Endoscopic resection versus esophagectomy for early esophageal cancer: a meta-analysis

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Background: Esophagectomy is the standard treatment for early-stage esophageal cancer but is associated with high morbidity and mortality. Thus, endoscopic resection is increasingly used as an alternative option. However, the literature is inconsistent regarding the efficacy of these treatments. This meta-analysis aimed to compare the efficacy and safety of these two treatments.

Methods: A systematic electronic search of PubMed, EMBASE, and the Cochrane Library was performed for studies comparing endoscopic resection and surgery for early-stage esophageal cancer. The overall survival, tumor recurrence, major adverse events, procedure-related mortality, and R0 resection rates were investigated. Forest plots were constructed based on the random-effects model.

Results: We found 15 studies involving 2,467 and 2,264 patients who underwent endoscopic resection and surgery, respectively. The meta-analysis showed that patients undergoing endoscopic resection had significantly fewer major adverse events (relative risk, 0.46; 95% confidence interval, 0.33–0.64) and a lower procedure-related mortality rate (relative risk, 0.27; 95% confidence interval, 0.10–0.73) than those undergoing surgery. The number of postprocedural stricture events did not significantly differ between the two treatments (relative risk, 0.89; 95% confidence interval, 0.53–1.49). Endoscopic resection was associated with higher recurrence rates (relative risk, 1.69; 95% confidence interval, 0.99–2.89) and lower R0 resection rates (relative risk, 0.92; 95% confidence interval, 0.86–0.98) than surgery. There may be some advantage conferred by esophagectomy in the long-term survival outcomes (hazard ratio, 1.21; 95% confidence interval, 1.02–1.43).

Discussion: Endoscopic resection is a minimally invasive and safe treatment for early-stage esophageal cancer. However, esophagectomy may be associated with better long-term survival.

Keywords: Endoscopic resection; esophagectomy; early esophageal cancer (EEC)

Introduction

Early esophageal cancer (EEC), defined as tumors are limited to the basement membrane (Tis), mucosa (T1a), or submucosal layer (T1b) of the esophageal wall, constitutes approximately 20% of all cases of esophageal cancer (1). Although the prognosis of locally advanced esophageal

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cancer is poor, the early detection and treatment will be associated with a much better outcome for patients with early disease. The reported 5-year survival rate is >90% in post-surgical T1a patients (2).

Esophagectomy plus lymph node dissection is generally associated with significant postoperative morbidity and mortality (3), and poor long-term quality of life (4), even in high volume and centers with multi-disciplinary care (5). Therefore, endoscopic resection (ER) might be an alternative option for the treatment of EEC as it is minimally invasive, promotes rapid recovery, and is relatively low-cost. However, ER is limited in that it is not accompanied by lymph node dissection. Although the risk of lymph node metastasis is very low when the tumor is limited to the mucosa, it can rise to 20% in cases of tumors involving the submucosa (6). This issue has challenged the effectiveness of ER as an alternative pathway to esophagectomy for EEC.

While several studies have evaluated the efficacy of ER and surgery for EEC, the results were inconsistent. Unfortunately, due to the high frequency of adverse events in those undergoing esophagectomy, it would be difficult to perform a randomized controlled trial to determine which of these two treatments is safer and more effective. To our knowledge, no meta-analysis has been conducted for this purpose. Therefore, we performed a meta-analysis to further evaluate the efficacy and safety of ER and esophagectomy in the treatment of EEC. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-182).

Methods

Study identification and selection criteria

A systematic literature search was conducted to identify relevant studies that compared ER and surgery for EEC. PubMed, EMBASE, and the Cochrane Library were independently searched by two authors (H Zheng and N Kang). The following search terms were used: ("endoscopic mucosal resection" OR "EMR" OR "endoscopic submucosal dissection" OR "ESD" OR "endoscopic resection" OR "ER") AND (surgery OR operation) AND (early esophageal cancer). The literature search had no language restriction and ended on August 13, 2020. This meta-analysis was registered in PROSPERO (CRD42020181615).

The inclusion criteria were as follows: randomized

controlled trials and non-randomized prospective and retrospective studies, analyses of both ER (endoscopic mucosal resection, endoscopic submucosal dissection (ESD), or both) and surgery for the treatment of EEC, and patients histologically diagnosed with EEC. The exclusion criteria were as follows: letters, case reports, comments, reviews, and studies with no full text or incomplete data available for analysis. If duplicate and multiple articles from the same team were retrieved, the most recent and informative publication was included in the meta-analysis.

Data extraction

All included studies and extracted the relevant data were assessed by two authors (H Zheng and N Kang), and a third author (Y Huang) decided the eligibility of any studies that these two authors did not agree upon. The following information was extracted: first author; year of publication; number, age, and sex of patients; follow-up duration; and outcome measures such as recurrence rate, R0 resection rate, procedure-related mortality, adverse event rates, postprocedural stricture events, and overall survival (OS) rates.

Quality assessment

The quality of the included studies was assessed by using the Newcastle-Ottawa scale, with some modifications to match the needs of this meta-analysis (7). Quality assessment was independently carried out by two authors (H Zheng and N Kang). The quality of the studies was evaluated via the examination of four items: representativeness of the exposed cohort, comparability of the study groups, adequacy of follow up, and assessment of outcome. A quality score was awarded to each study, with a maximum of 10 points indicating the highest possible score. Studies achieving ≥5 points were considered high quality.

Statistical analysis

We combined extracted data using R 3.6.1 software (version 3.6.1; https://www.r-project.org/). The hazard ratios (HRs) were extracted by using previously reported methods (8); one to obtain the HR value from the original paper, and another to estimate the HR value from related data. The estimated heterogeneity of the included researches were based on I^2 test, with levels of heterogeneity defined as minor (I^2 =0–30%), moderate (I^2 =30–50%), or significant
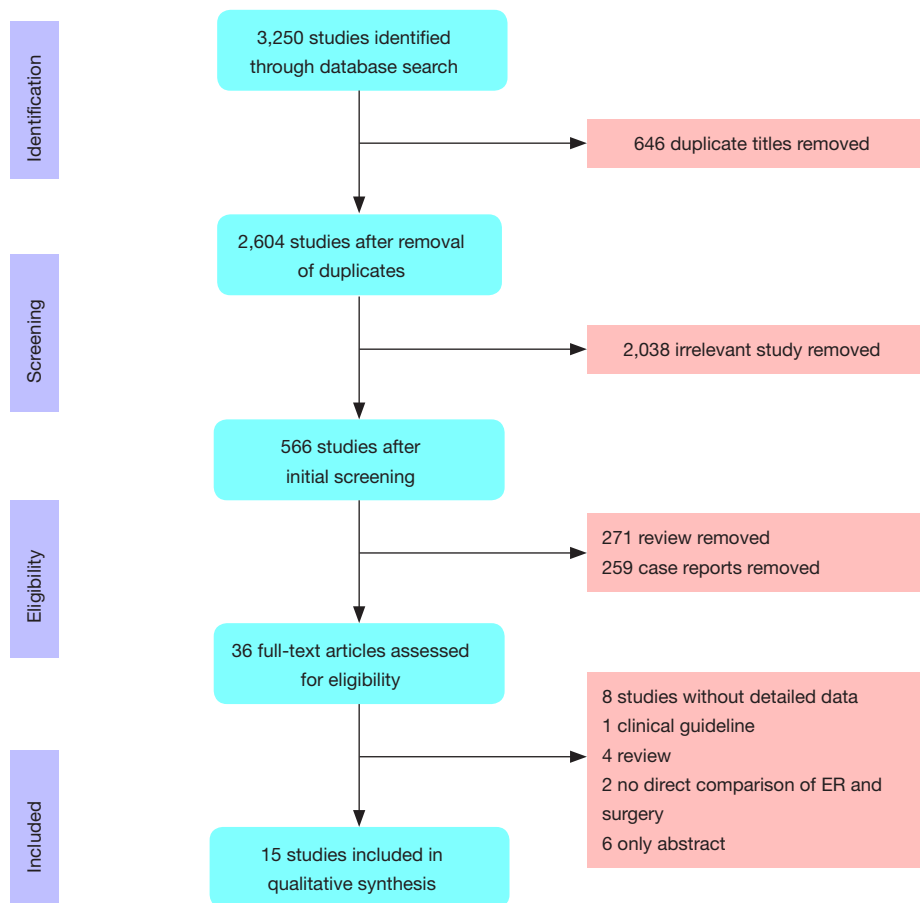
Figure 1 Schemata of the systematic review.

(I^2 >50%). The χ^2 test was used for the same purpose, with a statistical significance level of P<0.05 indicating the presence of statistical heterogeneity. A sensitivity analysis was conducted to explore potential heterogeneity. Due to the expected clinical heterogeneity of the included studies, we chose to use only the random effects model before pooling the data.

Results

A total of 3,250 studies were identified by a search of the PubMed, EMBASE, and Cochrane Library databases. Of these, 2,684 irrelevant or duplicate studies were excluded, and an additional 530 studies were removed because they were reviews, abstracts, or case reports. A total of 36 records were eligible for full-text review, and 17 articles were excluded. Finally, 19 studies met the inclusion criteria and were thus included. The study flow chart is presented in *Figure 1*. There were 12 retrospective studies (9-20),

three analyses using large national databases (21-23), and no randomized controlled trials (*Table 1*). Three studies were conducted in the United States, one in Germany, four in Korea, six in China, and one in Canada. This meta-analysis involved 4,731 patients, with 2,467 patients in the ER arm and 2,264 patients in the surgery arms.

Twelve studies reported major postprocedural adverse events. The incidence of major postprocedural adverse events ranged from 8–36% in the surgery group and 0–15% in the ER group. The meta-analysis indicated that ER was associated with fewer major adverse events than surgery [relative risk (RR), 0.46; 95% confidence interval (CI), 0.33–0.64], with moderate heterogeneity (I^2 =36%, P=0.10) (*Figure 2A*). Procedure-related mortality was reported in five patients after ER and 30 patients after surgery. The meta-analysis showed that the ER group had a lower procedure-related mortality rate than the surgery group (RR, 0.27; 95% CI, 0.10–0.73; P<0.01), with no heterogeneity (I^2 =15%, P=0.31) (*Figure 2B*). Eight studies

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Table 1 Baseline characteristics of included studies

Study	Year	Country	Study interval	Study interval	Study type	Patients (ER/surgery)	Mean age (years) (ER/surgery)	Gender (male/female)	Histology type	Mean follow-up (months)	Quality score
Schembre	2008	USA	1998–2005	1998–2005	Retrospective	62/32	70/64	ER: 45/17; surgery: 30/2	EAC	ER: 20 (6–84); surgery: 48 (6–88)	5
Prasad	2009	USA	1998–2007	1998–2007	Retrospective	132/46	71.2/67.7	ER: 111/21; surgery: 43/3	EAC	ER: 43 (NA); surgery: 64 (NA)	6
Pech	2011	Germany	1996–2009	1996–2009	Retrospective	76/38	62.7/62.7	ER: 73/3; surgery: 37/1	EAC	ER: 49.2 (6–104); surgery: 44.4 (6–156)	7
Gong	2016	Korea	2005–2010	2005–2010	Retrospective	40/39	65/60	ER: 35/5; surgery: 35/4	AEG	ER: 63.2 (53.6–83.5); surgery: 60.3 (58.4–68.7)	6
Jin	2016	China	2007–2011	2007–2011	Retrospective	59/40	NA	ER: 36/23; surgery: 28/12	ESCC/EAC	ER: 48; surgery: 48	6
Li	2017	Canada	2005–2013	2005–2013	Retrospective	11/12	65.3/64.8	ER: 59; surgery: 40	EAC	NA	5
Kim	2018	Korea	2006–2011	2006–2011	Retrospective	38/28	66.9/58.5	ER: 29/9; surgery: 23/5	AEG	ER: 50.4 (42–70); surgery: 59.0 (49–68)	6
Yuan	2018	China	2010–2016	2010–2016	Retrospective	69/47	63.7/61.1	ER: 51/18; surgery: 36/11	ESCC	ER: 43.8 (16–86); surgery: 49.4 (1–91)	6
Zhang	2018	China	2011–2016	2011–2016	Retrospective	322/274	63.5/62.4	ER: 258/64; surgery: 193/81	ESCC	ER: 23; surgery: 21	8
Min	2018	Korea	1994–2014	1994–2014	Retrospective	120/120	63.9/63.3	ER: 111/9; surgery: 111/9	ESCC	ER: 43.0 (14–72); surgery: 63.5 (34.8–92.2)	7
Gong	2019	China	2015–2018	2015–2018	Retrospective	78/128	60.5/59.5	ER: 65/13; surgery: 105/23	ESCC	NA	6
Lee	2020	Korea	2011–2017	2011–2017	Retrospective	34/34	67.5/67.3	ER: 31/3; surgery: 31/3	ESCC	ER: 33.0 (21.0–62.0); surgery: 40.5 (23.0–69.0)	7
Zeng	2017	China	1998–2013	1998–2013	Database (SEER)	621/621	NA	ER: 511/110; surgery: 516/105	EA/ESCC/other	NA	7
Marino	2018	US	2006–2012	2006–2012	Database (NCDB)	735/735	66.5/66.9	ER: 624/111; surgery: 625/110	EA	NA	7
Qin	2019	China	2004–2014	2004–2014	Database (SEER)	70/70	NA	ER: 60/10; surgery: 61/9	EA/ESCC/other	NA	6

AEG, adenocarcinoma of the esophagogastric junction; EA, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ER, endotherapy.

A

Study	Experimental Events	Total	Control Events	Total	Risk Ratio	RR	95%-CI	Weight
Schembre 2008	5	62	4	32		0.65	[0.19; 2.24]	5.7%
Prasad 2009	18	132	17	46		0.37	[0.21; 0.65]	15.1%
Pech 2011	0	76	12	38		0.02	[0.00; 0.33]	1.4%
Gong 2016	3	40	4	39		0.73	[0.17; 3.06]	4.5%
Jin 2016	4	59	3	40		0.90	[0.21; 3.82]	4.5%
Li 2017	1	11	2	12		0.55	[0.06; 5.21]	2.0%
Kim 2018	5	38	8	28		0.46	[0.17; 1.26]	7.9%
Yuan 2018	6	69	8	47		0.51	[0.19; 1.38]	8.0%
Zhang 2018	20	127	35	127		0.57	[0.35; 0.93]	17.1%
Min 2018	14	157	63	191		0.27	[0.16; 0.46]	15.9%
Gong 2019	14	78	31	128		0.74	[0.42; 1.30]	15.3%
Lee 2020	1	34	10	34		0.10	[0.01; 0.74]	2.5%
Random effects model		**883**		**762**		**0.46**	**[0.33; 0.64]**	**100.0%**

Heterogeneity: $I^2 = 36\%$, $\tau^2 = 0.1066$, $p = 0.10$
Test for overall effect: $z = -4.59$ ($p < 0.01$)

0.01 0.1 1 10 100

B

Study	Experimental Events	Total	Control Events	Total	Risk Ratio	RR	95%-CI	Weight
Schembre 2008	1	62	0	32		1.56	[0.07; 37.23]	8.9%
Prasad 2009	0	132	1	46		0.12	[0.00; 2.82]	8.9%
Pech 2011	0	76	1	38		0.17	[0.01; 4.02]	8.9%
Gong 2016	0	40	0	39				0.0%
Jin 2016	0	59	0	40				0.0%
Li 2017	0	11	0	12				0.0%
Kim 2018	0	38	1	28		0.25	[0.01; 5.84]	9.0%
Yuan 2018	0	69	2	47		0.14	[0.01; 2.78]	9.8%
Zhang 2018	1	127	0	127		3.00	[0.12; 72.95]	8.9%
Min 2018	0	157	0	191				0.0%
Lee 2020	2	34	4	34		0.50	[0.10; 2.55]	26.2%
Marino 2018	1	735	23	735		0.04	[0.01; 0.32]	19.4%
Random effects model		**1540**		**1369**		**0.27**	**[0.10; 0.73]**	**100.0%**

Heterogeneity: $I^2 = 15\%$, $\tau^2 = 0.3101$, $p = 0.31$
Test for overall effect: $z = -2.59$ ($p < 0.01$)
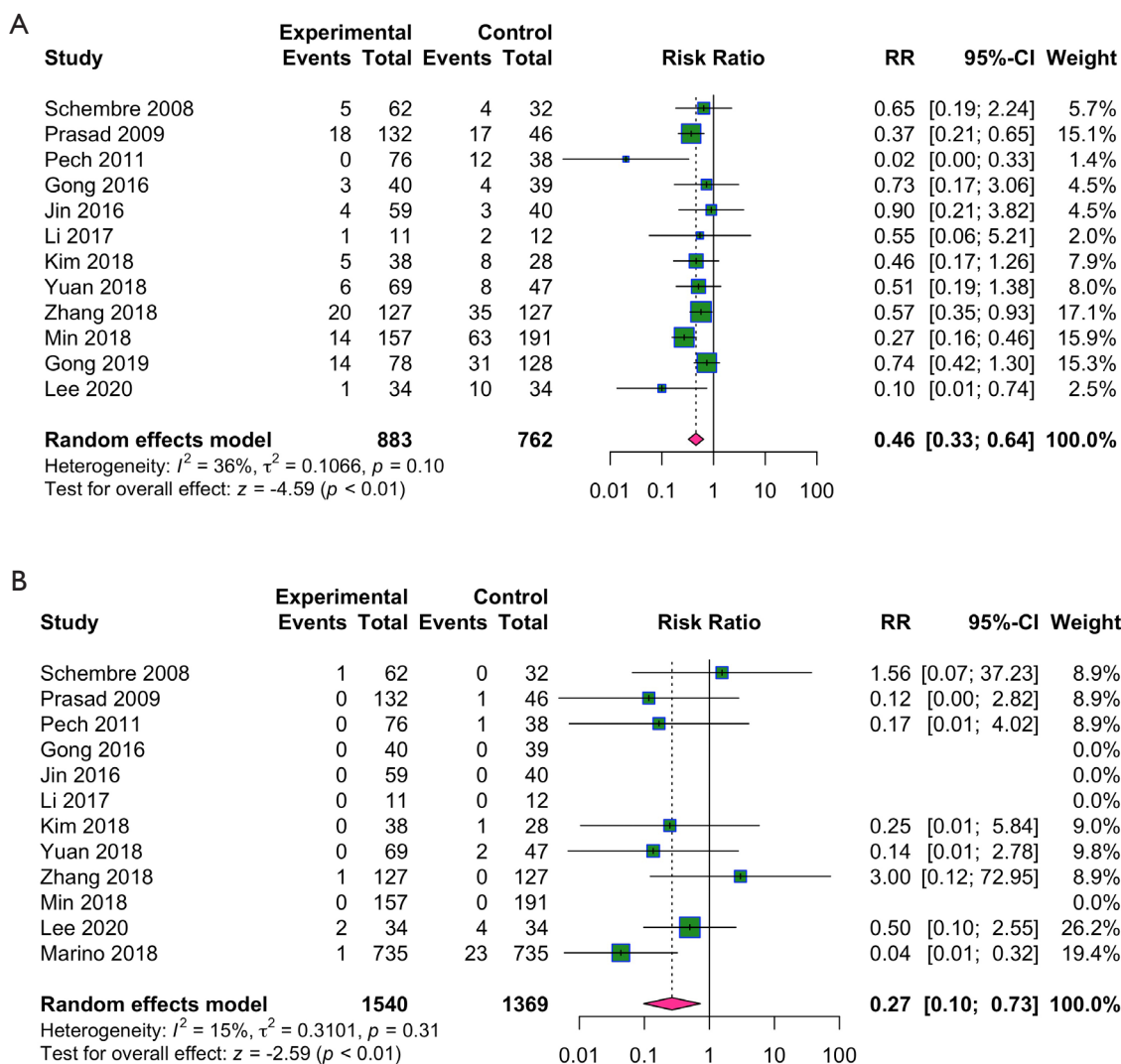
0.01 0.1 1 10 100

Figure 2 Meta-analysis showed that endoscopic resection (ER) was associated with fewer major adverse events (RR, 0.46; 95% CI, 0.33–0.64) and a lower procedure-related mortality rate (RR, 0.27; 95% CI, 0.10–0.73) than the surgery group. (A) The comparison of major postprocedural adverse events between endoscopic resection and surgery. (B) The comparison of procedure-related mortality between endoscopic resection and surgery. RR, relative risk; CI, confidence interval.

reported postprocedural stricture events. The meta-analysis revealed that the frequency of postprocedural stricture events did not significantly differ between ER and surgery (RR, 0.89; 95% CI, 0.53–1.49), with significant heterogeneity (I^2 =53%, P=0.04) (*Figure 3*). The sensitivity analysis was performed to explore the heterogeneity. After deletion, the pooled result did not deviate beyond the 95% CI of the whole estimate (Figure S1).

The R0 resection rate is a vital parameter for evaluating the efficacy of treatment and recurrence. In this meta-

analysis, nine studies reported the R0 resection rate after treatment. The R0 resection rate was 97–100% in patients who underwent esophagectomy and 73–100% in patients who underwent ER treatment. The pooled outcomes indicated that the R0 resection rate was lower in the ER group than in the surgery group (RR, 0.92; 95% CI, 0.86–0.98), with significant heterogeneity (I^2 =91%, P<0.01) (*Figure 4A*). According to the sensitivity analysis, although the data from the study by Gong *et al.* were seen as a potential source of heterogeneity, the combined RR
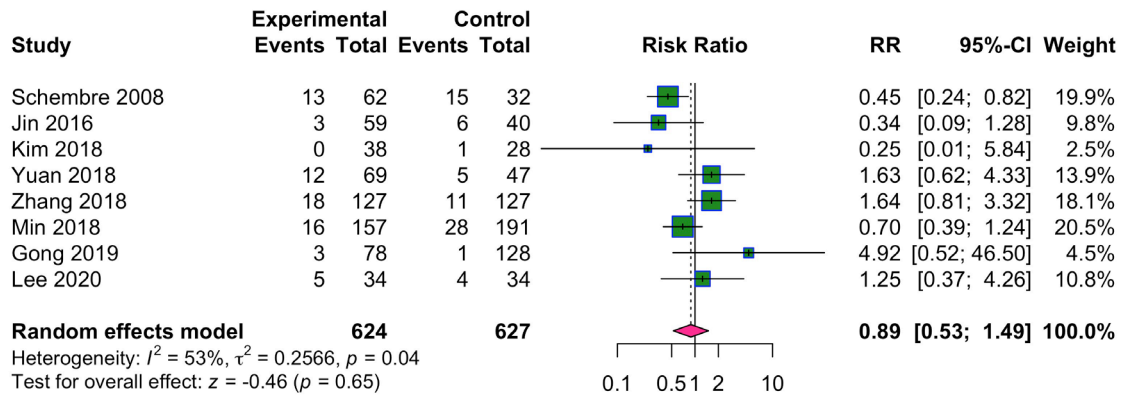
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Study	Experimental Events	Total	Control Events	Total	Risk Ratio	RR	95%-CI	Weight
Schembre 2008	13	62	15	32		0.45	[0.24; 0.82]	19.9%
Jin 2016	3	59	6	40		0.34	[0.09; 1.28]	9.8%
Kim 2018	0	38	1	28		0.25	[0.01; 5.84]	2.5%
Yuan 2018	12	69	5	47		1.63	[0.62; 4.33]	13.9%
Zhang 2018	18	127	11	127		1.64	[0.81; 3.32]	18.1%
Min 2018	16	157	28	191		0.70	[0.39; 1.24]	20.5%
Gong 2019	3	78	1	128		4.92	[0.52; 46.50]	4.5%
Lee 2020	5	34	4	34		1.25	[0.37; 4.26]	10.8%
Random effects model		**624**		**627**		**0.89**	**[0.53; 1.49]**	**100.0%**

Heterogeneity: $I^2 = 53\%$, $\tau^2 = 0.2566$, $p = 0.04$
Test for overall effect: $z = -0.46$ ($p = 0.65$)

0.1 0.5 1 2 10

Figure 3 The comparison of postprocedural stricture events between endoscopic resection and surgery. RR, relative risk; CI, confidence interval.

A

Study	Experimental Events	Total	Control Events	Total	Risk Ratio	RR	95%-CI	Weight
Prasad 2009	124	132	46	46		0.94	[0.90; 0.98]	12.9%
Pech 2011	75	76	38	38		0.99	[0.96; 1.01]	13.4%
Gong 2016	35	40	39	39		0.88	[0.78; 0.98]	9.8%
Jin 2016	56	59	39	40		0.97	[0.90; 1.05]	11.6%
Kim 2018	38	38	28	28		1.00	[0.94; 1.06]	12.3%
Yuan 2018	64	69	47	47		0.93	[0.87; 0.99]	12.1%
Zhang 2018	118	127	124	127		0.95	[0.90; 1.01]	12.5%
Gong 2019	57	78	128	128		0.73	[0.64; 0.84]	8.9%
Lee 2020	25	34	34	34		0.74	[0.61; 0.90]	6.3%
Random effects model		**653**		**527**		**0.92**	**[0.86; 0.98]**	**100.0%**

Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.0088$, $p < 0.01$
Test for overall effect: $z = -2.54$ ($p = 0.01$)

0.75 1 1.5

B

Study	Experimental Events	Total	Control Events	Total	Risk Ratio	RR	95%-CI	Weight
Schembre 2008	4	62	0	32		4.68	[0.26; 84.28]	3.4%
Prasad 2009	16	132	1	46		5.58	[0.76; 40.88]	7.2%
Pech 2011	1	76	0	38		1.51	[0.06; 36.20]	2.8%
Gong 2016	0	40	0	39				0.0%
Jin 2016	6	59	3	40		1.36	[0.36; 5.11]	16.2%
Li 2017	1	11	1	12		1.09	[0.08; 15.41]	4.1%
Kim 2018	2	38	0	28		3.70	[0.18; 74.16]	3.2%
Yuan 2018	6	69	2	47		2.04	[0.43; 9.69]	11.8%
Zhang 2018	12	127	9	127		1.33	[0.58; 3.05]	41.6%
Lee 2020	3	34	2	34		1.50	[0.27; 8.42]	9.6%
Random effects model		**648**		**443**		**1.69**	**[0.99; 2.89]**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.94$
Test for overall effect: $z = 1.93$ ($p = 0.05$)
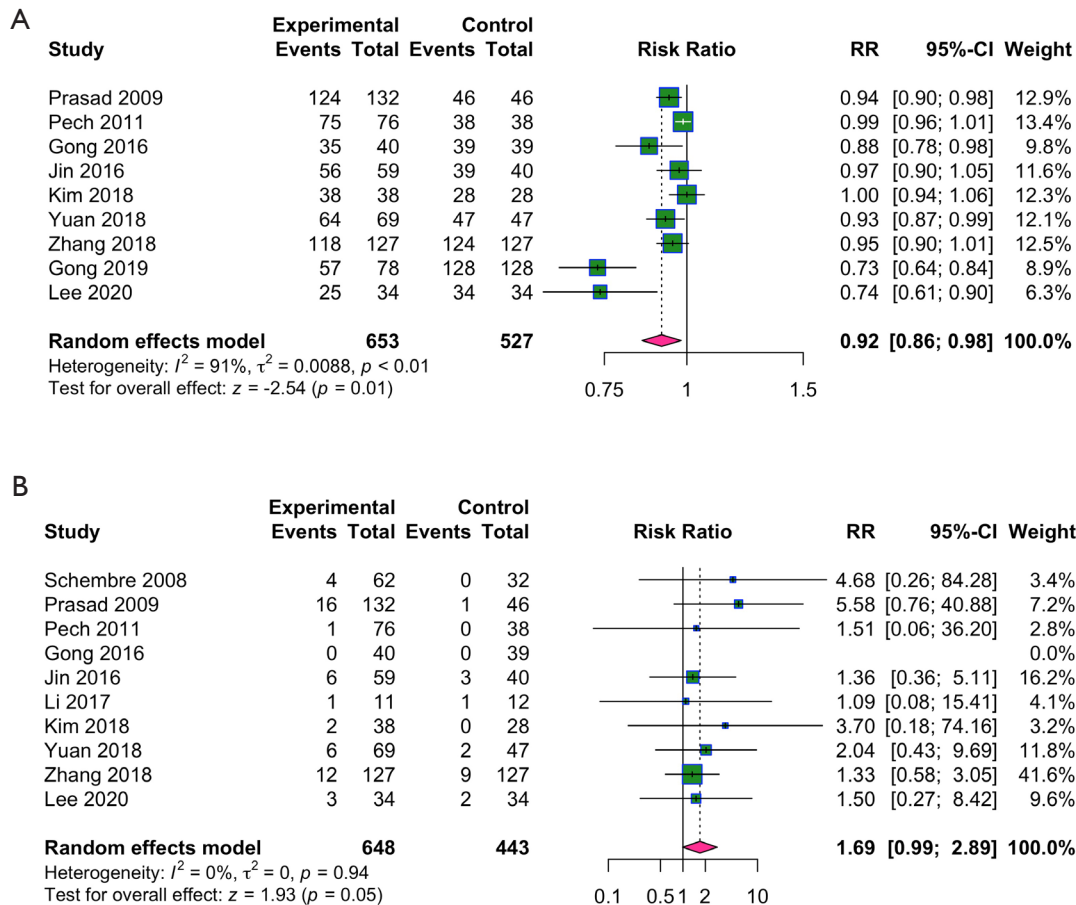
0.1 0.5 1 2 10

Figure 4 Meta-analysis showed that endoscopic resection (ER) was associated with a lower R0 resection rate (RR, 0.92; 95% CI, 0.86–0.98) and a higher tumor recurrence rate (RR, 1.69; 95% CI, 0.99–2.89) than the surgery group. (A) The comparison of R0 resection rate between endoscopic resection and surgery. (B) The comparison of recurrence rate between endoscopic resection and surgery. RR, relative risk; CI, confidence interval.
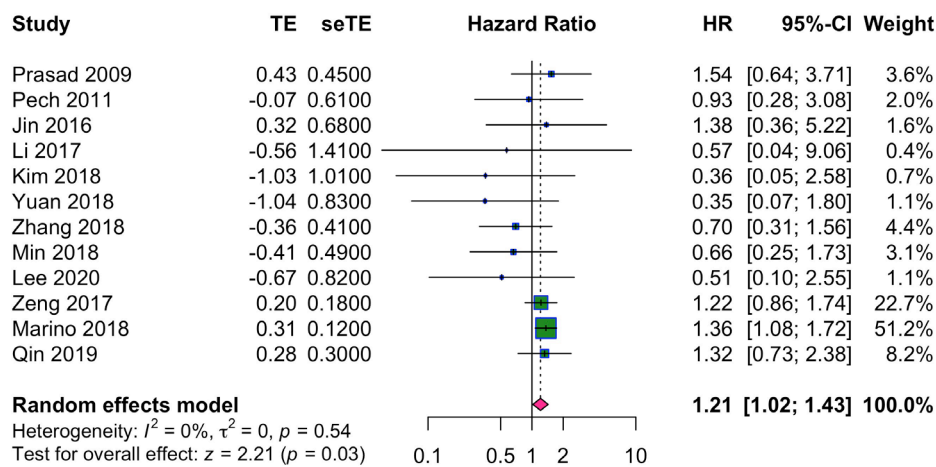
Figure 5 The comparison of overall survival between endoscopic resection and surgery. HR, hazard ratio; CI, confidence interval.

was very close to the original RR and the pooled result did not deviate beyond the 95% CI of the whole estimate (Figure S2). Ten studies reported tumor recurrence during follow-up. The meta-analysis demonstrated that the ER group had a higher tumor recurrence rate than the surgery group (RR, 1.69; 95% CI, 0.99–2.89), with no heterogeneity (I^2 =0%, P=0.94) (*Figure 4B*).

Twelve studies compared the OS between ER and surgery. The pooled result indicated poorer OS in the ER group than in the surgery group (HR, 1.21; 95% CI, 1.02–1.43), with no heterogeneity (I^2 =0%, P=0.54) (*Figure 5*).

Discussion

In this meta-analysis, we aimed to compare the efficacy and safety of ER and surgery for EEC and found that the OS rate was better among patients who underwent surgery, and the recurrence rate was higher among those who underwent ER. More major adverse events were recorded and the procedure-related mortality was higher among those who underwent surgery, but the R0 resection rate was lower among those who underwent ER. However, the rate of postprocedural stricture events did not significantly differ between the two treatments.

Based on favorable safety and oncologic outcomes in suitable indications, ER therapy is increasing in popularity worldwide for T1 esophageal cancer (24). In contrast to the high incidence of major adverse events in esophagectomy, ER is associated with few adverse events and almost never results in perioperative death. In addition, the major

adverse events of ER such as bleeding and stenosis also can be successfully treated with endoscopic procedures. Our results indicated that ER was associated with fewer major adverse events and a lower procedure-related mortality rate. Esophageal stricture as a major complication that manifests as varying degrees of dysphagia, which greatly increases medical costs and reduces quality of life. In our research, the pooled results indicated that the postoperative stricture rate was comparable between the ER group and the surgery group (11.2% *vs.* 11.3%, P=0.65).

Endoscopic ultrasound (EUS) is the most commonly used clinical staging modality but has an overall accuracy of only ~65% (25), which may affect treatment choice or outcomes. Even in clinical T1a patients, 20.2% of patients with deep invasion after esophagectomy and 8.7% of patients with occult lymph node metastasis were missed by EUS (24). Further, once a tumor breaches the muscularis mucosae, the incidence of lymphatic involvement exceeds 30%, and it is generally accepted that ER therapy no longer provides curative ability (26). In addition, our study found that the recurrence rate was significantly higher in the ER group than in the surgery group (P=0.05). Therefore, accurate clinical staging is crucial to treatment selection and the overall outcome. For patients treated with ER, postoperative monitoring is critical for detecting local tumor recurrence, which can be treated with esophagectomy. It is worth noting that, among the included studies, Jin *et al.* (13) compared the ER therapy and minimally invasive esophagectomy (MIE) and found no significant differences in the incidence of major complications between the two

treatment groups (P=1.0). Gong *et al.* (19) compared 128 patients who underwent MIE with 78 patients treated with ESD, of which 77% were T1a in the ESD group and 34% T1a in the MIE group. Again, there was no difference in overall postoperative complication rates (24.22% *vs.* 23.08%; P=1.000). According to these findings, under the premise of the completeness of resection and radical lymphadenectomy, MIE would not significantly increase the main complications. Therefore, ER therapy is a less invasive treatment for T1a patients, whereas MIE therapy may be more suitable for T1b patients or patients at greater risk of lymph node metastases.

Some studies comparing the long-term survival rate associated with the two procedures used the Surveillance Epidemiology and End Results (SEER) registry or the National Cancer Database (NCDB). Most studies reported no difference in OS or cancer-specific survival between the two treatment groups. However, Marino *et al.* (22) used the NCDB after propensity matching and found that ER therapy positively affected survival during the first 90 days (HR, 0.15; P=0.003), whereas esophagectomy was associated with better survival after 90 days (HR, 1.34; P=0.02). Similarly, Zeng *et al.* (21) used the SEER registry and also found poorer OS (HR, 1.690; P<0.001) in the ER group than in the esophagectomy group. Nevertheless, all single-center retrospective studies included in this meta-analysis reported no difference in the long-term survival rate. Only one study by Prasad *et al.* (10) found that cancer-free survival was lower in the ER group than in the surgery group (80% *vs.* 97%, P=0.01). In our study, the pooled results showed that the OS was poorer in the ER group than in the surgery group (HR, 1.21; 95% CI, 1.02–1.43; P=0.03). Most of the included studies were single-center retrospective studies, and the number of included cases was relatively small. Some studies used public databases that did not include propensity-score matching, which may have resulted in significant selection bias. However, our research revealed a higher survival rate in the surgery group than the ER group, which may have been due to the higher risk of occult positive lymph nodes in T1b disease and the improved locoregional control with esophagectomy.

Several limitations of this meta-analysis need to be considered. First, all of the included studies were retrospective and uncontrolled. The relatively small number of cases in some studies may have reduced the reliability of the findings. Second, the large database studies have several common shortcomings. One of the more important limitations is the inability to verify important data points, such as pathologic diagnosis and comorbidities. In addition, the databases do not contain records of local therapies used before surgery, including whether or not ER was performed. Third, some of the HRs were extracted by calculations, which inevitably introduces bias. Finally, different types of esophageal tumors, ER procedures, and surgical approaches may have resulted in biased results, but the included studies were limited and subgroup analyses could not be performed.

In conclusion, ER for EEC is associated with fewer major adverse events and lower procedure-related mortality rate than surgery, but this therapy does not address potential lymphatic spread. On the contrary, esophagectomy with lymph node dissection has a higher R0 resection rate and lower tumor recurrence rate, which may result in improved survival. Thus, ER cannot completely replace radical surgery for EEC. Long-term follow-up is critical for patients undergoing ER.

Acknowledgments

Footnote

formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

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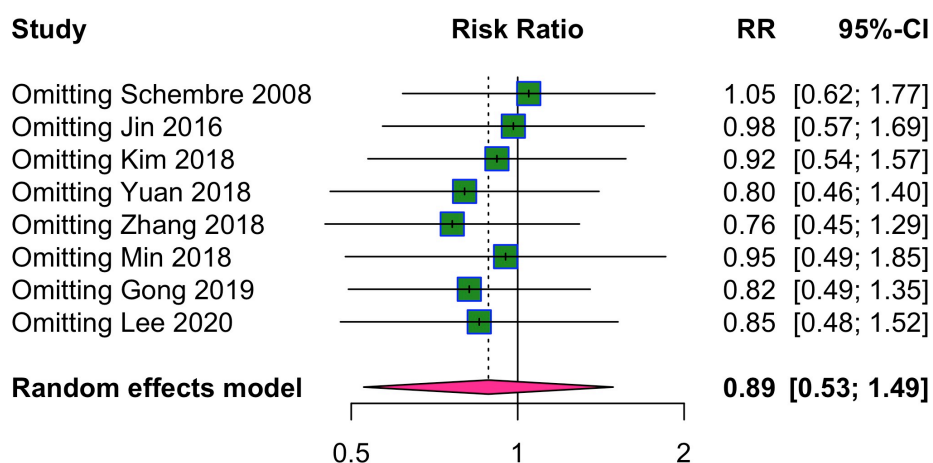| Study	Risk Ratio	RR	95%-CI
Omitting Schembre 2008		1.05	[0.62; 1.77]
Omitting Jin 2016		0.98	[0.57; 1.69]
Omitting Kim 2018		0.92	[0.54; 1.57]
Omitting Yuan 2018		0.80	[0.46; 1.40]
Omitting Zhang 2018		0.76	[0.45; 1.29]
Omitting Min 2018		0.95	[0.49; 1.85]
Omitting Gong 2019		0.82	[0.49; 1.35]
Omitting Lee 2020		0.85	[0.48; 1.52]
Random effects model		**0.89**	**[0.53; 1.49]**

0.5   1   2

Figure S1 Sensitivity analysis of postprocedural stricture events. RR, relative risk; CI, confidence interval.

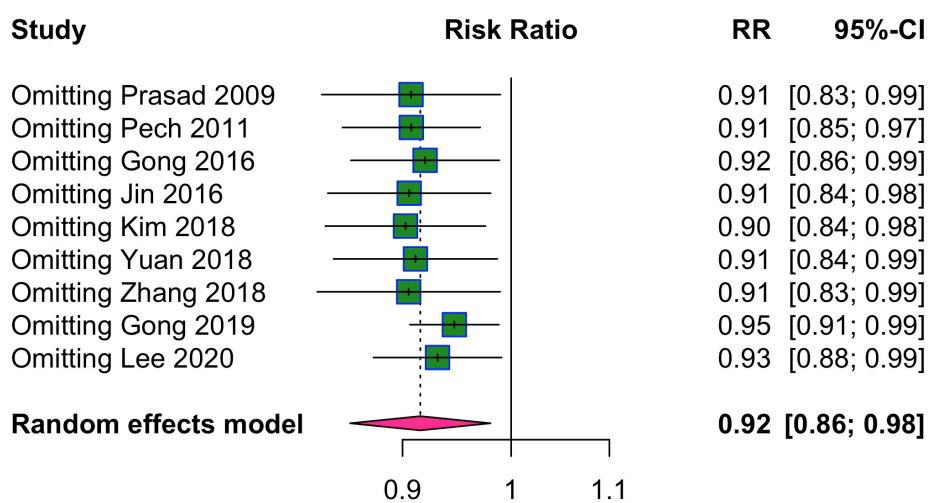| Study	Risk Ratio	RR	95%-CI
Omitting Prasad 2009		0.91	[0.83; 0.99]
Omitting Pech 2011		0.91	[0.85; 0.97]
Omitting Gong 2016		0.92	[0.86; 0.99]
Omitting Jin 2016		0.91	[0.84; 0.98]
Omitting Kim 2018		0.90	[0.84; 0.98]
Omitting Yuan 2018		0.91	[0.84; 0.99]
Omitting Zhang 2018		0.91	[0.83; 0.99]
Omitting Gong 2019		0.95	[0.91; 0.99]
Omitting Lee 2020		0.93	[0.88; 0.99]
Random effects model		**0.92**	**[0.86; 0.98]**

0.9   1   1.1

Figure S2 Sensitivity analysis of R0 resection rate. RR, relative risk; CI, confidence interval.