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Critical Review

Effects of Local Treatment in Combination with Systemic Therapy for Advanced Esophageal Cancer: A Systematic Review and Meta-analysis

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Purpose: Initial studies investigating the combination of local and systemic treatments in advanced esophageal cancer (EC) have conflicting conclusions regarding survival benefits. The objective of this systematic review and meta-analysis is to assess the efficacy of the addition of local therapy to systemic treatments in patients with advanced EC.

Methods and Materials: A systematic literature search was conducted in the PubMed, EMBASE, and CENTRAL databases. Key eligibility criteria included studies that enrolled patients with histologically confirmed EC or esophagogastric junction cancer with metastasis or recurrence and compared survival benefits between the combined local and systemic treatment group and the systemic treatment alone group. Survival outcomes, represented by hazard ratios (HRs) of progression-free survival (PFS) and overall survival (OS), were pooled using a random effects model. The MINORS score was adopted for quality assessment. Risk of bias was statistically examined by Begg's and Egger's tests.

Results: A total of 1 randomized controlled trial (RCT) and 10 qualified retrospective studies including 14,489 patients were identified. Addition of local therapy to systemic treatment significantly improved PFS (HR, 0.52; 95% CI, 0.37-0.73; $P < .001$) and OS (HR, 0.69; 95% CI, 0.58-0.81; $P < .0001$) compared with systemic treatment alone. The subgroup analysis revealed that combined local and systemic treatment conferred a significant survival advantage in both patients with oligometastasis (PFS: HR, 0.45; 95% CI, 0.31-0.64; $P < .0001$; OS: HR, 0.62; 95% CI, 0.48-0.79; $P < .0001$) and recurrence (OS: HR, 0.55; 95% CI, 0.37-0.81; $P = .002$).

Conclusions: In conclusion, addition of local treatment to systemic therapy can improve survival in patients with advanced EC, particularly in those with oligometastasis or recurrent diseases.

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The data used to support the findings of this study are included in the article. The study protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023406556.

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Introduction

Approximately 20% to 30% of patients with esophageal cancer (EC) present with metastatic disease at the time of diagnosis, with a 5-year relative survival rate of 6%.[1] Systemic treatment, which includes chemotherapy, immunotherapy, and targeted therapy, has become the standard

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treatment option for metastatic EC, while local treatments such as radiation therapy and surgery typically serve as palliative measures.[2] Continually updated strategies incorporating systemic drugs have significantly extended the survival of patients in the advanced stage, potentially offering more opportunities for local treatments.

Advanced EC comprises newly diagnosed metastatic cases and recurrent EC following treatment. In this context, a subset distinguished by comparatively early-stage presentations is termed oligometastatic. Nevertheless, a standardized definition for this classification is currently lacking. A disease burden of 1 extraregional lymph node station or 1 organ with 3 or fewer metastases is commonly defined as oligometastatic disease in esophagogastric cancer, according to a systemic review.[3]

Previous research has also yielded conflicting findings on the survival benefit of local tumor therapy in advanced EC. A retrospective analysis found that radiation therapy of the primary tumor is associated with prolonged overall survival (OS) in patients with metastatic EC.[4] Similarly, a systematic review and meta-analysis of 16 nonrandomized studies reported that local treatment of oligometastatic disease was associated with superior OS compared with systemic therapy alone, although the analysis was limited by a high risk of bias.[3] These results are consistent with other studies demonstrating a survival benefit of local therapy in recurrent EC.[5,6] A recently published randomized study has nearly conclusively determined that additional local therapy extends both progression-free survival (PFS) and OS.[7] However, several other analyses have failed to demonstrate a statistically significant survival advantage with the addition of local treatment to systemic therapy.[8,9]

The evidence for local tumor therapy as a supplement to standard systemic treatment in advanced EC remains unclear. No publication has yet integrated the controversial results. Therefore, we conducted a meta-analysis evaluating OS to determine whether additional local treatment is an optimal approach for patients with advanced EC.

Methods and Materials

Search strategy

A systematic literature search was conducted in the PubMed, EMBASE, and CENTRAL databases using the keywords "esophageal cancer," "metastasis/recurrence/advanced," "local treatment/surgery/radiotherapy," "chemotherapy/drug," and synonyms. The detailed search strategies for each database are provided in Table E1. The study protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023406556.

Study selection

Studies were considered eligible if they met the following criteria: (1) histologically confirmed EC or esophagogastric junction cancer (EGJC), (2) metastatic disease at initial diagnosis or recurrence after curative treatments, (3) comparison of survival benefits between combined systemic and local treatments versus systemic treatments alone, and (4) publication date after January 1, 2000. Exclusion criteria included (1) insufficient data (lacking available hazard ratios (HRs) for PFS and OS); (2) case reports, letters, reviews, and meta-analyses; and (3) non-English language. In this context, advanced EC referred to patients with nonregional lymph node or distant organ metastasis, or recurrence following initial treatment with curative intent.

After removing duplicates, 2 authors (J.J. and Y.L.) independently screened titles and abstracts for eligibility, extracted data, and assessed the risk of bias and the quality of the evidence. Disagreements were resolved through consensus. References of the included publications and relevant review articles were also examined to identify any potentially relevant articles that may have been missed.

Data extraction

Data were extracted from the included studies for the following variables: first author, publication year, country of origin, inclusion years, study type (retrospective or prospective, single- or multicenter), population characteristics (eg, age), metastatic or recurrent disease status, primary tumor histology, and the number of patients receiving combined systemic and local treatments or systemic therapy alone. Additionally, HRs comparing PFS and OS after combined systemic and local treatments versus systemic therapy alone were collected. PFS and OS were defined in accordance with the respective articles. They were typically calculated from the initiation of treatment or diagnosis of metastasis, or from the diagnosis of recurrence until the occurrence of either disease progression or death, whichever happened first (PFS), or until death (OS). Available subgroup analyses were conducted, including analyses of metastatic or recurrent disease status, histologic subtypes, and types of local treatments.

Outcomes

The primary outcomes measured were the pooled HRs comparing PFS and OS after combined systemic and local treatments versus systemic therapy alone for metastatic or

recurrent EC or EGJC. The secondary outcome was to identify the population that benefits most from combined therapy.

Evaluation of quality and bias

The quality of nonrandomized studies was assessed using the Methodological Index for Nonrandomized Studies (MINORS) score (Table E3).[10] The items were scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The global ideal score was 16 for noncomparative studies and 24 for comparative studies. Publication bias was illustrated by funnel plots and quantitatively assessed by Begg's and Egger's tests for all outcomes.

Statistical analysis

R software (version 4.2.3; R Foundation for Statistical Computing) with "meta" package (version 6.2-1) was used for pooled HR estimation, heterogeneity tests (I^2 and τ), prediction interval generation, subgroup analysis, sensitivity analysis, and publication bias tests. The larger the I^2 and τ values, the greater the heterogeneity among studies. Weighted random effects models were adopted to calculate overall summary estimates for each outcome measure, considering the potential disparity among studies in different centers and the retrospective nature. Results were presented as forest plots with corresponding 95% confidence intervals (CIs) and 95% prediction intervals. A P value less than 0.05 was considered statistically significant.

A sensitivity analysis was performed based on the leave-one-out method, to assess the influence of each study on the overall results by removing them individually. The robustness of the outcome measure was confirmed if the exclusion of any individual study did not result in an obvious alteration in the meta-analytical effect size or CI.

Results

Literature review and characteristics of included studies

A total of 1 randomized controlled trial (RCT)[7] and 10 retrospective studies with 14,489 patients met the predefined criteria and were included in our final analysis.[4-6,8,11-16] The selection process and characteristics of these eligible studies are depicted in Fig. 1 and Table 1, respectively. Five studies based on the Surveillance, Epidemiology, and End Results (SEER) database were included in the initial screening, of which 4 with a smaller scope were excluded as duplicate data.[9,17-19] The MINORS assessment result of the included studies, which received relatively high-quality scores ranging from 16 to 20, is presented in Fig. E1.

Among the enrolled studies, radiation therapy, including both conventional and hypo-fractionated regimens, was the most frequently employed local treatment modality. Table E4 provides a comprehensive summary of radiation treatment regimens, incorporating detailed information on radiation dose and fractions as reported by 7 studies. Four of the studies used concurrent chemoradiotherapy, while the rest implemented sequential chemoradiotherapy or did not specify the treatment order. Conventional fractionation with a total dose exceeding 50 Gy was predominantly used for primary lesions, while hypo-fractionated regimens were frequently employed for metastatic lesions in distant organs. Owing to insufficient information in the original studies, specific details regarding systemic treatments were not provided. Additionally, 9 studies incorporated chemotherapy with or without targeted therapy in their respective control arms, while the remaining 2 studies included patients treated with immunotherapy.

Impact of additional local treatment on PFS and OS

Across 7 studies, a total of 1739 patients had available information on PFS.[7,11-16] The combination of local and systemic treatments resulted in a significant PFS improvement compared with the systemic treatment alone group (pooled HR, 0.52; 95% CI, 0.37-0.73; $P < .001$; $I^2 = 86\%$; Fig. 2A). Moreover, a survival benefit was also observed in OS (pooled HR, 0.69; 95% CI, 0.58-0.81; $P < .0001$; $I^2 = 86\%$; Fig. 2B) across 11 studies enrolling 14,489 patients.

Subgroup analyses

Subgroup analyses revealed that the PFS and OS benefit of combined therapies varied considerably across subgroups stratified by oligometastasis, metastasis, or recurrence. As shown in Fig. 3A, both patients with oligometastasis (HR, 0.62; 95% CI, 0.48-0.79; $P < .0001$) and recurrence (HR, 0.55; 95% CI, 0.37-0.81; $P = .002$) experienced superior survival outcomes through the combination of local and systemic treatments, while no significant improvement in those with metastatic disease was observed (HR, 0.80; 95% CI, 0.60-1.08; $P = .148$). Differential survival outcomes due to disease status variations might be the origin of heterogeneity. No significant differences were detected in subgroups delineated by types of local treatment (Fig. 3B) and histologic classifications (Fig. 3C). The survival benefit was observed in both studies focusing on squamous cell carcinoma and studies

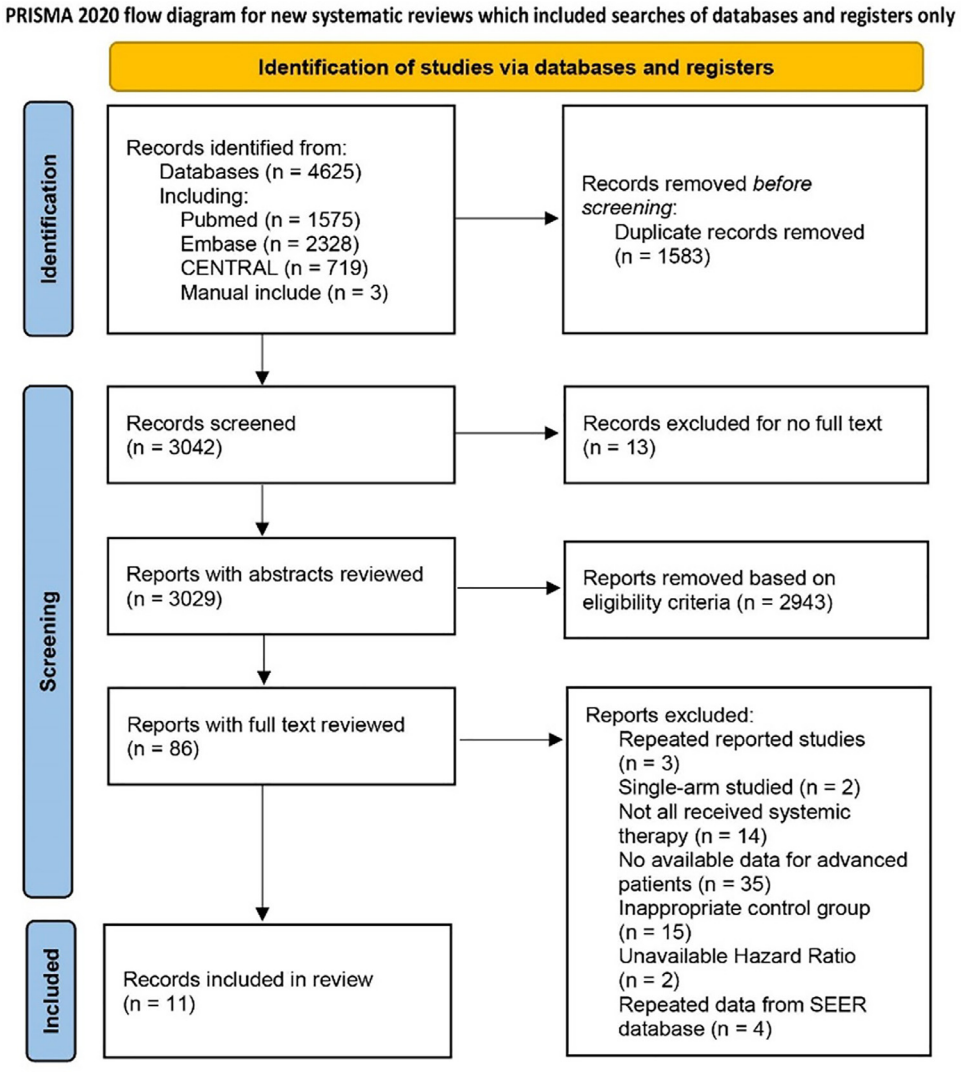

Figure 1 Flowchart of study selection.
Abbreviations: PRISMA = preferred reporting items for systematic reviews and meta−analyses.

without restricted pathologic type subgroups. The results of the subgroup analysis for PFS (Fig. 4) and OS were largely consistent. The addition of local therapy significantly prolonged PFS in the oligometastatic subgroup (HR, 0.45; 95% CI, 0.31-0.64; $P < .0001$; Fig. 4A).

Sensitivity analysis and risk of bias assessment

Sensitivity analyses conducted by successively excluding each specific study from the overall data set, indicated that the newly calculated HRs for PFS and OS were consistent with the original pooled HRs (Fig. E2).

No evidence of publication bias was detected by Begg's test or Egger's test in both PFS and OS, with the funnel plots shown in Fig. E3.

Discussion

In this systematic review and meta-analysis, we assessed the efficacy of combining local and systemic treatments in patients with advanced EC. Our findings suggest that the addition of local treatment to systemic therapy significantly improves PFS and OS, especially in patients with oligometastasis and recurrence.

Our conclusion regarding the survival benefits of additional local treatment is partially supported by several pioneering studies. A systematic analysis including 4 clinical studies demonstrated that in patients with locally advanced or metastatic EC, the pooled response rate (CR or PR) of pemetrexed-based radiation therapy was 51% (24/47), suggesting that chemoradiotherapy is associated with reasonable activity and good tolerability in selected patients.[20] A retrospective study based on the SEER

Table 1 General information from the included studies

Article	Inclusion				metastasis/ recurrence	No. of patients	Comparisons		No. of patients		HR of PFS			HR of OS		
	Country	Type	Center	Period			Combined	Systemic	Combined	Systemic	HR	LCI	UCI	HR	LCI	UCI
Liu 2023	China	RCT	Multi	2019-2021	both	104	R/S/TA	I/C/I + C	53	51	0.26	0.16	0.42	0.42	0.24	0.74
Wu 2022	China	retrospective	Single	2017-2021	both	127	R	I±C	87	40	1.10	0.73	1.64	0.97	0.61	1.54
Shi 2022	China	retrospective	Double	2012-2018	metastasis	532	CCRT	C	240	292	0.685	0.565	0.832	0.750	0.607	0.926
Kroese 2022	the Netherlands	retrospective	Single	2010-2021	metastasis	36	R/S/(R + S) + (C±T)	C±T	12	24	0.452	0.176	0.935	0.439	0.165	0.962
Shao 2021	China	retrospective	SEER database	2010-2016	metastasis	2862	R + C	C	1431	1431	-	-	-	1.05	0.96	1.14
Morinaga 2021 (OLR)	Japan	retrospective	Single	2005-2019	recurrence	40	R/S/RFA + C	C	25	15	-	-	-	0.35	0.14	0.87
Morinaga 2021 (non-OLR)						50	R/S/RFA + C	C	16	34	-	-	-	0.694	0.325	1.481
Li 2020 (concurrent)	China	retrospective	Single	2013-2018	metastasis	153	CCRT	C	59	94	0.35	0.24	0.50	0.53	0.34	0.83
Li 2020 (sequential)						185	R + C	C	91	94	0.33	0.24	0.45	0.50	0.34	0.74
Chen 2019	China	retrospective	Double	2012-2015	metastasis	461	CCRT	C	196	265	0.735	0.602	0.893	0.833	0.671	1.031
Lyu 2018	China	retrospective	Single	2010-2015	metastasis	141	CCRT	C	55	86	0.611	0.426	0.875	0.631	0.438	0.907
Guttmann 2017	USA	retrospective	NCDB database	2004-2012	metastasis	9700	R + C	C	2426	7274	-	-	-	0.72	0.70	0.74
Depypere 2017	Belgium	retrospective	Single	1990-2012	recurrence	98	R + C	C	32	66	-	-	-	0.565	0.335	0.956

Abbreviations: C = chemotherapy; CCRT = concurrent chemoradiotherapy; I = immunotherapy; OS = overall survival; R = radiation therapy; RCT = randomized controlled trial; RFA = radiofrequency ablation; S = surgery; T = targeted therapy; TA = thermal ablation.

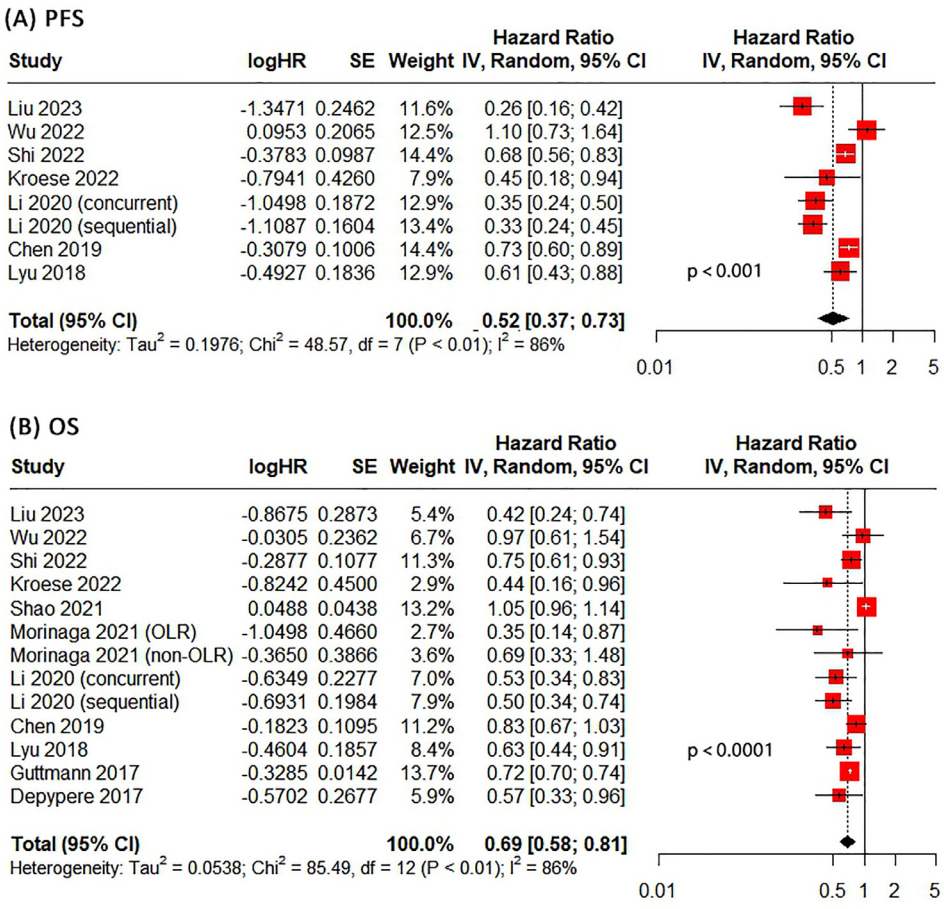

Figure 2 Forest plots for (A) progression-free survival (PFS) and (B) overall survival (OS) comparing local treatment plus systemic treatment with systemic treatment alone in patients with advanced esophageal cancer.
Abbreviations: non-OLR = nonoligometastatic recurrence; OLR = oligometastatic recurrence. "Concurrent" and "sequential" refer to chemoradiation therapy administered concurrently or sequentially, respectively.

database revealed that radiation therapy improved OS and cancer-specific survival in patients with metastatic EC.[21] However, the proportion of patients who received chemotherapy remained greater in the radiation therapy group even after propensity score matching, which may partly contribute to the survival benefit of the radiation therapy group. Therefore, our meta-analysis only included original studies in which all patients received systemic therapy to reduce such effects. Another 2 retrospective studies of the SEER database studied elderly patients with esophageal squamous cell carcinoma[18] and adenocarcinoma,[9] respectively, and did not show a survival benefit of adding local treatment to chemotherapy. This may be explained by the fact that both studies were limited to patients with stage IVB disease and excluded nonregional lymph node metastasis, which could have benefitted from additional local treatments. However, these studies did not control for a baseline of systemic therapy or had a mixture of locally advanced disease. Consequently, our findings offer additional evidence supporting the role of aggressive local treatments as a potential component of a multimodal approach to improve prognosis in advanced EC withstanding systemic treatment.

Subgroup analysis in our study indicated that the benefits of combined therapies were more pronounced in patients with oligometastasis and recurrent disease, which highlights the significance of patient selection in determining the optimal treatment strategy. This observation is consistent with the growing recognition of the oligometastatic state as a distinct clinical status with the potential for curative-intent treatment.[22] Local treatments such as radiation therapy and surgery may be particularly effective in controlling limited metastatic disease, which may ultimately lead to improved survival outcomes. A previous meta-analysis by Kroese et al[3] found that oligometastasis-directed treatment improved OS compared with systemic therapy alone for oligometastatic esophagogastric cancer, based on 8 studies without multivariable adjustment (pooled HR for OS, 0.36; 95% CI, 0.22-0.58) and 6 studies with multivariable adjustment (pooled adjusted HR for OS, 0.47; 95% CI, 0.30-0.74). Another meta-analysis included multi-institutional RCTs of

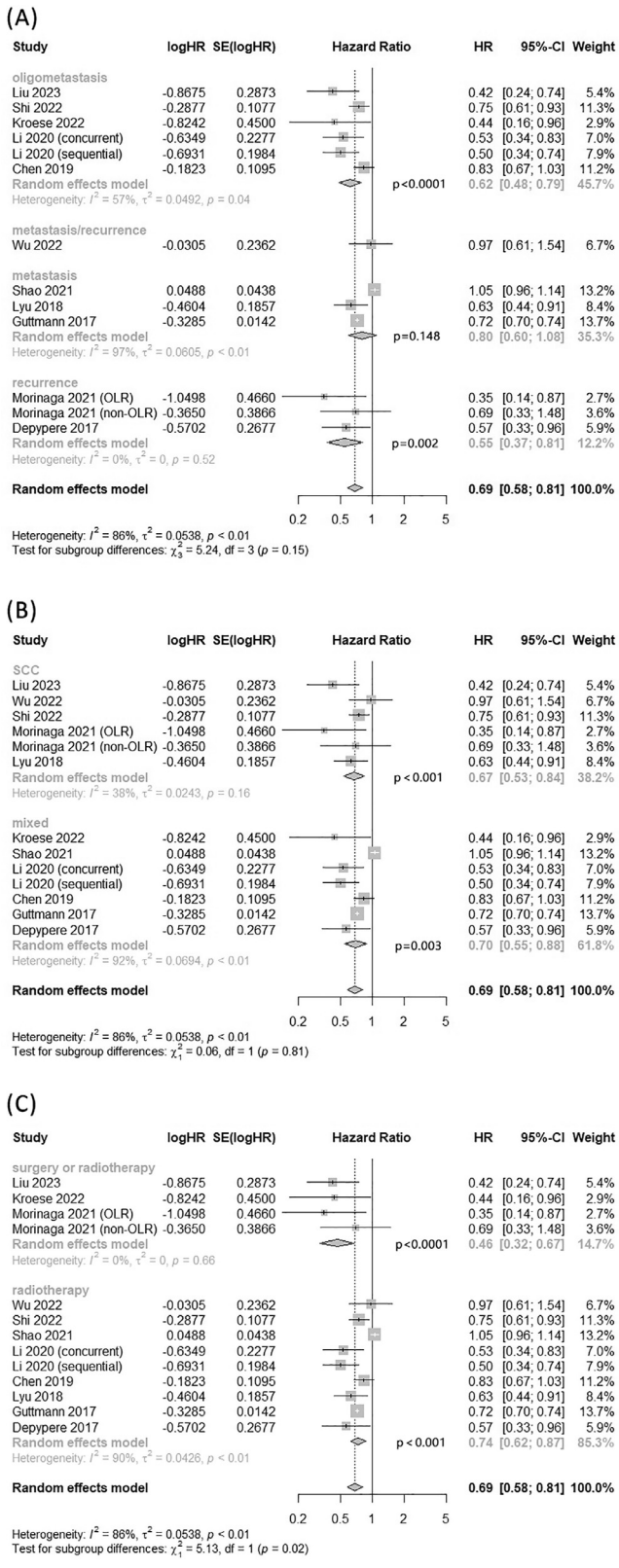

Figure 3 Subgroup analyses of overall survival stratified by (A) oligometastasis, metastasis, or recurrence; (B) types of local treatment; and (C) histology. The *P* value represents the significance of differences between subgroups.
Abbreviations: non-OLR = nonoligometastatic recurrence; OLR = oligometastatic recurrence; SCC = esophageal squamous cell carcinoma. "Concurrent" and "sequential" refer to chemoradiation therapy administered concurrently or sequentially, respectively.

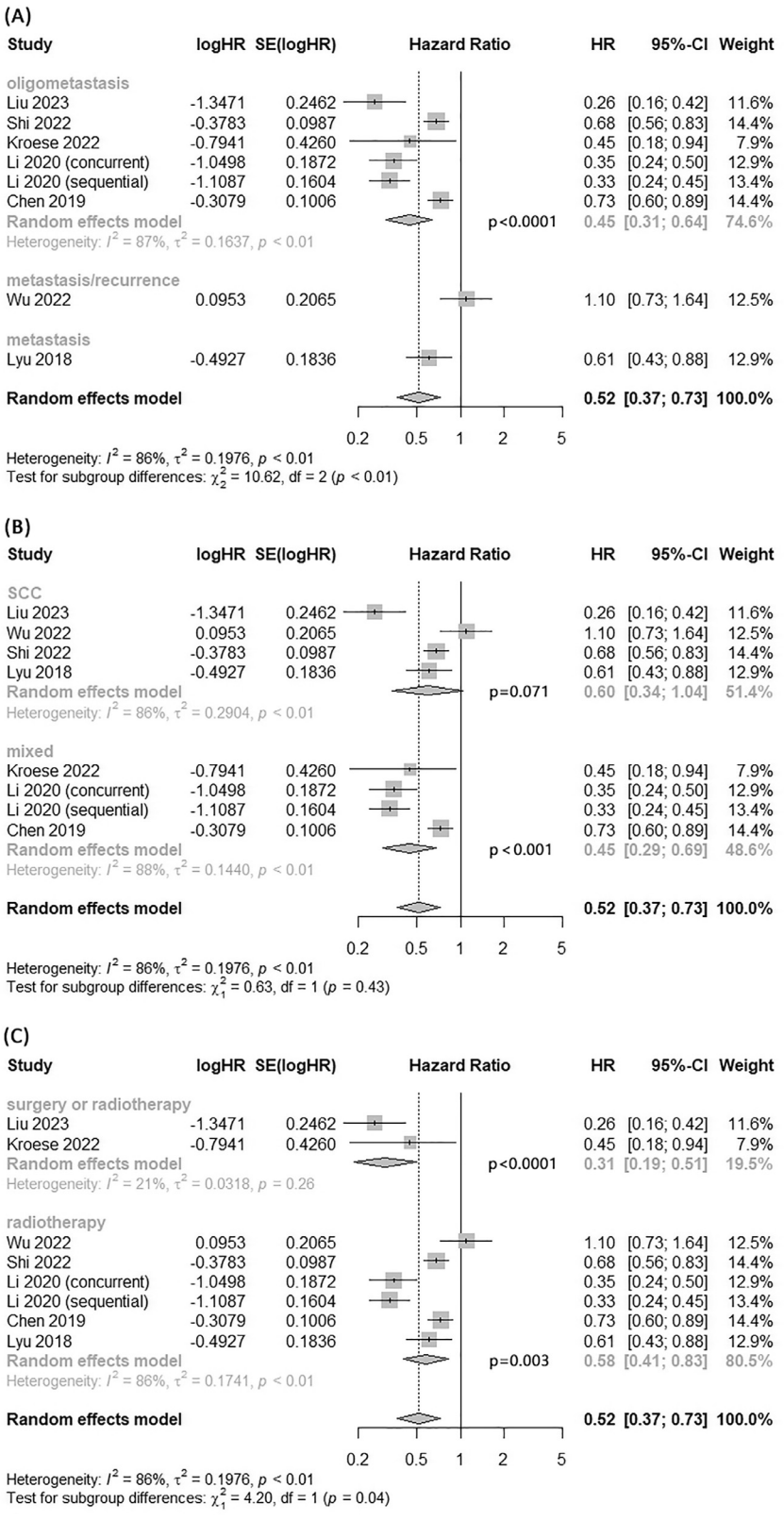

Figure 4 Subgroup analyses of progression-free survival stratified by (A) oligometastasis, metastasis, or recurrence; (B) types of local treatment; and (C) histology. The *P* value represents the significance of differences between subgroups.
Abbreviations: SCC = esophageal squamous cell carcinoma. "Concurrent" and "sequential" refer to chemoradiation therapy administered concurrently or sequentially, respectively.

patients with metastatic disease receiving systemic therapy with or without addition of local treatment to the primary tumor in various types of cancer (ie, breast, colorectal, gastric, lung, nasopharyngeal, prostate cancers, and renal cell carcinoma). Although the addition of local therapy did not consistently improve PFS or OS in unselected patients with metastatic disease, it did improve OS significantly in patients with a low metastatic burden or those who received radiation therapy compared with surgery.[23] In our analysis, no significant differences in survival outcomes were detected across subgroups stratified by types of local treatment and histologic classifications. The variability in outcomes regarding local treatment may be explained by the fact that the original studies included in our analysis allowed for either surgery alone or surgery combined with radiation therapy. None of the studies exclusively examined the effects of surgery on its own, thus limiting our ability to draw definitive conclusions regarding the comparative effects of radiation therapy versus surgery.

Owing to the fact that the majority of the studies were conducted before the prevalence of immunotherapy, most of the original studies (9 out of 11) included in our meta-analysis solely used chemotherapy as the systemic treatment. Currently, there are limited studies investigating the addition of local therapy to immunotherapy. A recent retrospective study has demonstrated that combining immunotherapy with radiation therapy can provide survival benefits to patients with locoregional recurrence and improve dysphagia compared with immunotherapy alone.[16] However, there was no improvement in PFS and OS in the overall population. In this study, palliative radiation therapy was administered to 44% of patients (30-48 Gy/10-24 f), and the proportion of patients with lymph node recurrence who received only radiation therapy was lower than in previous studies, which may explain the lack of a significant efficacy difference between groups. The recently published ESO-Shanghai 13 represents the first prospective randomized controlled study in this field.[24] It enrolled patients with PS 0 to 1, squamous cell carcinoma, stable primary lesions for at least 3 months after curative treatment, and oligometastatic lesions defined as 1 to 4 metastases in 1 to 3 sites. The patients were randomly divided into a locoregional combined systemic therapy group and a systemic therapy alone group, with radiation therapy eventually administered to over 80% of patients and immunotherapy, to approximately half of the patients in both groups. At a median follow-up of 30.5 months, the addition of local therapy extended the median PFS from 6.4 months to 15.3 months (HR, 0.26; $P < .0001$) and the median OS from 18.6 months to not reached (HR, 0.42; $P = .0020$). However, among patients who received immunotherapy, the addition of local therapy significantly improved PFS but not OS. Another prospective, single-arm study[25] involving patients with oligometastatic squamous cell carcinoma and first-line treatment failure demonstrated that low-dose radiation therapy (esophageal lesion, 40 Gy/20 f; metastases, 30 Gy/10 f) combined with immunochemotherapy still provided some survival benefits. The median PFS was 6.9 months, and the median OS was 12.8 months. However, the incidence of treatment-related grade 3 or above adverse events was relatively high, accounting for 63.3%. As immunotherapy continues to evolve and gain wider application, it is essential to further investigate the potential effectiveness of combining local treatment strategies with immunotherapy.

Some other endpoints in the original literature, such as local recurrence, disease control rate, and treatment toxicities, deserve attention despite their challenging quantitative analysis. Local recurrence was addressed by a single study,[7] reporting initial local control rates of 83% in the systemic and local therapy group compared with 26% in the systemic therapy-only group. Disease control rate, documented by 2 studies,[11,14] ranged from 83.2% to 84.2% in combined therapy groups and from 65.8% to 75.5% in systemic therapy-only groups, with P values of <0.05. Treatment toxicities, reported in 4 articles,[7,11,14,15] generally demonstrated good tolerance to additional local treatment. Grade 3 or greater toxicities, predominantly leukocytopenia, occurred in 29.6% to 41.8% of patients in combined therapy groups compared with 22.3% to 35% in systemic therapy-only groups. Incidences of radiation pneumonitis ranged from 0% to 7.6%, and radiation esophagitis, from 2% to 14.5%, with the minimum rates reported in a small prospective study. However, esophageal fistula resulted in the death of 2 (4%) patients in this study. Therefore, in certain populations of patients with advanced EC, the addition of systemic therapy to standard treatment regimens has been shown to improve local control, prolong survival, and demonstrate good safety profiles. However, it is essential to remain cautious of potential severe adverse effects, such as esophageal fistula.

This meta-analysis has several limitations. First, as most of the included studies were retrospective, our findings may be subject to inherent biases associated with this study design. However, the consistent survival benefit observed across the included studies, coupled with the robust sensitivity analysis results, implied relatively credibility to our conclusions. Second, the considerable heterogeneity observed among the included studies may influence the pooled estimates, although the use of random effects models and subgroup analyses aimed to account for this variability. Lastly, the absence of individual patient data, along with insufficient information regarding treatment regimens and related toxicities, has hindered a more comprehensive analysis of the safety and identification of the optimal group for maximum therapeutic benefit.

Conclusion

The addition of local treatment to systemic therapy significantly improves OS in patients with advanced esophageal cancer, particularly in those with oligometastasis or recurrent disease. Future prospective, randomized controlled trials are needed to confirm these findings and further refine patient selection criteria for the optimal integration of local and systemic treatments.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2024.101522.

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