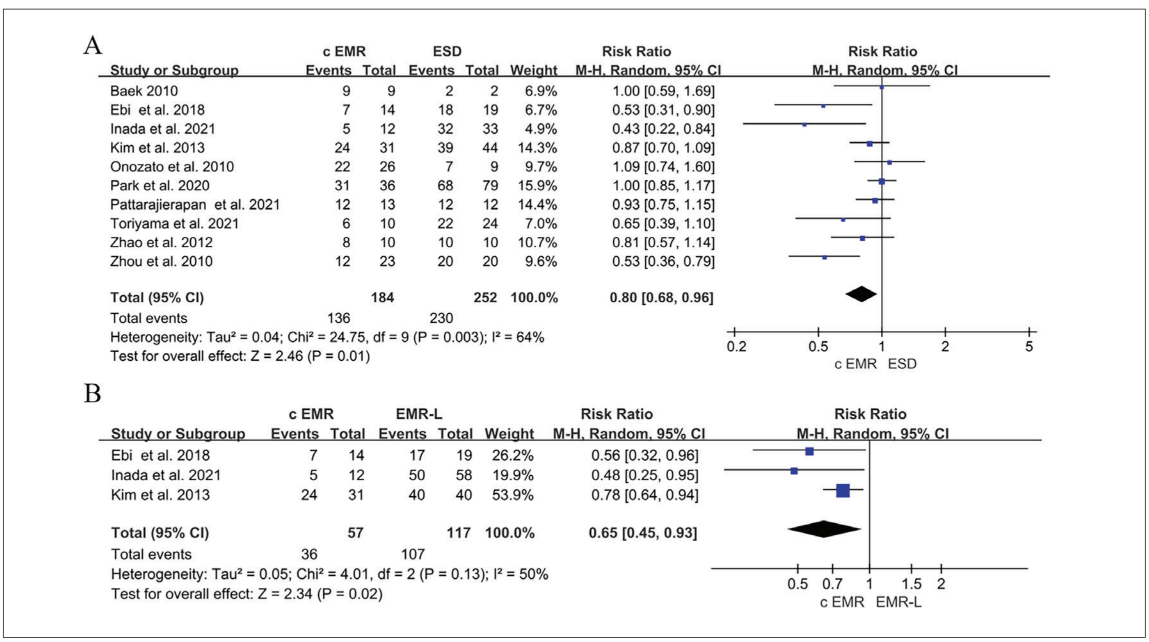


Figure 3. EMR subgroup analysis on complete resection (R0) rate comparison. A: cEMR versus ESD; B: c EMR versus EMR-L.

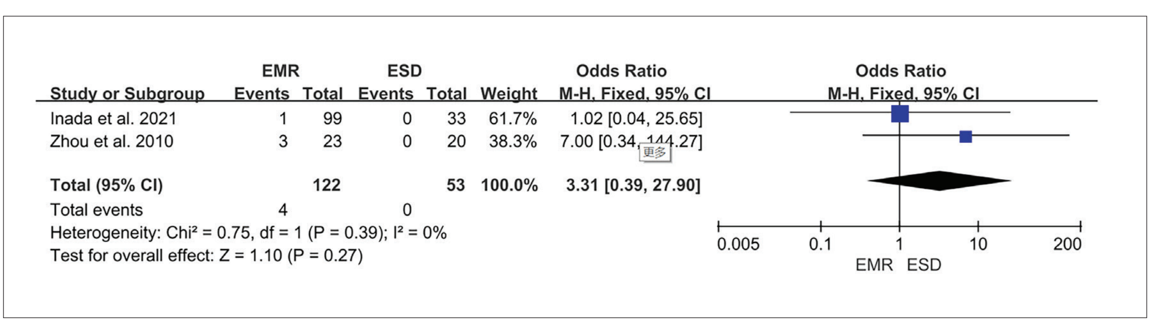


Figure 4. Recurrence rate comparison of EMR versus ESD.

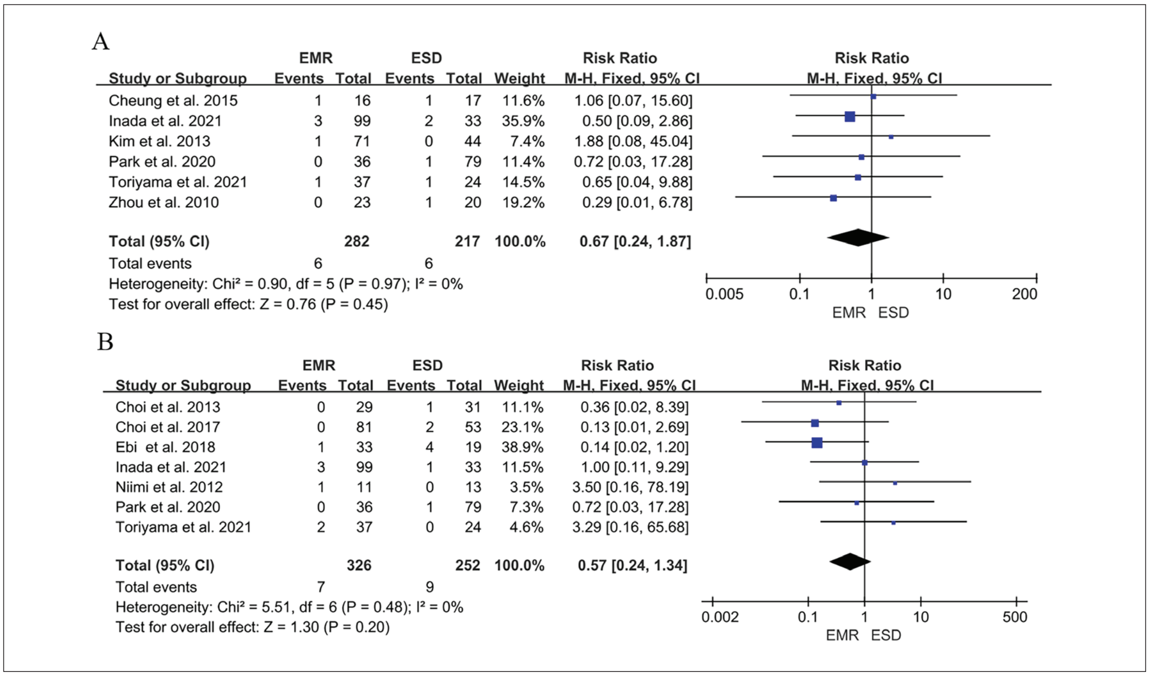


Figure 5. Perforation and bleeding rate comparison of EMR versus ESD. A: Perforation rate comparison of EMR versus ESD; B: Bleeding rate comparison of EMR versus ESD.

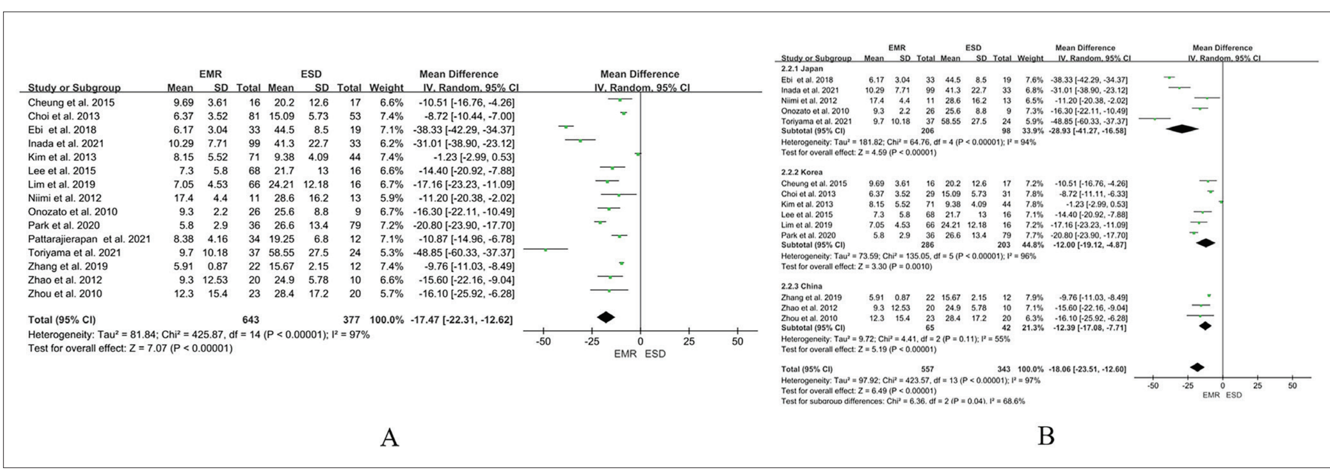


Figure 6. Procedure time comparison of EMR versus ESD. A: EMR group versus ESD group; B: Subgroup analysis by country (Japan, Korea, and China).

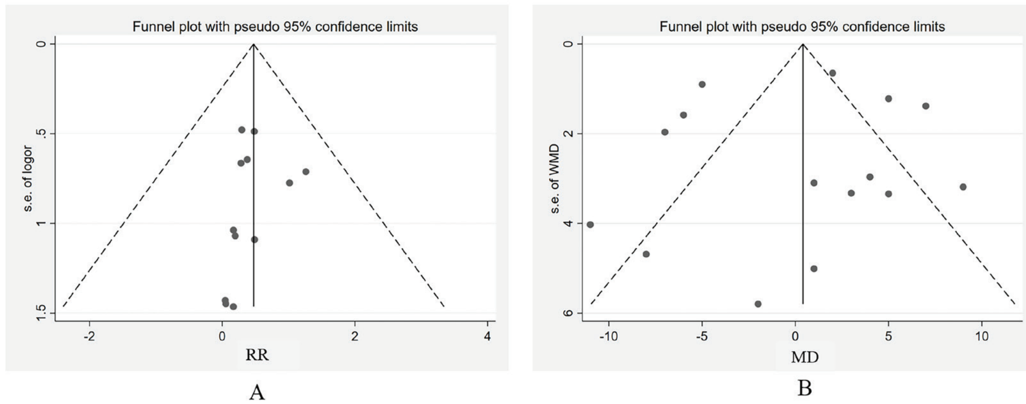


Figure 7. Funnel plot for publication bias assessment. A: Funnel plot of complete resection (Egger's test *P*=.587); B: Funnel plot of procedure time (Egger's test *P*=.839). RR: relative risk; MD: mean difference.

This consensus for combining these procedures is based on the fact that there is an 18.7%-30.4% increased rate of lymphatic metastasis with rectal NETs.[10] For rectal NETs ≤10 mm, endoscopic approaches are suggested by guidelines. Endoscopic approaches include several procedures, such as EMR and ESD; although they share a similar efficacy, other factors, such as safety and expenditure, should be considered while making a clinical decision. Therefore, we conducted this meta-analysis that focused on observational studies on individual tumor sizes ≤10 mm in diameter rather than those with average-sized tumors; in this respect, our study differed from the abovementioned previous studies.[39,40] Observational studies are less conclusive than RCTs. However, few RCTs have been reported on this topic; the sparsity of RCTs is mainly because performing high-quality RCTs are demanding and involve higher medical costs.[41] Owing to the limited number of previous studies focusing on this area, we conducted this study using 18 observational studies.

Based on the results of our study, both EMR and ESD showed good efficacy and safety profiles for treating rectal NETs no larger than mm 10 in diameter. EMR-L and EMR-C showed comparable efficacies to ESD as for complete and en bloc resections. In addition, both EMR and ESD showed lower incidences of perforation and gastrointestinal bleeding. Nevertheless, EMR had a shorter procedure time and a similarly lower recurrence rate than ESD. Additionally, owing to the advantages of operation convenience, fewer skill requirements for surgeons, lower medical costs, and availability in day surgery,[42-44] EMR is superior to ESD in treating rectal NETs no larger than 10 mm from the perspective of health economics.

Rectal NETs are tumors growing slowly with malignant potential, whose prognosis is often determined by the R0. There should be differences between ESD and EMR in terms of complete resection and rate of recurrence,[45,46] yet we failed to differentiate between them in this study, partly because we focused on tumors less than 10 mm in diameter. According to clinical experience, the difference between the two surgical methods will gradually emerge as the tumor diameter increases. In previous studies, the complete resection rate of the less than 5 mm subgroup was significantly higher than that of the 5–10 mm subgroup,[20,25,29,36] a finding that concurs with that of clinical practice. Two previous meta-analyses found that m-EMR has a better complete resection rate than cEMR, with an equivalent safety profile. More specifically, the studies found that the complete resection rates of EMR-L and ESD were higher than those of EMR, whereas the EMR-C, EMR-L, EMR-P, and ESD had similar complete resection rates, with which the above-mentioned meta-analyses concluded similarly. Our subgroup analysis found that the heterogeneity I^2 of the R0 rates in China, Japan, and Korea decreased; these results were not statistically significant. However, we noted a trend suggesting that the effect of endoscopic treatment varied between countries. Although previous studies reported incomplete resections, the final recurrence rate was low because remedial surgeries were performed.[20,25,30,32,34] Additionally, a low incidence of adverse events was also observed in this study, and no statistical differences were found for bleeding and perforation. This study also found that the recurrence rates of both EMR and ESD were low.

Rectal NETs ≤10 mm are less likely to develop into lymphatic metastasis or invade the muscular layer.

Endoscopic ultrasonography improves the complete resection rate.[47,48] Rectal NETs are indolent, slow-growing tumors. Thus, short follow-up periods may fail to detect the differences between the procedures. In addition, the National Comprehensive Cancer Network (NCCN) guidelines state that rectal NETs <10 mm do not require follow-up,[49] while the Japanese Society of Gastroenterology guidelines suggest that postoperative surveillance should be used for colorectal cancer.[10] The disparity in follow-up may lie in the different incidence rates between the East and West and different levels of available medical resources. At present, NETs still lack biomarkers of high sensitivity and specificity; therefore the diagnosis, pathology, and prognosis are greatly limited.[50] A NETs recurrence rate of only 3.1% and a disease-specific survival rate of 96.9% were reported in a 5-year follow-up study.[51] However, there is a significant difference in the 5-year survival rate between NETs in the rectum and those at the rectosigmoid junction, suggesting that differential treatment and management should be applied.[52] In all cases, however, long-term systematic follow-ups of patients with rectal NETs are recommended based on different risk factors. The duration of follow-up time should be further investigated.

In terms of procedure time, there was a statistical difference between EMR and ESD, with a large I^2 value (97%), which indicates great heterogeneity. The results showed that EMR had a shorter procedure time than ESD. Subgroup analysis demonstrated that cEMR, EMR-C, EMR-L, and EMR-P had reduced procedure times compared to ESD. The largest difference between EMR and ESD is the submucosal dissection, which is difficult to operate, highly demanding, and time-consuming for surgeons.[6] The heterogeneity in this study may be due to factors such as different timing standards, the skill level of the surgeon, differences in device manufacturers, and tumor location. The analysis of the Japan-Korea-China group showed high heterogeneity. In addition, ESD incurs higher costs than EMR. In Korea, EMR costs approximately $300, while transanal endoscopic microsurgery (TEM) and ESD cost more than $1500.[26] Medical expenditure is related to the charge for treatment and the length of hospital stay. In Asia, ESD often requires hospitalization, whereas EMR does not. According to Niimi et al, the duration of the hospital stay of patients with ESD (6.2 [2.1]) days was significantly longer than that for EMR-L (1.8 [3.1]) days.[22] Thus, EMR is more cost-effective than ESD for the removal of rectal NETs.

Sensitivity analysis was conducted using the leave-one-out approach. The results for this approach were similar and indicated the accuracy of our findings. However, there are several limitations in this study. First, only one prospective study was included, while the other studies were retrospective ones where doctors or patients decided on the surgical procedures instead of random allocation. Second, most of the included studies were conducted in China, Japan, and Korea, which limited their external validity. Third,the operation of endoscopic rectal NETs resection varies between regions and countries. Therefore, the occurrence of adverse events and the length of the operation may be subjectively influenced by the choices of the surgeon. In addition, publication bias was detected in this study, which may limit its reliability. Therefore, further well-designed, large-scale, multi-centered RCTs with long-term follow-ups are needed to facilitate high-quality verification of the efficacy, safety profile, and cost-effectiveness of using EMR and ESD for rectal NETs ≤10 mm.

In summary, the clinical efficacy and safety of EMR and ESD for resecting rectal NETs ≤10 mm are comparable. Combined with current clinical practice and article reports, it can be concluded, with some caution, that EMR is superior in terms of operation time and cost. In addition, the complete resection rates of EMR-L and ESD were higher than those of cEMR, and the complete resection rates of EMR-C, EMR-L, and EMR-P were comparable to those of ESD. The authors hope these findings will inform future research, especially prospective studies focused on evaluating the cost-effectiveness and clinical decision-making for endoscopists.

REFERENCES

1. Xie W, Yang T, Zuo J, Ma Z, Yu W, Hu Z, et al. Chinese and Global Burdens of Gastrointestinal Cancers From 1990 to 2019. Frontiers in public health. 2022; 10:941284.

2. Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, et al. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(7):839-68.

3. Cives M, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors. CA Cancer J Clin. 2018;68(6):471-87.

4. Frilling A, Akerström G, Falconi M, Pavel M, Ramos J, Kidd M, et al. Neuroendocrine tumor disease: an evolving landscape. Endocrine-related cancer. 2012;19(5): R163-85.

5. Osagiede O, Habermann E, Day C, Gabriel E, Merchea A, Lemini R, et al. Factors associated with worse outcomes for colorectal neuroendocrine tumors in radical versus local resections. Journal of gastrointestinal oncology. 2020;11(5):836-46.

6. Maione F, Chini A, Milone M, Gennarelli N, Manigrasso M, Maione R, et al. Diagnosis and Management of Rectal Neuroendocrine Tumors (NETs). Diagnostics (Basel, Switzerland). 2021;11(5).

7. Shah MH, Goldner WS, Halfdanarson TR, Bergsland E, Berlin JD, Halperin D, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw. 2018;16(6):693-702.

8. Chablaney S, Zator ZA, Kumta NA. Diagnosis and Management of Rectal Neuroendocrine Tumors. Clinical endoscopy. 2017;50(6):530-6.

9. Ito T, Masui T, Komoto I, Doi R, Osamura RY, Sakurai A, et al. JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis. J Gastroenterol. 2021;56(11):1033-44.

10. Tanaka S, Saitoh Y, Matsuda T, Igarashi M, Matsumoto T, Iwao Y, et al. Evidence-based clinical practice guidelines for management of colorectal polyps. J Gastroenterol. 2021;56(4):323-35.

11. McDermott FD, Heeney A, Courtney D, Mohan H, Winter D. Rectal carcinoids: a systematic review. Surgical endoscopy. 2014;28(7):2020-6.

12. McCarty TR, Bazarbashi AN, Thompson CC, Aihara H. Hybrid endoscopic submucosal dissection (ESD) compared with conventional ESD for colorectal lesions: a systematic review and meta-analysis. Endoscopy. 2021;53(10):1048-58.

13. Mistry S, Alaber O, Chandar AK, Perez LKM, Dumot J, Bhatt A, et al. A survey of physician training and credentialing in endoscopic submucosal dissection in the United States. Surg Endosc. 2022;36(5):2794-800.

14. Godwin JD, 2nd. Carcinoid tumors. An analysis of 2,837 cases. Cancer. 1975;36(2):560-9.

15. Park HW, Byeon JS, Park YS, Yang DH, Yoon SM, Kim KJ, et al. Endoscopic submucosal dissection for treatment of rectal carcinoid tumors. Gastrointest Endosc. 2010;72(1):143-9.

16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.

17. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2020. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

19. Baek IH. Endoscopic submucosal dissection or conventional endoscopic mucosal resection is an effective and safe treatment for rectal carcinoid tumors: a retrospective study. Journal of laparoendoscopic & advanced surgical techniques Part A. 2010;20(4):329-31.

20. Onozato Y, Kakizaki S, Iizuka H, Sohara N, Mori M, Itoh H. Endoscopic treatment of rectal carcinoid tumors. Diseases of the colon and rectum. 2010;53(2):169-76.

21. Zhou PH, Yao LQ, Qin XY, Xu MD, Zhong YS, Chen WF, et al. Advantages of endoscopic submucosal dissection with needle-knife over endoscopic mucosal resection for small rectal carcinoid tumors: a retrospective study. Surgical endoscopy. 2010;24(10):2607-12.

22. Niimi K, Goto O, Fujishiro M, Kodashima S, Ono S, Mochizuki S, et al. Endoscopic mucosal resection with a ligation device or endoscopic submucosal dissection for rectal carcinoid tumors: an analysis of 24 consecutive cases. Digestive endoscopy: official journal of the Japan Gastroenterological Endoscopy Society. 2012;24(6):443-7.

23. Zhao ZF, Zhang N, Ma SR, Yang Z, Han X, Zhao YF, et al. A comparative study on endoscopy treatment in rectal carcinoid tumors. Surg Laparosc Endosc Percutan Tech. 2012;22(3):260-3.

24. Choi CW, Kang DH, Kim HW, Park SB, Jo WS, Song GA, et al. Comparison of endoscopic resection therapies for rectal carcinoid tumor: endoscopic submucosal dissection versus endoscopic mucosal resection using band ligation. Journal of clinical gastroenterology. 2013;47(5):432-6.

25. Kim KM, Eo SJ, Shim SG, Choi JH, Min BH, Lee JH, et al. Treatment outcomes according to endoscopic treatment modalities for rectal carcinoid tumors. Clinics and research in hepatology and gastroenterology. 2013;37(3):275-82.

26. Cheung DY, Choi SK, Kim HK, Kim SS, Chae HS, Seo KJ, et al. Circumferential submucosal incision prior to endoscopic mucosal resection provides comparable clinical outcomes to submucosal dissection for well-differentiated neuroendocrine tumors of the rectum. Surgical endoscopy. 2015;29(6):1500-5.

27. Lee SJ, Song GA, Kim DU, Baek DH, Jeon HK, Shin DH, et al. Endoscopic Treatment Options for Rectal Neuroendocrine Tumor: ESD Versus EMR. Gastrointest Endosc. 2015;81(5): AB297-AB.

28. Bang BW, Park JS, Kim HK, Shin YW, Kwon KS, Kim JM. Endoscopic Resection for Small Rectal Neuroendocrine Tumors: Comparison of Endoscopic Submucosal Resection with Band Ligation and Endoscopic Submucosal Dissection. Gastroenterology research and practice. 2016; 2016:6198927.

29. Choi CW, Park SB, Kang DH, Kim HW, Kim SJ, Nam HS, et al. The clinical outcomes and risk factors associated with incomplete endoscopic resection of rectal carcinoid tumor. Surgical endoscopy. 2017;31(12):5006-11.

30. Ebi M, Nakagawa S, Yamaguchi Y, Tamura Y, Izawa S, Hijikata Y, et al. Endoscopic submucosal resection with an endoscopic variceal ligation device for the treatment of rectal neuroendocrine tumors. International journal of colorectal disease. 2018;33(12):1703-8.

31. Lim HK, Lee SJ, Baek DH, Park DY, Lee BE, Park EY, et al. Resectability of Rectal Neuroendocrine Tumors Using Endoscopic Mucosal Resection with a Ligation Band Device and Endoscopic Submucosal Dissection. Gastroenterology research and practice. 2019; 2019:8425157.

32. Zhang DG, Luo S, Xiong F, Xu ZL, Li YX, Yao J, et al. Endoloop ligation after endoscopic mucosal resection using a transparent cap: A novel method to treat small rectal carcinoid tumors. World J Gastroenterol. 2019;25(10):1259-65.

33. Park SS, Han KS, Kim B, Chang Kim B, Hong CW, Sohn DK, et al. Comparison of underwater endoscopic mucosal resection and endoscopic submucosal dissection of rectal neuroendocrine tumors (with videos). Gastrointestinal endoscopy. 2020;91(5):1164-71. e2.

34. Inada Y, Yoshida N, Fukumoto K, Hirose R, Inoue K, Dohi O, et al. Risk of lymph node metastasis after endoscopic treatment for rectal NETs 10 mm or less. International journal of colorectal disease. 2021;36(3):559-67.

35. Pattarajierapan S, Khomvilai S. Recurrence After Endoscopic Resection of Small Rectal Neuroendocrine Tumors: A Retrospective Cohort Study. Ann Coloproctol. 2021.

36. Toriyama K, Yamamura T, Nakamura M, Maeda K, Sawada T, Mizutani Y, et al. An evaluation of resectability among endoscopic treatment methods for rectal neuroendocrine tumors <10 mm. Arab journal of gastroenterology: the official publication of the Pan-Arab Association of Gastroenterology. 2021;22(2):104-10.

37. Zhong DD, Shao LM, Cai JT. Endoscopic mucosal resection vs endoscopic submucosal dissection for rectal carcinoid tumours: a systematic review and meta-analysis. Colorectal disease: the official journal of the Association of Coloproctology of Great Britain and Ireland. 2013;15(3):283-91.

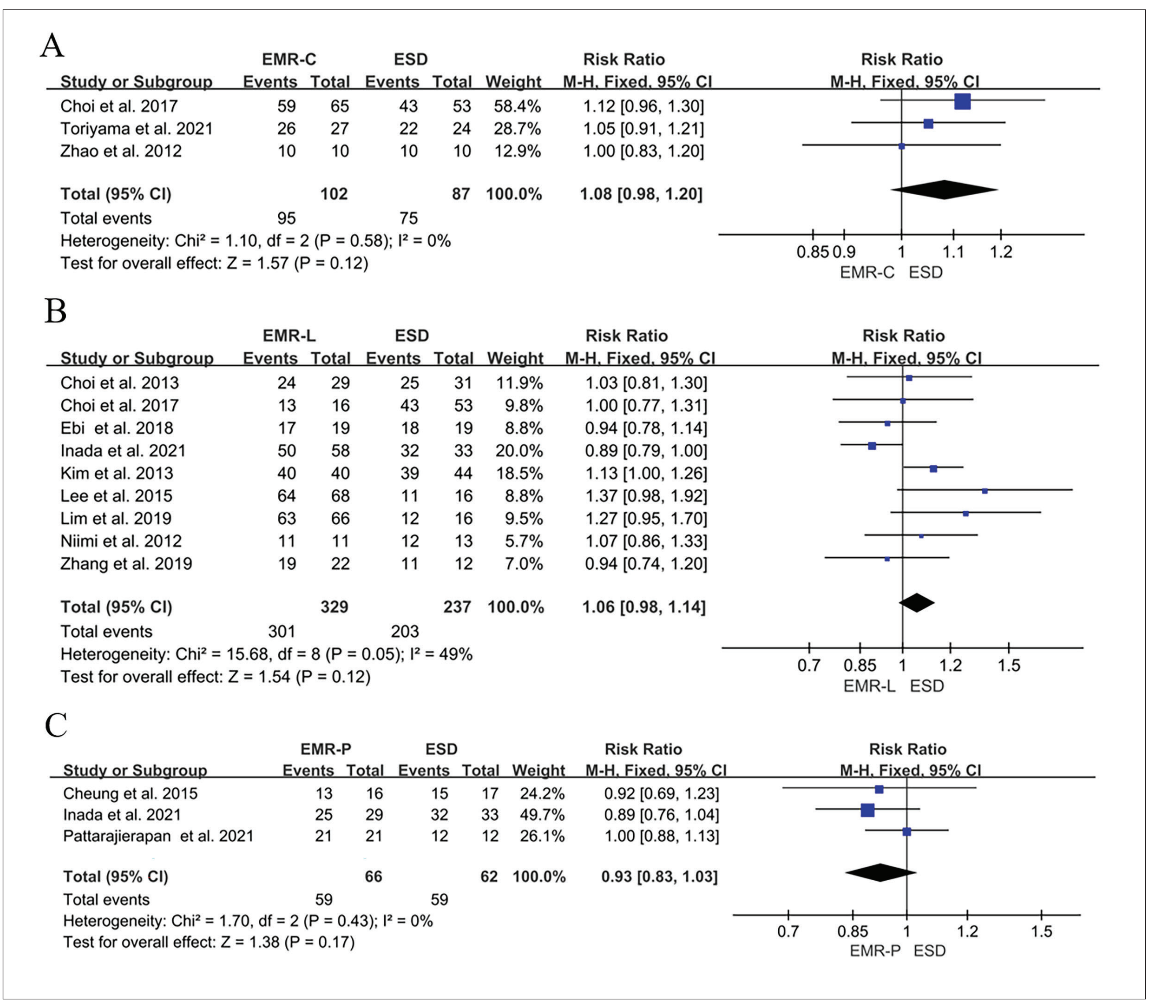
38. He L, Deng T, Luo H. Efficacy and safety of endoscopic resection therapies for rectal carcinoid tumors: a meta-analysis. Yonsei medical journal. 2015;56(1):72-81.

39. Pan J, Zhang X, Shi Y, Pei Q. Endoscopic mucosal resection with suction vs. endoscopic submucosal dissection for small rectal neuroendocrine tumors: a meta-analysis. Scand J Gastroenterol. 2018;53(9):1139-45.

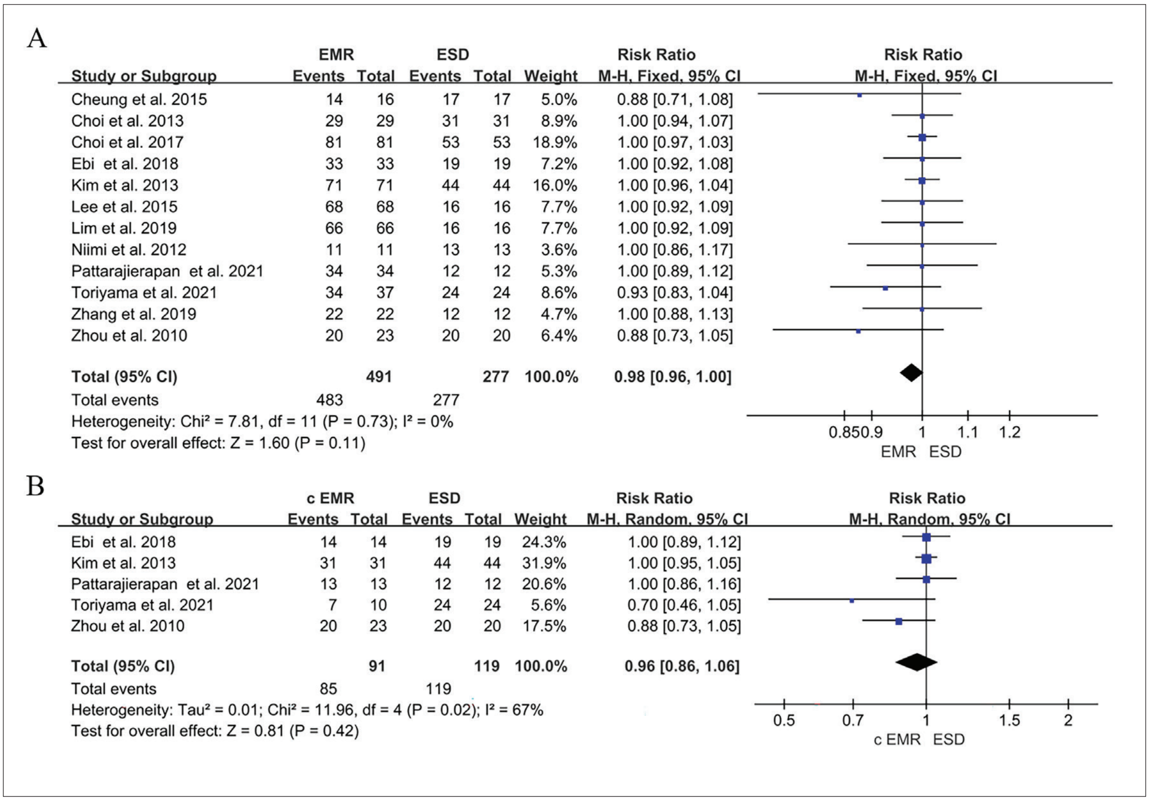
40. Yong JN, Lim XC, Nistala KRY, Lim

LKE, Lim GEH, Quek J, et al. Endoscopic submucosal dissection versus endoscopic mucosal resection for rectal carcinoid tumor. A meta-analysis and meta-regression with single-arm analysis. J Dig Dis. 2021;22(10):562-71.
41. Singh S, Sivajohanathan D, Asmis T, Cho C, Hammad N, Law C, et al. Systemic therapy in incurable gastroenteropancreatic neuroendocrine tumours: a clinical practice guideline. Curr Oncol. 2017;24(4):249-55.
42. Dalgic T, Senlikci A, Bostanci EB. Submucosal Endoscopic Resection of Rectal GEP-NETs Is Curative-a Case Series Analysis. Indian J Surg. 2020;82(5):927-9.
43. Sivandzadeh GR, Ejtehadi F, Shoaee S, Aminlari L, Niknam R, Taghavi AR, et al. Endoscopic mucosal resection: still a reliable therapeutic option for gastrointestinal neuroendocrine tumors. BMC gastroenterology. 2021;21(1):238.
44. Okada M, Shinozaki S, Ikeda E, Hayashi Y, Takezawa T, Fukuda H, et al. Underwater Endoscopic Mucosal Resection of Small Rectal Neuroendocrine Tumors. Frontiers in medicine. 2022; 9:835013.
45. Draganov PV, Aihara H, Karasik MS, Ngamruengphong S, Aadam AA, Othman MO, et al. Endoscopic Submucosal Dissection in North America: A Large Prospective Multicenter Study. Gastroenterology. 2021;160(7):2317-27. e2.
46. Ono H, Yao K, Fujishiro M, Oda I, Uedo N, Nimura S, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc. 2021;33(1):4-20.
47. Mandair D, Caplin ME. Colonic and rectal NET's. Best practice & research Clinical gastroenterology. 2012;26(6):775-89.
48. Murino A, Lazaridis N. T1 rectal NET resection: Does size really matter? Gastrointest Endosc. 2021;94(2):416-8.
49. Kulke MH, Benson AB, 3rd, Bergsland E, Berlin JD, Blaszkowsky LS, Choti MA, et al. Neuroendocrine tumors. J Natl Compr Canc Netw. 2012;10(6):724-64.
50. Modlin IM, Bodei L, Kidd M. Neuroendocrine tumor biomarkers: From monoanalytes to transcripts and algorithms. Best Pract Res Clin Endocrinol Metab. 2016;30(1):59-77.
51. Kojima M, Chen Y, Ikeda K, Tsukada Y, Takahashi D, Kawano S, et al. Recommendation of long-term and systemic management according to the risk factors in rectal NETs patients. Scientific reports. 2019;9(1):2404.
52. Cai W, Ge W, Hu H, Mao J. Rectal NETs and rectosigmoid junction NETs may need to be treated differently. Cancer medicine. 2020;9(3):971-9.

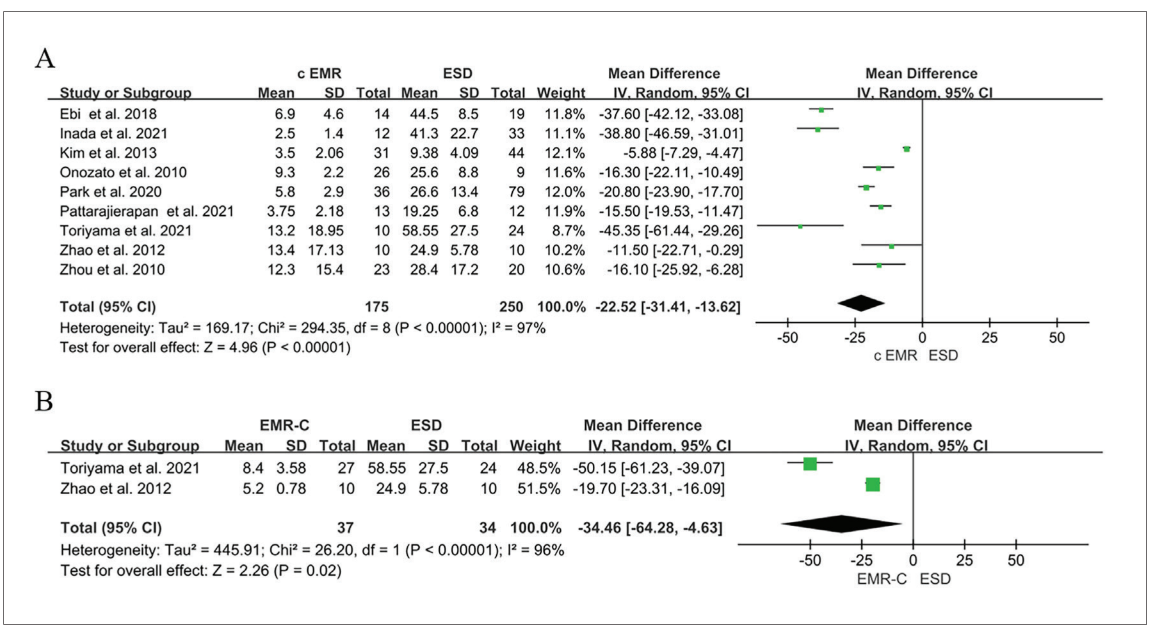
SUPPLEMENTARY FIGURES



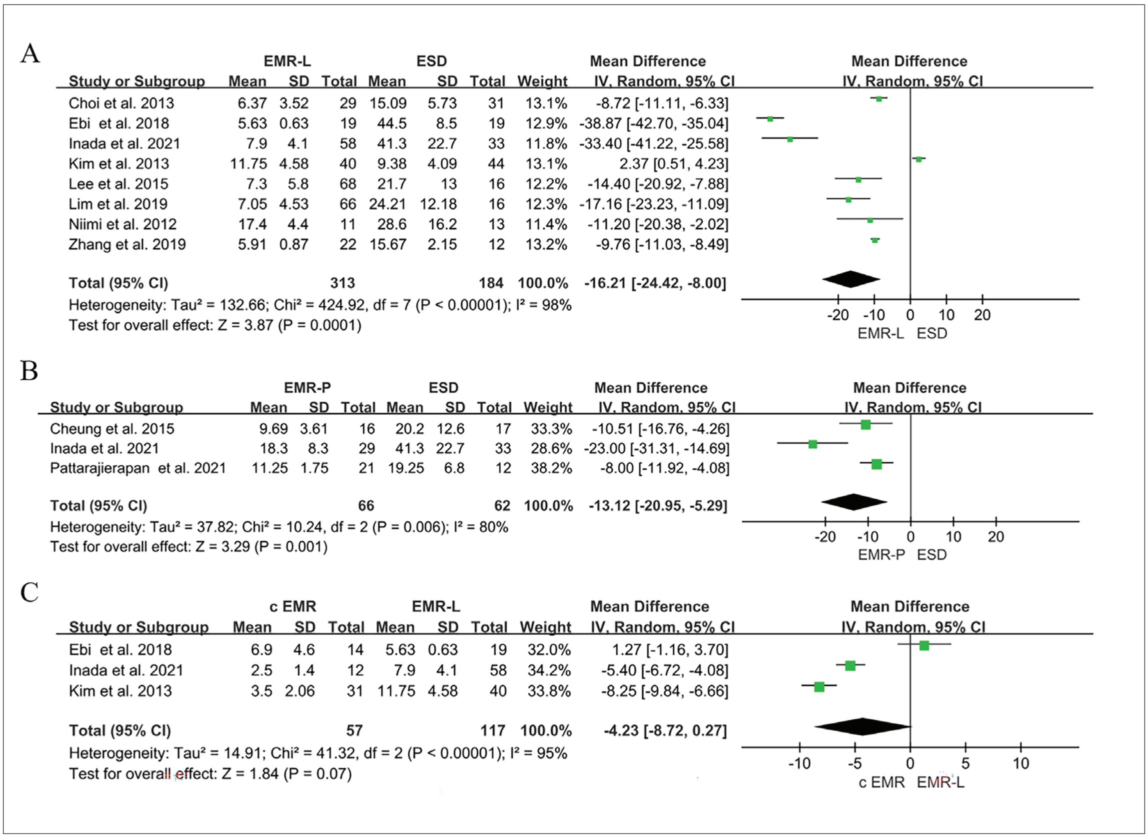
Supplementary Figure S1. EMR subgroup analysis on complete resection (R0) rate comparison. A: EMR-C versus ESD, B: EMR-L versus ESD, C: EMR-P versus ESD.



Supplementary Figure S2. En bloc resection rate comparison of EMR versus ESD. A: EMR group versus ESD group, B: c EMR versus ESD.



Supplementary Figure S3. EMR subgroup analysis on procedure time: A. c EMR versus ESD, B: EMR-C versus ESD.



Supplementary Figure S4. EMR subgroup analysis on procedure time: A: EMR-L versus ESD, B: EMR-P versus ESD,C: c EMR versus EMR-L.

Newcastle–Ottawa quality scale of studies included

Study	Year	Selection				Comparability		Outcome assessment			Total score
		1	2	3	4	1	2	1	2	3	
Baek	2010	★	★	★	★	★		★	★	★	★★★★★★★★
Onozato et al.	2010	★	★	★	★	★		★	★		★★★★★★★
Zhou et al.	2010	★	★	★	★	★		★			★★★★★★
Niimi et al.	2012	★	★	★	★	★		★	★		★★★★★★★
Zhao et al.	2012	★	★	★	★			★			★★★★★
Choi et al.	2013	★	★	★	★	★		★			★★★★★★
Kim et al.	2013	★	★	★	★	★		★	★	★	★★★★★★★★
Cheung et al.	2015	★	★	★	★	★		★			★★★★★★
Lee et al.	2015	★	★					★			★★★
Bang et al.	2016	★	★	★		★		★			★★★★★
Choi et al.	2017	★	★	★	★	★		★	★		★★★★★★★
Ebi et al.	2018	★	★	★	★	★		★	★		★★★★★★★
Lim et al.	2019	★	★	★	★	★		★	★	★	★★★★★★★★
Zhang et al.	2019	★	★	★	★	★		★			★★★★★★
Park et al.	2020	★	★	★	★	★		★	★		★★★★★★★
Inada et al.	2021	★	★	★	★	★		★			★★★★★★
Pattarajierapan et al.	2021	★	★	★	★	★		★	★	★	★★★★★★★★
Toriyama et al.	2021	★	★	★	★	★		★	★		★★★★★★★

Supplementary Figure S5. Newcastle–Ottawa quality scale of studies included.