Original Article

Long-term survival in esophagectomy for early-stage esophageal cancer versus endoscopic resection plus additional chemoradiotherapy: a systematic review and meta-analysis

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Background: Esophagectomy is still advised as an additional treatment for patients with superficial esophageal cancer (EC, T1a-T1b) after endoscopic resection (ER). However, esophagectomy often deteriorates the general condition of EC patients. In recent years, adjuvant chemoradiotherapy (CRT) has been recognized as a reliable, non-surgical treatment that can improve the prognosis. How to combine ER with adjuvant therapy to bring maximal benefits to patients has become a hot clinical research hot topic. However, the current studies have mostly been conducted retrospectively, in single centers, and with small clinical samples; there have been few prospective and large sample size randomized controlled trials (RCTs). The aim of this systematic review and meta-analysis was to compare the outcomes of adjuvant CRT versus esophagectomy in the treatment of early EC, and to provide a reference for clinical research and practice.

Methods: A comprehensive and extensive literature search was performed via the databases of PubMed, Cochrane Library, Embase, and Web of Science online and all randomized cohort studies and retrospective cohort studies were collected. The quality of research was evaluated according to Cochrane's quality standards, and statistical analysis was conducted with Stata 13.0 and RevMan 5.3 software and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Results: A total of 9 cohort studies, including 790 patients, were included for meta-analysis. The long term effects of the esophagectomy group were better than those of the CRT after ER group [odds ratio (OR) =6.08, 95% confidence interval (CI): 1.96 to 18.84, P=0.002] in disease-free survival (DFS) [hazard ratio (HR) =0.24, 95% CI: 0.07 to 0.85, P=0.03] and overall survival (OS) (HR =1.02, 95% CI: 0.57 to 1.82, P=0.94). Other survival indicators showed no significant difference (P>0.05).

Conclusions: The 2 groups showed no significant results in OS. Although we found that CRT may be suitable for patients with high-risk of relapse or unable to tolerate surgery, it cannot totally replace surgical treatment; further randomized trials are required to verify this view.

Keywords: Endoscopic resection (ER); esophagectomy; chemoradiotherapy; meta-analysis; esophageal cancer (EC)

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Introduction

As one of the most severe malignant digestive neoplasms, esophageal cancer (EC) is highly aggressive, has a poor prognosis, and the 5-year overall survival (OS) is less than 25% (1,2). Recently, endoscopic resection (ER) has been recognized for its ability to diagnose and even cure early-stage superficial EC, which can increase the 5-year survival rate to about 85% (3,4). Mönig *et al.* (5) proposed that the lymph node metastasis rate at T1a stage is 0–13% in esophageal squamous cell carcinoma (ESCC), the lymph node metastasis rate at T1b stage is 8–26.5% in the superficial submucosa (SM1), and the risk of lymph node metastasis can increase to 22–61% when infiltrated into the submucosal layer (SM2) and below. Shen *et al.* (6) declared that the risk factors of lymph node metastasis were tumor differentiation, vascular invasion, and depth of tumor invasion. Therefore, it is essential to conduct esophagectomy or adjuvant chemoradiotherapy (CRT) after ER.

Traditionally, esophagectomy combined with lymph node dissection has been accepted as the standard treatment for cT1a/bN0M0 early EC. Although it has a reliable long-term effect, patients usually must accept the risk of postoperative complications and downtrend of living quality. According to a retrospective analysis by Saeki *et al.* (7), during the 87-month follow-up period, a total of 34 patients with early-stage EC were included without any recurrence and metastasis; the 3- and 5-year OS rates were 97.4% and 89.9%, respectively, whereas the postoperative complication rates were 18% and 10%, respectively. Additionally, the whole effect of treatment was found to largely depend on the experience of the surgical team and the patient's physical condition.

Compared to esophagectomy, CRT after ER involves less trauma and a lower risk of postoperative complications and is gradually becoming another acceptable treatment choice. A multi-center, single-arm prospective study by Minashi *et al.* (8) reported that among 176 enrolled patients, the metastasis recurrence rate was 8.5% when the pathological stage was T1b (SM1-2) N0M0; the 3-year progression-free survival rate was 89.7%, and the 3-year OS rate was 90.7%. This long-term treatment effect was considered equivalent to that of radical surgery, but not limited to surgical patients only on account of the unilateral results.

A recent phase II trial revealed that combined ER and CRT is equally effective for clinical stage ESCC as esophagectomy, however, the long-term survival rate and the risk of recurrence and metastasis between the 2 methods have not been reported in detail (9). Furthermore, the current literature is mostly composed of retrospective, single center, and small sample clinical studies. Therefore, it is fundamental to conduct further comparisons of the pros and cons of the 2 treatment methods. Meta-analysis provides a summary of clinical research data by implementing statistical methods and a quantitative and comprehensive analysis of the results, which is widely used to solve clinical problems and provide corresponding decision-making and guidance. Therefore, we aimed to use meta-analysis methods to comprehensively analyze the long-term effect of esophagectomy compared with CRT after ER, and to contribute to the body of evidence-based medicine for the scientific management of early EC. We present this article in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-376/rc).

Highlight box

Key findings

- The research showed that CRT may be suitable for EC patients with high-risk relapse or unable to tolerate surgery, but cannot totally replace surgical treatment.

What is known and what is new?

- This study intended to comprehensively compare the long-term effects of esophagectomy with CRT after ER for the first time.
- Previous research has mostly comprised retrospective, single center, and small sample clinical studies. Therefore, it is fundamental to make more comparisons on the pros and cons of the 2 treatment methods for further investigation.

What is the implication, and what should change now?

- This study found that esophagectomy remained a higher priority for patients with early-stage EC, as evidenced by a longer disease-free survival, while CRT after ER was indicated for patients who were known to be at high risk of recurrence and could not tolerate surgery.

Methods

Search strategy

A comprehensive systematic literature search was conducted for all suitable controlled trials and observational studies in electronic databases including PubMed, Cochrane library, Embase, and Web of Science from inception to September 2020. The search terms and relative variants presented in the title and abstract were as follows: "esophageal neoplasms", "esophageal cancer", "esophagectomy", "chemoradiotherapy", "chemoradiation", "radiochemotherapy", "esophagoscopy", "endoscopic

mucosal resection", and logical combinations of these terms using the Boolean operators "AND" and "OR". Based on the identified study reference list, a manual search was conducted to identify any studies that may have been missed in the initial search.

Inclusion criteria

The following inclusion criteria were established before collecting articles: (I) studies comparing survival data of esophagectomy with CRT after ER. (II) participants: patients had EC with pT1a-pT1b; (III) intervention: esophagectomy versus additional CRT; (IV) study design: randomized controlled trials (RCTs) or observational studies including cohort and case-control studies; (V) outcomes: complete data.

Exclusion criteria

(I) case reports or studies that did not perform a comparison; (II) letters and expert opinions; (III) meta-analyses or animal studies; (IV) reviews, news, comments, and other literature without original data; (V) incomplete literature and overlapped studies.

Data extraction and quality assessment

The formal full-length publications of studies which met the inclusion criteria previously described were independently skimmed through by 2 reviewers independently. Data were extracted from article texts, tables, and figures. The primary endpoints included any patterns of recurrence: locoregional recurrence rate (LRR), distant metastases rate (DMR), and LRR plus DMR. The secondary endpoints were OS and disease-free survival (DFS). OS was defined as the time from the date of ER to that of death from any cause or interruption of follow-up. DFS was defined as the duration of patient survival following ER without signs or symptoms of cancer recurrence. Discrepancies between the 2 reviewers were mutually resolved through discussion with a third reviewer.

Since many trials did not report this information directly, the time-to-event data were extracted from the survival curves. Kaplan–Meier curves were read by Engauge Digitizer version 4.1 (free software downloaded from http://sourceforge.net). Data combining was performed by RevMan 5.3 software (Cochrane Collaboration, Oxford, UK).

The quality evaluation of included studies was performed using the modified Newcastle-Ottawa Scale (NOS) (10,11), and the evaluation criteria included 3 main parts: the selection of research objects, comparability between the groups, and outcome measurement (total NOS score: 9 points). Any disagreements between the 2 extracting authors were settled by consensus. If consensus could not be reached between the 2 reviewers after discussion, a third author was invited for final arbitration.

Sensitivity and publication of bias assessment

The sensitivity analysis was evaluated using the odds ratio (OR) value with the 95% confidence interval (CI) of the random effects model, and the stability of the OR and 95% CI were observed by sequentially eliminating the literature. If little effect was observed after elimination, the combined result was considered relatively stable. Publication bias was tested using Funnel plots tests, Egger's and Begg's tests, and a P-value >0.05 was taken to indicate no significant publication bias (12,13). Data analyses were conducted by Stata 13.0 (Stata Corp., College Station, TX, USA), with $P \leq 0.05$ considered statistically significant.

Statistical analysis

All statistical analyses were assessed by RevMan 5.3 software. We calculated the pooled hazard ratio (HR) and 95% CI for OS and DFS and the pooled OR difference with 95% CI for recurrence or metastasis rate. A random effects model was used when substantial heterogeneity ($I^2>50\%$) was detected, and a fixed effects model was used in the absence of significant heterogeneity ($I^2<50\%$) (14,15). Statistical significance was considered when $P<0.05$. Furthermore, when a study included medians and interquartile ranges, we calculated the mean ± standard deviation via a method proposed by Hozo *et al.* (12).

Results

Study selection and characteristics

Our search strategy yielded a total of 39 publications suitable for full-text screening. After screening according to the inclusion criteria, a total of 9 suitable articles remained (16-24). *Figure 1* illustrates the literature retrieval process. A total of 6 of the 9 included articles had been conducted in Japan. The total number of participants was 790. ESCC was the predominant condition, whose primary treatments were endoscopic submucosal dissection; the chemotherapy

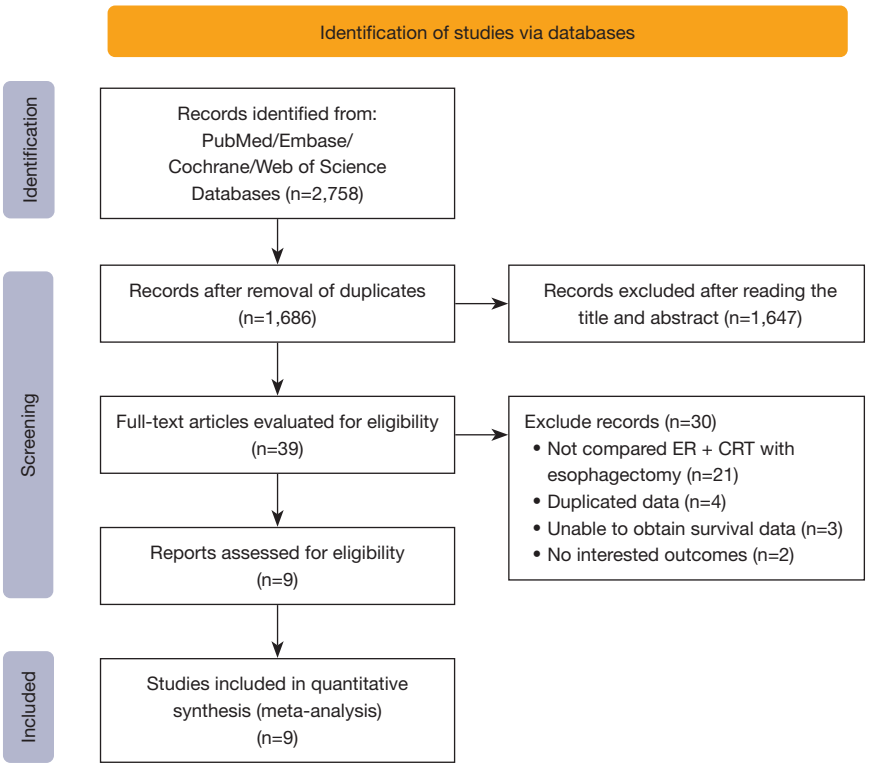

Figure 1 Systematic reviews and meta-analysis flow chart detailing the study selection process (PRISMA 2020 flow diagram). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ER, endoscopic resection; CRT, chemoradiotherapy.

regimen included 5-fluorouracil and cisplatin. We conducted NOS on the non-RCTs with a score of 5–8, based on the scoring system. A study with a NOS score of 5 or higher was regarded as of high quality. The baseline characteristics of the selected studies are summarized in *Table 1*.

Recurrence and metastasis

Recurrence and metastasis analysis included a total of 234 patients from 7 studies (16,17,19-24). A statistically significant improvement in the recurrence and metastasis rate was observed for esophagectomy when compared to CRT after ER (OR =6.08, 95% CI: 1.96 to 18.84, P=0.002). No heterogeneity was revealed in the result (I^2=0%, P=0.79) (*Figure 2*).

OS

A total of 6 studies contributed a total of 225 patients, including 113 who underwent esophagectomy and 112 controls (CRT after ER group) (16-17,20,22-24). No statistically significant OS difference could be established between these groups (HR =1.02, 95% CI: 0.57 to 1.82, P=0.94), with a low between-study heterogeneity (I^2=0%, P=0.42) (*Figure 3*). A fixed effects model was chosen for remaining groups because of the minimal heterogeneity.

DFS

There were 2 studies that reported data on DFS rates, consisting of a total of 91 patients, 44 in the esophagectomy and 47 in the CRT after ER (19,20). Despite the small sample size, the results demonstrated the significant superiority of the esophagectomy over the control group (HR =0.24, 95% CI: 0.07 to 0.85, P=0.03) with insignificant heterogeneity (I^2=0%, P=0.39) (*Figure 4*).

Sensitivity analysis and evaluation of publication bias

The included literature had good stability. Funnel plots

Table 1 Study characteristics

Author	Publication year	Country	Study type	Sample size	T stage	Pathology	Treatment regimen	Dose of RT	NOS
Tanaka (16)	2019	Korea	Re	52	T1b	SCC	ER + CRT/ER + surgery	>50	7
Lorenzo (17)	2019	France	Re	10	T1	SCC	ESD + CRT/ESD + surgery	NA	5
Lu (18)	2019	America	Re	501	T1b	AC	ER + RT ± CT/surgery	NA	5
Suzuki (19)	2018	Japan	Re	32	T1b	SCC + AC	ESD + CRT/ESD + surgery	40/50	6
Takeuchi (21)	2018	Japan	Re	32	M3–T1b	SCC + AC	ER + CRT/ER + surgery	50.4	7
Koterazawa (20)	2018	Japan	Re	59	T1	SCC	ESD + CRT/ESD + surgery	41.4/50.4	8
Ohki (22)	2018	Japan	Re	23	T1	NA	ESD + CRT/ESD + surgery	NA	6
Ikeda (23)	2015	Japan	Re	26	T1	NA	ESD + CRT/ESD + surgery	41.4/50.4	5
Shimizu (24)	2004	Japan	Re	55	T1	SCC	EMR + CRT/surgery	40–46	6

RT, radiotherapy; NOS, Newcastle-Ottawa Scale; Re, retrospective; SCC, squamous cell carcinoma; AC, adenocarcinoma; NA, not available; ER, endoscopic resection; CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.

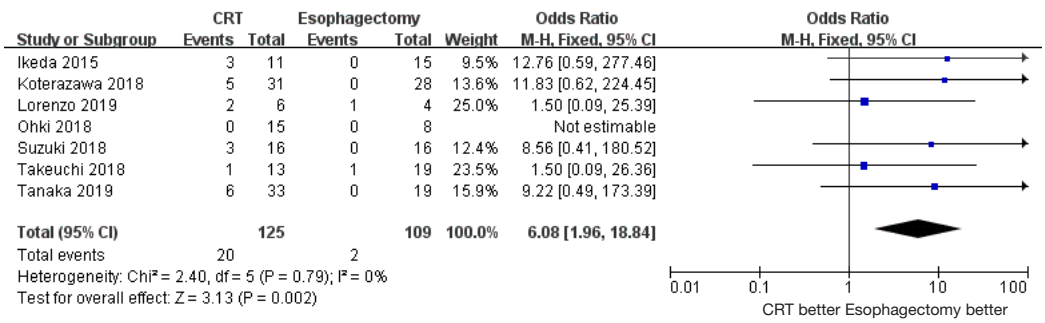

Figure 2 Forest plot of meta-analysis and cumulative meta-analysis in recurrence and metastasis rate. CRT, chemoradiotherapy; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

were created for the primary outcome measures of recurrence and metastasis and OS (*Figure 5A*,*5B*), both of which revealed no publication bias. The results of recurrence and metastasis were from Begg's test (P=0.072) and Egger's test (P=0.649); the result of OS was from Begg's test (P=1.000) and Egger's test (P=0.847). No statistically significant difference was detected, suggesting a small bias in publication.

Discussion

The treatment of early EC is largely based on radical surgery and endoscopic treatment. The treatment plan for EC is mainly determined according to its stage. The clinical effect of ER is equivalent to that of radical surgery, but the former can be used as the first choice of treatment due to it being associated with less trauma, fewer postoperative complications, and shorter hospital stay. Moreover, for some patients with T1b stage who are at risk of lymph node metastasis, ER cannot achieve lymph node sampling or dissection, and the tumor may be incompletely removed (25). Adjuvant therapy is accepted to improve long-term survival and reduce recurrence rates. At present, the main adjuvant treatment methods are esophagectomy and CRT after ER (26). However, some controversies still exist. For one thing, we must consider the safety and effectiveness of CRT after ER before deciding whether it can completely replace radical surgery. For another, for patients with pathological high-risk factors such as lymph node metastasis or vascular nerve invasion, it must be

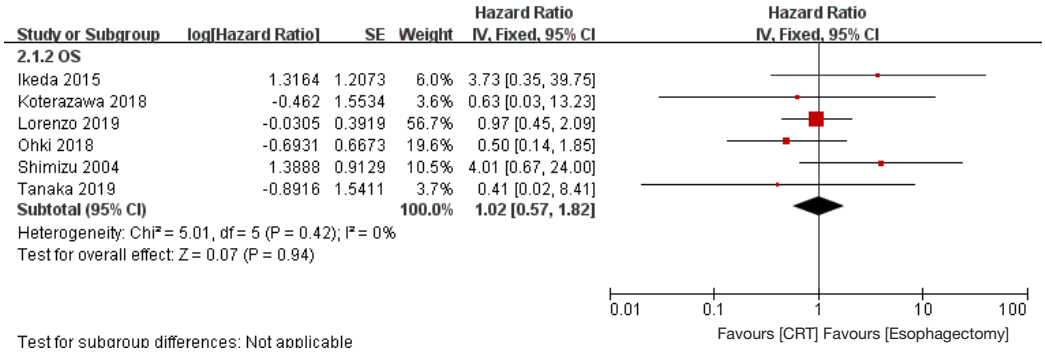

Figure 3 Forest plot of meta-analysis and cumulative meta-analysis in OS. OS, overall survival; CRT, chemoradiotherapy; CI, confidence interval; df, degrees of freedom; SE, standard error.

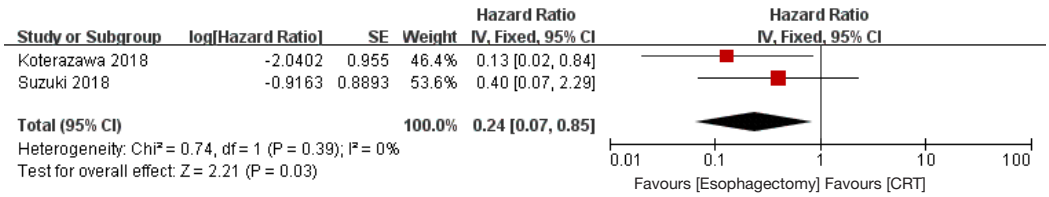

Figure 4 Forest plot of meta-analysis and cumulative meta-analysis in DFS. DFS, disease-free survival; CRT, chemoradiotherapy; CI, confidence interval; df, degrees of freedom; SE, standard error.

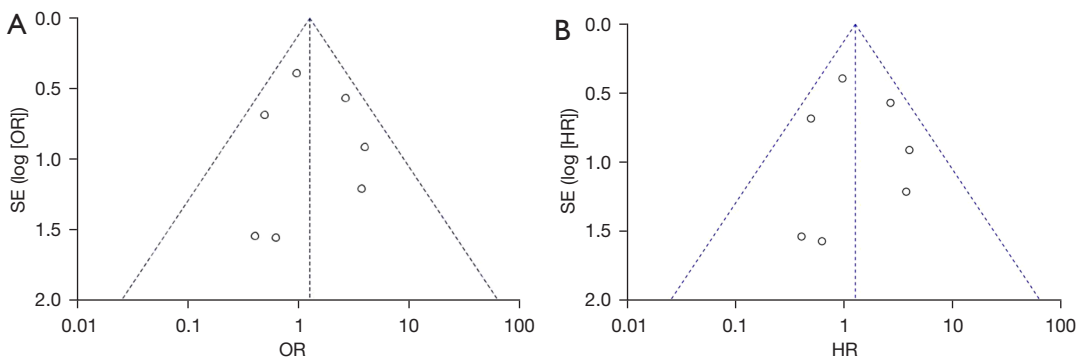

Figure 5 Funnel plots for primary outcome measures. (A) Recurrence and metastasis, (B) OS. OS, overall survival; SE, standard error; OR, odds ratio; HR, hazard ratio.

clarified whether radical surgery can provide better long-term benefits. In this meta-analysis, we focused on analyzing the details of both sides of intervention.

Traditionally, radical esophagectomy for early EC has been a standard treatment method but with obvious treatment risks, such as lung infection or stenosis, anastomotic leakage, and even death. Yang *et al.* (27) conducted a retrospective study including a total of 179 patients. Lung infection and esophageal perforation occurred in the radical surgery group, yet no serious complications occurred in the CRT after ER group. In the radical surgery group, the local recurrence rate was 1%, the LRR was 5%, and DMR was 4%; in addition, both local and regional recurrences in the CRT after ER group were 8%, and no distant metastasis was found. No significant differences were identified in the 5-year OS rate between the 2 groups (P=0.405). A was shown in *Figure 2*, the 9 articles included in our study involved a total of

790 patients with early EC, and the recurrence and metastasis rate of the CRT after ER group was 6.08 times that of the radical surgery group. Further, in the radical surgery group, DFS was also better than CRT after ER (HR =0.24, 95% CI: 0.07 to 0.85, P=0.03). There were 2 studies that reported radical surgery can achieve better disease control for tumors ≥ SM2 with lymphatic vascular invasion (19,20). We identified 2 reasons to explain why radical surgery can achieve better performance. Firstly, compared to ER, esophagectomy can completely remove the lesion and perform lymph node dissection, thereby obtaining a more accurate pathological staging and long-term prognosis judgment. Secondly, the lack of accurate pathological staging after ER contributed to insufficient radiation field exposure. The study by Lee *et al.* also reported similar views (28). Additionally, the included literature showed that no significant differences were found in OS. The results were basically consistent with the retrospective study conducted by Yang *et al.* (27). A single arm confirmatory Japanese study (JCOG0508) (29) reported on 176 patients with stage I ESCC treated with ER (combined with CRT or not) in 2016. A total of 96 patients were treated with CRT; the 3-year OS was 92.6% among all patients and 90.7% in the CRT group. Therefore, the study concluded that the efficacy of ER combined with adjuvant CRT for T1b esophageal SCC is equivalent to that of radical surgery. In 2020, Tsou *et al.* (30) conducted a review study, summarizing and reviewing 3 previous related studies, and concluded that patients with a high risk of recurrence should be recommended to use radical surgery. Although the thoughts and conclusions of the current analysis are similar to previously reported results, a total of 9 documents were included herein, making the conclusions more credible and practical.

No differences in survival benefits were found between the 2 treatment strategies according to our study. Compared to adjuvant CRT, radical esophagectomy, as a highly invasive operation with a high incidence rate of postoperative complications (40–50%) and mortality (2.0–9.5%), is not suitable for elderly patients or patients with more complications, yet it can prolong the hospital stay and reduce the quality of life of patients after operation, and these patients should consider adjuvant CRT (31). This study analyzed the application value of CRT after ER of early EC, and argued that CRT can be the preferred choice for the elderly, and patients who are in poor physical condition or unable to tolerate surgery. However, there are no large-scale RCTs to confirm these observations and an ongoing multicenter RCT from China is expected to provide new insights into treatment options for patients with early-stage esophageal cancer (Chest 201908, ClinicalTrials.gov number: NCT04135664) (32). Meanwhile, early EC should be evaluated by a multidisciplinary team, including the participation of gastroenterology, oncology, and thoracic surgeons, all striving to select a reasonable treatment plan.

This study has certain limitations. First, the included studies are basically non-RCTs, most studies are limited to single-institution case series, small sample size, and retrospective study design. Large amounts of retrospective data in studies can create uncertainties and questions about final conclusions that should be addressed with more RCTs. Selection bias in retrospective studies may be unavoidable unless the propensity score matching method is employed. Besides, due to trust in the efficacy of traditional surgery, patients with a greater risk of tumor recurrence are more likely to undergo esophagectomy, whereas those with a relatively low probability of recurrence may undergo CRT after ER. This difference in subjective choice may be increasing the observable curative effect of CRT after ER, thereby weakening the observable curative effect of radical surgery. Nevertheless, our research results show that surgical resection has better DFS and less probability of metastasis and recurrence, which highlights the reliability of our results. Similarly, in the included literature, the total number of participants from Lu *et al.* (18) is 501, but the number of patients in the radical surgery group is as high as 477 (78%). Considering the overall stability of the research results, the relevant research results were not included for overall comparison. This reduced the overall sample size of the study. In addition, of the 9 articles included in this study, 6 articles are from Japan, and relatively few are from Europe and America. Furthermore, the included articles mainly focus on long-term effects and do not provide detailed short-term effects, such as postoperative complications, radiotherapy and chemotherapy toxicity. Therefore, it is impossible to detect the difference in the recent treatment effects of the 2 methods in a more comprehensive manner. Last, due to the limitations of the included literature data, this study did not conduct further subgroup analysis on the tumor staging of patients, and failed to clarify the difference in the efficacy of radical surgery and CRT after ER for specific substages.

Conclusions

For the adjuvant treatment after ER of early EC, CRT

cannot completely replace esophagectomy, and both are equally essential treatments in survival benefits. For patients with tumor invasion ≥ SM2 or high risk of lymph node metastasis, radical surgery is recommended. Moreover, for patients with high risk factors for surgery or intolerance, CRT is the preferred option, but this conclusion still needs to be supported by more large-scale and sample RCTs.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-376/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-376/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-376/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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