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Endoscopic submucosal dissection (ESD) versus transanal endoscopic microsurgery (TEM) for treatment of rectal tumors: a comparative systematic review and meta-analysis

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Abstract

Background While multiple studies have evaluated endoscopic submucosal dissection (ESD) and transanal endoscopic microsurgery (TEM) to remove large rectal tumors, there remains a paucity of data to evaluate their comparative efficacy and safety. The primary aim of this study was to perform a structured systematic review and meta-analysis to compare efficacy and safety of ESD versus TEM for the treatment of rectal tumors.

Methods Individualized search strategies were developed from inception through November 2018 in accordance with PRISMA guidelines. Measured outcomes included pooled *en bloc* resection rates, margin-negative (R_0) resection rates, procedure-associated adverse events, and rates of recurrence. This was a cumulative meta-analysis performed by calculating pooled proportions. Heterogeneity was assessed with Cochran Q test and I^2 statistics, and publication bias by funnel plot using Egger and Begg tests.

Results Three studies ($n = 158$ patients; 55.22% male) were included in this meta-analysis. Patients with ESD compared to TEM had similar age ($P = 0.090$), rectal tumor size ($P = 0.108$), and diagnosis rate of adenoma to cancer ($P = 0.53$). ESD lesions were more proximal as compared to TEM (8.41 ± 3.49 vs. 5.11 ± 1.43 cm from the anal verge; $P < 0.001$). Procedure time and hospital stay were shorter for ESD compared to TEM [(79.78 ± 24.45 vs. 116.61 ± 19.35 min; $P < 0.001$) and (3.99 ± 0.32 vs. 5.83 ± 0.94 days; $P < 0.001$), respectively]. No significant differences between *en bloc* resection rates [OR 0.98 (95% CI 0.22–4.33); $P = 0.98$; $I^2 = 0.00\%$] and R_0 resection rates [OR 1.16 (95% CI 0.36–3.76); $P = 0.80$; $I^2 = 0.00\%$] were noted between ESD and TEM. ESD and TEM reported similar rates of adverse events [OR 1.15 (95% CI 0.47–2.77); $P = 0.80$; $I^2 = 0.00\%$] and rates of recurrence [OR 0.46 (95% CI 0.07–3.14); $P = 0.43$; $I^2 = 0.00\%$].

Conclusion ESD and TEM possess similar rates of resection, adverse events, and recurrence for patients with large rectal tumors; however, ESD is associated with significantly shorter procedure times and duration of hospitalization. Future studies are needed to evaluate healthcare utilization for these two strategies.

Keywords Endoscopy · Endoscopic surgery · Endoscopic submucosal dissection (ESD) · Transanal endoscopic microsurgery (TEM)

In the United States, it is estimated there will be 44,180 new diagnoses of rectal cancer in 2019 alone [1]. Although standard treatment for advanced rectal cancer has traditionally been considered anterior resection (AR) or abdominoperineal resection (APR), less invasive alternative modalities such as endoscopic submucosal dissection (ESD) and transanal endoscopic microsurgery (TEM) have emerged as effective treatments to achieve local excision of rectal tumors with a reduced associated morbidity compared to traditional surgery. Compared with conventional surgery, ESD and TEM are less traumatic, resulting in less post-procedure pain, faster recovery, shorter hospital duration, and more rapid return to daily life [2–4].

While ESD is a specialized resection technique that enables endoscopic *en bloc* resection of colorectal lesions using a modified needle knife for submucosal dissection, TEM is a surgical procedure that employs an operative rectoscope

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and allows for full-thickness resection of tumors located 5 to 18 cm from the anal verge [5–7]. Both techniques are considered minimally invasive procedures to treat benign rectal adenomas, intramucosal cancer, and superficial submucosal cancer and have largely replaced AR and APR for these lesions. However, there are limited data available to determine if one approach is superior to the other [2, 8, 9].

As such, the primary aim of this study was to perform a structured systematic review and meta-analysis to compare efficacy and safety of ESD versus TEM for the treatment of rectal tumors.

Materials and methods

Study design and search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline for reporting systematic reviews and meta-analyses and was conducted following a prior established protocol [10]. Individualized searches of PubMed, EMBASE, Web of Science, and Cochrane databases were performed from inception through November 30, 2018. The following medical subject heading (MESH) terms included: *rectal tumor* or *rectal cancer*. For articles related to rectal tumor, subject heading search terms and title and abstract were reviewed for *endoscopic surgery*, *endoscopic removal, endoscopic submucosal dissection (ESD)*, and *transanal endoscopic microsurgery (TEM)*.

All relevant articles irrespective of year of publication, type of publication, or publication status were included. The titles and abstracts of all potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles by cross checking bibliographies. Two reviewers (TRM and ANB) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any differences were resolved by mutual agreement and in consultation with the third reviewer (KEH). In the case of studies with incomplete information, contact was attempted with the principal authors to obtain additional data. Institutional IRB approval and written consent was not required given the design of this systematic review and meta-analysis.

Study selection criteria

Randomized controlled trials, observational studies, and case series evaluating ESD and TEM were included in this analysis. Studies were included if patients were adults ≥ 18 years of age, had a diagnosis of rectal tumor, and underwent ESD and TEM procedures for tumor removal. Included studies were required to be directly comparative studies including both removal techniques. Alterative tumor removal procedures such as endoscopic mucosal resection (EMR) were not included. Mandatory outcomes to merit study inclusion were pooled *en bloc* resection rates, margin-negative (R_0) resection rates, procedure-associated adverse events, or rates of recurrence. Only human subject studies were considered for this meta-analysis. Multiple published works from similar authors were evaluated for overlapping enrollment times to preserve independence of observations. A study was excluded if deemed to have insufficient data, as were review articles, editorials, and correspondence letters that did not report independent data. Case series and reported studies with < 5 patients were excluded in effort to limit selection bias.

Outcome measures

The primary outcome was a comparative review of ESD versus TEM with regard to pooled *en bloc* resection rates, margin-negative (R_0) resection rates, procedure-associated adverse events, and rates of recurrence. Secondary outcomes included baseline patient and procedure characteristics including rectal tumor size and location, diagnosis rate (defined as adenoma to cancer rate), duration of procedure (min), and mean duration of hospitalization.

Risk of bias and quality assessment

Risk of bias was assessed using the Cochrane Collaboration's risk of bias in non-randomized studies of interventions (ROBINS-I) tool for observational studies [11]. In this meta-analysis, publications were deemed low risk of bias if ≥ 50% of the above domains were judged as low risk. The quality of observational studies was evaluated using the Newcastle–Ottawa Quality Assessment Scale [12]. Two authors (TRM and ANB) independently extracted data and assessed the risk of bias and study quality for each of the articles. Any disagreements were resolved by discussion and consensus, and in consultation with the third reviewer (KEH).

Investigations of heterogeneity

Heterogeneity was assessed for the individual meta-analyses using the Chi-squared test and the I^2 statistic [13]. Significant heterogeneity was defined as $P < 0.05$ using the Chi-squared or $I^2 > 50\%$. A random effects model was used except for when statistical heterogeneity was not significant. Differences in subgroups were assessed using a Chi-squared test for interaction with a $P < 0.05$ defined as statistically significant. To assess for publication bias, a funnel plot was created and visually inspected for asymmetry [14].

Statistical analysis

This meta-analysis was performed by calculating pooled proportions. After appropriate studies were identified through systematic review, the individual study proportion was transformed into a quantity using the Freeman–Tukey variant of the arcsine square root transformed proportion. Then the pooled proportion was calculated as the back transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian–Laird weights for the random effect model [15, 16]. All weighted pool rates involved 95% confidence intervals and were analyzed using fixed or random effects models based on the heterogeneity of the sample. Tabular and graphical displays were performed in Review Manager 5 (RevMan 5.3). Combined weighted proportions and additional analyses were determined by the use of the Stata 13.0 software package (Stata Corp LP, College Station, TX).

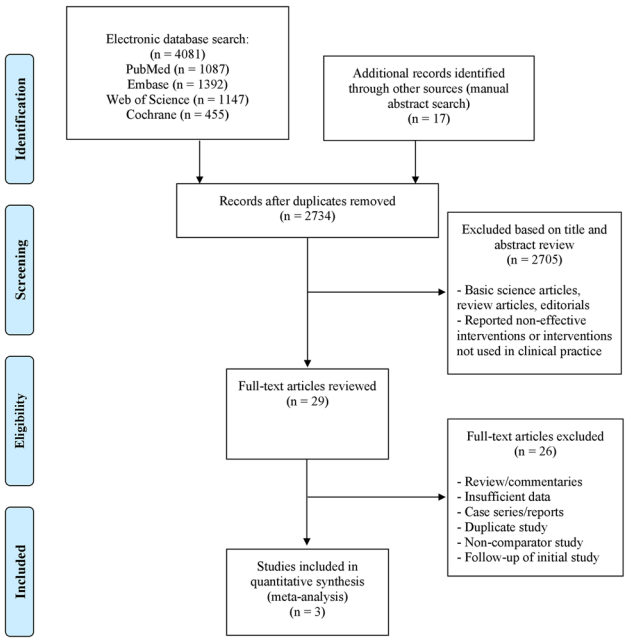

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of search results for ESD versus TEM for treatment of rectal tumors

Results

Characteristics of included studies

This systematic review and meta-analysis included a total of 3 studies ($n = 158$) [2, 8, 9]. A PRISMA flow chart of search results is shown in Fig. 1. All included studies were retrospective cohort studies with no prospective or randomized control trials found via the above search criteria. One study by Jung et al. separated cohorts based upon epithelial and subepithelial lesions [9]. Mean age of included patients was 61.94 ± 4.84 years with 55.22% males. Average study follow-up of both ESD and TEM was 15.87 ± 9.45 months. Mean tumor rectal size overall was 31.33 ± 11.17 mm at a mean distance of 6.67 ± 3.08 cm from the anal verge. Additional study characteristics are highlighted in Table 1.

ESD versus TEM

Among included comparative studies, mean age of patients in the ESD cohort was similar to patients who underwent TEM (62.52 ± 4.91 vs. 61.20 ± 4.69 years; $P = 0.090$). Mean follow-up duration for TEM was almost double that of ESD (20.47 ± 10.33 vs. 12.31 ± 6.88 months; $P < 0.001$). With regard to ESD compared to TEM, the size of rectal tumor was similar between two groups (32.58 ± 13.29 vs. 29.70 ± 7.41 mm; $P = 0.108$), respectively. Location of ESD lesions was more proximal as compared to TEM (8.41 ± 3.49 vs. 5.11 ± 1.43 cm from the anal verge; $P < 0.001$).

With regard to primary outcome measures, there were no significant differences between *en bloc* resection rates [OR 0.98 (95% CI 0.22 to 4.33); $P = 0.98$; $I^2 = 0.00\%$] and R_0 resection rates [OR 1.16 (95% CI 0.36 to 3.76); $P = 0.80$; $I^2 = 0.00\%$] between ESD and TEM groups—Figs. 2 and 3. Rate of adenoma to cancer diagnosis was similar between the ESD and TEM groups as well [OR 0.80 (95% CI 0.41 to 1.58); $P = 0.53$; $I^2 = 80.00\%$]. ESD and TEM also reported similar rates of procedure-associated adverse events [OR 1.15 (95% CI 0.47 to 2.77); $P = 0.80$; $I^2 = 0.00\%$] and rates of tumor recurrence [OR 0.46 (95% CI 0.07 to 3.14); $P = 0.43$; $I^2 = 0.00\%$]—Figs. 4 and 5. Cumulative pooled rates for ESD and TEM are shown in Table 2. Despite similar primary outcome measures, procedure time and hospital stay were significantly shorter for ESD as compared to TEM [(79.78 ± 24.45 vs. 116.61 ± 19.35 min; $P < 0.001$) and (3.99 ± 0.32 vs. 5.83 ± 0.94 days; $P < 0.001$), respectively].

Risk of bias assessment

All studies were assessed using ROBINS-I, and the Newcastle–Ottawa Quality Assessment Scale with authors' judgements about each risk of bias item for all included studies is highlighted in Fig. 6A. A risk of bias summary graph is also available in Fig. 6B. Testing for publication bias with funnel plot asymmetry was not performed given the limited number of included studies.

Table 1 Baseline characteristics of included studies involving ESD versus TEM for treatment of rectal tumors

Author	Year	Study design	No of patients	No of males (%)	Age (year)	Follow-up (months)	Tumor size (mm)	Distance from anal verge (cm)	Procedure time (min)	Hospital stay (days)	Adenoma-to-cancer ratio	En bloc resection rates (%)	R_0 resection rates (%)	Adverse events (%)	Recurrence rate (%)
ESD															
Park et al.	2012	Retrospective	30	14 (46.67%)	58.6 ± 8.3	20.1 ± 14.1	25.4 ± 11.0	10.5 ± 4.6	84 ± 51.2	3.6 ± 1.2	18:12	29/30 (96.67%)	29/30 (96.67%)	1/30 (3.33%)	0/30 (0.00%)
Kawaguti et al.	2014	Retrospective	11	–	62.3 ± 4.6	18.6 ± 5.4	64.6 ± 57.9	2.72 ± 2.19	133 ± 94.8	3.8 ± 3.3	1:10	10/11 (90.91%)	9/11 (81.82%)	5/11 (45.45%)	1/11 (9.09%)
Jung et al. (epithelial)	2018	Retrospective	40	22 (55.00%)	67.4 ± 9.3	6	33 ± 13	–	71.5 ± 51.3	4.3 ± 1.2	24:16	38/40 (95.00%)	37/40 (92.50%)	11/40 (27.50%)	1/40 (2.50%)
Jung et al. (subepithelial)	2018	Retrospective	8	5 (62.50%)	53.1 ± 16.8	6	13.7 ± 5.1	–	32.13 ± 13.4	4.1 ± 4.1	–	8/8 (100.00%)	7/8 (87.50%)	2/8 (25.00%)	0/8 (0.00%)
TEM															
Park et al.	2012	Retrospective	33	17 (51.52%)	59.5 ± 11.0	27.2 ± 11.6	27.8 ± 15.0	6 ± 3.6	116.4 ± 58.5	6.6 ± 3.5	24:9	33/33 (100.00%)	32/33 (96.97%)	2/33 (6.06%)	0/33 (0.00%)
Kawaguti et al.	2014	Retrospective	13	–	61.5 ± 9.5	29 ± 13.4	43.9 ± 30.7	2.85 ± 2.88	150 ± 66.3	4.08 ± 1.7	8:5	11/13 (84.62%)	11/13 (84.62%)	5/13 (38.46%)	2/13 (15.38%)
Jung et al. (epithelial)	2018	Retrospective	16	9 (56.25%)	68.4 ± 8.9	6	27 ± 15	–	105.6 ± 28.2	5.8 ± 1.8	5:11	15/16 (93.75%)	14/16 (87.50%)	4/16 (25.00%)	1/16 (6.25%)
Jung et al. (subepithelial)	2018	Retrospective	7	7 (100.00%)	52.2 ± 8.2	6	18.5 ± 17.6	–	80.71 ± 18.35	5.5 ± 2.0	–	7/7 (100.00%)	6/7 (85.61%)	1/7 (14.29%)	0/7 (0.00%)

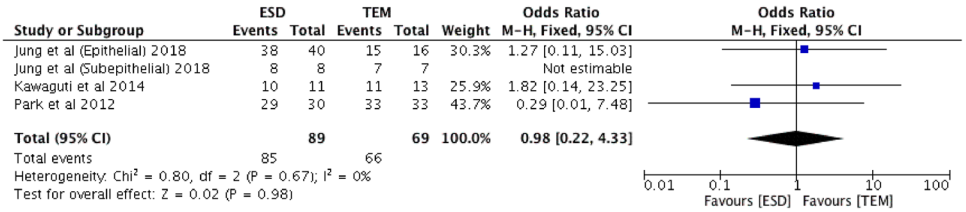

Fig. 2 Comparative en bloc resection rate of ESD versus TEM for treatment of rectal tumors

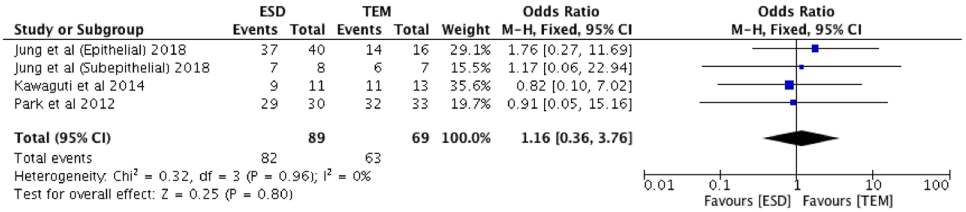

Fig. 3 Comparative R_0 resection rate of ESD versus TEM for treatment of rectal tumors

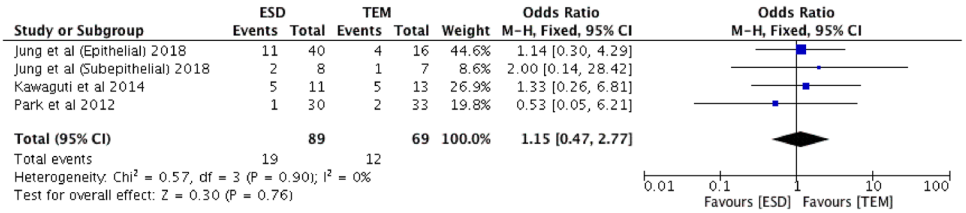

Fig. 4 Comparative adverse event rate of ESD versus TEM for treatment of rectal tumors

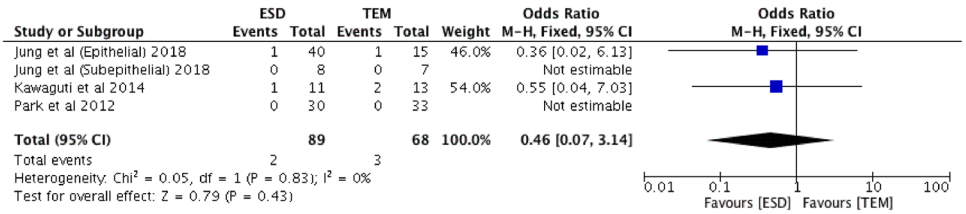

Fig. 5 Comparative recurrence rate of ESD versus TEM for treatment of rectal tumors

Table 2 Efficacy and safety of ESD versus TEM for treatment of rectal tumors: cumulative and comparative meta-analysis

	Cumulative data for ESD		Cumulative data for TEM		Comparative data for ESD vs. TEM	
	Pooled rate (95% CI)	Heterogeneity (I^2) (%)	Pooled rate (95% CI)	Heterogeneity (I^2) (%)	Odds ratio (95% CI)	Heterogeneity (I^2) (%)
En bloc resection rate	97% (95% CI 91 to 100)	0.00	97% (95% CI 87 to 100)	43.46	0.98 (95% CI 0.22 to 4.33)	0.00
R_0 resection rate	94% (95% CI 87 to 99)	0.00	93% (95% CI 84 to 99)	43.46	1.16 (95% CI 0.36 to 3.76)	0.00
Adverse event rate	21% (95% CI 5 to 44)	76.26	18% (95% CI 4 to 37)	59.40	1.15 (95% CI 0.47 to 2.77)	0.00
Rate of recurrence	1% (95% CI 0 to 5)	0.00	3% (95% CI 0 to 13)	43.46	0.46 (95% CI 0.07 to 3.14)	0.00

Discussion

Overall, the results of this systematic review and meta-analysis demonstrate that ESD and TEM are similar in efficacy and safety for patients with large rectal lesions. Pooled *en bloc* resection rate and R_0 resection rate for ESD and TEM were comparable [(97% versus 97%) and (94% versus 93%), respectively]. Adverse event rate and rate of recurrence for ESD versus TEM was also similar [(21% versus 18%) and (1% versus 3%), respectively]. Secondary aims of this study highlight that ESD resulted in decreased procedure time as compared to TEM with shorter duration of hospital stay. Although both modalities provide effective and safe alternatives to traditional radical surgery, the technique and indication to achieve these results is different. Due to use of a rigid rectoscope, TEM is typically limited to lesions 5 cm proximal to the anal verge, while

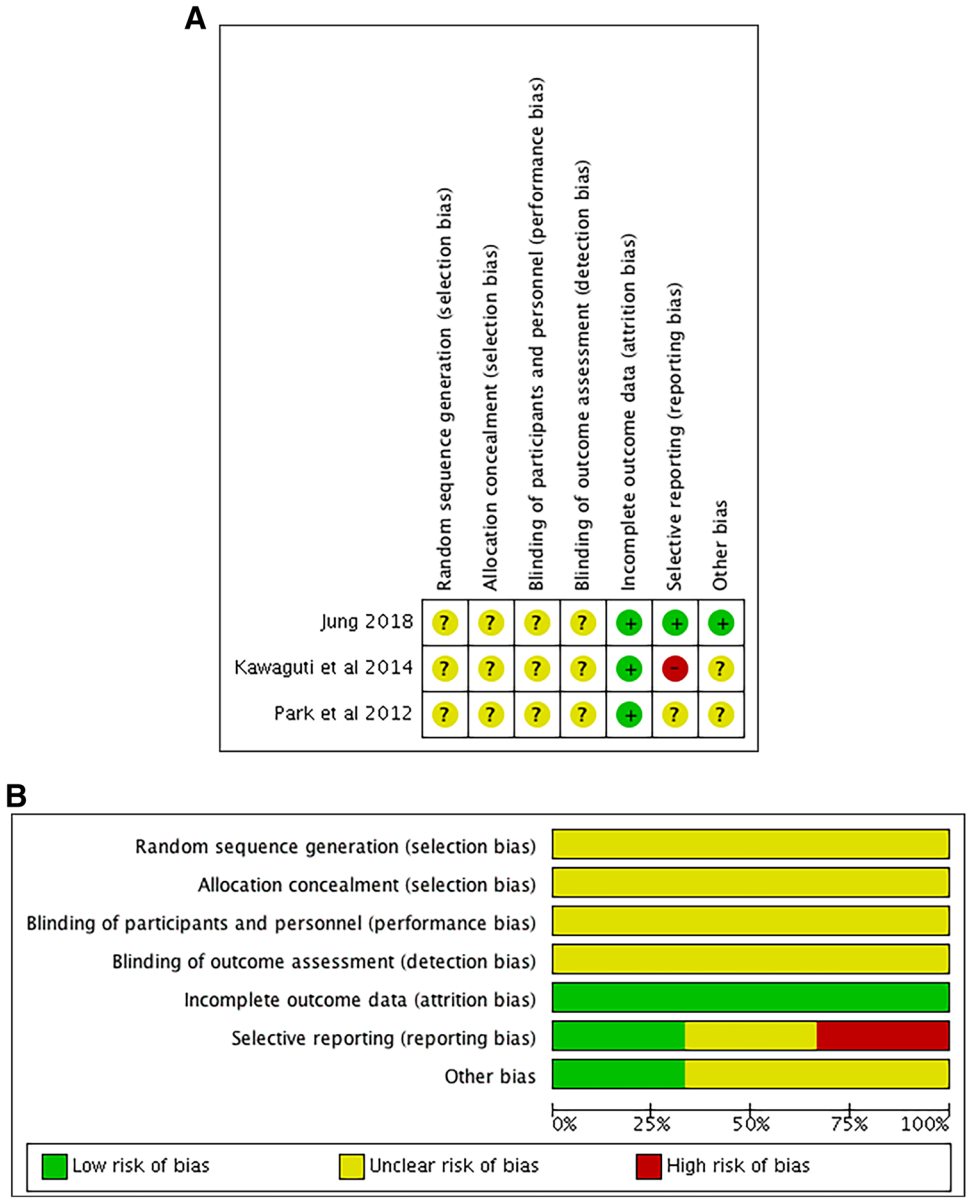

Fig. 6 **A** Risk of bias summary: review authors' judgements about each risk of bias item for each included study. **B** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

ESD relies upon a standard endoscope allowing for forward-view or retroflexed resection of lesions near the anus or at the dentate line [7, 17, 18]. The ability to treat more distal lesions provides added benefit for ESD as compared to TEM, despite comparable efficacy and safety.

A previous systematic review of non-comparator studies including 21 articles and 2077 patients revealed a significantly lower *en bloc* resection rate and R_0 resection rate for ESD as compared to TEM [87.8% (95% CI 84.3 to 90.6) versus 98.7% (95% CI 97.4 to 99.3) $P < 0.001$] and [74.6% (95% CI 70.4 to 78.4) versus 88.5% (95% CI 85.9 to 90.6) $P < 0.001$], respectively [19]. The post-procedure adverse rate was similar between the two procedures; however, the recurrence rate for ESD was better than TEM despite lower resection rates as above [2.6% (95% CI 1.3 to 5.2) versus 5.2% (95% CI 4.0 to 6.9); $P < 0.001$]. While these results contradict our current meta-analysis, it is important to note these were non-comparator observational studies and all published prior to 2010—with inherent bias and inability to reflect current ESD practices, technique, and procedure evolution [9]. All studies in our analysis span from 2012 to 2018, which may account for improved proficiency of ESD practitioners, development of novel endoscopic devices for safe and accurate resections, and use of high-definition endoscopes [9, 20–22].

Another important consideration with regard to a preferred procedure is cost. The TEM procedure, characterized by full-thickness resection, requires the procedure to be performed under either general or spinal anesthesia, whereas ESD may be performed with conscious or deep sedation

in the endoscopy unit. TEM additionally requires expensive surgical instruments which make the procedure a more expensive modality compared to ESD, even despite being an older modality [23]. A previous cost comparison study by Nam and colleagues aimed to compare costs associated with TEM versus ESD, finding median total hospital costs were significantly lower in the ESD than in the TEM group ($1214 versus $1686; $P < 0.001$) [4]. This is an important realization and may explain our findings of TEM being associated with a longer duration of hospitalization.

Limitations to this present study include the inherent heterogeneity bias of pooled systematic reviews and meta-analyses. Although this was evaluated with I^2 and appeared to be minimal in this analysis, we cannot rule out the risk of inherent study bias, specific differences in patient population, and inter-operator variability in procedure outcomes. For this reason, published data may not fully reflect current practice and endoscopic or surgical expertise. For example, some patients undergoing TEM may be discharged from the post-anesthesia care unit after the procedure similar to patients in the endoscopy suite post-ESD. Furthermore, studies of TEM had a significantly longer follow-up period—almost double that of ESD studies, potentially allowing for more adverse events to occur. Procedure time was also not standardized among studies. The quality of included studies is also limited as no randomized controlled studies were included in this analysis, with 3 small, single-center retrospective studies included. Publication bias was also not assessed with funnel plot asymmetry as typically a minimum of 8–10 studies should be included in the meta-analysis [24].

An additional limitation relates to location of rectal lesions. Although TEM is typically recommended for tumors located 5 to 18 cm from the anal verge, the study by Kawaguti et al. reported a mean distance of 2.85 cm for lesions treated with TEM [8]. Although many surgeons perform TEM for lesions as low as the dentate line (i.e., not limiting use to lesions proximal to 5 cm from the anal verge), risk of selective bias for this study was significant. Subgroup analysis excluding this study was not possible due to limited number of studies. Ideally, it would be highly relevant to stratify our results based upon adenoma and cancer findings on pathology; however, this was not possible due to limited data and reporting style. This is very pivotal as full-thickness excision TEM can resect some T2 rectal cancers while ESD does not. It is also important to understand a large limitation of this study relates to generalizability. There is a significant learning curve or clinical expertise needed to perform an effective ESD or TEM procedure, with some institutions perhaps more adept at performing one procedure over the other—especially with regard to centers with less familiarity or proven expertise. This may result in large differences, including margin status, *en bloc* resection, recurrence, and other outcomes [25].

Despite these limitations, this study has several strengths. While there remains a paucity of literature, this structured systematic review and meta-analysis methodologically summarizes all available data to evaluate the comparative effectiveness of ESD versus TEM for the treatment of localized rectal tumors. Through inclusion of direct comparator studies, we also aimed to minimize selection bias. One study by Hitzler et al. appeared to be a comparator study upon initial review; however, the study was excluded as German patients undergoing TEM were compared to a literature review of ESD outcomes among Japanese patients [26]. Therefore, in effort to limit potential selection bias, this study was excluded from our meta-analysis. In addition to technical measures such as en bloc resection rates, R_0 resection rates, adverse events, and rates of recurrence, we also aimed to assess surrogates of cost-effectiveness including procedure-associated times and length of hospital stay.

In conclusion, ESD and TEM appear to possess similar rates of resection, adverse events, and rate of recurrence for patients with rectal tumors. Although both have comparable efficacy and safety, ESD is associated with significantly shorter procedure times and duration of hospitalization. Future studies are needed to evaluate healthcare utilization for these two strategies and determine what subset of patients may respond better to ESD or TEM.

Compliance with ethical standards

Disclosures Chris C. Thompson is a consultant for Boston Scientific, Olympus America, and Apollo Endosurgery. Hiroyuki Aihara is a consultant for Olympus America, Boston Scientific, and Fujifilm Medical Systems. Thomas R. McCarty, Ahmad Najdat Bazarbashi, and Kelly E. Hathorn have no conflicts to disclose.

Ethical approval Institutional IRB approval and written consent was not required given the design of this systematic review and meta-analysis.

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