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Chemotherapy in esophageal cancer, 2nd Edition

Edited by
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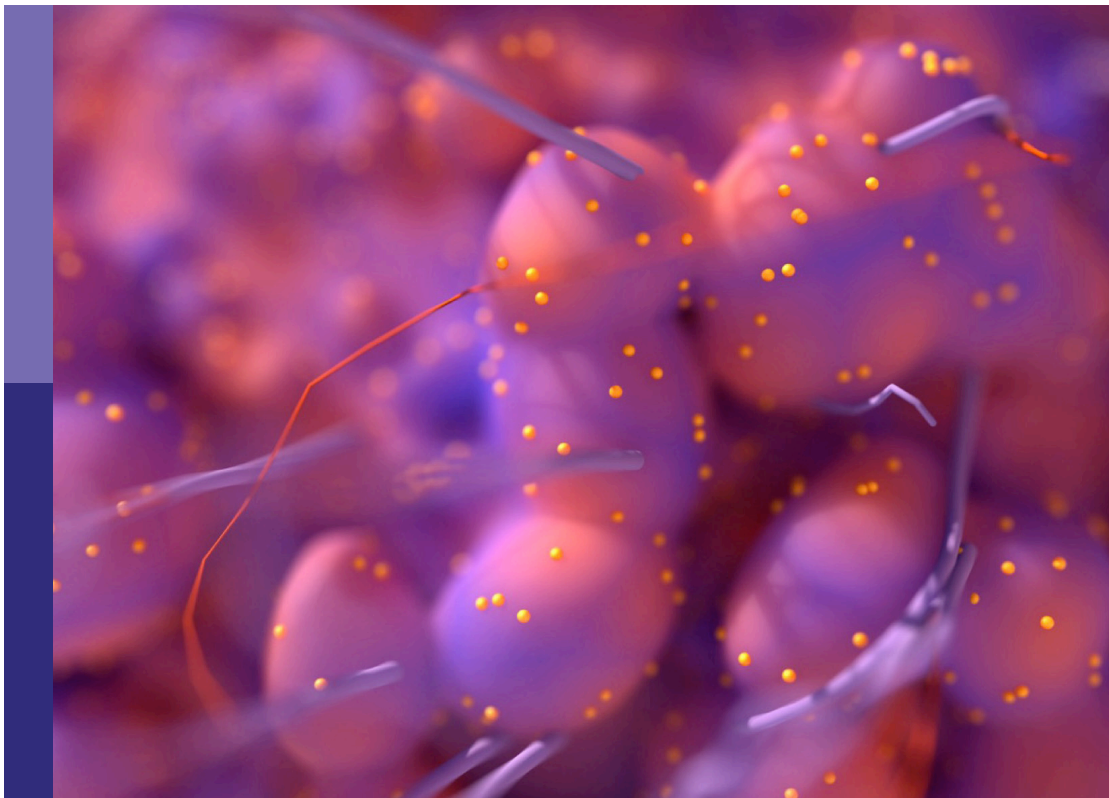

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Chemotherapy in esophageal cancer, 2nd Edition

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Editorial: Chemotherapy in esophageal cancer

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KEYWORDS

chemotherapy, esophageal cancer, drugs, metastasis, cancer

Editorial on the Research Topic
Chemotherapy in esophageal cancer

Esophageal cancer is the cancer of esophagus and is one of the most deleterious cancers and sixth most common cause of carcinogenesis related mortality worldwide (1). Although incidence rates of esophageal cancer vary based on geographic locations, the major causes for this malady includes tobacco chewing, smoking, excess alcohol consumption, practicing western sedentary lifestyle and dietary habits and associated obesity (2) (3). These causes activate various signalling pathways at cellular levels and initiate esophageal cancer development (4) (Elliott and Reynolds). Although there are many treatment options for esophageal cancer this issue mainly focused on chemotherapy. In this special issue we received many research and review articles on chemo and associated therapies to treat this cancer and two of these review articles by Luo et al and Huang et al sheds light on the role of PI3K/Akt/mTOR signalling pathway in development and pathophysiology of esophageal squamous cell carcinoma (ESCC). They also suggested that either PI3K/Akt/mTOR or their downstream eukaryotic translation initiation factors (eIFs) may act as potential therapeutic targets to treat this disease. A study by Xiao et al discussed the possible brain metastasis of ESCC and concluded that development of characteristics of brain metastases is rare in these patients and suggested that local or specific territorial (locoregional) treatment is associated with improved overall survival. Another *in silico* study by Zhao et al predicted the overall survival and benefits of chemotherapy using Deep Learning (DL)-based protein features in gastric cancer and they also demonstrated the advantages of DL-based workflow in gastric cancer molecular subtyping along with its possible therapeutic application. Study by Yang et al suggested that the esophageal cancer patients who are intolerable to surgery or who are under the impact of old age or geriatric patients (aged ≥80 years), should prefer chemoradiotherapy (CRT) as a preferable treatment option compared to other therapies.

A retrospective, propensity score-matched short-term study by Feng et al discussed the clinical efficacy of neoadjuvant chemotherapy (NACT) combined with Laparoscopic

gastrectomy (LG) for locally advanced adenocarcinoma of the esophagogastric junction and concluded that these combined therapies does not increase the risk of postoperative morbidity and mortality when compared with LG alone (https://pubmed.ncbi.nlm.nih.gov/34660265/). A population study associated SEER analysis by Yang et al revealed that ESCC subjects with organ specific metastasis other than liver or bone have more benefits from local ablative treatment (LAT) with systemic chemotherapy. A study by Kermani et al concluded that in ESCC patients' predictive or anticipating value of endoscopic results, observations, impressions and biopsy after neoadjuvant CRT are insufficient for assessing overall complete pathological response after neoadjuvant treatment and they also suggested that additional methods are required for overall assessment of the treatment and its impact. A phase II randomized study by Wang et al compared the preoperative concurrent CRT versus NACT or neoadjuvant chemotherapy for locally well-developed later stage gastric cancer (LAGC) patients in a single center-based data. In contrast to this report another study by Zheng et al compared the side effects and effectiveness of chemical drugs Lobaplatin-based versus Cisplatin-based adjuvant chemotherapy data from multicenter study and based on their analysis, Lobaplatin plus docetaxel might be a better choice of drug for adjuvant chemotherapy particularly for ESCC. Finally, A systematic review and meta-analysis by Xia et al. concluded that consolidation chemotherapy (CCT) after Concurrent chemoradiotherapy (CCRT) significantly increases over all long-term survival and disease progression-free survival of patients with nonsurgical esophageal cancer and could provide them astonishing overall survival benefits.

Finally, these elegant research and review articles increased the current knowledge and added additional information about benefits and drawbacks of different therapeutic options for patients with advanced esophageal cancer.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Come J, Castro C, Morais A, Cossa M, Modcoicar P, Tulsidâs S, et al. Clinical and pathologic profiles of esophageal cancer in Mozambique: A study of consecutive patients admitted to Maputo central hospital. *J Glob Oncol* (2018) 4:1–9. doi: 10.1200/JGO.18.00147

2. Zhao X, Lim F. Lifestyle risk factors in esophageal cancer: An integrative review. *Crit Care Nurs Q* (2020) 43(1):86–98. doi: 10.1097/CNQ.0000000000000295

3. Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. *Gastroenterol Clin North Am* (2009) 38(1):27–57. doi: 10.1016/j.gtc.2009.01.004

4. Osei-Sarfo K, Urvalek AM, Tang XH, Scognamiglio T, Gudas LJ. Initiation of esophageal squamous cell carcinoma (ESCC) in a murine 4-nitroquinoline-1-oxide and alcohol carcinogenesis model. *Oncotarget* (2015) 6(8):6040–52. doi: 10.18632/oncotarget.3339

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SYSTEMATIC REVIEW
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Long-Term Survival in Nonsurgical Esophageal Cancer Patients Who Received Consolidation Chemotherapy Compared With Patients Who Received Concurrent Chemoradiotherapy Alone: A Systematic Review and Meta-Analysis

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Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for nonsurgical esophageal cancer (EC). However, esophageal cancer patients receiving CCRT alone are still unsatisfactory in terms of local control and overall survival (OS) benefit. Clinicians generally add consolidation chemotherapy (CCT) after CCRT. It remains controversial whether CCT following CCRT is beneficial for esophageal cancer. We, therefore, undertook a meta-analysis to assess the need for CCT in inoperable esophageal cancer.

Materials and Methods: We combed PubMed, Embase, Cochrane Library, Web of Science, and CNKI for relevant published articles up to July 2020 that compared CCRT plus CCT to CCRT alone for patients with nonsurgical EC. Our primary endpoint was OS and progression-free survival (PFS), and the secondary endpoint was treatment toxicity. We analyzed the hazard ratio (HR) to estimate the time-to-event data and the odds ratio (OR) to compare the treatment-related effect. To assess heterogeneity, we performed the I^2 test and examined publication bias using funnel plots analysis.

Results: The 11 retrospective studies involved 2008 patients. Of these 2008 patients, 1018 received CCRT plus CCT, and 990 received CCRT. Compared to CCRT alone, CCT after CCRT did not improve disease control rate (DCR) (OR 1.66; 95% CI 0.53–5.15, p=0.384) and objective response rate (ORR) (OR 1.44; 95% CI 0.62–3.35, p=0.393). However, OS (HR 0.72; 95% CI 0.59–0.86, $p < 0.001$) and PFS (HR 0.61; 95% CI 0.44–0.84, p=0.003) did increase. Our results show that CCT plus CCRT had a clear survival

advantage over CCRT alone. The risk of treatment toxicity did not increase for EC patients who received CCT.

Conclusion: CCT after CCRT significantly increases OS and PFS in patients with nonsurgical EC and could provide them remarkable survival benefits. The results provide an evidence-based framework for the use of CCT after CCRT.

Keywords: esophageal cancer, consolidation chemotherapy, chemoradiotherapy, meta-analysis, toxicity

INTRODUCTION

Esophageal cancer (EC) is one of the most common malignant tumors of the digestive system. It ranks seventh in terms of tumor incidence and is the sixth leading cause of cancer-related death (1). Esophageal squamous cell carcinoma (ESCC) is the predominant histological type reported in Asian countries although adenocarcinoma is more common in Western countries (2). Most patients with EC are diagnosed in an advanced stage due to a lack of specificity of early symptoms and have lost the opportunity to undergo radical surgery (3). Concurrent chemoradiotherapy (CCRT) is considered as the standard treatment for patients with unresectable EC, especially for elderly patients (4). However, the 5-year survival rate of EC patients receiving CCRT is about 10%–30% due to local tumor recurrence and distant metastasis (5). Therefore, there is need for a more effective method to further improve the survival rate of EC patients who receive CCRT.

As far as we know, there are no large-scale clinical trials to explore the efficacy of consolidation chemotherapy (CCT) after CCRT in EC patients. Studies have confirmed that CCT plays a significant role in the treatment of nasopharyngeal cancer, lung cancer, and other tumors (6, 7). Some studies (8, 9) find that CCT did prolong the survival time of patients with EC although others (10, 11) show that CCT has nothing to do with improving patient prognosis. It is not clear whether CCT can improve the survival rate of EC patients, and there are no relevant and exhaustive studies to determine whether CCT is related to patient prognosis.

CCT aims to inhibit tumor cell proliferation by eliminating subclinical lesions after CCRT. To date, several case-control studies have been published, but no randomized controlled studies have been conducted to explore the effect of CCT on EC after receiving CCRT. The results of each case-control study differ and are not sufficient to detect the role of CCT. In such circumstances, we first performed a meta-analysis to estimate the survival benefit of CCT in EC patients.

MATERIAL AND METHODS

Search Strategy

In May 2020 and July 2020, we did two comprehensive searches on the Pubmed, Embase, Cochrane Library, Web of Science, and CNKI databases to make sure we collected all the literature related to CCT of EC. The keywords used for the online search were "esophageal neoplasms," "concurrent chemoradiotherapy," and "consolidation chemotherapy." Apart from searching the databases, we did a manual search for potential studies from the cited documents of the included studies. Two researchers independently carried out the search.

Study Selection

Studies were eligible if they met the following inclusion criteria: (1) participants diagnosed with pathologically inoperable EC; (2) studies including survival outcomes between the CCRT-alone and CCRT–CCT groups; (3) case reports, reviews, letters, comments, and editorials were excluded; (4) treatment response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), and adverse events were evaluated based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE); (5) hazard ratio (HR) and 95% confidence interval (95% CI) were available directly or indirectly; (6) the language of the included documents was English or Chinese.

Data Collection and Quality Assessment

Data were extracted from eligible studies based on systemic review, and the meta-analysis was reported according to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12) and the Observational Studies in Epidemiology (MOOSE) guidelines (13). Two researchers independently extracted the following data: author, year of publication, trial region, sample size, number in CCRT-alone group, number in CCRT–CCT group, pathological type, clinical stage, staging standard, follow-up time, univariate or multivariate analysis, survival outcome, treatment regimen, HR and 95% CI, adverse events, and treatment response. If both univariate and multivariate results were available, univariate was preferred for the following reasons. Only 27.3% (univariate=10, multivariate=3, both=2) of all studies report results of multivariate analysis, and none of them describes the multivariate analysis method. The difference in numbers and types of variables entered also increased the bias in multivariate analysis results.

The Newcastle–Ottawa Scale (NOS) (14), which was developed for nonrandomized studies, was applied to assess the studies' quality based on three categories: selected cases, comparability of groups, and assessment of outcomes. Two researchers obtained independent scores according to the classification prompts for the three categories. Scores ranged from 0 to 9 with higher scores indicating better quality of literature. Studies scoring higher than 6 were considered to be of high quality. Any disagreements regarding

study selection, data collection, and quality assessment were resolved through discussion.

Statistical Analysis

HR and 95% CI were used to assess survival outcomes. The definition of HR was CCRT–CCT group versus CCRT-alone group, and we took the reciprocal of HR and 95% CI in studies whose HR was CCRT-alone group versus CCRT–CCT group. When possible, HR and 95% CI were obtained directly from the studies. HRs were calculated from survival curves in cases in which studies did not report the exact HR values with the methods previously reported by Tierney (15). If 95% CI of HR covered 1, it was considered insignificant. The meaning of HR < 1 was defined as CCT decreasing the risk of death, and HR > 1 indicated CCT increased the risk of death. Response rate and adverse events were assessed by odds ratios (ORs). The definition of OR was CCRT–CCT group versus CCRT-alone group.

I^2 statistics were used to assess heterogeneity between studies, which estimated the total percentage variation across studies due to heterogeneity rather than chance (16). A fixed effect model was used in the absence of significant heterogeneity (I^2 < 50%). Otherwise, a random effect model was applied. We also performed a subgroup analysis and a sensitivity analysis to find the source of the heterogeneity. Publication bias was assessed by Begg's and Egger's tests (17) and funnel plots. *P* less than 0.05 was considered as existing publication bias. The trim-and-fill method was applied to adjust the HR for publication bias among studies. A two-sided *p* value less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata statistical software 15.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Study Selection

As summarized in **Figure 1**, 1007 records of relevant studies were obtained from PubMed (n=685) and other databases (n=322). Of these, 68 studies passed the title and abstract screening. After full text screening, 57 studies were excluded for reasons such as lack of relevant data or data duplication. Finally, 11 case-control studies were included in this meta-analysis (8–11, 18–24).

Characteristics of Included Studies and Quality Assessment

There were 2008 unresectable EC patients in the 11 retrospective trials with 1018 in the intervention groups (CCRT–CCT) and 990 in the control groups (CCRT-alone). The basic characteristics of the included literature and the treatment regimens used are described in **Table 1**. Eligible studies were published in the past 7 years. All 11 trials were retrospective

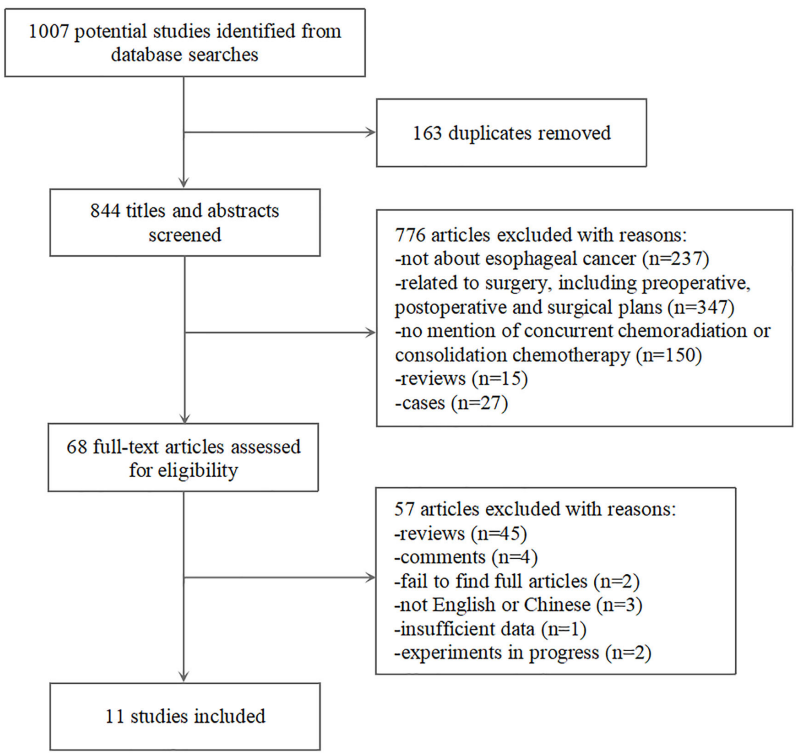

FIGURE 1 | Flow chart of the study selection process.

TABLE 1 | Characteristics of included studies.

Author	Year	Region	Sample Size	Number CCRT/ CCRT-CCT	Tumour type	Clinical stage	Staging standard	Treatment regimen			Median follow-up period (months)	Survival analysis	Outcome	Quality scores
								concurrent chemotherapy	radiotherapy	consolidation chemotherapy				
Chen, M (11).	2018	China	187	98/89	ESCC	II37/ III47/ IVA61/ IVB42	8th AJCC	PF/TP	40-50.4Gy (1.8-2.2Gy/ fractions)	NR 1-4 cycles	20	Univariate analysis	OS/LFFS/ DFFS	6
Koh, H. K (18).	2020	Korea	73	17/56	ESCC	NR	NR	PF	50-70Gy(1.8-2Gy/fractions)	PF	13.3	Multivariate analysis	OS/PFS/ LFFS	6
Chen, Y (19).	2018	China	524	262/262	ESCC	II218/ III306	7th AJCC/ UICC	PF: 5-FU (500 mg/ m2) d1-d5+ cisplatin(15 mg/m2) d1-d5 q4w	>50.4Gy(1.8-2Gy/fractions)	PF: 5-FU (750 mg/ m2) d1-d4+ cisplatin(75 mg/m2) d1 q4w 2cycles	42.5	Univariate analysis	OS/PFS	7
Luo, H (20).	2016	China	79	41/38	Mixed	II28/III51	6th AJCC/ UICC	TP: docetaxel (25 mg/m2) d1+cisplatin(25 mg/m2) d1-d3 qw	56-60Gy(1.8-2Gy/fractions)	TP: docetaxel (60 mg/m2) d1,d8+cisplatin(75 mg/m2) d1-d5 q3w 4 cycles	NR	Univariate analysis	OS/PFS	6
Wu, S. X (21).	2017	China	209	142/67	ESCC	I41/II82/ III86	NR	PF: 5-FU (7500 mg/ m2) d1-d4+ cisplatin(20-25 mg/ m2) d1-d3 q3w	>50.4Gy (2Gy/ fractions)	(1) PF: 5-FU (7500 mg/m2) d1-d4+ cisplatin(20-25 mg/ m2) d1-d3 2cycles; (2) TP:docetaxel (60-70 mg/m2) d1+cisplatin(20-25 mg/m2) d1-d3/ nedaplatin (60-70 mg/m2) d1; 2cycles based on platinum 2-4 cycles	NR	Multivariate analysis/ Univariate analysis	OS/PFS	7
Chen, H (22).	2018	China	124	59/65	ESCC	NR	6th AJCC/ UICC	(1)PF: 5-FU (500 mg/m2) d1-d5+ cisplatin(75-80 mg/ m2) d1-d3 q3w; (2) TP:paclitaxel (135-175 mg/m2) d1+cisplatin(75-80 mg/m2) d1-d3 q3w	50-74Gy(1.8-2.2Gy/ fractions)		18.5	Univariate analysis	OS/PFS	6
Zhang, A. D (8).	2020	China	222	109/113	ESCC	NR	7th AJCC/ UICC	(1)LPF: 5-FU (450-500 mg/m2) d1-d5 + cisplatin(25 mg/ m2) d1-d3 + calcium folinate(200 mg/m2) d1-d5 1-2 cycles; (2)PF: 5-FU (450-500 mg/m2) d1-d5+ cisplatin(25 mg/m2) d1-d3 1-2 cycles; (3) TP: paclitaxel (135-175	50.4-66Gy (1.8-2Gy/ fractions)	(1)LPF: 5-FU (450-500 mg/m2) d1-d5 + cisplatin(25 mg/ m2) d1-d3 + calcium folinate(200 mg/m2) d1-d5 1-4 cycles; (2)PF: 5-FU (450-500 mg/m2) d1-d5+ cisplatin(25 mg/m2) d1-d3 1-4 cycles; (3) TP: paclitaxel (135-175	93	Univariate analysis	OS	7

(Continued)

TABLE 1 | Continued

Author	Year	Region	Sample Size	Number CCRT/ CCRT-CCT	Tumour type	Clinical stage	Staging standard	Treatment regimen			Median follow-up period (months)	Survival analysis	Outcome	Quality scores
								concurrent chemotherapy	radiotherapy	consolidation chemotherapy				
								mg/m2) d1+cisplatin(25 mg/m2) d1-d3 1-2 cycles		mg/m2) d1+cisplatin(25 mg/m2) d1-d3 1-4 cycles				
Kim, D. E (9).	2013	Korea	59	16/43	ESCC	III/IVA	6th AJCC/ UICC	(1)PF: 5-FU (1000 mg/m2) d1-d4+ cisplatin(75 mg/m2) d1 2 cycles; (2) TP: docetaxel (20 mg/m2) +cisplatin(25 mg/m2) d1,d15,d18 2 cycles	50.4-64.8Gy (1.8Gy/ fractions)	based on platinum 2-6 cycles	18.4	Univariate analysis	OS	6
Li, Y. M (10).	2017	China	102	53/49	ESCC	II41/III61	Analysis on the applicability of the nonsurgical clinical staging for esophageal carcinoma	(1)PF: 5-FU (500 mg/m2) d1-d5+ cisplatin(80 mg/m2) d1-d3 q4w; (2) TP:paclitaxel (135 mg/m2) +cisplatin(75 mg/m2) d1-d3 q3w	50.4-57.6Gy (1.8Gy/ fractions)	(1)PF: 5-FU (500 mg/m2) d1-d5+ cisplatin(80 mg/m2) d1-d3 q4w; (2) TP:paclitaxel (175 mg/m2) +cisplatin(75 mg/m2) d1-d3 q3w 1-6 cycles	NR	Univariate analysis	OS/PFS	6
Tian, J (23).	2017	China	68	32/36	ESCC	II46/ III19/ IVA3	6th AJCC/ UICC	(1)S-1: TS-1(50 mg bid) d1-d14 q3w;(2) PF: 5-FU (750 mg/m2) d1-d5+ cisplatin(20 mg/m2) d1-d5 q3w; (3) TP:docetaxel (40 mg/m2)/paclitaxel (90 mg/m2) d1,d8,d15+ cisplatin(40 mg/m2) d1,d8,d15 q4w	60 Gy(2Gy/ fractions)	(1)S-1: TS-1(50 mg bid) d1-d14 q3w;(2) PF: 5-FU (750 mg/m2) d1-d5+ cisplatin(20 mg/m2) d1-d5 q3w; (3) TP:docetaxel (40 mg/m2)/paclitaxel (90 mg/m2) d1,d8,d15+ cisplatin(40 mg/m2) d1,d8,d15 q4w 1-4 cycles	20	Multivariate analysis/ Univariate analysis	OS/PFS	7
Chen, Y (24).	2016	China	361	161/200	ESCC	II119/ III242	7th AJCC/ UICC	based on platinum	>50.4Gy(1.8-2Gy/fractions)	based on platinum 2-4 cycles	NR	Univariate analysis	OS	5

CCRT, concurrent chemoradiotherapy; CCRT-CCT, consolidation chemotherapy following concurrent chemoradiotherapy; ESCC, esophageal squamous cell carcinoma; NR, not report. AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; PF, 5-FU + cisplatin; TP, docetaxel + cisplatin. LPF, 5-FU + cisplatin + calcium folinate; OS, overall survival; PFS, progression-free survival, DFFS, distant failure-free survival; LFFS, locoregional failure-free survival.

studies from a single center, and participants were from Korea and China. The clinical TNM stage of patients in most studies was diagnosed according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system. Most of the EC patients participating in the enrolled studies were at an advanced stage except for one study. The stage of patients published by Wu, S. X. et al. were from stage I to III (21). The total radiation dose in the enrolled studies ranged from 40 to 70 Gy in fractionated doses of 1.8 or 2 Gy per day. Synchronized chemotherapy regimens were based on platinum, including paclitaxel combined with platinum or 5-FU combined with platinum. The regimens for CCT were 1–6 cycles of paclitaxel or 5-FU combined with platinum. The estimated NOS scores of all included studies were higher than 5, and the median quality score of included studies was 6.

Survival Analysis

We included all 11 case-control studies in the overall survival (OS) analysis, giving 2008 EC patients in total. The forest plot for HR of OS is shown in **Figure 2A**. Patients treated with CCRT followed by CCT had a better survival rate than those treated with CCRT alone (HR 0.72; 95% CI 0.59–0.86, $p < 0.001$). Statistics suggest that EC patients who have not undergone surgery may benefit from CCT after CCRT. However, obvious

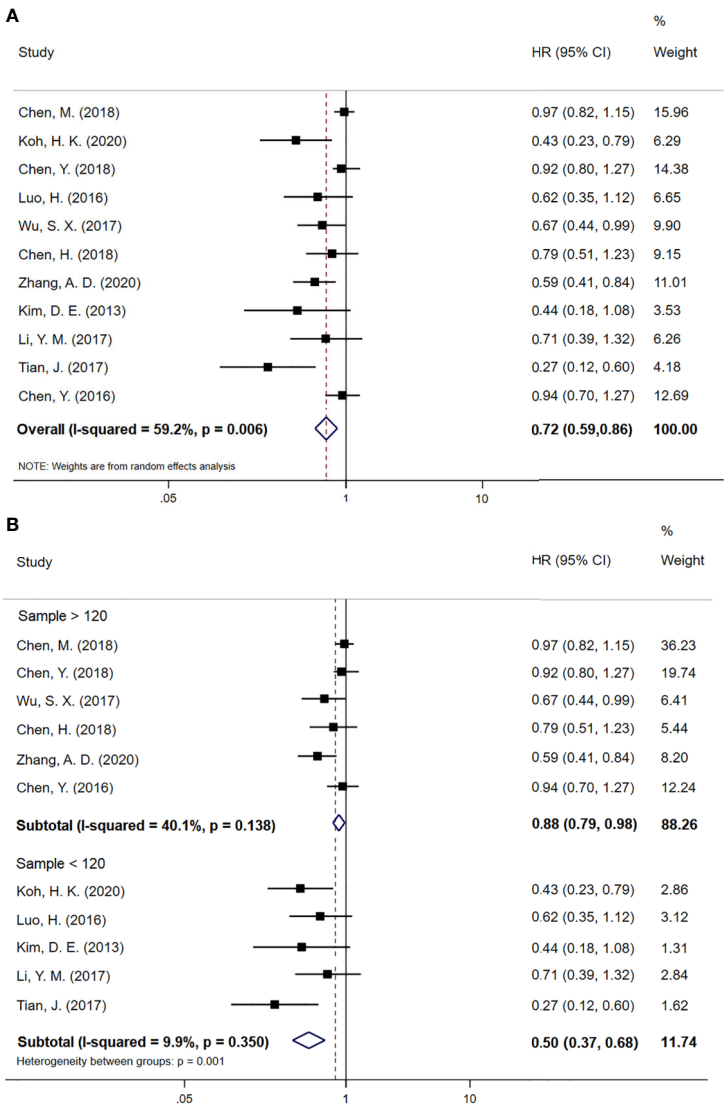

FIGURE 2 | **(A)** Meta-analysis of the associated HRs of OS for CCRT–CCT compared with CCRT alone. **(B)** Subgroup analysis of the associated HRs of OS for CCRT–CCT compared with CCRT alone. HR, hazard ratio; OS, overall survival; 95% CI, 95% confidence interval; CCRT–CCT, consolidation chemotherapy following concurrent chemoradiotherapy; CCRT alone, only concurrent chemoradiotherapy.

heterogeneities were found between studies (P=0.006, I^2=59.2%). Subsequently, we performed a subgroup analysis based on the sample size of patients with EC. The subgroup analysis results for OS are shown in **Figure 2B**. Nevertheless, six case-control studies with a sample size above 120 (HR 0.88; 95% CI 0.79–0.98, p=0.018) and five case-control studies with a sample size below 120 (HR 0.50; 95% CI 0.37–0.68, p < 0.001) revealed OS was improved with CCT following CCRT compared to CCRT alone. There was no evidence of significant heterogeneity between studies with high sample size (P=0.138, I^2=40.1%) or with low sample size (P=0.350, I^2=9.9%).

Progression-free survival (PFS) data was extracted from six studies, including 1111 EC patients, in which 537 patients received CCT after CCRT and 574 patients received CCRT alone. The meta-analysis result for PFS is shown in **Figure 3**. PFS in the CCT group was significantly better than that in the CCRT group (HR 0.61; 95% CI 0.44–0.84, p=0.003). There was obvious heterogeneity among these studies (P=0.006, I^2=69.1%).

In the included studies, only 2 articles reported the survival outcome of locoregional failure-free survival (LFFS). Koh, H. K (18). report that CCT prolonged LFFS, and Chen, M (11). thought there was no difference in LFFS between both groups. Considering the high degree of heterogeneity, no merger was carried out. Chen, M. likewise reports the insignificant result of distant failure-free survival (DFFS).

Tumor Response

Three studies involving 368 cases reported sufficient data on objective response rate (ORR) and disease control rate (DCR). As shown in **Figure 4**, the pooled ORs demonstrate that there was no statistical difference between the CCT followed by CCRT group and the CCRT-alone group (OR 1.66; 95% CI 0.53–3.15, p=0.384 and OR 1.44; 95% CI 0.62–3.35, p=0.393 for DCR and ORR, respectively). No obvious heterogeneity was found in the DCR and ORR analysis (P=0.329, I^2=10%). Although there were moderate differences in the ORR analysis (I^2=55.6%), there was no evidence of significant heterogeneity between groups (P=0.105).

Toxicity

Adverse events occurring during the treatment period were available in only three studies involving 708 patients. Gastrointestinal reactions included nausea, emesis, and anorexia. There were no significant differences between the CCRT–CCT group and the CCRT-alone group regarding hematological or nonhematological adverse events. The risk of adverse event grades of 1–2 and 3–4 were similar. There was no evidence of significant heterogeneity between the trials regarding treatment toxicity. The detailed merger results are shown in **Table 2**.

Sensitivity Analysis and Publication Bias

We used a sensitivity analysis to assess the stability of our overall results. The outcomes of the primary overall analysis were not converted although we removed each study in turn (**Figure 5**). In a pooled analysis of all 11 trials, the funnel plot for OS indicates the existence of publication bias. Two trials were outside the precision line, and one trial was on the line as shown in **Figure 6**. The p values of Begg's and Egger's tests (both Ps < 0.05) also indicate the evidence of publication bias. However, further analysis through the trim-and-fill test shows that publication bias did not significantly affect the estimated results (HR 0.72; 95% CI 0.59–0.86, p < 0.001).

DISCUSSION

Due to the lack of specificity of early symptoms, EC patients are frequently diagnosed at an advanced stage and are mainly elderly patients (25). CRT followed by surgery is considered the optional treatment for resectable EC (26). Patients with late stage or weak constitution generally lose the opportunity to undergo radical surgery. CCRT is the standard therapy for unresectable EC and RTOG 85-01 determines the position of CCRT (27). The 5-year survival rate of EC patients receiving CCRT is still below 30% at present. Clinicians are keen to find optional methods in combination with CCRT to improve survival of EC patients.

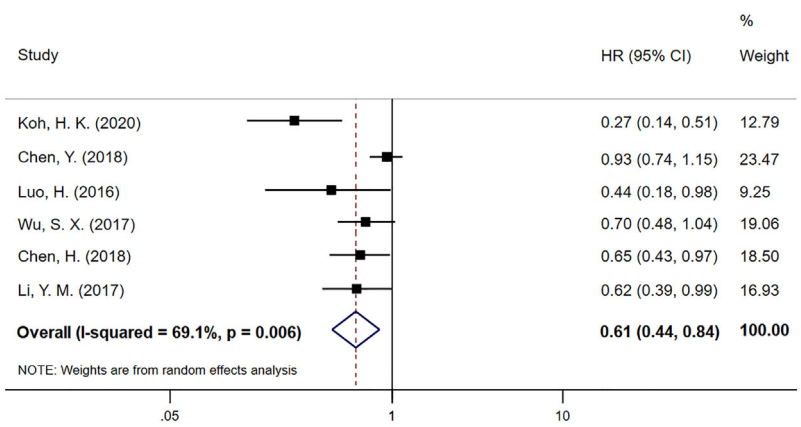

FIGURE 3 | Meta-analysis of the associated HRs of PFS for CCRT–CCT compared with CCRT alone. HR, hazard ratio; PFS, progression-free survival; CCRT–CCT, consolidation chemotherapy following concurrent chemoradiotherapy; CCRT alone only concurrent chemoradiotherapy.

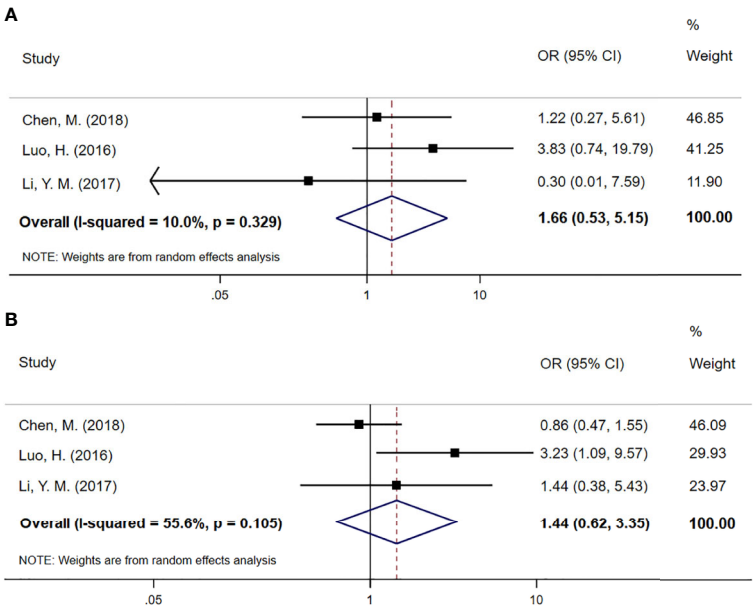

FIGURE 4 | **(A)** Meta-analysis of the associated ORs of DCR for CCRT–CCT compared with CCRT alone. **(B)** Meta-analysis of the associated ORs of ORR for CCRT–CCT compared with CCRT alone. OR, odds ratio; DCR, disease control rate; ORR, objective response rate; 95% CI, 95% confidence interval; CCRT–CCT, consolidation chemotherapy following concurrent chemoradiotherapy; CCRT alone, only concurrent chemoradiotherapy.

TABLE 2 | Adverse events during the CCRT-CCT or CCRT-alone period.

Adverse events	Grade	No. of studies	No. of patients	Pooled OR and its 95% CI	Meta-regression (*P* value)	Heterogeneity	
						I^2(%)	*P* value
Leukopenia	0-2	2	178	0.62 (0.26-1.47)	0.28	0	0.80
	3-4	2	178	1.62 (0.68-3.89)	0.28	0	0.80
Thrombocytopenia	0-2	2	178	0.93 (0.18-4.76)	0.93	0	0.42
	3-4	2	178	1.07 (0.21-5.45)	0.93	0	0.42
Neutropenia	0-2	3	702	0.86 (0.59-1.25)	0.42	0	0.89
	3-4	3	702	1.16 (0.80-1.68)	0.42	0	0.89
Anemia	0-2	2	178	0.93 (0.26-3.33)	0.91	0	0.50
	3-4	2	178	1.08 (0.30-3.87)	0.91	0	0.50
Gastrointestinal tract	0-2	3	702	1.35 (0.61-2.98)	0.46	0	0.95
	3-4	3	702	0.74 (0.34-1.64)	0.46	0	0.95
Radiation esophagitis	0-2	3	702	0.94 (0.67-1.31)	0.72	0	0.70
	3-4	2	178	1.84 (0.42-8.01)	0.42	0	0.67
Radiation pneumonia	0-2	3	702	1.05 (0.73-1.50)	0.81	17	0.30
	3-4	3	178	0.71 (0.12-4.31)	0.71	32	0.23

CCRT-CCT, consolidation chemotherapy following concurrent chemoradiotherapy; CCRT-alone, only concurrent chemoradiotherapy. OR, odds ratio; 95% CI, 95% confidence interval.

Because induction chemotherapy before CCRT has been shown to increase the risk of radiation-induced lung tissue damage in EC patients (28), CCT after CCRT has been assumed to improve the therapeutic effect. However, there is still no unanimous conclusion on whether CCT increases the efficacy of nonsurgical EC. In this context, we were the first to conduct this research to estimate the effect of CCT followed by CCRT.

The results of our meta-analysis show that the addition of CCT following CCRT increased OS in patients with nonsurgical EC (HR 0.72; 95% CI 0.59–0.86; p < 0.001). However, the overall result for OS indicates evident heterogeneity (P=0.006, I^2 = 59.2%). Subgroup analysis based on sample size eliminated significant heterogeneity, and the results of subgroup analysis further confirm this finding. Our sample size is quite large with 2008 patients, and the median NOS score of the 11 case-control studies included is 6, indicating the reliability of our OS results. We further analyzed the data eligible in our articles and found that the clinical features of 7 of those articles are similar in the CCT and the CCRT-alone groups. The clinical features in 4 articles were not detailed (9, 18, 23, 24). The numbers of patients

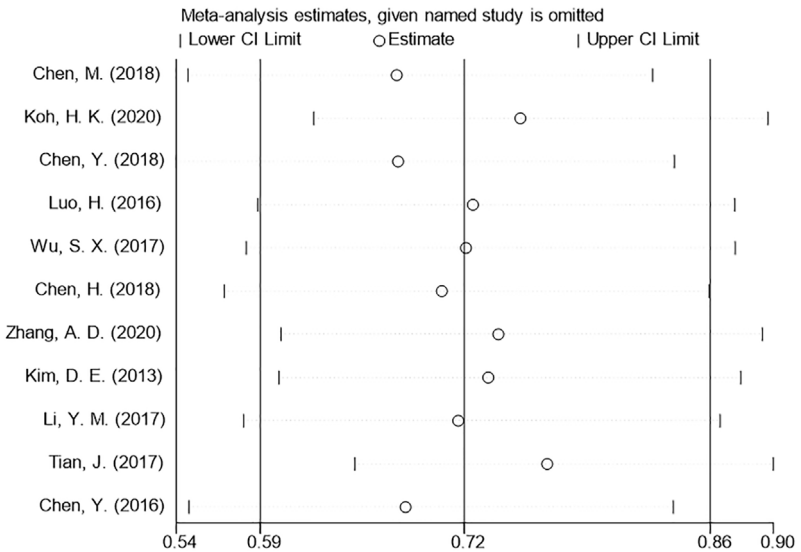

FIGURE 5 | Sensitivity analysis of HRs of OS. HR, hazard ratio.

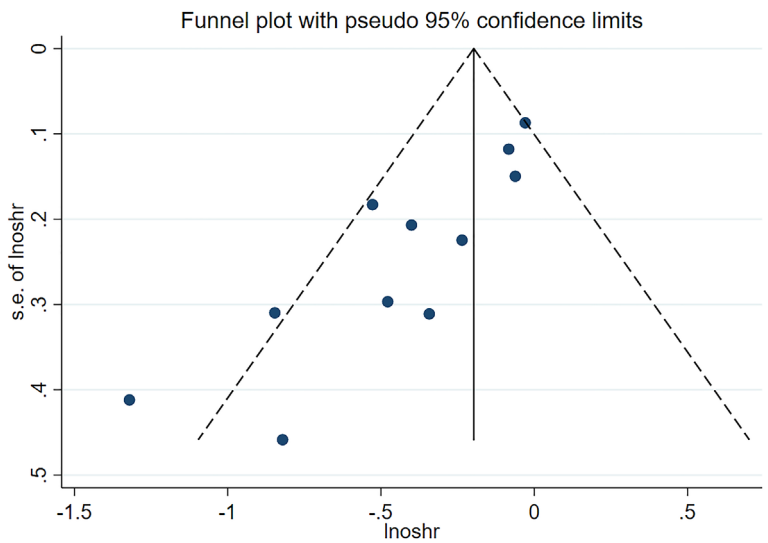

FIGURE 6 | Funnel plot of publication bias for OS.

who did not accept CCT after CCRT reported by Koh, H. K. et al (18). and Dae-Eun Kim, et al. (9) are 17 and 16, respectively. Those two articles contained 136 people in total, 103 of whom received CCT. Given that the patients in both articles are late stage and mostly have lymph node metastasis, we found that the number of EC patients with positive lymph nodes receiving CCT is much larger, and this may be an important external factor affecting the results of our meta-analysis. Research has found that EC patients with a poor clinical response to CCRT could benefit from CCT with improved 3-year OS rates in the consolidation group (29). It is known that the clinical response of tumor patients depends largely on the initial stage of cancer. Patients with higher clinical T and N stages generally have a poor response. Those with higher clinical T and N stages have consistently lower pathological CR and OS rates after neoadjuvant CRT (30, 31). Chen Y et al. reveal that the lower esophageal tumor location may have a worse clinical response to CCRT (32). Therefore, we hypothesize that EC patients with high T stage, N stage, and lower tumor location have a poor response to CCRT and may be prone to benefit from CCT. Consistent with

our hypothesis, stage III non-small cell lung cancer patients with a good response to CCRT did not benefit from CCT after CCRT (33).

CCT is complementary to synchronous chemoradiation and has a continuous cytotoxic effect on subclinical lesions that cannot be eliminated by CCRT to inhibit tumor cell proliferation (20). It primarily removes cancer cells remaining in the blood to prevent distant tumor metastasis. We hypothesize that this is an intrinsic factor that enables CCT after CCRT to improve patient survival. Because 10 of the 11 articles were limited to squamous cell carcinoma, we did not perform a subgroup analysis based on pathological types of EC. In our meta-analysis, 1111 patients in 6 included articles demonstrated that CCT followed by CCRT can prolong PFS of EC patients (HR 0.61; 95% CI 0.44–0.84; p=0.003). Except for trials conducted by Chen, Y. et al (24). and Wu, S. X. et al. (21), the other 4 trials reported positive PFS results. The results reveal that there was no significant difference in DCR (OR 1.66; 95% CI 0.53–5.15) and ORR (OR 1.44; 95% CI 0.62–3.35) between the CCRT–CCT and CRT-alone groups. Because both results only include 3 experimental results, so the sample size is small and has some degree of heterogeneity, we consider the reliability of these results to be low, and additional research should be required for further analysis. Fortunately, a prospective, open-label, multicenter, randomized, and controlled Phase III trial comparing CCRT plus CCT to CCRT alone for locally advanced ESCC is ongoing in China (34).

The main chemotherapy regimens used in the included studies were docetaxel plus cisplatin (TP) and 5-FU plus cisplatin (PF), and there was a trend in favor of cisplatin-based therapy. However, we were unable to reach a consensus to recommend any chemotherapy regimen due to the limited number of articles exploring a specific chemotherapy regimen, and the patients involved in these studies showed considerable heterogeneity. The chemotherapy regimen in CCT is generally consistent with CCRT in our included research. A published phase III clinical trial shows the 3-year OS of the cisplatin plus fluorouracil regimen was essentially higher than that in the RTOG 8501 trial (51% vs. 30%), and the paclitaxel plus fluorouracil regimen was not superior in terms of OS compared to the standard cisplatin plus fluorouracil regimen in CCRT for patients with locally advanced EC (35). The prevalence of the use of paclitaxel-based regimens for CCRT in EC patients was due to the higher rates of pathologic CR compared to the use of the cisplatin plus fluorouracil regimen (35–37). However, paclitaxel-based regimens in retrospective studies showed an increased risk of radiation pneumonitis in CCRT (38, 39). To date, the cisplatin plus fluorouracil regimen has remained the standard regimen in EC patients, and future clinical trials should focus on finding the optimal chemotherapy regimen.

The pooled ORs of adverse events involving 708 patients in three trials reveal that CCT did not increase treatment toxicity. The main chemotherapy regimen used in the research was paclitaxel combined with platinum or 5-FU combined with platinum. Fluoropyrimidine plus platinum is the standard chemotherapy regimen in East Asia, and 5-fluorouracil, cisplatin, S-1, and docetaxel are chemotherapy drugs commonly used to treat esophagogastric cancer (40). The study of Zhu, Y. et al (41). shows that CCRT with docetaxel plus cisplatin had comparable OS and PFS to CCRT with the 5-Fluorouracil plus cisplatin regimen. Each of these 3 studies (10, 18, 20) shows that CCT can prolong patient survival time without increasing treatment-related toxicity, and the results of the data aggregation in our meta-analysis are consistent with their results.

Our meta-analysis provides favorable evidence on the benefits of CCT followed by CCRT, but our study has several limitations. First, because the articles included are retrospective studies, some biases inevitably generate steps in data integration. Second, some literature does not directly provide HR, and we obtained related data using the method suggested by Tierney (15). These values may differ slightly from the actual values. Third, there is obvious heterogeneity among some results, but this cannot be eliminated by certain methods, such as subgroup analysis, etc. Finally, our meta-analysis shows some publication bias because articles with positive results are easily accepted. Fortunately, publication bias was not significantly affected by the trim-and-fill test, and the sensitivity analysis demonstrates the stability of our results.

CONCLUSIONS

In conclusion, the limited published data demonstrate that the addition of CCT could be of significant benefit in terms of survival in nonsurgical EC cases receiving definitive CCRT. At the same time, the toxicities of therapy are similar between the CCRT–CCT and the CCRT-alone groups. More clinical studies, especially large, randomized, controlled trials are warranted to assess its effectiveness and identify patients who could benefit from CCT. We are looking forward to finding more effective methods to prolong the survival rate of nonsurgical EC patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XX: Roles/writing—original draft, data curation, investigation, methodology. ZL: Roles/writing—original draft, resources, formal analysis, methodology. QQ: Roles/writing—original draft, software, investigation, methodology. XD: Roles/writing—original draft, validation. ZZ: Roles/writing—original draft, visualization. XS: Writing—review and editing, conceptualization, project administration, funding acquisition. XG: Writing—review and editing, conceptualization, supervision, funding acquisition.

All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2018) 68(6):394–424. doi: 10.3322/caac.21492
2. Short MW, Burgers KG, Fry VT. Esophageal Cancer. *Am Fam Physician* (2017) 95(1):22–8.
3. Sasaki Y, Kato K. Chemoradiotherapy for esophageal squamous cell cancer. *Jpn J Clin Oncol* (2016) 46(9):805–10. doi: 10.1093/jjco/hyw082
4. Davies L, Lewis WG, Arnold DT, Escofet X, Blackshaw G, Gwynne S, et al. Prognostic significance of age in the radical treatment of oesophageal cancer with surgery or chemoradiotherapy: a prospective observational cohort study. *Clin Oncol (R Coll Radiol)* (2010) 22(7):578–85. doi: 10.1016/j.clon.2010.05.023
5. Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer–a standard of care in patients with non-metastatic oesophageal cancer. *Clin Oncol (R Coll Radiol)* (2011) 23 (3):182–8. doi: 10.1016/j.clon.2010.12.001
6. Liu YC, Wang WY, Twu CW, Jiang RS, Liang KL, Wu CT, et al. Prognostic impact of adjuvant chemotherapy in high-risk nasopharyngeal carcinoma patients. *Oral Oncol* (2017) 64:15–21. doi: 10.1016/j.oraloncology.2016.11.008
7. Wang X, Ding X, Kong D, Zhang L, Guo Y, Ren J, et al. The effect of consolidation chemotherapy after concurrent chemoradiotherapy on the survival of patients with locally advanced non-small cell lung cancer: a meta-analysis. *Int J Clin Oncol* (2017) 22(2):229–36. doi: 10.1007/s10147-016-1074-x
8. Zhang AD, Su XH, Shi GF, Han C, Wang L, Liu H, et al. Survival Comparision of Three-dimensional Radiotherapy Alone with Chemoradiotherapy for Esophageal Squamous Cell Carcinoma. *Arch Med Res* (2020) 51(5):419–28. doi: 10.1016/j.arcmed.2020.04.013
9. Kim DE, Kim UJ, Choi WY, Kim MY, Kim SH, Kim MJ, et al. Clinical prognostic factors for locally advanced esophageal squamous carcinoma treated after definitive chemoradiotherapy. *Cancer Res Treat* (2013) 45 (4):276–84. doi: 10.4143/crt.2013.45.4.276
10. Li Y, Huang J, Chen L, Yang Y, Ying X. Comparison of efficacy and safety between concurrent chemoradiotherapy combined with adjuvant chemotherapy and concurrent chemoradiotherapy alone for treatment of unresectable locally advanced esophageal squamous cell carcinoma. *Guangxi Med J* (2017) 39(09):1341–5. doi: 10.11675/j.issn.0253-4304.2017.9.15
11. Chen M, Shen M, Lin Y, Liu P, Liu X, Li X, et al. Adjuvant chemotherapy does not benefit patients with esophageal squamous cell carcinoma treated with definitive chemoradiotherapy. *Radiat Oncol* (2018) 13(1):150. doi: 10.1186/s13014-018-1086-y
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* (2009) 339:b2700. doi: 10.1136/bmj.b2700
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* (2000) 283(15):2008–12. doi: 10.1001/jama.283.15.2008
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* (2010) 25(9):603–5. doi: 10.1007/s10654-010-9491-z
15. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* (2007) 8:16. doi: 10.1186/1745-6215-8-16
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557
17. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* (1997) 315(7109):629–34. doi: 10.1136/bmj.315.7109.629
18. Koh HK, Park Y, Koo T, Park HJ, Lee MY, Chang AR, et al. Adjuvant Chemotherapy and Dose Escalation in Definitive Concurrent Chemoradiotherapy for Esophageal Squamous Cell Carcinoma. *Anticancer Res* (2020) 40(3):1771–8. doi: 10.21873/anticanres.14131
19. Chen Y, Guo L, Cheng X, Wang J, Zhang Y, Wang Y, et al. With or without consolidation chemotherapy using cisplatin/5-FU after concurrent chemoradiotherapy in stage II-III squamous cell carcinoma of the esophagus: A propensity score-matched analysis. *Radiother Oncol* (2018) 129(1):154–60. doi: 10.1016/j.radonc.2017.10.031
20. Luo H, Qiao L, Liang N, Xie J, Yu X, Zhang J. Concurrent chemoradiotherapy followed by docetaxel and cisplatin consolidation chemotherapy in elderly patients with esophageal carcinoma. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* (2016) 41(10):1024–30. doi: 10.11817/j.issn.1672-7347.2016.10.003
21. Wu SX, Li XY, Xu HY, Xu QN, Luo HS, Du ZS, et al. Effect of consolidation chemotherapy following definitive chemoradiotherapy in patients with esophageal squamous cell cancer. *Sci Rep* (2017) 7(1):16870. doi: 10.1038/s41598-017-17254-9
22. Chen H, Zhou L, Yang Y, Yang L, Chen L. Clinical Effect of Radiotherapy Combined with Chemotherapy for Non-Surgical Treatment of the Esophageal Squamous Cell Carcinoma. *Med Sci Monit* (2018) 24:4183–91. doi: 10.12659/MSM.910326
23. Tian J, Zhang J, Wang X, Cui B, Wang N, Deng W, et al. Analysis of prognostic factors in patients with locally advanced esophageal squamous cell carcinoma treated with concurrent chemoradiotherapy. *Chin J Cancer Prev Treat* (2017) 24(22):1573–7. doi: 10.16073/j.cnki.cjcpt.2017.22.006
24. Chen Y, Cheng X, Liu Y, Zhang Y, Wu X, Hao D, et al. With or without consolidation chemotherapy for clinical responder to definitive concurrent chemoradiation in stage II-III esophageal squamous cell carcinoma. *Radiother Oncol* (2016) 96(2):E160–1. doi: 10.1016/j.ijrobp.2016.06.995
25. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* (2016) 66(2):115–32. doi: 10.3322/caac.21338
26. Mayanagi S, Irino T, Kawakubo H, Kitagawa Y. Neoadjuvant treatment strategy for locally advanced thoracic esophageal cancer. *Ann Gastroenterol Surg* (2019) 3(3):269–75. doi: 10.1002/ags3.12243
27. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JJ, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* (1999) 281(17):1623–7. doi: 10.1001/jama.281.17.1623
28. Wang S, Liao Z, Wei X, Liu HH, Tucker SL, Hu C, et al. Association between systemic chemotherapy before chemoradiation and increased risk of

treatment-related pneumonitis in esophageal cancer patients treated with definitive chemoradiotherapy. *J Thorac Oncol* (2008) 3(3):277–82. doi: 10.1097/JTO.0b013e3181653ca6
29. Zhao Z, Zhang Y, Wang X, Geng X, Zhu L, Li M. Clinical response to chemoradiotherapy in esophageal carcinoma is associated with survival and benefit of consolidation chemotherapy. *Cancer Med* (2020) 9(16):5881–8. doi: 10.1002/cam4.3273
30. Blum MM, Xiao L, Patel VR, Maru DM, Correa AM, AF G, et al. Pathological complete response in patients with esophageal cancer after the trimodality approach: The association with baseline variables and survival-The University of Texas MD Anderson Cancer Center experience. *Cancer* (2017) 123 (21):4106–13. doi: 10.1002/cncr.30953
31. Vallböhmer D, Hölscher AH, DeMeester S, DeMeester T, Salo J, Peters J, et al. A multicenter study of survival after neoadjuvant radiotherapy/chemotherapy and esophagectomy for ypT0N0M0R0 esophageal cancer. *Ann Surg* (2010) 252(5):744–9. doi: 10.1097/SLA.0b013e3181fb8dde
32. Chen Y, Guo L, Cheng X, Wang J, Zhang Y, Wang Y, et al. With or without consolidation chemotherapy using cisplatin/5-FU after concurrent chemoradiotherapy in stage II-III squamous cell carcinoma of the esophagus: A propensity score-matched analysis. *Radiother Oncol* (2018) 129(1):154–60. doi: 10.1016/j.radonc.2017.10.031
33. Ahn JS, Ahn YC, Kim JH, Lee CG, Cho EK, Lee KC, et al. Multinational Randomized Phase III Trial With or Without Consolidation Chemotherapy Using Docetaxel and Cisplatin After Concurrent Chemoradiation in Inoperable Stage III Non-Small-Cell Lung Cancer: KCSG-LU05-04. *J Clin Oncol* (2015) 33(24):2660–6. doi: 10.1200/JCO.2014.60.0130
34. ChiCTR. *A prospective, open-label, multicenter, randomized and controlled Phase III trial to compare radical concurrent chemoradiotherapy alone with radical concurrent chemoradiotherapy followed by consolidation chemotherapy for the locally advanced esophageal squamous cell carcinoma [EB].* Cochrane library (2019). Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01908111/ (Accessed March 31, 2019).
35. Urba SG, Orringer MB, Ianettonni M, Hayman JA, Satoru H. Concurrent cisplatin, paclitaxel, and radiotherapy as preoperative treatment for patients with locoregional esophageal carcinoma. *Cancer* (2003) 98(10):2177–83. doi: 10.1002/cncr.11759
36. Meluch AA, Greco FA, Gray JR, Thomas M, Sutton VM, Davis JL, et al. Preoperative therapy with concurrent paclitaxel/carboplatin/infusional 5-FU and radiation therapy in locoregional esophageal cancer: Final results of a minnie pearl cancer research network phase II trial. *Cancer J* (2003) 9(4):251–60. doi: 10.1097/00130404-200307000-00007
37. Lin CC, Hsu CH, Cheng JC, Wang HP, Lee JM, Yeh KH, et al. Concurrent chemoradiotherapy with twice weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal cancer. *Ann Oncol* (2007) 18 (1):93–8. doi: 10.1093/annonc/mdl339
38. McCurdy M, McAleer MF, Wei W, Ezhil M, Johnson V, Khan M, et al. Induction and concurrent taxanes enhance both the pulmonary metabolic radiation response and the radiation pneumonitis response in patients with esophagus cancer. *Int J Radiat Oncol Biol Phys* (2010) 76(3):816–23. doi: 10.1016/j.ijrobp.2009.02.059
39. Palma DA, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* (2013) 85(2):444–50. doi: 10.1016/j.ijrobp.2012.04.043
40. Ku GY. Systemic therapy for esophageal cancer: chemotherapy. *Chin Clin Oncol* (2017) 6(5):49. doi: 10.21037/cco.2017.07.06
41. Zhu Y, Zhang W, Li Q, Li Q, Qiu B, Liu H, et al. A Phase II Randomized Controlled Trial: Definitive Concurrent Chemoradiotherapy with Docetaxel Plus Cisplatin versus 5-Fluorouracil plus Cisplatin in Patients with Oesophageal Squamous Cell Carcinoma. *J Cancer* (2017) 8(18):3657–66. doi: 10.7150/jca.20053

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Multicentre Comparison of the Toxicity and Effectiveness of Lobaplatin-Based *Versus* Cisplatin-Based Adjuvant Chemotherapy in Oesophageal Carcinoma

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Objectives: Lobaplatin (LBP), a third-generation cisplatin derivative has shown promising activity and few side effects in oesophageal squamous cell carcinoma (ESCC) in previous reports. We compared LBP plus docetaxel with cisplatin plus docetaxel as adjuvant chemotherapy in ESCC patients to determine the effects on overall survival (OS) and toxicity.

Methods: A multicentre retrospective study was performed using propensity score matching (PSM) with the Medicine-LinkDoc database. Patients diagnosed with stage II-III ESCC treated with adjuvant chemotherapy (cisplatin plus docetaxel or LBP plus docetaxel) between January 2013 and December 2016 were selected from 6 centres in China.

Results: There were 733 eligible ESCC patients. After PSM (1:1 ratio), 458 patients remained. The 5-year OS rates of the cisplatin and LBP groups were 25.9% and 23.6%, respectively (P=0.457). Leukopenia (grade III-IV/I-II/0: 2.62%/34.5%/59.39% *versus* 5.24%/43.23%/45.85%; P=0.0176), neutropenia (grade III-IV/I-II/0: 6.55%/37.56%/51.09% *versus* 4.37%/53.28%/36.34%; P=0.0015), nephrotoxicity (grade I-II/0: 13.97%/76.86% *versus* 26.64%/65.94%; P<0.001) and gastrointestinal symptoms (grade III-IV/I-II/0: 2.18%/54.59%/32.31% *versus* 6.55%/65.07%/20.88%; P=0.0011) were more frequent in the cisplatin group.

Conclusions: Compared with cisplatin plus docetaxel, LBP plus docetaxel provided the same survival benefits but lower side effects of myelosuppression and gastrointestinal symptoms. LBP plus docetaxel might be a choice for adjuvant chemotherapy in ESCC.

Clinical Trial Registration: Lobaplatin or Cisplatin in Adjuvant Chemotherapy for Oesophageal Carcinoma, identifier NCT03413436.

Keywords: ESCC, adjuvant chemotherapy, lobaplatin, adverse reactions, cisplatin

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INTRODUCTION

Over the past two decades, the combination of preoperative chemotherapy and chemoradiotherapy has become the standard of care for the systemic therapy of oesophageal squamous cell carcinoma (ESCC) in Western countries and Japan. In China, where more than half of the ESCC cases in the world occur, adjuvant chemotherapy (AC) or chemoradiotherapy has mainly been adopted (1). Because of postoperative complications and nutrition problems, AC in Western countries has rarely been administered. Lobaplatin (LBP), which has few side effects, has been adopted in AC to reduce side effects and increase the complete rate. Cisplatin-based regimens have been widely accepted as standard chemotherapy regimens worldwide and remain the standard of care for ESCC in China. However, the LBP regimen with less toxicity has subsequently emerged for older patients and is being evaluated for patients with low performance scores (PSs) (2).

The use of first- and second-generation platinum drugs such as cisplatin, carboplatin, and nedaplatin is often associated with drug resistance, nephrotoxicity, and bone marrow suppression. How to reduce chemotherapy-related toxicity without reducing the antitumour effect is an urgent problem to be solved. LBP, as a third-generation platinum compound, is basically similar to cisplatin in terms of DNA damage and cell apoptosis and does not need to be hydrated (3). LBP has played a reliable antitumour role in solid tumours such as lung cancer, nasopharyngeal cancer, breast cancer and gastric cancer (4–7). In *in vivo* animal experiments of ESCC, LBP has been shown to induce apoptosis and significantly inhibit the growth of ESCC. In the first-line treatment of patients with advanced ESCC, LBP has been shown to have certain efficacy and safety (8). However, due to the small sample sizes and lack of controlled trials, the existing studies cannot reflect the efficacy and safety advantages of LBP compared with chemotherapy regimens containing cisplatin. Therefore, our team conducted a retrospective study to understand AC combined with LBP after radical resection for ESCC in China and the difference in efficacy and safety between LBP and cisplatin. In addition, we aimed to understand the distribution characteristics of chemotherapy regimens and the characteristics of ESCC patients after treatment with radical resection combined with LBP AC.

The Medicine-LinkDoc database network provides a multicentre database of this topic for observational comparative-effectiveness studies of ESCC. We sought to compare the completion rates, toxicities and survival outcomes of ESCC patients receiving cisplatin- and LBP-based regimens as AC in real-world settings, employing propensity-matching methods to mitigate selection bias.

Abbreviations and Acronyms: LBP, lobaplatin; ESCC, oesophageal squamous cell carcinoma; OS, overall survival; PSM, propensity score matching; AC, adjuvant chemotherapy; PSs, performance scores; BMI, body mass index; DL, docetaxel +LBP; DC, docetaxel+ cisplatin; WHO, World Health Organization; ECG, electrocardiogram.

MATERIALS AND METHODS

This study was approved by the ethics review committee of the Affiliated Cancer Hospital of ZhengZhou University/Henan Cancer Hospital and approved officially with approval number 2017405. Data from The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Anyang Cancer Hospital, Anhui Provincial Hospital, The First Affiliated Hospital of Anhui Medical University, Tangdu Hospital of the Fourth Military Medical University, and The First Affiliated Hospital of Xi'an Jiaotong University were combined to perform this retrospective study by using the Medicine-LinkDoc database network. A retrospective analysis was performed on patients with ESCC from the 6 centres who underwent radical resection from January 2013 to December 2016 (**Figure 1**). The inclusion criteria were as follows: pathological diagnosis of ESCC stage II/III, no surgical contraindications found, radical resection of ESCC performed as the primary treatment, at least 1 cycle of postoperative AC, and no radiotherapy performed in the same period. The exclusion criteria were as follows: history of other malignancies, preoperative treatment, and history of chemotherapy. The clinical data of the patients included the following: date of admission, sex, age, body mass index (BMI), past history, laboratory examination, clinical stage, tumour site, tumour size, degree of differentiation, lymph node metastasis, surgical history, number of chemotherapy cycles, etc.

In the full cohort, the frequency distribution of chemotherapy regimens containing LBP was calculated (**Figures 2A, B**), in which the docetaxel combined with cisplatin regimen (docetaxel+ cisplatin, DC) had the highest frequency (276 cases, 37.76%), followed by paclitaxel combined with LBP (237 cases, 32.42%). Therefore, the docetaxel+LBP (DL) regimen was selected as the test group, and the DC regimen was selected as the control group (**Figure 1**). The dosages were usually docetaxel, 75–80 mg/m^2 and cisplatin, 75 mg/m^2; in the DL regimen, the dosages were docetaxel, 75–80 mg/m^2 and lobaplatin, 50 mg/m^2. Usually, 4 rounds of postoperative adjuvant chemotherapy are recommended. Total and subtotal thoracic oesophagectomies were performed. Right, left thoracotomy and thoracoscopic oesophagectomy were included. The transhiatal oesophagectomy was not used. Regional lymph nodes included mediastinal lymph nodes (paraesophageal, paratracheal, subcarinal, supradiaphragmatic and posterior mediastinal) and perigastric nodes. Bilateral recurrent laryngeal nerve lymph nodes were dissected if the right-side approach was adopted. Dissection of distant lymph nodes such as cervical nodes was reported in the cervical ultrasound test.

Chemotherapy-Related Toxicities

The inpatient claims were all evaluated during the AC period. Chemotherapy-related toxicities were based on the World Health Organization (WHO) grading; bone marrow suppression, gastrointestinal side effects, liver and kidney function disorders, and electrocardiogram (ECG) changes were mainly evaluated during chemotherapy. Routine blood test results (white blood cells, platelets, lymphocytes and neutrophils), liver and kidney function test results (alanine

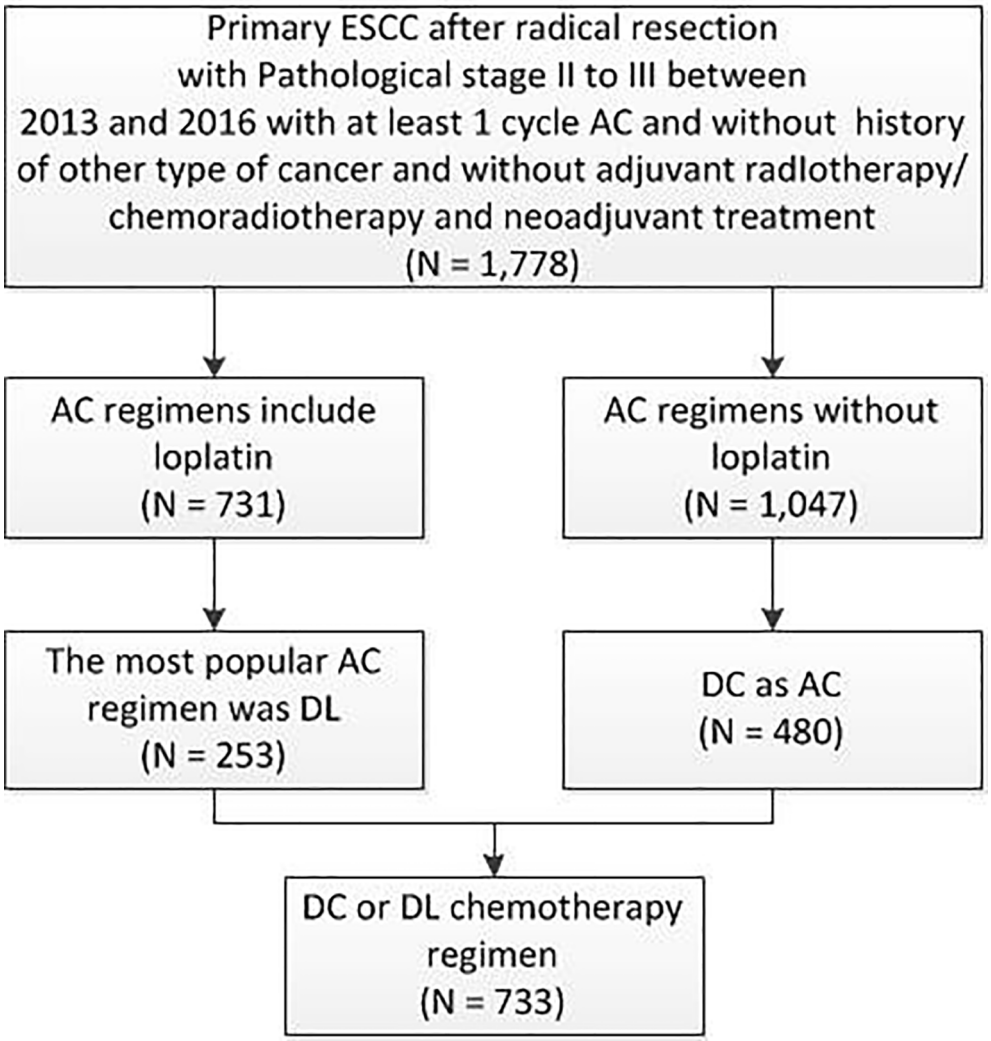

FIGURE 1 | Patient distribution diagram. ESCC, oesophageal squamous cell carcinoma; AC, adjuvant chemotherapy; DL, docetaxel+ lobaplatin; DC, docetaxel+ cisplatin; N, number.

aminotransferase, aspartate aminotransferase, creatinine, etc.) and ECG results were based on the WHO standards for severity classification of the outcome measure.

Any conditions before AC (heart failure, cerebrovascular accident, liver or kidney failure) were not included in the toxicity evaluation. The toxicity records were collected in the hospital. The model was performed with propensity matching and was adjusted for sex, tumour differentiation, pathological lymph node metastases, number of cycles of AC, and age.

Survival

We measured overall survival (OS) as the days from the date of the operation to the date of death from any cause.

Propensity Score Matching

Propensity score matching (PSM) is widely used to reduce selection bias in observational studies (9). The PSM method was used to match the two groups with a ratio of the test group to the control group of 1:1, considering the bias caused by confounding factors. The matching variables were based on clinical and methodological considerations, including sex, degree of differentiation, lymph node metastasis and the cycles of AC. We used PSM to create comparable cohorts of resected ESCC patients receiving DL and DC regimens on the basis of clinical and pathological characteristics.

Analysis

Descriptive statistical methods were used to assess the baseline characteristics of the patients, and SAS 9.4 software was used for statistical analysis of the data. For continuous indicators, t-test or the Wilcoxon rank sum test was used for comparisons between two groups, and the chi-square test was used for classification data comparisons. For adverse events, the severity was graded, and the number and percentage of adverse events with different

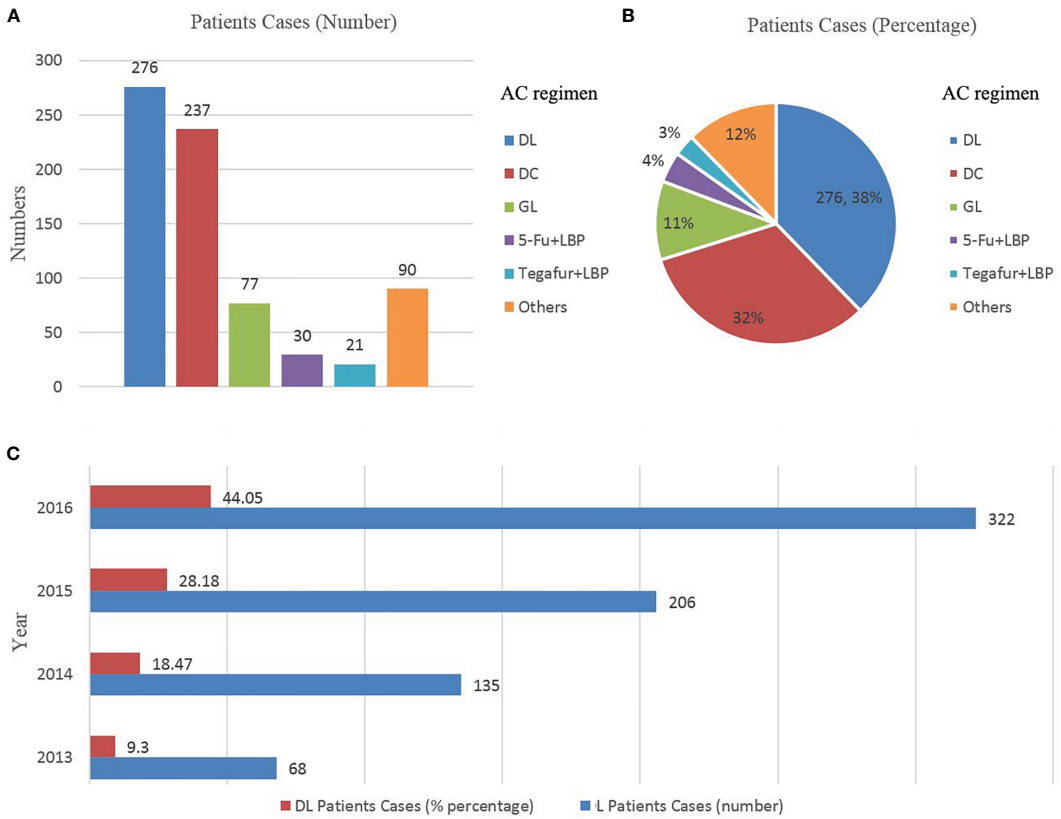

FIGURE 2 | **(A, B)**, Scheme distribution of the combined lobaplatin regimens (N = 731); **(C)** Trends in the use of lobaplatin regimens by year, ESCC patients treated with a combined lobaplatin regimen from 2013 to 2016 and its percentage in all ESCC patients after AC (N = 731). DL, docetaxel+ lobaplatin; DC, docetaxel+ cisplatin; GL, gemcitabine + lobaplatin; LBP, lobaplatin; LBP, lobaplatin; N, number; AC, adjuvant chemotherapy; ESCC, oesophageal squamous cell carcinoma.

grades were obtained. Two-sided tests were used for all statistical tests, and $P < 0.05$ was considered statistically significant. We compared the Kaplan-Meier curves of the 5-year survival rates for DL and DC in the matched cohort. The Kaplan-Meier method was used to draw survival curves, and the log-rank test was used to compare the survival curves.

RESULTS

Predictors of Regimen Choice

The full cohort included 733 patients (**Table 1**). Before PSM, patients receiving DL tended to be male, have grade 1 tumours, have pathological lymph node metastases and undergo more than 3–4 cycles of AC. The increasing practice patterns of DL changed over time; DL use increased from 68 patients in 2013 to 322 in 2016 (**Figure 2C**). There were 276 patients receiving DL as AC. However, twenty-three patients did not have any safety records of AC or were lost to follow-up. Finally, two hundred and fifty-three patients receiving DL were included in the PSM and followed with safety and survival analyses. The characteristics of 458 patients were similar between the two groups after PSM. Details regarding the distribution of patients treated with DL, DC and other chemotherapy regimens are shown in **Table 1** and **Figures 2A, B**.

Toxicity of Therapy

After matching, leukopenia, neutropenia, nephrotoxicity and gastrointestinal symptoms were more frequent in the DC group. There were no significant differences in haemoglobin levels, platelet counts or hepatotoxicity between the two groups. For the ECG test, significantly more abnormal reports were recorded in the DC group. The details are provided in **Table 2**.

In the subgroup analysis of 1–2 cycles *versus* more than 2 cycles of DL, there was significantly less toxicity in the DL group for gastrointestinal symptoms (P=0.047) (**Table 3**). In the subgroup analysis of 1–2 cycles of AC, there was significantly less toxicity in the DL group for neutropenia (P=0.0113), ECG test reports (P=0.0052), nephrotoxicity (P=0.0031) and gastrointestinal symptoms (P=0.0018). The other factors were not different (**Table 4**). In the subgroup analysis of three to four cycles of AC, there was significantly less toxicity in the DL group for neutropenia (P=0.028) (**Table 5**).

Survival

In the matched subset, the follow-up was conducted from 1.6 to 77.0 months. The mean follow-up period was 31.2 months.

TABLE 1 | Characteristics of full and propensity score–matched cohorts.

Characteristics	Full Cohort			Propensity Score Matched		
	DL (n = 253)	DC (n = 480)	P	DL (n = 229)	DC (n = 229)	P
Sex			0.0069			1.000
Male	217 (85.77)	370 (77.08)		198 (86.46)	199 (86.9)	
Female	36 (14.23)	110 (22.92)		31 (13.54)	30 (13.1)	
Age (years)			0.949			1.000
<60	130 (51.38)	244 (50.83)		117 (51.09)	118 (51.53)	
>=60	123 (48.62)	236 (49.17)		112 (48.91)	111 (48.47)	
BMI			0.6533			0.948
<18.5	23 (9.09)	44 (10.67)		22 (9.61)	24 (10.48)	
18.5~24	194 (76.67)	356 (74.17)		174 (75.98)	171 (74.67)	
>=24	33 (13.04)	75 (15.63)		31 (13.54)	31 (13.54)	
Missing	3 (1.19)	5 (1.04)		2 (0.87)	3 (1.31)	
Smoking			0.093			0.179
Never	37 (14.62)	106 (22.08)		39 (17.03)	43 (18.78)	
Ever/current	201 (79.44)	335 (69.79)		176 (76.85)	167 (72.93)	
Missing	15 (5.93)	39 (8.13)		14 (6.12)	19 (8.29)	
Alcohol			0.599			0.273
Never	115 (23.96)	70 (27.67)		70 (30.57)	57 (24.89)	
Ever/current	336 (70.00)	172 (67.98)		148 (64.63)	163 (71.18)	
Missing	29 (6.04)	11 (4.35)		11 (4.80)	9 (3.93)	
Clinical stage			0.4642			0.500
Stage II	159 (62.85)	316 (65.83)		146 (63.76)	138 (60.26)	
Stage III	94 (37.15)	164 (34.17)		83 (36.24)	91 (39.74)	
Location of tumour			0.6268			0.336
Upper thoracic	45 (17.79)	72 (15.0)		36 (15.72)	36 (15.72)	
Middle thoracic	140 (55.34)	257 (53.54)		134 (58.52)	114 (49.78)	
Lower thoracic	60 (23.72)	122 (25.42)		55 (24.02)	65 (28.38)	
Missing	8 (3.16)	29 (6.04)		4 (1.75)	14 (6.11)	
Thickness of tumour			0.7347			0.589
<3 m	37 (14.62)	63 (13.13)		35 (15.29)	29 (12.67)	
>=3 cm	207 (81.82)	384 (80)		189 (82.53)	186 (81.22)	
Missing	9 (3.56)	33 (6.88)		5 (2.18)	14 (6.11)	
Histological grade			0.0399			0.715
Well differentiated (G1)	40 (15.81)	44 (9.17)		40 (17.47)	37 (16.16)	
Moderately differentiated (G2)	157 (62.06)	315 (65.63)		157 (68.56)	165 (72.05)	
Poorly differentiated (G3)	32 (12.65)	65 (13.54)		32 (13.97)	27 (11.79)	
Missing	24 (9.49)	56 (11.67)		0	0	
Lymphocyte infiltration			0.0164			0.844
No	162 (64.03)	319 (66.46)		149 (65.07)	152 (66.38)	
Yes	83 (32.81)	107 (22.29)		80 (34.93)	77 (33.62)	
Missing	8 (3.16)	54 (11.25)		0	0	
Cycles of AC			0.0021			0.933
1~4	231 (91.3)	396 (82.5)		210 (91.7)	208 (90.83)	
5~8	21 (8.30)	72 (15.0)		18 (7.86)	20 (8.73)	
>8	1 (0.40)	12 (2.5)		1 (0.44)	1 (0.44)	

The median follow-up period was 31.1 months in the DL group and 32.9 months in the DC group. In the matched subset, 23.6% of DL users and 25.9% of DC users were alive at 5 years, log-rank test P=0.457 (median survival time, DL 36.2 months, 95% CI, 32.8 to 44.6; DC 38.4 months, 95% CI, 33.9–43.4; **Figure 3A**). In the first year, the DC group had a slightly higher OS (87.3%) than the DL group (83.0%); the same situation was observed for the 3-year OS (DC 54.0% and DL 50.7%). There were no statistically significant differences (**Figure 3A**). In the subgroup analysis of 1–2 cycles *versus* more than 2 cycles of DL, the five-year OS was 22.9% *versus* 26.0% (P=0.269; **Figure 3B**). In the subgroup analysis of 1–2 cycles of AC, the 5-year OS was 22.9% for DL users and 30.8% for DC users (P=0.588; **Figure 3C**). In the subgroup analysis of 3–4 cycles of AC, the 5-year OS was 22.1% for DL users and 30.3% for DC users (P=0.526; **Figure 3D**).

DISCUSSION

In this national project of AC after radical resection for ESCC, among matched patients, we found no significant differences in the 5-year OS between DL and DC users. However, according to WHO-based chemotherapy-related toxicities, DC users had significantly worse leukopenia, nephrotoxicity and gastrointestinal symptoms. Regarding the ECG test, DC users also had significantly more abnormal reports. In the DL

TABLE 2 | Side effects of adjuvant therapy in the matched full cohort.

Toxicity	DL (n = 229)	DC (n = 229)	P
Leukopenia			0.0176
0	136 (59.39)	105 (45.85)	
I-II	79 (34.5)	99 (43.23)	
III-IV	6 (2.62)	12 (5.24)	
Missing	8 (3.49)	13 (5.68)	
Haemoglobin decreased			0.4042
0	112 (48.91)	124 (54.15)	
I-II	95 (41.49)	82 (35.81)	
III-IV	14 (6.11)	11 (4.8)	
Missing	8 (3.49)	12 (5.24)	
Thrombocytopenia			0.0600
0	95 (41.49)	112 (48.91)	
I-II	103 (44.98)	98 (42.79)	
III-IV	20 (8.73)	9 (3.93)	
Missing	11 (4.80)	10 (4.37)	
Neutropenia			0.0015
0	117 (51.09)	83 (36.24)	
I-II	86 (37.56)	122 (53.28)	
III-IV	15 (6.55)	10 (4.37)	
Missing	11 (4.80)	14 (6.11)	
Hepatotoxicity			0.3687
0	160 (69.87)	177 (77.29)	
I-II	40 (17.47)	34 (14.85)	
Missing	29 (12.66)	18 (7.86)	
Nephrotoxicity			<0.001
0	176 (76.86)	151 (65.94)	
I-II	32 (13.97)	61 (26.64)	
Missing	21 (9.17)	17 (7.42)	
Gastrointestinal symptoms			0.0011
0	74 (32.31)	46 (20.88)	
I-II	125 (54.59)	149 (65.07)	
III-IV	5 (2.18)	15 (6.55)	
Missing	25 (10.92)	19 (8.30)	
ECG			0.0068
Normal	135 (58.95)	111 (48.47)	
Abnormal	68 (29.69)	98 (42.79)	
Missing	26 (11.35)	20 (8.74)	

ECG, Electrocardiograph.

TABLE 3 | Subgroup analysis of side effects of adjuvant therapy (DL ≥ 2 cycles *versus* DL < 2 cycles).

Toxicity	DL < 2 Cycles (n = 118)	DL ≥ 2 Cycles (n = 111)	P
Leukopenia			0.7546
0	70 (59.32)	66 (59.46)	
I-II	39 (33.05)	40 (36.04)	
III-IV	4 (3.39)	2 (1.8)	
Missing	5 (4.24)	3 (2.7)	
Haemoglobin decreased			0.5342
0	53 (44.92)	59 (53.15)	
I-II	52 (44.07)	43 (38.74)	
III-IV	8 (6.78)	6 (5.41)	
Missing	5 (4.23)	3 (2.70)	
Thrombocytopenia			0.2884
0	55 (46.61)	40 (36.04)	
I-II	49 (41.53)	54 (48.65)	
III-IV	9 (7.63)	11 (9.91)	
Missing	5 (4.23)	6 (5.4)	
Neutropenia			0.186
0	61 (51.69)	56 (50.45)	
I-II	41 (34.75)	45 (40.55)	
III-IV	11 (9.32)	4 (3.6)	
Missing	5 (4.24)	6 (5.4)	
Liver disorder			0.1104
0	89 (75.42)	71 (63.96)	
I-II	16 (13.56)	24 (21.62)	
Missing	13 (11.02)	16 (14.42)	
Renal disorder			0.2485
0	94 (79.66)	82 (73.87)	
I-II	13 (11.02)	19 (17.12)	
Missing	11 (9.32)	10 (9.01)	
Gastrointestinal symptoms			0.047
0	46 (38.98)	28 (25.23)	
I-II	56 (47.46)	69 (62.16)	
III-IV	3 (2.54)	2 (1.8)	
Missing	13 (11.02)	12 (10.81)	
ECG			0.1053
Normal	74 (62.71)	61 (54.95)	
Abnormal	29 (24.58)	39 (35.14)	
Missing	15 (12.71)	11 (9.91)	

ECG, Electrocardiograph.

subgroup, patients receiving more than 2 cycles of DL had the same survival benefits as those receiving 1–2 cycles of DL. The difference in toxicity between the two groups involved worse gastrointestinal symptoms in the DL group with more than 2 cycles.

A study showed no significant difference in the survival of LBP-based regimens *versus* cisplatin for metastatic breast cancer (10), which is consistent with our results. Although survival with cisplatin was slightly high, there was still no significant difference in this large sample size cohort. In the DL subgroup analysis, we found that the survival of patients treated with more than two cycles was perhaps better than that of patients treated with 1–2 cycles of AC, without statistical significance, while more cycles of DL increased gastrointestinal symptoms. Four cycles of AC are the standard treatment for lung cancer (11). Four cycles were better than 2 cycles (11). However, since retrospective data were used, the results should be interpreted with caution. Patients with poor physical condition may be less able to complete 3–4 cycles of AC. Patients with different chemotherapy cycles may be screened. Patients with multiple cycles may have better physical, financial and family support. These data are not within the range of our analysis. Therefore, the same survival benefit of different chemotherapy cycles cannot be fully interpreted, as the 2 cycles were sufficient. Randomized controlled clinical trials are still needed to identify and exclude potential confounders.

The lower toxicity of LBP has been demonstrated in breast cancer (12), lung cancer (13), oesophageal carcinoma (14), and hepatic cancer (15). Patients with ESCC after surgery usually have worse PSs than those with other types of cancer. Previous research has reported the use of LBP in ESCC (16), but no study has compared the effectiveness and safety of DL and DC in the AC setting of ESCC. Lower toxicity is very important for patients to complete 4 cycles of AC. LBP, a third-generation platinum anticancer drug developed by the German company ASTA, has been reported in the international literature to have limited nephrotoxicity without the need to perform hydration during

TABLE 4 | Subgroup analysis of side effects of 1–2 cycles of adjuvant therapy (DL *versus* DC).

Toxicity	DL (n = 118)	DC (n = 90)	P
Leukopenia			0.0664
0	70 (59.32)	38 (42.22)	
I-II	39 (33.05)	40 (44.44)	
III-IV	4 (3.39)	5 (5.56)	
Missing	5 (4.24)	7 (7.78)	
Haemoglobin decreased			0.7341
0	53 (44.91)	46 (51.11)	
I-II	52 (44.07)	36 (40.00)	
III-IV	8 (6.78)	6 (6.67)	
Missing	5 (4.24)	2 (2.22)	
Thrombocytopenia			0.5729
0	55 (46.60)	42 (46.67)	
I-II	49 (41.53)	42 (46.67)	
III-IV	9 (7.63)	4 (4.44)	
Missing	5 (4.24)	2 (2.22)	
Neutropenia			0.0113
0	61 (51.69)	29 (32.22)	
I-II	41 (34.75)	47 (52.22)	
III-IV	11 (9.32)	5 (5.56)	
Missing	5 (4.24)	9 (10.00)	
Liver disorder			0.5598
0	89 (75.42)	68 (75.56)	
I-II	16 (13.56)	16 (17.77)	
Missing	13 (11.02)	6 (6.67)	
Renal disorder			0.0031
0	94 (79.66)	58 (64.44)	
I-II	13 (11.02)	25 (27.78)	
Missing	11 (9.32)	7 (7.78)	
Gastrointestinal symptoms			0.0018
0	46 (38.98)	18 (20.00)	
I-II	56 (47.46)	57 (63.33)	
III-IV	3 (2.54)	8 (8.89)	
Missing	13 (11.02)	7 (7.78)	
ECG			0.0052
Normal	74 (62.71)	40 (44.45)	
Abnormal	29 (24.58)	39 (43.33)	
Missing	15 (12.71)	11 (12.22)	

ECG, Electrocardiograph.

TABLE 5 | Subgroup analysis of side effects of 3–4 cycles of adjuvant therapy (DL *versus* DC).

Toxicity	DL (n = 92)	DC (n = 118)	P
Leukopenia			0.5475
0	54 (58.7)	61 (51.69)	
I-II	33 (35.87)	46 (38.98)	
III-IV	2 (2.17)	5 (4.25)	
Missing	3 (3.26)	6 (5.08)	
Haemoglobin decreased			0.7844
0	49 (53.26)	65 (55.08)	
I-II	36 (39.13)	40 (33.9)	
III-IV	5 (5.43)	5 (4.24)	
Missing	2 (2.18)	8 (6.78)	
Thrombocytopenia			0.1135
0	36 (39.13)	57 (48.31)	
I-II	41 (44.57)	48 (40.68)	
III-IV	10 (10.87)	5 (4.24)	
Missing	5 (5.43)	8 (6.77)	
Neutropenia			0.028
0	51 (55.43)	47 (39.83)	
I-II	34 (36.96)	64 (54.24)	
III-IV	1 (1.09)	3 (2.54)	
Missing	6 (6.52)	4 (3.39)	
Liver disorder			0.2567
0	62 (67.39)	93 (78.81)	
I-II	18 (19.57)	17 (14.41)	
Missing	12 (13.04)	8 (6.78)	
Renal disorder			0.1254
0	70 (76.09)	80 (67.80)	
I-II	15 (16.30)	31 (26.27)	
Missing	7 (7.61)	7 (5.93)	
Gastrointestinal symptoms			0.1657
0	24 (26.09)	25 (21.19)	
I-II	58 (63.04)	75 (63.56)	
III-IV	1 (1.09)	7 (5.93)	
Missing	9 (9.78)	11 (9.32)	
ECG			0.7674
Normal	49 (53.26)	62 (52.54)	
Abnormal	33 (35.87)	47 (39.83)	
Missing	10 (10.87)	9 (7.63)	

ECG, Electrocardiograph.

chemotherapy (3). The major dose-limiting toxicity of LBP was thrombocytopenia in a past report (3, 17, 18). Similarly, the most frequent grade 3–4 toxicity in our study was thrombocytopenia (8.73%). However, compared with the DC group, the toxicity of thrombocytopenia in the DL group was not different (P=0.060) in our data. Overall, the grade 3–4 toxicity of LBP was less than 10%, which was acceptable. No grade 3 or 4 hepatotoxicity or nephrotoxicity was observed. Renal toxicity and cardiac dysfunction may be reduced. Compared with DC, DL had much lower incidences of nephrotoxicity and fewer abnormal ECG reports during AC. Some previous reports of LBP showed neutropenia (17, 19). However, in our study, the incidence of neutropenia with LBP was much lower than that with cisplatin. AC with cisplatin brings high pressure to patients because of its toxicity (20). It can easily induce drug resistance (20). LBP has no crossing drug resistance with other platinum-based drugs (3).

In the year-by-year OS results of DC *versus* DL, the DC group consistently had better survival rates but without statistical significance. The toxicity of DC was much worse than that of DL. In a previous report, compared with cisplatin, LBP had lower toxicity, lower physical and mental pressure, and less stimulation of the vasculature (21). To control and reduce the toxicity of AC in certain patients after oesophagectomy, DL may be a good choice since it has the same survival outcomes with less toxicity.

Several limitations that are common to observational analyses could be found in this study. All toxicity data were collected in the inpatient department. The full extent of toxicities, especially after discharge, could not be collected. Second, there was no information on recurrence. Thus, it was impossible to analyse disease-free survival (DFS). Similarly, this retrospective observational study did not collect the cause of death. We were unable to calculate the tumour-related OS. Although propensity score adjustment was used, the unmeasured factors may still have remained confounding factors. Although the multicentre study had a large sample size, the standardization of all data was much more difficult than that for a single centre study. Finally, for the evaluation of the toxicity of AC, the Common Terminology Criteria for Adverse Events (CTCAE) was not adopted.

There was no information available to clinicians choosing between cisplatin and LBP in the adjuvant setting for ESCC.

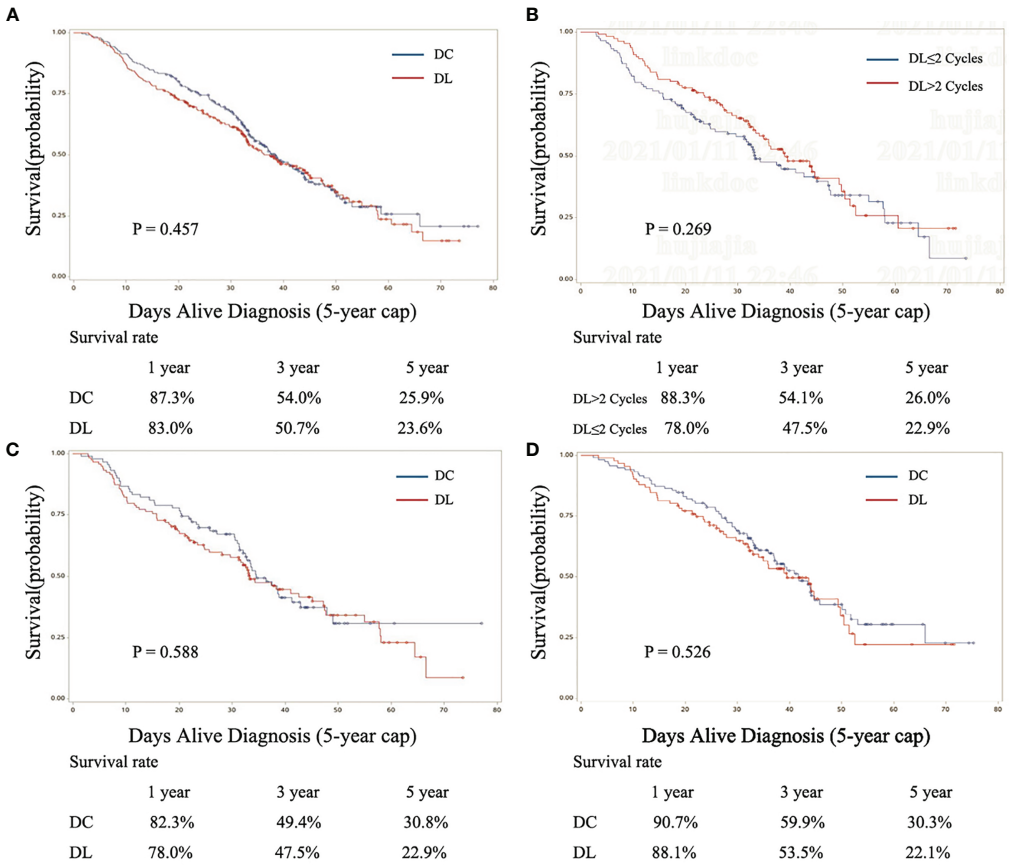

FIGURE 3 | Kaplan-Meier curves for the 3-year survival outcomes of propensity score–matched patients by regimen (DL and DC). **(A)** Fully matched cohort, **(B)** DL subgroup, **(C)** 1–2 cycles of AC group of DL and DC, and **(D)** 3–4 cycles of AC group of DL and DC. DL, docetaxel+ lobaplatin; DC, docetaxel+ cisplatin.

Some studies have demonstrated the safety and effectiveness of LBP in advanced ESCC. No head-to-head clinical trial has compared DC and DL in terms of efficacy or toxicity. Prospective randomized studies are unlikely to be conducted in the near future. The large population from multiple centres and rigorous retrospective studies can inform clinical care by offering information about the outcomes of different treatments. The results of this study can fill a crucial knowledge gap.

In conclusion, DL has the same long-term survival benefit and lower chemotherapy-related toxicity than DC as AC in the treatment of ESCC. However, the data included in this retrospective study come from different research centres. It is inevitable that some data are missing, which made it impossible to evaluate the DFS of patients. The results need to be confirmed by large prospective controlled studies.

AUTHOR'S NOTE

The abstract was accepted as an oral presentation at the 26th European Conference on General Thoracic Surgery at Ljubljana, Slovenia, in May 2018.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data was in LinkDoc company. The access of the dataset should be approved by ethics review committee of all the included multiple centers. Requests to access these datasets should be directed to dingjing201305@163.com.

ETHICS STATEMENT

This study was approved by the ethics review committee of the Affiliated Cancer Hospital of ZhengZhou University/Henan Cancer Hospital approved officially with the approval number 2017405. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL and YZ designed the study. XL, HS, JH, and LL performed the experiments. JH and LL analysed the data. ZY and GL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Mao YS, He J, Xue Q, Shao K, Su K, Li N, et al. Nationwide Speaking Tour of Standardized Diagnosis and Treatment for Esophageal Cancer. *Zhonghua Wei Chang Wai Ke Za Zhi* (2013) 16:801–4.
2. Zhai X, Zheng Q, Yang L, Zhu Y, Li J, Liu Y, et al. Impact of Platinum/Pemetrexed Combination *Versus* Other Platinum-Based Regimens on Adjuvant Chemotherapy in Resected Lung Adenocarcinoma. *Sci Rep* (2017) 7:1453. doi: 10.1038/s41598-017-01347-6
3. McKeage MJ. Lobaplatin: A New Antitumour Platinum Drug. *Expert Opin Investig Drugs* (2001) 10:119–28. doi: 10.1517/13543784.10.1.119
4. Zhang H, Chen R, Wang X, Zhang H, Zhu X, Chen J. Lobaplatin-Induced Apoptosis Requires P53-Mediated P38mapk Activation Through ROS Generation in non-Small-Cell Lung Cancer. *Front Oncol* (2019) 9:538. doi: 10.3389/fonc.2019.00538
5. Chen Z, Xu G, Wu D, Wu S, Gong L, Li Z, et al. Lobaplatin Induces Pyroptosis Through Regulating Ciap1/2, Ripoptosome and ROS in Nasopharyngeal Carcinoma. *Biochem Pharmacol* (2020) 177:114023. doi: 10.1016/j.bcp.2020.114023
6. Wu Y, Xu XY, Yan F, Sun WL, Zhang Y, Liu DL, et al. Retrospective Study of the Efficacy and Toxicity of Lobaplatin in Combined Chemotherapy for Metastatic Breast Cancer. *Onco Targets Ther* (2019) 12:4849–57. doi: 10.2147/OTT.S192373
7. Hua S, Kong X, Chen B, Zhuang W, Sun Q, Yang W, et al. Anticancer Mechanism of Lobaplatin as Monotherapy and in Combination With Paclitaxel in Human Gastric Cancer. *Curr Mol Pharmacol* (2018) 11:316–25. doi: 10.2174/1874467211666180813095050
8. Chen MQ, Chen C, Lu HJ, Xu BH. The Efficacy and Toxicities of Combined Lobaplatin With Paclitaxel as a First-Line Chemotherapy for Advanced Esophageal Squamous Cell Carcinoma. *J Thorac Dis* (2015) 7:1749–55. doi: 10.3978/j.issn.2072-1439.2015.10.23
9. Sox HC, Goodman SN. The Methods of Comparative Effectiveness Research. *Annu Rev Public Health* (2012) 33:425–45. doi: 10.1146/annurev-publhealth-031811-124610
10. Wang Z, Xu L, Wang H, Li Z, Lu L, Li X, et al. Lobaplatin-Based Regimens Outperform Cisplatin for Metastatic Breast Cancer After Anthracyclines and Taxanes Treatment. *Saudi J Biol Sci* (2018) 25:909–16. doi: 10.1016/j.sjbs.2018.01.011
11. Liang Y, Wakelee HA. Adjuvant Chemotherapy of Completely Resected Early Stage non-Small Cell Lung Cancer (NSCLC). *Transl Lung Cancer Res* (2013) 2:403–10. doi: 10.3978/j.issn.2218-6751.2013.07.01
12. Engel JB, Martens T, Hahne JC, Häusler SF, Krockenberger M, Segerer S, et al. Effects of Lobaplatin as a Single Agent and in Combination With TRAIL on the Growth of Triple-Negative P53-Mutated Breast Cancers *In Vitro*. *Anticancer Drugs* (2012) 23:426–36. doi: 10.1097/CAD.0b013e32834fb8ce
13. Xie CY, Xu YP, Jin W, Lou LG. Antitumor Activity of Lobaplatin Alone or in Combination With Antitubulin Agents in Non-Small-Cell Lung Cancer. *Anticancer Drugs* (2012) 23:698–705. doi: 10.1097/CAD.0b013e328352cc10
14. Yang JS, Wang T, Qiu MQ, Li QL. Comparison of Efficacy and Toxicity Profiles Between Paclitaxel/Lobapoatin- and Cisplatin/5-Fluorouracil-Based Concurrent Chemoradiotherapy of Advanced Inoperable Oesophageal Cancer. *Intern Med J* (2015) 45:757–61. doi: 10.1111/imj.12773
15. Wang N, Lv YZ, Xu AH, Huang YR, Peng L, Li JR. Application of Lobaplatin in Trans-Catheter Arterial Chemoembolization for Primary Hepatic Carcinoma. *Asian Pac J Cancer Prev* (2014) 15:647–50. doi: 10.7314/APJCP.2014.15.2.647
16. Pan S, Sun Y, Sui D, Yang T, Fu S, Wang J, et al. Lobaplatin Promotes Radiosensitivity, Induces Apoptosis, Attenuates Cancer Stemness and Inhibits Proliferation Through PI3K/AKT Pathway in Esophageal Squamous Cell Carcinoma. *BioMed Pharmacother* (2018) 102:567–74. doi: 10.1016/j.biopha.2018.03.109
17. Ke LR, Xia WX, Qiu WZ, Huang XJ, Yang J, Yu YH, et al. Safety and Efficacy of Lobaplatin Combined With 5-Fluorouracil as First-Line Induction Chemotherapy Followed by Lobaplatin-Radiotherapy in Locally Advanced Nasopharyngeal Carcinoma: Preliminary Results of a Prospective Phase II Trial. *BMC Cancer* (2017) 17:134. doi: 10.1186/s12885-017-3080-4
18. Gietema JA, De Vries EG, Sleijfer DT, Willemse PH, Guchelaar HJ, Uges DR, et al. A Phase I Study of 1,2-Diamminomethyl-Cyclobutane-Platinum (II)-Lactate (D-19466; Lobaplatin) Administered Daily for 5 Days. *Br J Cancer* (1993) 67:396–401. doi: 10.1038/bjc.1993.73
19. Miyawaki Y, Nakajima Y, Kawada K, Okada T, Tokairin Y, Kawano T. Efficacy of Docetaxel, Cisplatin, and 5-Fluorouracil Chemotherapy for Superficial Esophageal Squamous Cell Carcinoma. *Dis Esophagus* (2017) 30:1–8. doi: 10.1111/dote.12485
20. Waissbluth S, Daniel SJ. Cisplatin-Induced Ototoxicity: Transporters Playing a Role in Cisplatin Toxicity. *Hear Res* (2013) 299:37–45. doi: 10.1016/j.heares.2013.02.002
21. Dilruba S, Kalayda GV. Platinum-Based Drugs: Past, Present and Future. *Cancer Chemother Pharmacol* (2016) 77:1103–24. doi: 10.1007/s00280-016-2976-z

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Short-Term Clinical Efficacy of Neoadjuvant Chemotherapy Combined With Laparoscopic Gastrectomy for Locally Advanced Siewert Type II and III Adenocarcinoma of the Esophagogastric Junction: A Retrospective, Propensity Score-Matched Study

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Background: Laparoscopic gastrectomy (LG) has been increasingly used for the treatment of locally advanced Siewert type II and III adenocarcinoma of the esophagogastric junction (AEG). However, whether LG can achieve the same short-term efficacy in the treatment of patients who receive neoadjuvant chemotherapy (NACT) remains controversial. Thus, the aim of this study was to investigate the clinical outcomes of NACT combined with LG for Siewert type II and III AEG.

Methods: This retrospective study identified patients with locally advanced Siewert type II and III AEG diagnosed between May 2011 and October 2020 using the clinical tumor-node-metastasis (cTNM) staging system. The short-term outcomes were compared between the matched groups using a 1:3 propensity score matching (PSM) method, which was performed to reduce bias in patient selection.

Results: After PSM, 164 patients were selected, including 41 in the NACT group and 123 in the LG group. The baseline characteristics were similar between the two groups. Compared with the LG group, the NACT group exhibit a smaller tumor size and significantly less advanced pathological tumor classification and nodal classification stages. The time to first flatus of the NACT group was significantly shorter, but the hospital stay was significantly longer than that of the LG group. The NACT group showed similar overall (29.3% *vs* 25.2%, P=0.683), systemic (24.4% *vs* 21.1%, P=0.663), local (12.2% *vs* 9.8%, P=0.767), minor (19.5% *vs* 19.5%, P=1.000) and major (9.8% *vs* 5.7%,

P=0.470) complications as the LG group. Subgroup analyses showed no significant differences in most stratified parameters. Operation time≥ 300 minutes was identified as an independent risk factor for overall complications. Age≥ 60 years was identified as an independent risk factor for major complications.

Conclusion: NACT combined with LG for AEG does not increase the risk of postoperative morbidity and mortality compared with LG.

Keywords: esophagogastric junction, neoadjuvant chemotherapy, laparoscopic, postoperative complication, Siewert II and III

INTRODUCTION

The incidence of adenocarcinoma of the esophagogastric junction (AEG) is rapidly increasing, especially Siewert II and III AEG (1, 2). Surgery remains the only radical cure for AEG (3). Since laparoscopic gastrectomy (LG) was first introduced by Kitano in 1994 (4), it has been widely used for early gastric cancer and advanced gastric cancer with the advantages of less injury, faster recovery, and lower morbidity of postoperative complications (5–8). For Siewert type II and III AEG, Liao's meta-analysis (9) revealed that LG can achieve short-term surgical outcomes comparable to open gastrectomy (OG). However, the development of surgical procedures did not improve long-term outcomes (10). In addition, due to the special location of this tumor, most cases are diagnosed at an advanced stage (11), seriously impacting on the prognosis of patients and resulting in a lower overall survival.

Accumulating evidence has revealed that neoadjuvant therapy improves the efficacy of AEG compared with surgery alone (12–14). However, chemotherapy-induced tissue fibrosis and oedema provide new technical challenges for minimally invasive procedures and increase the difficulty of the operation. It remains controversial whether LG is suitable for AEG patients after NACT. Therefore, we conducted a single-centre retrospective, propensity score-matched study to determine whether LG is suitable for AEG patients after NACT.

MATERIALS AND METHODS

Patients

A total of 256 Siewert type II or III AEG patients who underwent laparoscopic gastrectomy were identified from a prospectively maintained database containing all gastric cancers diagnosed at The First Affiliated Hospital of Army Medical University in China between May 2011 and October 2020. The decision for NACT was discussed in the Department of General Surgery and determined by the patients who were informed of the possible complications of the procedure and the potential benefits and harms of NACT compared with the LG approach. Written informed consent was obtained from all patients before the operation.

The inclusion criteria were as follows: patients aged 18 to 85 years who were diagnosed with Siewert type II/III AEG by computed tomography (CT); patients who received gastroscopy and were pathologically confirmed by postoperative biopsy; patients who adopted a complete trans-abdominal approach; patients with no distant metastasis or invasion to adjacent organs; and patients who underwent D2 radical laparoscopic gastrectomy. The exclusion criteria included non-radical operation, emergent operation previous gastrectomy, endoscopic mucosal resection, or endoscopic submucosal dissection. In total, 41 and 192 patients were included in the NACT and LG groups, respectively. Clinical stage was evaluated for all patients using intravenous contrast-enhanced CT before and after NACT. Before the study was conducted, CT data were evaluated by a professional radiologist who was blinded to the clinical information of the patient. This study was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University, PLA (Approval number: KY2021059).

Neoadjuvant Chemotherapy and Evaluation of Clinical Response and Toxicity

Patients received different cycles of NACT preoperatively, and a median of 3 (2, 4) cycles was administered. Among the 41 patients in the NACT group, 37 (90.2%) received the SOX (oxaliplatin + S-1) regimen, 2 (4.9%) received the XELOX (oxaliplatin + capecitabine) regimen, and 2 (4.9%) received the FOLFOX (oxalipatin + fluorouracil + leucovorin) regimen. The toxicity and adverse events of NACT were evaluated according to the World Health Organization (WHO) standard criteria (15). The response to chemotherapy was endoscopically and radiologically evaluated by endoscopy and CT scans. Post-NACT evaluation of the target lesions was divided into four categories: complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) (16).

Surgery and Postoperative Outcome

Patients in the NACT group underwent radical gastrectomy after the completion of NACT (3-4 weeks). All patients who underwent laparoscopic gastrectomy with D2 lymphadenectomy were treated by three experienced surgeons according to the Japanese Gastric Cancer Treatment Guidelines (17, 18). Specific surgical gastrectomy procedures, including proximal and total gastrectomy, were selected depending on the location of the primary tumor. Reconstruction of the gastrointestinal tract was performed according to the type of gastrectomy. Postoperative outcomes, including the results of the

pathological outcomes, postoperative recovery (i.e., the times to first flatus and length of overall and postoperative hospital stay), and morbidity and mortality rates, were evaluated. Pathologic evaluations and staging were updated according to the 8th American Joint Committee on Cancer (AJCC) TNM staging system (19). Postoperative complications were defined as complications that occurred within 30 days after surgery. One month after the operation, outpatient and telephone follow-ups were conducted to determine the survival and severity of the patients after discharge.

Statistical Analysis

To minimize the bias between the NACT group and the LG group, we performed PSM with the R (x64 3.5.0) MatchIt package. Age, sex, body mass index (BMI) on admission, American Society of Anaesthesiologists (ASA) grade, Siewert classification, cT stage, cN stage, cTNM stage, resection range and tumor differentiation were chosen to perform 1:3 matching using the "nearest" method. Data are presented as proportions for categorical variables and as the mean ± SD for continuous variables. Variables with high skew are presented as the median (IQR). Categorical variables were compared using the $\chi 2$ test or Fisher's exact test, whereas continuous variables were compared using Student's t-test or the Mann-Whitney U test. Variables with P-values<0.10 in univariate analysis were included in the multivariate analysis. Multivariate analysis was conducted with the binary logistic regression model to identify independent risk factors for postoperative complications. A P-value (two-sided)<0.05 was considered statistically significant. Data analyses were conducted using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

RESULTS

Patients' Characteristics

Flow of patient enrolment is presented in **Figure 1**. **Table 1** summarizes the clinicopathological characteristics of the patients in the two groups. Clinical T stage, clinical N stage and tumor differentiation significantly differed between the NACT and LG

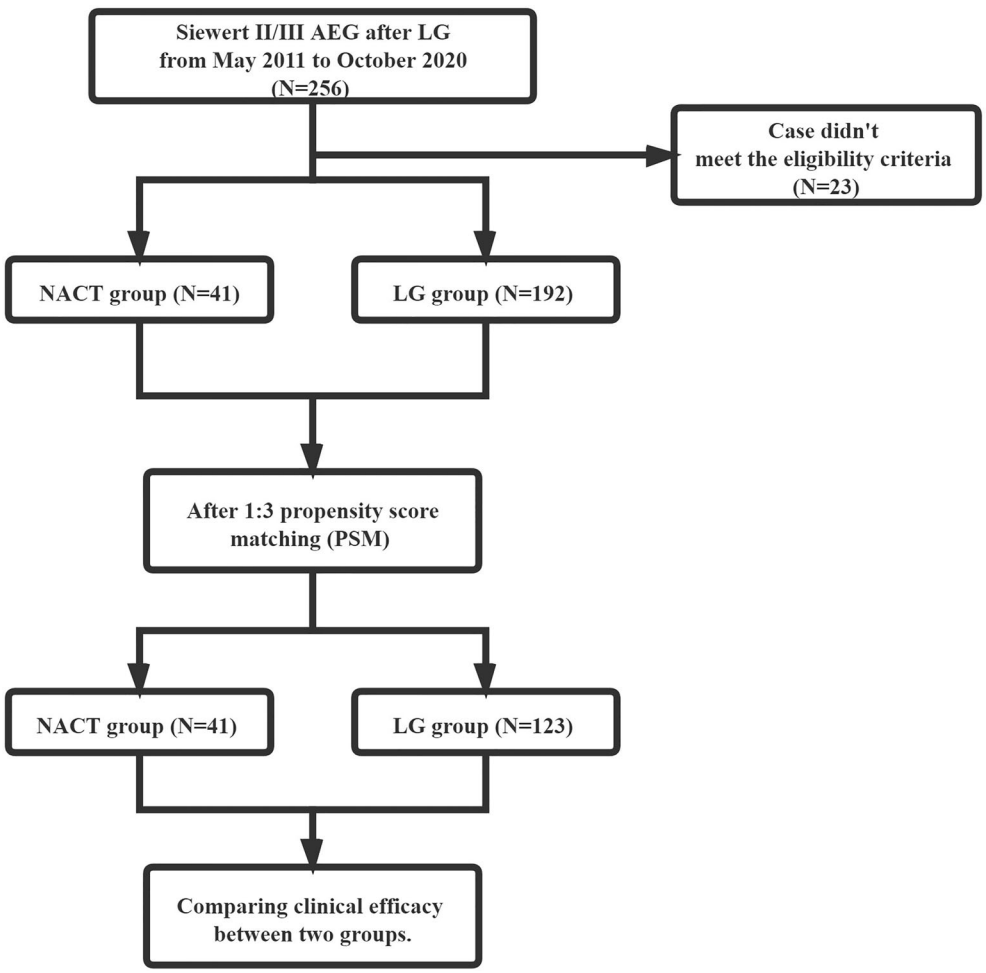

FIGURE 1 | Patient selection diagram based on PSM.

TABLE 1 | Characteristics of patients before and after PSM.

Characteristic	Crude Cohort (n = 233)			PSM Cohort (n = 123)		
	NACT group (n = 41)	LG group (n = 192)	P value	NACT group (n = 41)	LG group (n = 123)	P value
Age (years)			0.202			0.991
<60	20	73		20	55	
≥60	21	119		21	68	
Sex			0.615			0.663
Male	31	152		31	97	
Female	10	40		10	26	
BMI (kg/m2) on admission			0.614			0.695
<18.5	4	11		2	9	
≥18.5 and <25	30	146		30	96	
≥25	7	35		9	18	
ASA score			***0.025***			0.207
1	32	111		32	85	
2	8	78		8	37	
3	1	3		1	1	
Siewert classification			0.145			0.278
Type II	16	99		16	60	
Type III	25	93		25	63	
Clinical T stage			0.078			0.399
T2	0	20		0	1	
T3	13	46		13	25	
T4a	28	126		28	97	
Clinical N stage			***0.014***			0.562
0	0	37		0	0	
1	10	46		10	30	
2	22	69		22	56	
3	9	40		9	37	
Clinical TNM stage			***0.008***			1.000
I	0	15		0	0	
IIA	0	4		0	0	
IIB	0	22		0	0	
III	41	151		41	123	
Resection range			0.056			1.000
Proximal	1	26		1	2	
Total	40	166		40	121	
Differentiation			***0.025***			0.349
Well/moderately	12	93		12	48	
Poorly/undifferentiated	29	99		29	75	

PSM, propensity score matching; NACT, neoadjuvant chemotherapy; BMI, body mass index; ASA, American Society of Anesthesiologists. Italicized and bold values represent significant differences.

groups. On the basis of 1:3 PSM, 164 patients (41 in the NACT group and 123 in the LG group) were selected for analysis. After PSM, no significant differences in age, sex, BMI on admission, ASA, Siewert classification, cT stage, cN stage, cTNM stage, resection range and tumor differentiation were noted between the two groups.

NACT Response and Toxicity Analysis

In this study, 27 (65.8%) patients exhibited PR, 12 (29.3%) exhibited SD, and 2 (4.9%) patients exhibited PD according to contrast-enhanced CT before and after NACT (**Table 2**). The BMI of the NACT group after NACT was significantly greater than that on admission (22.50 *vs* 21.90 P=0.016). 8 (19.5%) of the 41 treated patients experienced at least grade 3-4 toxicity during NACT treatment. The most common grade 3-4 toxicities were leukopenia/neutropenia (9.8%) and nausea and vomiting (12.2%) (**Table 2**).

Comparison of Operative Findings

The proximal margin of one patient in the NACT group and four patients in the LG group was found to be positive. R0 resection was performed for 97.8% of patients in the NACT group and 93.5% of patients in the LG group (P = 0.453). The amount of blood loss, transfused patient number, and operation time were comparable between the two groups. During the procedure, 6 patients (14.6%) in the NACT group were converted to open gastrectomy, whereas 12 patients (9.8%) in the LG group showed no significant differences (P=0.395). No statistically significant difference was found between the two groups regarding the length of incision, distal margin or proximal margin (**Table 3**). After PSM, the median time to first flatus of the NACT group was significantly shorter than that of the LG group (3 *vs* 4 days, P=0.004). Both the total hospital stay and postoperative hospital stay of the NACT group were significantly longer than those of the LG group.

TABLE 2 | Characteristics of neoadjuvant chemotherapy, n (%).

Chemotherapy regimen	
SOX	37 (90.2%)
FOLFOX	2 (4.9%)
XELOX	2 (4.9%)
Cycles of NACT completed	
2 cycles	10 (24.4%)
3 cycles	19 (46.3%)
4 cycles	7 (17.1%)
More than 4 cycles	5 (12.2%)
Clinical response per RECIST criteria	
PR	27 (65.8%)
SD	12 (29.3%)
PD	2 (4.9%)
Grade 3 or 4 adverse effects	
Leukopenia/neutropenia	4 (9.8%)
Nausea/vomiting	5 (12.2%)
Skin disease	2 (4.9%)
Anaemia	1 (2.4%)
Thrombocytopenia	1 (2.4%)
Chemotherapy-surgical procedure interval, week (median, IQR)	4 (3,6)

NACT, neoadjuvant chemotherapy; PR, partial remission; SD, stable disease; PD, progressive disease. IQR, interquartile range.

Analyses of Pathological Outcomes

The average number of harvested lymph nodes (LNs) did not significantly differ (P=0.225) in the NACT (30.54) and LG groups (33.51), whereas the number of metastatic LNs was significantly lower in the NACT group (**Table 3**). The tumor size of the NACT group was smaller than that of the LG group (P<0.001). Following PSM, both the (y)pT and (y)pN stage categories of the NACT group were significantly less advanced than those of the LG group.

Analyses of Postoperative Complications

The postoperative morbidity and mortality of patients in the PSM cohort are shown in **Table 4**. Morbidity was comparable between the two groups (29.3% *vs* 25.2%, P=0.683). No differences in systemic complications (24.4% *vs* 21.1%, P=0.663) and local complications (12.2% *vs* 9.8%, P=0.767) were noted between the groups. No significant differences in the comparison of specific complications (all P>0.05) were noted between the groups. More infectious complications were noted in the NACT group compared with the LG group; however, the difference was not significant (24.4% *vs* 18.7%, P=0.431). No

TABLE 3 | Comparison of operative and postoperative parameters between the NACT group and LG group, n (%).

Variable	NACT group (n = 41)	LG group (n = 123)	P value
Resection			0.453
R0	40 (97.8%)	115 (93.5%)	
R1	1 (2.4%)	8 (6.5%)	
Operation time, min (mean ± SD)	280.34 ± 53.61	273.73 ± 48.87	0.466
Blood loss, ml (median, IQR)	150 (100, 200)	160 (110, 200)	0.480
Blood transfusion			1.000
Yes	5 (12.2%)	13 (10.6%)	
No	36 (87.8%)	108 (89.4%)	
Lymph node dissection range			0.640
D2	39 (95.1%)	119 (96.7%)	
D2+	2 (4.9%)	4 (3.3%)	
Conversion to open from laparoscopic gastrectomy	6 (14.6%)	12 (9.8%)	0.395
Length of incision, cm (median, IQR)	7 (6,9)	6 (5,8)	0.070
Distal margin, cm (median, IQR)	8 (5,14.5)	8 (5,10)	0.306
Proximal margin, cm (median, IQR)	3 (2,4.5)	3 (2,3)	0.161
Tumor size, cm (median, IQR)	3 (2,4.5)	4 (3,5)	***<0.001***
The number of resected lymph nodes (mean ± SD)	30.54 ± 14.20	33.68 ± 13.42	0.202
The number of metastatic lymph nodes (median, IQR)	0 (0,4)	5 (1,9)	***<0.001***
Pathological tumor classification			***<0.001***
(y)pT0-2	16 (39.0%)	14 (11.4%)	
(y)pT3	0	2 (1.6%)	
(y)pT4a/4b	25 (61.0%)	107 (87.0%)	
Pathologic nodal classification			***<0.001***
(y)pN0	22 (53.7%)	13 (10.6%)	
(y)pN1	7 (17.1%)	31 (25.2%)	
(y)pN2	8 (19.5%)	28 (22.8%)	
(y)pN3	4 (9.8%)	37 (30.1%)	
Total hospital stay, d (median, IQR)	18 (14,22)	15 (13,18)	***0.012***
Postoperative hospital stay, d (median, IQR)	11 (9,14)	9 (8,11)	***0.003***
Time to first flatus, d (median, IQR)	3 (3,4)	4 (3,5)	***0.004***

NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy; SD, standard deviation; IQR, interquartile range. Italicized and bold values represent significant differences.

TABLE 4 | Postoperative Complications of the patients in NACT group and LG group, n (%).

Variable	NACT group (n = 41)	LG group (n = 123)	P-value
Postoperative complications	12 (29.3%)	31 (25.2%)	0.683
Systemic complication	10 (24.4%)	26 (21.1%)	0.663
Heart failure	1 (2.4%)	1 (0.8%)	0.439
Respiratory failure	2 (4.9%)	4 (3.3%)	0.640
Pulmonary infection	6 (14.6%)	17 (13.8%)	0.897
Pleural effusion	3 (7.3%)	11 (8.9%)	1.000
Urinary tract infection	0	1 (0.8%)	1.000
Hepatic malfunction	0	3 (2.4%)	1.000
Local complication	5 (12.2%)	12 (9.8%)	0.767
Duodenal stump leakage	1 (2.4%)	1 (0.8%)	0.439
Anastomotic leakage	2 (4.9%)	2 (1.6%)	0.260
Intra-abdominal infection	3 (7.3%)	5 (4.1%)	0.414
Abdominal bleeding	0	4 (3.3%)	0.573
Wound infection	0	2 (1.6%)	1.000
Infectious complication	10 (24.4%)	23 (18.7%)	0.431
Clavien-Dindo Classification			
Grades I-II	8 (19.5%)	24 (19.5%)	1.000
Grade I	1 (2.4%)	4 (3.3%)	1.000
Grade II	7 (17.1%)	20 (16.3%)	0.707
Grades III-V	4 (9.8%)	7 (5.7%)	0.470
Grade III	1 (2.4%)	3 (2.4%)	1.000
Grade IV	3 (7.3%)	4 (3.3%)	0.368
Grade V	0	0	NA
Reoperation	1 (2.4%)	2 (1.6%)	1.000

NACT, neoadjuvant chemotherapy; LG, laparoscopic gastrectomy; NA, not available.

significant differences in complication severity according to the Clavien-Dindo grade were noted (20, 21). Four patients (9.8%) in the NACT group and 7 patients (5.7%) in the LG group experienced grade III or higher complications (P=0.470). One patient in the NACT group and 2 patients in the LG group underwent reoperation due to abdominal bleeding.

Subgroup Analyses

Subgroup analyses were performed for overall complications in the PSM cohort. No significant differences in any stratified parameters in terms of overall complications were noted between the two groups (**Figure 2**).

Risk Factor for Overall and Major Complications

Univariate analysis showed that BMI ≥25, BMI <18.5, operation time≥ 300 minutes and blood loss ≥200 ml were positively correlated with overall complications (**Table 5**). Multivariate analysis revealed that operation time≥ 300 minutes (P=0.049) was an independent risk factor for overall complications (**Table 5**). Regarding major complications, age≥ 60 years, operation time≥ 300 and blood loss ≥200 were correlated with major complications in univariate analysis. In multivariate analysis, age≥ 60 years (P=0.042) was identified as an independent risk factor for major complications.

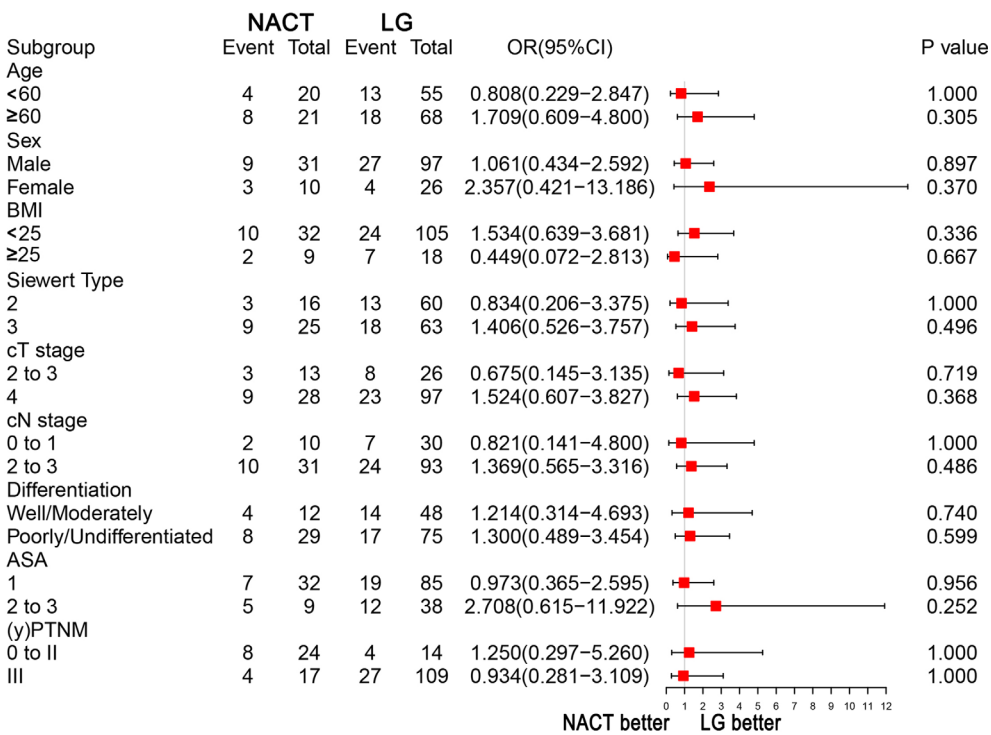

FIGURE 2 | Subgroup analyses of overall complications.

TABLE 5 | Analysis of risk factors for overall and severe complications in the crude cohort.

Variables	Overall complication				Severe complication			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex								
Male	Ref				Ref			
Female	0.711 (0.338-1.493)	0.367			0.771 (0.212-2.794)	0.692		
Age (years)								
<60	Ref				Ref		Ref	
≥60	1.110 (0.613-2.010)	0.730			3.333 (0.931-11.940)	***0.064***	3.881 (1.051-14.330)	***0.042***
ASA Grade								
I	Ref				Ref			
II-III	1.605 (0.892-2.888)	0.115			1.511 (0.561-4.073)	0.414		
BMI								
≥18.5 and <25	Ref		Ref		Ref			
<18.5	2.864 (0.912-8.999)	***0.072***	3.011 (0.925-9.801)	0.067	3.055 (0.595-15.686)	0.181		
≥25	2.056 (1.007-4.199)	***0.048***	1.886 (0.910-3.910)	0.088	2.270 (0.733-7.035)	0.155		
Neoadjuvant chemotherapy								
No	Ref				Ref			
Yes	1.144 (0.543-2.410)	0.723			1.489 (0.460-4.821)	0.507		
Siewert type								
II	Ref				Ref			
III	1.310 (0.733-2.342)	0.362			1.429 (0.524-3.891)	0.485		
Clinical TNM stage								
I-II	Ref				Ref			
III	0.661 (0.321-1.361)	0.261			0.672 (0.207-2.176)	0.507		
Histopathological grade								
Well/moderately	Ref				Ref			
Poorly/undifferentiated	0.868 (0.486-1.551)	0.633			1.551 (0.554-4.346)	0.403		
Converted to open gastrectomy								
No	Ref				Ref			
Yes	1.757 (0.691-4.464)	0.236			1.382 (0.294-6.505)	0.682		
Transfusion								
No	Ref				Ref			
Yes	1.393 (0.535-3.628)	0.498			1.382 (0.294-6.505)	0.682		
Tumor Size (cm)								
<6	Ref				Ref			
≥6	0.896 (0.500-1.606)	0.731			1.060 (0.389-2.899)	0.909		
Operation Time (min)								
<300	Ref		Ref		Ref		Ref	
≥300	2.094 (1.149-3.815)	***0.016***	1.870 (1.004-3.483)	***0.049***	2.557 (0.945-6.918)	***0.065***	2.545 (0.907-7.139)	0.076
Blood Loss (ml)								
<200	Ref		Ref		Ref		Ref	
≥200	1.667 (0.931-2.987)	***0.086***	1.484 (0.802-2.747)	0.208	2.771 (0.988-7.773)	***0.053***	2.482 (0.863-7.137)	0.092

ASA, American Society of Anesthesiologists; BMI, Body mass index. Italicized and bold values represent significant differences.

DISCUSSION

In our study, NACT did not increase the operation time, blood loss, transfusion during or after surgery or the rate of conversion to open surgery. Although NACT could trigger stomach and metastatic lymph node fibrosis (27) and the tissues of patients with NACT are more likely to bleed (28), the laparoscopic monitoring amplification effect, careful intraoperative procedures and the use of laparoscopic high-resolution imaging help reduce unnecessary damage to prevent accidental bleeding. The wide application of intraoperative ultrasound scalpels can also effectively solve these problems. Therefore, no increase in surgical difficulty was noted after chemotherapy.

Lymph node dissection is a key radical gastrectomy for advanced AEG, and the number of lymph nodes dissected is an important prognostic factor for the surgical treatment of advanced gastric cancer (29). In our study, the average number of lymph nodes dissected in both groups of patients undergoing radical resection was greater than 30, which meets the requirements of current guidelines suggesting that LG is feasible in lymph node dissection (30). No significant difference in the number of dissected lymph nodes was noted between the two groups. The number of metastatic LNs was significantly lower in the NACT group (median 0 *vs* 5). After NACT, 5% of the total MLNs could achieve complete tumor regression (31), which may explain the difference.

Postoperative complications are the main indicator for evaluating the safety and feasibility of surgery. In our analysis, the incidence of postoperative complications in the NACT group was slightly higher than that in the LG group; however, the

difference was not significant (29.3% *vs.* 25.6%, P= 0.535). Further analysis showed no difference in systemic complications, local complications, minor complications (CD grade<3) or major complications (CD grade≥3). Pulmonary complications obviously accounted for most of the complications in our study, and no difference was noted between the two groups. In their stratified analysis of 92 patients after PSM, Amir et al. (32) found that the NACT group had similar postoperative complications with the surgery alone group. However, in a study of 90 patients, Wei et al. (33) revealed that the NACT group had a higher risk of postoperative infectious complications. Possible explanations for the differences may be that the baselines of the two studies were inconsistent. The cT stage and cN stage in Amir's study were matched well; however, Wei's study did not take this factor into consideration. Indeed, a reduction in tumor volume allows less extensive procedures, and nutritional improvement before surgery is helpful to reduce the incidence of complications. Although chemotherapy-induced tissue fibrosis can make surgery more difficult (27) and perhaps increase postoperative complications, LG can provide visual magnification, better exposure, and more detailed organ, blood vessel, and nerve operations, reducing unnecessary intra-operative damage. These problems can be effectively solved by laparoscopy. All patients in this study followed a 3-week rest and nutritional support programme after completing preoperative NACT before surgery. Furthermore, we also performed subgroup analysis to further evaluate complications in different parameters. The results of subgroup analyses showed no significant increase in all types of complications of NACT compared with LG.

Patients with progressive disease and stable disease after neoadjuvant chemotherapy represent a special group of patients, and few studies have been conducted on this group before. However, previous studies (34–37) have shown that approximately 32.1% to 58% of patients inevitably underwent SD or PD after neoadjuvant chemotherapy based on fluorouracil + oxaliplatin, so it is necessary to study the short-term efficacy of this group of patients. Subgroup analysis of complications showed no significant difference in the complications between the SD and PD groups compared with either the PR group or LG group (**Appendix, Tables 1, 2**). Subgroup analysis of postoperative results revealed no significant differences in operative time, intraoperative blood loss or other results between the SD and PD groups compared with either the PR group or LG group (**Appendix, Tables 3, 4**). We also noticed a significant increase in the transfer rate of open abdominal surgery and a longer incisional length in the SD and PD groups compared with the direct LG group (**Appendix, Table 4**). In the SD and PD groups, neoadjuvant chemotherapy was not effective, and some patients experienced tumor progression. Moreover, the oedema of tissues around tumors and metastatic lymph nodes might increase the difficulty of laparoscopic surgery, thus increasing the conversion rate of laparotomy. The increase in the rate of conversion to laparotomy subsequently increased the incision length.

In our analysis, NACT was not an independent risk factor for total complications or for major complications in advanced AEG laparoscopic therapy; thus, the applicability of LG for patients after NACT was further verified. An operation time ≥ 300 minutes was identified as a risk factor for overall complications. A longer operation time always indicates a more complicated situation. In addition, prolonged anaesthesia increases the risk of postoperative complications. According to published studies, old age is a leading risk factor for postoperative complications in gastric cancer surgery (38–40). In our study, old age was an independent risk factor for major complications rather than for overall complications. The reason for this difference may be that LG can effectively reduce the total complications in elderly patients. A previous meta-analysis showed that LG could effectively reduce total complications and minor complications (41). We should also realize that gastrectomy still has higher risks of major complications for elderly patients, and more attention should be given when this procedure is used in elderly patients in clinical practice.

In this study, we also compared the total hospital stay, postoperative hospital stay and time to first flatus between the two procedures. The results showed that the hospital stay was significantly longer in the NACT group. The reason for this finding may be that complications in the NACT group were slightly higher than those in the LG group, and surgeons took a longer time to manage the complications. However, the time to first flatus of the NACT group was significantly shorter than that of the LG group. To investigate whether the difference in the time to first flatus was related to the anastomosis method, we performed a statistical analysis of the anastomosis method between the two groups (**Appendix, Tables 5–7**). We first conducted statistics on the two groups of anastomosis methods. The results revealed no significant difference between the NACT group and the LG group (**Appendix, Table 5**). Then, we compared the time to first flatus of the two most common anastomosis methods within the two groups. The results indicated no significant difference in the time to first flatus of end-to-side anastomosis and semi-end-to-end anastomosis in either the NACT group or the LG group (**Appendix, Table 6**). In addition, in a previous study at our centre, 176 cases of end-to-side esophagojejunostomy and 92 cases of semi-end-to-end esophagojejunostomy were included and compared, and no significant difference in the first time to flatus was noted between the two groups (P = 0.957) (42). Finally, we performed an intergroup comparison between the NACT group and the LG group. The results revealed that the time to first flatus of end-to-side anastomosis in the NACT group was significantly shorter than that in the LG group, and the time to first flatus of semi-end-to-end anastomosis in the NACT group was also significantly shorter than that in the LG group (**Appendix, Table 7**). Therefore, we hypothesized that the difference in the time to first flatus between the NACT group and the LG group was caused by neoadjuvant chemotherapy rather than the difference in anastomosis. In our study, the BMI of the NACT group before surgery was significantly greater than that on admission. AEG is often accompanied by symptoms of obstruction, leading to poor preoperative nutritional status. NACT can effectively improve the obstruction state preoperatively supplemented with enteral nutrition preparation and prove the preoperative nutritional status.

Nevertheless, there are several limitations in the current study. First, as a retrospective analysis conducted at a single centre, this study is subject to possible selection bias despite the use of PSM to reduce bias, which was intended to mimic randomized controlled trials. Second, the regimens and indications for NACT were not standardized; therefore, the effects of different NACT regimens were not analysed.

In conclusion, the findings of this study suggest that NACT combined with LG is safe and feasible in treating locally advanced Siewert type II and III AEG in terms of morbidity and short-term surgical outcomes. Multicentre, prospective, clinical trials with large sample sizes are still warranted to verify our findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Southwest Hospital (Chongqing, China). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YS and P-wY contributed to the conception and design of the study. M-sD, FQ, Y-Lz, and YW organized the database. DL and QF performed the statistical analysis. QF wrote the first draft of the manuscript. X-sW and Z-sL wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.690662/full#supplementary-material

REFERENCES

1. Imamura Y, Watanabe M, Toihata T, Takamatsu M, Kawachi H, Haraguchi I, et al. Recent Incidence Trend of Surgically Resected Esophagogastric Junction Adenocarcinoma and Microsatellite Instability Status in Japanese Patients. *Digestion* (2019) 99(1):6–13. doi: 10.1159/000494406
2. Buas MF, Vaughan TL. Epidemiology and Risk Factors for Gastroesophageal Junction Tumors: Understanding the Rising Incidence of This Disease. *Semin Radiat Oncol* (2013) 23(1):3–9. doi: 10.1016/j.semradonc.2012.09.008
3. Saka M, Morita S, Fukagawa T, Katai H. Present and Future Status of Gastric Cancer Surgery. *Jpn J Clin Oncol* (2011) 41(3):307–13. doi: 10.1093/jjco/hyq240
4. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-Assisted Billroth I Gastrectomy. *Surg Laparosc Endosc* (1994) 4(2):146–8.
5. Kinoshita T. Minimally Invasive Approaches for Early Gastric Cancer in East Asia: Current Status and Future Perspective. *Transl Gastroenterol Hepatol* (2020) 5:20. doi: 10.21037/tgh.2019.10.08
6. Kim W, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW, et al. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-Term Outcomes From a Multicenter Randomized Controlled Trial (KLASS-01). *Ann Surg* (2016) 263(1):28–35. doi: 10.1097/SLA.0000000000001346
7. Hu Y, Huang C, Sun Y, Su X, Cao H, Hu J, et al. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. *J Clin Oncol* (2016) 34(12):1350–7. doi: 10.1200/JCO.2015.63.7215
8. Park YK, Yoon HM, Kim YW, Park JY, Ryu KW, Lee YJ, et al. Laparoscopy-Assisted Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: Results From a Randomized Phase II Multicenter Clinical Trial (COACT 1001). *Ann Surg* (2018) 267(4):638–45. doi: 10.1097/SLA.0000000000002168
9. Liao C, Feng Q, Xie S, Chen J, Shi Y. Laparoscopic Versus Open Gastrectomy for Siewert Type II/III Adenocarcinoma of the Esophagogastric Junction: A Meta-Analysis. *Surg Endosc* (2021) 35(2):860–71. doi: 10.1007/s00464-020-07458-y
10. Zhang P, Zhang X, Xue H. Long-Term Results of Hand-Assisted Laparoscopic Gastrectomy for Advanced Siewert Type II and Type III Esophagogastric Junction Adenocarcinoma. *Int J Surg* (2018) 53:201–5. doi: 10.1016/j.ijsu.2018.03.004
11. Barbour AP, Rizk NP, Gonen M, Tang L, Bains MS, Rusch VW, et al. Adenocarcinoma of the Gastroesophageal Junction: Influence of Esophageal Resection Margin and Operative Approach on Outcome. *Ann Surg* (2007) 246(1):1–8. doi: 10.1097/01.sla.0000255563.65157.d2
12. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial. *J Clin Oncol* (2011) 29(13):1715–21. doi: 10.1200/JCO.2010.33.0597
13. Coccolini F, Nardi M, Montori G, Ceresoli M, Celotti A, Cascinu S, et al. Neoadjuvant Chemotherapy in Advanced Gastric and Esophago-Gastric Cancer. Meta-Analysis of Randomized Trials. *Int J Surg* (2018) 51:120–7. doi: 10.1016/j.ijsu.2018.01.008
14. Miao ZF, Liu XY, Wang ZN, Zhao TT, Xu YY, Song YX, et al. Effect of Neoadjuvant Chemotherapy in Patients With Gastric Cancer: A PRISMA-Compliant Systematic Review and Meta-Analysis. *BMC Cancer* (2018) 18(1):118. doi: 10.1186/s12885-018-4027-0
15. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting Results of Cancer Treatment. *Cancer Am Cancer Soc* (1981) 47(1):207–14. doi: 10.1002/1097-0142(19810101)47:1<207::aid-cncr2820470134>3.0.co;2-6
16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). *Eur J Cancer* (2009) 45(2):228–47. doi: 10.1016/j.ejca.2008.10.026

17. Nakajima T. Gastric Cancer Treatment Guidelines in Japan. *Gastric Cancer* (2002) 5(1):1–5. doi: 10.1007/s101200200000
18. Japanese Gastric Cancer Association. Japanese Gastric Cancer Treatment Guidelines 2010 (Ver. 3). *Gastric Cancer* (2011) 14(2):113–23. doi: 10.1007/s10120-011-0042-4
19. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to Build a Bridge From a Population-Based to a More "Personalized" Approach to Cancer Staging. *CA Cancer J Clin* (2017) 67(2):93–9. doi: 10.3322/caac.21388
20. Clavien PA, Sanabria JR, Strasberg SM. Proposed Classification of Complications of Surgery With Examples of Utility in Cholecystectomy. *Surgery* (1992) 111(5):518–26.
21. Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. *Ann Surg* (2004) 240(2):205–13. doi: 10.1097/01.sla.0000133083.54934.ae
22. Siewert JR, Stein HJ. Classification of Adenocarcinoma of the Oesophagogastric Junction. *Br J Surg* (1998) 85(11):1457–9. doi: 10.1046/j.1365-2168.1998.00940.x
23. Sugita S, Kinoshita T, Kaito A, Watanabe M, Sunagawa H. Short-Term Outcomes After Laparoscopic Versus Open Transhiatal Resection of Siewert Type II Adenocarcinoma of the Esophagogastric Junction. *Surg Endosc* (2018) 32(1):383–90. doi: 10.1007/s00464-017-5687-6
24. Huang CM, Lv CB, Lin JX, Chen QY, Zheng CH, Li P, et al. Laparoscopic-Assisted Versus Open Total Gastrectomy for Siewert Type II and III Esophagogastric Junction Carcinoma: A Propensity Score-Matched Case-Control Study. *Surg Endosc* (2017) 31(9):3495–503. doi: 10.1007/s00464-016-5375-y
25. Shi Y, Li L, Xiao H, Guo S, Wang G, Tao K, et al. Feasibility of Laparoscopic Gastrectomy for Patients With Siewert-Type II/III Adenocarcinoma of the Esophagogastric Junction: A Propensity Score Matching Analysis. *PLoS One* (2018) 13(9):e0203125. doi: 10.1371/journal.pone.0203125
26. Zhang YC, Wu QB, Yang XY, Yang TH, Wang ZQ, Wang ZQ, et al. Laparoscopic-Assisted Transhiatal Esophagogastrectomy Without Thoracic or Cervical Access: A Series of One Hundred Three Consecutive Cases. *J Laparoendosc Adv Surg Tech A* (2018) 28(7):845–52. doi: 10.1089/lap.2017.0692
27. An JY, Kim KM, Kim YM, Cheong JH, Hyung WJ, Noh SH. Surgical Complications in Gastric Cancer Patients Preoperatively Treated With Chemotherapy: Their Risk Factors and Clinical Relevance. *Ann Surg Oncol* (2012) 19(8):2452–8. doi: 10.1245/s10434-012-2267-9
28. Wu L, Ge L, Qin Y, Huang M, Chen J, Yang Y, et al. Postoperative Morbidity and Mortality After Neoadjuvant Chemotherapy Versus Upfront Surgery for Locally Advanced Gastric Cancer: A Propensity Score Matching Analysis. *Cancer Manag Res* (2019) 11:6011–8. doi: 10.2147/CMAR.S203880
29. Koh YW, Park YS, Ryu MH, Ryoo BY, Park HJ, Yook JH, et al. Postoperative Nodal Status and Diffuse-Type Histology are Independent Prognostic Factors in Resectable Advanced Gastric Carcinomas After Preoperative Chemotherapy. *Am J Surg Pathol* (2013) 37(7):1022–9. doi: 10.1097/PAS.0b013e31828778fd
30. Lu J, Wang W, Zheng CH, Fang C, Li P, Xie JW, et al. Influence of Total Lymph Node Count on Staging and Survival After Gastrectomy for Gastric Cancer: An Analysis From a Two-Institution Database in China. *Ann Surg Oncol* (2017) 24(2):486–93. doi: 10.1245/s10434-016-5494-7
31. Kinoshita O, Ichikawa D, Ichijo Y, Komatsu S, Okamoto K, Kishimoto M, et al. Histological Evaluation for Chemotherapeutic Responses of Metastatic Lymph Nodes in Gastric Cancer. *World J Gastroenterol* (2015) 21(48):13500–6. doi: 10.3748/wjg.v21.i48.13500
32. Charruf AZ, Ramos M, Pereira MA, Dias AR, de Castria TB, Zilberstein B, et al. Impact of Neoadjuvant Chemotherapy on Surgical and Pathological Results of Gastric Cancer Patients: A Case-Control Study. *J Surg Oncol* (2020) 121(5):833–9. doi: 10.1002/jso.25839
33. Wei Z, Tan B, Cao S, Liu S, Tan X, Yao Z, et al. The Influence of Neoadjuvant Chemotherapy on Gastric Cancer Patients' Postoperative Infectious Complications: What Is the Negative Role Played by the Intestinal Barrier Dysfunction? *Oncotarget* (2017) 8(26):43376–88. doi: 10.18632/oncotarget.14758
34. Zhao Q, Lian C, Huo Z, Li M, Liu Y, Fan L, et al. The Efficacy and Safety of Neoadjuvant Chemotherapy on Patients With Advanced Gastric Cancer: A Multicenter Randomized Clinical Trial. *Cancer Med* (2020) 9(16):5731–45. doi: 10.1002/cam4.3224
35. Zhang X, Huang H, Wei Z, Zhu Z, Yang D, Fu H, et al. Comparison of Docetaxel + Oxaliplatin + S-1 vs Oxalipatin + S-1 as Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: A Propensity Score Matched Analysis. *Cancer Manag Res* (2020) 12:6641–53. doi: 10.2147/CMAR.S258360
36. Sah BK, Zhang B, Zhang H, Li J, Yuan F, Ma T, et al. Neoadjuvant FLOT Versus SOX Phase II Randomized Clinical Trial for Patients With Locally Advanced Gastric Cancer. *Nat Commun* (2020) 11(1):6093. doi: 10.1038/s41467-020-19965-6
37. Zhao Q, Li Y, Huang J, Fan L, Tan B, Tian Y, et al. Short-Term Curative Effect of S-1 Plus Oxaliplatin as Perioperative Chemotherapy for Locally Advanced Gastric Cancer: A Prospective Comparison Study. *Pharmazie* (2017) 72(4):236–40. doi: 10.1691/ph.2017.6865
38. Zhou J, Yu P, Shi Y, Tang B, Hao Y, Zhao Y, et al. Evaluation of Clavien-Dindo Classification in Patients Undergoing Total Gastrectomy for Gastric Cancer. *Med Oncol* (2015) 32(4):120. doi: 10.1007/s12032-015-0573-3
39. Li Z, Bai B, Zhao Y, Yu D, Lian B, Liu Y, et al. Severity of Complications and Long-Term Survival After Laparoscopic Total Gastrectomy With D2 Lymph Node Dissection for Advanced Gastric Cancer: A Propensity Score-Matched, Case-Control Study. *Int J Surg* (2018) 54(Pt A):62–9. doi: 10.1016/j.ijsu.2018.04.034
40. Hamakawa T, Kurokawa Y, Mikami J, Miyazaki Y, Takahashi T, Yamasaki M, et al. Risk Factors for Postoperative Complications After Gastrectomy in Gastric Cancer Patients With Comorbidities. *Surg Today* (2016) 46(2):224–8. doi: 10.1007/s00595-015-1175-6
41. Chen X, Feng X, Wang M, Yao X. Laparoscopic Versus Open Distal Gastrectomy for Advanced Gastric Cancer: A Meta-Analysis of Randomized Controlled Trials and High-Quality Nonrandomized Comparative Studies. *Eur J Surg Oncol* (2020) 46(11):1998–2010. doi: 10.1016/j.ejso.2020.06.046
42. Duan W, Liu K, Fu X, Shen X, Chen J, Su C, et al. Semi-End-to-End Esophagojejunostomy After Laparoscopy-Assisted Total Gastrectomy Better Reduces Stricture and Leakage Than the Conventional End-to-Side Procedure: A Retrospective Study. *J Surg Oncol* (2017) 116(2):177–83. doi: 10.1002/jso.24637

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Treatment Patterns and Outcomes of Elderly Patients With Potentially Curable Esophageal Cancer

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Objectives: The proportion of elderly patients with esophageal cancer (EC) is increasing due to prolonged life expectancy and aging process. The aim of the study is to explore the optimal treatment strategy for elderly patients (aged ≥70 years) with locally advanced EC.

Methods: Eligible patients with cT2-4aNxM0 EC were identified in the Surveillance, Epidemiology, and End Results database from 2010 to 2016. Treatment patterns were divided into six groups: surgical resection (S), chemoradiotherapy (CRT), trimodality therapy (CRT+S), radiotherapy (RT), chemotherapy (CT), or observation with no treatment (Obs). Survival between groups was compared using the log-rank test, and the Cox proportional hazards model was used to identify factors associated with overall survival (OS).

Results: A total of 2917 patients with potentially curable EC were identified. Of all the patients included, 6.7%, 51.8%, 18.0%, 9.4% and 3.6%received S, CRT, CRT+S, RT, and CT, respectively, whereas 10.6% underwent Obs. The 3-year OS estimates were 30.2% (95% confidence interval [CI]: 23.5–38.9%), 25.4% (95% CI: 22.8–28.3%),44.3% (95% CI: 39.3–49.9%), 11.4% (95% CI: 7.7–17.0%), 16.1% (95% CI: 9.1–28.3%), and 5.6% (95% CI: 3.2–9.8%) for S, CRT, CRT+S RT, CT, and Obs (p<0.001), respectively. Overall, patents underwent CRT+S had the longest OS, compared to other treatment patterns, and the survival difference was not significant between patients receiving CRT and S (p=0.12) in the elderly population. However, the survival benefits of trimodality therapy over CRT gradually weakened with the increase in age, and became statistically non-significant for EC patients aged ≥80 years (p=0.35). Multivariate analysis showed that treatment patterns, age, sex, tumor grade, T stage, N stage, and marital status were significantly associated with OS.

Conclusion: Generally, the use of trimodality therapy was associated with the longest OS, the survival benefits were comparable between CRT and S alone, and CRT was superior to RT or CT alone in elderly patients with curable EC. For patients intolerable to surgery or aged ≥80 years, definitive CRT should be considered as a preferable option.

Keywords: esophageal cancer, treatment patterns, surgery, chemoradiotherapy, SEER

INTRODUCTION

Esophageal cancer (EC) is one of the most common cancers worldwide. Moreover, 604,100 people were newly diagnosed with EC, whereas 544,076 people died of EC in 2020, according to Global Cancer Statistics (1). The peak age of EC incidence is between 60 and 70 years, and then, the incidence of EC decreases with age. According to the Global Burden of Disease report, approximately 30% of all newly diagnosed patients with EC are older than 70 years (2). The proportion of elderly patients with EC intends to increase gradually in the future due to prolonged life expectancy and aging process. However, evidence concerning treatment strategies in elderly patients with EC is still inadequate, since most data are from clinical trials with younger patients, in which the elderly have been often neglected and underrepresented (3).

Since the publication of the CROSS study (4), neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy is recommended for patients with potentially curable EC, according to the National Comprehensive Cancer Network and other guidelines (5). However, elderly patients tend to have poorer performance scores, more multiple comorbidities, and shorter life expectancy compared to young individuals. Moreover, they might be less tolerant to esophagectomy or definitive CRT, due to severe complications and side effects (6–8). Thus, treatment for elderly patients with esophageal carcinoma appears to be underutilized (9). Controversies on the selection of the optimal treatment strategy for elderly patients with curable EC, including esophagectomy versus CRT (10, 11) or CRT versus radiotherapy (RT) alone, still continue (8, 12). For example, Abrams JA et al. have reported that esophagectomy may be associated with better survival for early-stage EC patients aged ≥65 years compared to CRT (11), whereas Koeter M et al. have found that survival was comparable among elderly patients (aged ≥75 years) with esophageal squamous cell carcinoma (ESCC) who underwent surgery or received definitive CRT (10). However, most previous studies have included a relatively small number of samples or only compared the efficiency of two main treatment patterns (10, 11), with inconsistent definitions of "elderly population" from aged 65 years and older (11, 13) to ≥70 (12, 14) or 75 years (10) or more than 80 years (15). Given the conflicting and insufficient data on this population, the optimal treatment strategy for elderly patients with potentially curable EC needs to be further investigated.

In the present study, we systematically evaluated all treatment patterns and outcomes of elderly patients with potentially curable EC using the Surveillance, Epidemiology, and End Results (SEER) database. To provide a comprehensive understanding of the impact of age on treatment selections and survival outcomes, patients were further divided into four age groups as follows, age 70–74, 75–79, 80–84, and ≥85 years.

MATERIALS AND METHODS

Patient Selection

Data Source

This study involved extraction of eligible patient-level data on elderly EC cases from the SEER database, which collects data on cancer incidence, treatment, and survival from population-based cancer registries, covering 26% of the US population (16). In our study, elderly patients referred to those aged 70 years or older, mainly according to the definitions of elderly patients with NSCLC (17, 18). To reflect the modern radiation technology (intensity-modulated RT) and recent progress in EC treatment, patients aged ≥70 years diagnosed with stage T2-T4aNxM0 EC from 2010 to 2016 were identified from the SEER database, using SEER*Stat software (version 8.3.8, NIH, USA).

Inclusion and Exclusion Criteria

Potentially curable esophageal cancer in our study was recognized as localized disease without distant metastases, which can be treated by radical surgery or definitive CRT. The inclusion criteria were as follows: (1) patients with histologically confirmed EC, esophageal adenocarcinoma (EAC), or ESCC; (2) patients aged >70 years; (3) patients with stage T2-T4aNxM0, according to the guidelines of the American Joint Committee on Cancer 7th edition; (4) patients with treatment information, including surgery, radiation sequence with surgery, and chemotherapy (CT).The exclusion criteria were as follows: (1) patients who underwent endoscopic resection; (2) patients receiving resection through biopsy or regional lymph node aspiration; and (3) patients with missing or incomplete data on treatment information, including RT or survival status.

Study Definitions

In our study, treatment patterns for elderly patients were divided into six groups: surgical resection (S), CRT, CRT+S, RT, CT, or observation with no treatment (Obs). The treatment definitions were as follows: the treatment of surgery was defined as patients

Abbreviations: EC, esophageal cancer; SEER, the Surveillance, Epidemiology and End Results database; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; S, surgical resection; CRT, chemoradiotherapy; RT, radiotherapy; CT, chemotherapy; Obs, observation with no treatment; OS, overall survival; CSS, cancer-specific survival; AUC, area under the curve; ROC, receiver operating characteristic curve; CGA, comprehensive geriatric assessment.

who underwent esophagectomy alone or combined with RT or CT, whereas CRT referred to patients receiving RT with CT, concurrent or sequential. CRT+S referred to patients receiving CRT before or after surgery, RT or CT was defined as patients receiving RT or CT alone. The primary endpoint in our study was overall survival (OS), and the secondary endpoint was cancer-specific survival (CSS), which was defined as the intervals between the date of diagnosis and the occurrence of any-cause or cancer-specific death, respectively.

Statistical Analyses

Differences in baseline characteristics between patients treated with different patterns were compared using Pearson's chi-squared test or Fisher's exact test. Multinomial logistic regression was used to determine the predictors of the use of trimodality therapy (CRT+S). Survival was estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival curves. Univariate Cox regression analysis was performed to identify the significant variables associated with survival, and variables with a p value less than 0.10 were included in the multivariate Cox model. P for the interaction between subgroup analyses was calculated using the likelihood ratio test. All tests were two-sided, and p values <0.05 were considered statistically significant. Statistical analysis including Pearson's chi-squared test, logistic regression was performed by the International Business Machines (IBM) Statistical Package for the Social Sciences statistics software (version 22.0; IBM Corp., Armonk, NY, USA). R version 3.4.1, including ggplot2, survival, survminer, foreign, rms packages, was used for Cox regression analysis, Kaplan-Meier survival curve comparison and nomgram drawing.

RESULTS

Patient Characteristics and Patterns of Care

From 2010 to 2016, a total of 24006 newly diagnosed patients with EC were found in the SEER database; 43.55% (N=10455) of them were elderly patients aged > 70 years. According to the inclusion criteria, 2917 patients with potentially curable EC were identified in our study. Of all the patients included, 6.7% (n =194) received surgery alone, more than one half patients (N=1510, 51.8%) received CRT, 18.0% (N=524) received CRT+S, 9.4% (N=273) received RT, and 3.6% (N=106) received CT, whereas 10.6% (N=310) underwent Obs. A flowchart of patient selection was presented in **Figure 1**. Data were widely collected for each patient for analysis, including patient characteristics, clinicopathologic tumor parameters, treatment, and survival information. Baseline patient demographics and clinical characteristics are listed in **Table 1**. As shown in **Figure 2**, patients receiving CRT+S tended to be younger, and more patients underwent RT alone or Obs, with the increase in age (p<0.001). Other variables significantly associated with trimodality therapy included earlier T stage (odds ratio [OR] for T2 = 6.01, 95% confidence interval[CI]:2.62-1.78, p<0.001;

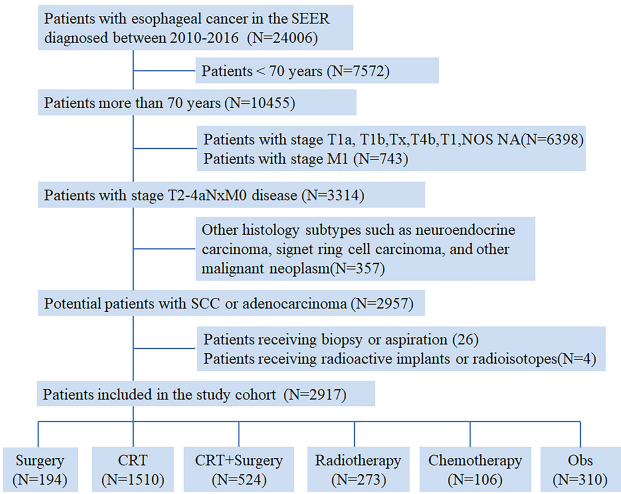

FIGURE 1 | Flow chart of patient selection from the Surveillance, Epidemiology, and End Results (SEER) database.

OR for T3 = 6.12, 95%CI:3.29-11.60, p<0.001), married status (OR=2.58, 95%CI:1.26-5.30, p=0.01), middle or lower third location of primary lesions (OR for middle location=2.93, 95% CI:1.47-5.87, p<,0.001; OR for lower location=3.53, 95% CI: 1.98–6.28, p<0.001) and white race(OR=2.8, 95%CI:1.23-6.36, p=0.014).

Survival Analyses

In the overall analysis for OS, patients receiving trimodality therapy showed significantly better survival than patients who underwent other treatment patterns, whereas observation resulted in the worst survival, as shown in **Figure 3A**. The 3-year OS estimates were 30.2% (95% confidence interval [CI]: 23.5–38.9%), 25.4% (95% CI: 22.8–28.3%),44.3% (95% CI: 39.3–49.9%), 11.4% (95% CI: 7.7–17.0%), 16.1% (95% CI: 9.1–28.3%), and 5.6% (95% CI: 3.2–9.8%) for S, CRT, CRT+S RT, CT, and Obs (p<0.001), respectively. Compared to Obs, any treatment pattern was associated with superior OS, and the hazard ratios (HRs) for S, CRT, CRT+S, RT, and CT were 0.25(95%CI: 0.20-0.31), 0.29(95%CI:0.25-0.33), 0.17(95%CI:0.14-0.20), 0.54(95% CI:0.45-0.65) and 0.43(95%CI:0.33-0.56) (p<0.001), respectively. Further pairwise comparisons between groups showed that CRT+S significantly was related to better outcomes compared to any other treatment patterns (p<0.01), and no significant differences were observed between patients who underwent CRT and S alone(p=0.12). Moreover, patients receiving CRT had a significant survival advantage over RT or CT alone (p<0.01). For CSS, similar results were found (**Figure 3B**), and the 3-year CSS estimates were 56.3%(95%CI:47.7-66.4%), 45.3%(95%CI:41.8-49.1%),61.1%(95%CI:55.8-67.0%),29.0%(95%CI:21.5-39.0%), 28.9%(95%CI:17.5-47.7%) and 19.0%(95%CI:12.4-29.0%) for S, CRT, CRT+S, RT, CT, and Obs (p<0.001), respectively. In this analysis, the use of surgery or CRT+S brought better survival benefits than CRT (p=0.024,<0.001 respectively), indicating the critical role of surgery.

When further stratified by age group, the superiority of CRT +S was observed in almost all age groups, as shown in **Figure 4**. However, the survival benefits of CRT+S or surgery over CRT gradually weakened with the increase in age, and the 3 year-OS estimates were 20.6%(95%CI:11.8-36.0%) for S, 27.5%(95% CI:23.0-32.9%) for CRT and 38.5%(25.6-57.9%) for CRT+S respectively in EC patients aged >80 years, and the survival benefit of trimodality therapy was statistically non-significant (p=0.36 compared to S, 0.35 compared to CRT). The results of definitive CRT remained fairly stable over the age groups. Subgroup analyses stratified by other factors, including race, pathology, grade, stage, location, and marital status also supported the superiority of trimodality therapy and the results were presented in **Table S1**.

Predictive Factors for OS in Elderly Patients With Esophageal Cancer

Univariate Cox regression analysis was performed to identify the variables associated with OS in the selected cohort, and the significant predictive factors are consisted ofage, grade, sex, T stage, N stage, marital status, and treatment patterns, whilerace, pathological subtype, and tumor location were not significantly associated with OS in univariate analysis. The results were presented in **Table 2**. In multivariate Cox regression analysis, treatment pattern was still a statistically significant factor for improved OS (p<0.001). Other significant factors identified by multivariate analysis included age, sex, tumor grade, T stage, N stage, and marital status (p<0.05). Based on these predictive factors found on multivariate analysis, predictive nomograms

TABLE 1 | Baseline Patient Demographics and Clinical and Tumor Characteristics.

Variables	Total N = 2917 (100%)	S N = 194 (6.7%)	CRT N = 1510 (51.8%)	CRT+S N = 524 (18.0%)	RT N = 273 (9.4%)	CT N = 106 (3.6%)	Obs N = 310 (10.6%)	P value
Age at diagnosis								<0.001
70-74 years	1081 (37.1%)	68 (35.1%)	540 (35.8%)	309 (59.0%)	45 (16.5%)	46 (43.4%)	73 (23.5%)	
75-79 years	836 (28.7%)	62 (32.0%)	463 (30.7%)	160 (30.5%)	53 (19.4%)	35 (33.0%)	63 (20.3%)	
80-84 years	591 (20.3%)	43 (22.2%)	325 (21.5%)	49 (9.4%)	80 (29.3%)	16 (15.1%)	78 (25.2%)	
85+ years	409 (14.0%)	21 (10.8%)	182 (12.1%)	6 (1.1%)	95 (34.8%)	9 (8.5%)	96 (31.0%)	
Sex								<0.001
Male	2170 (74.4%)	136 (70.1%)	1118 (74.0%)	442 (84.4%)	194 (71.1%)	78 (73.6%)	202 (65.2%)	
Female	747 (25.6%)	58 (29.9%)	392 (26.0%)	82 (15.6%)	79 (28.9%)	28 (26.4%)	108 (34.8%)	
Race								<0.001
White	2601 (89.2%)	178 (91.8%)	1339 (88.7%)	497 (94.8%)	232 (85.0%)	90 (84.9%)	265 (85.5%)	
Black	173 (5.9%)	5 (2.6%)	100 (6.6%)	16 (3.1%)	21 (7.7%)	7 (6.6%)	24 (7.7%)	
Others	143 (4.9%)	11 (5.7%)	71 (4.7%)	11 (2.1%)	20 (7.3%)	9 (8.5%)	21 (6.8%)	
Histological subtype								<0.001
Adenocarcinoma	1108 (38.0%)	67 (34.5%)	661 (43.8%)	97 (18.5%)	129 (47.3%)	39 (36.8%)	115 (37.1%)	
Squamous cell	1809 (62.05)	127 (65.5%)	849 (56.2%)	427 (81.5%)	144 (52.7%)	67 (63.2%)	195 (62.9%)	
Stage								<0.001
II	1404 (48.1%)	115 (59.3%)	736 (48.7%)	201 (38.4%)	164 (60.1%)	40 (37.7%)	148 (47.7%)	
III	1513 (51.9%)	79 (40.7%)	774 (51.3%)	323 (61.6%)	109 (39.9%)	66 (62.3%)	162 (52.3%)	
T stage								<0.001
T2	740 (25.4%)	65 (33.5%)	394 (26.1%)	116 (22.1%)	69 (25.3%)	22 (20.8%)	74 (23.9%)	
T3	1959 (67.2%)	122 (6.2%)	1030 (68.2%)	385 (73.5%)	185 (67.8%)	71 (67.0%)	166 (53.5%)	
T4a	218 (7.5%)	7 (3.6%)	86 (5.7%)	23 (4.4%)	19 (7.0%)	13 (12.2%)	70 (22.6%)	
N stage								<0.001
N0	1259 (43.2%)	104 (53.6%)	624 (41.3%)	164 (31.3%)	158 (57.9%)	39 (36.8%)	170 (54.8%)	
N1	1285 (44.1%)	47 (24.2%)	696 (46.1%)	278 (53.1%)	90 (7.0%)	54 (50.9%)	120 (38.7%)	
N2	310 (10.6%)	28 (14.4%)	166 (11.0%)	71 (13.5)	21 (7.7%)	10 (9.4%)	310 (10.6%)	
N3	63 (2.2%)	15 (7.7%)	24 (1.6%)	11 (2.1%)	4 (1.5%)	3 (2.8%)	63 (2.2%)	
Grade								<0.001
Well (G1)	170 (5.8%)	11 (5.7%)	86 (5.7%)	26 (5.0%)	17 (6.2%)	5 (4.7%)	25 (8.1%)	
Moderate (G2)	1094 (37.5%)	85 (43.8%)	573 (37.9%)	209 (39.9%)	93 (34.1%)	35 (33.0%)	99 (31.9%)	
Poorly (G3)	1124 (38.5%)	83 (42.8%)	548 (36.3%)	231 (44.1%)	110 (40.3%)	46 (43.4%)	106 (34.2%)	
Undifferentiated (G4)	26 (0.9%)	5 (19.2%)	13 (0.9%)	2 (0.4%)	1 (0.4%)	1 (0.9%)	4 (1.3%)	
Unknown	503 (17.2%)	10 (5.2%)	290 (19.2%)	56 (10.7%)	52 (19.0%)	19 (17.9%)	76 (24.5%)	
Tumor location								<0.001
Upper third	243 (8.3%)	15 (7.7%)	155 (10.3%)	9 (1.7%)	28 (10.3%)	8 (7.5%)	28 (9.0%)	
Middle third	602 (20.6%)	32 (16.5%)	360 (23.8%)	61 (11.6%)	79 (28.9%)	17 (16.0%)	53 (17.1%)	
Lower third	1841 (63.1%)	134 (69.1%)	879 (58.2%)	429 (81.9%)	149 (54.6%)	61 (57.5%)	189 (61.0%)	
Unknown	231 (7.9%)	13 (6.7%)	116 (7.7%)	25 (4.8%)	17 (6.2%)	20 (18.9%)	40 (12.9%)	
Marital status								<0.001
Married	1684 (57.7%)	96 (49.5%)	887 (58.7%)	372 (71.0%)	137 (50.2%)	65 (61.3%)	127 (41.0%)	
Unmarried	1087 (37.3%)	86 (44.3%)	554 (36.7%)	133 (25.4%)	122 (44.7%)	27 (25.5%)	165 (53.2%)	
Unknown	146 (5.0%)	12 (6.2%)	69 (4.6%)	19 (3.6%)	14 (5.1%)	14 (13.2%)\	18 (5.8%)	

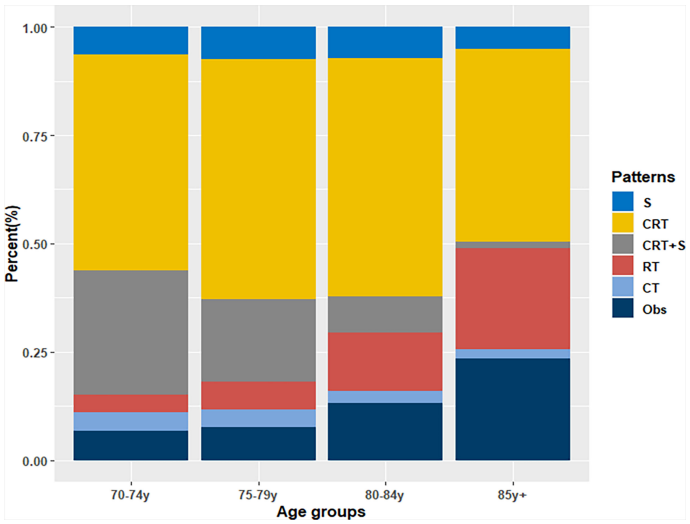

FIGURE 2 | Treatment patterns of elderly patients with EC by age group.

were constructed to predict the 3- and 5-year cumulative incidence of OS for elderly patients with potentially curable EC (**Figure 5**), and the concordance index for the prediction of OS was calculated (0.68, 95% CI:0.66–0.70). In addition, the areas under the curve of the receiver operating characteristic curves for 3-year and 5-year OS were 0.72 and 0.73, respectively (**Figures 6A, B**). The calibration plots for the 3-year and 5-year cumulative probabilities of OS are presented in **Figures 6C, D**, which showed good consistency between nomogram prediction and actual observation.

DISCUSSION

In this large, population-based study, patterns of treatment and outcomes of elderly patients with potentially curable EC were comprehensively analyzed. The results showed that the usage ratios of trimodality therapy were decreased with the increase in age, CRT was mostly adapted in patients with locally advanced-stage EC, and RT alone was also occasionally employed, especially in patients aged ≥80 years. The survival analysis indicated that all the treatment patterns had survival benefits in elderly patients compared to Obs. The use of surgery or CRT_+S was associated with improved OS in the elderly EC patients, and CRT was superior to RT or CT alone. The results were stable across subgroup analyses stratified by most factors, including sex, clinical stage, histological subtype, and tumor location, demonstrating the reliability of our conclusions.

In younger patients, surgery-based trimodality therapy has been the standard treatment for locally advanced EC (19, 20). However, elderly patients tend to have a decline in physiological function and a high prevalence of chronic diseases, such as high

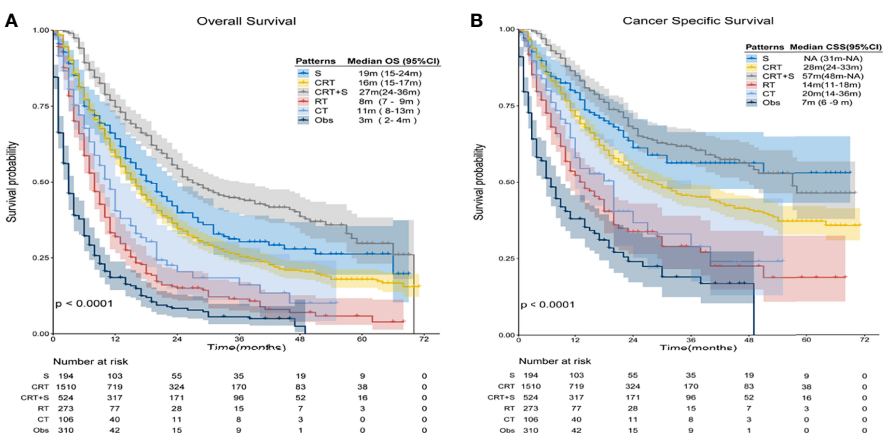

FIGURE 3 | Kaplan-Meier survival curves of OS and CSS for elderly patients with potentially curable EC. **(A)** Overall Survival(OS), **(B)** Cancer Specific Survival (CSS).

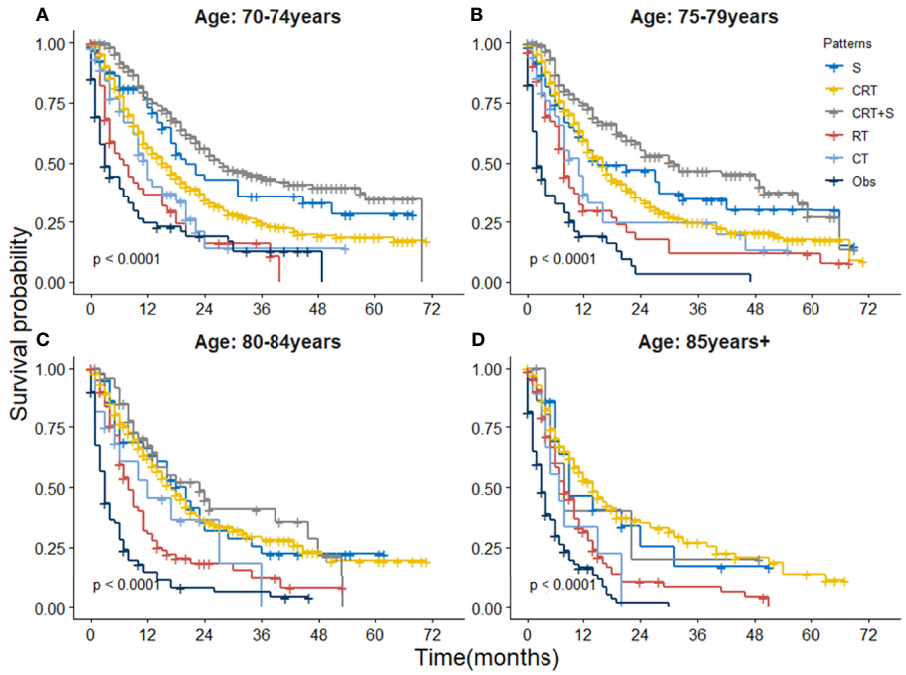

FIGURE 4 | Kaplan-Meier survival curves of OS for elderly patients with potentially curable EC stratified by age group. **(A)** 70-74 year, **(B)** 75-79 years, **(C)** 80-84 years and **(D)** ≥85 years.

blood pressure, diabetes, and cardiovascular system diseases, which make them difficult to respond to surgical trauma and recover slowly (21). Consequently, elderly patients undergoing esophagectomy for cancer are reported to have a significantly higher risk of postoperative mortality, especially in patients aged 75 years or older (7, 22, 23). Hence, elderly patients with EC should be cautiously evaluated and selected for surgery (24). In fact, only one-third of patients in our cohort underwent surgical resection, and the number of patients who underwent surgery decreased dramatically with increasing age. In this study, a significantly small number of patients (<10%) aged >80 years underwent surgery, reflecting concerns about postoperative morbidity and the underuse of surgery in elderly patients with EC.

In the survival analysis, elderly patients who underwent CRT+S lived significantly longer than those who received other treatment patterns, including CRT or surgery alone. The advantage of trimodality therapy was stable in both EAC and ESCC and across stages II to III.In consistence with our findings, a series of other retrospective studies also supported the use of surgery in elderly patients with EC, and esophagectomy was found to be associated with improved survival, even with increased risk of complications in elderly patients (6, 10, 11, 25, 26). In fact, it is also reported that trimodality therapy is a reasonable treatment option for properly selected elderly patients with EC, and can bring survival benefits (27). In addition to these findings, our study showed that the survival benefits of trimodality therapy or surgery disappeared in patients aged >80 years, while the benefit of definitive CRT remained fairly stable over the age groups, compared to RT or CT alone. Therefore, after comprehensive assessment and rigid screening, CRT+S should be preferentially recommended for elderly patients with good performance status and long expected life span, given the improved outcomes with treatment. For patients intolerable to surgery or aged >80 years, definitive CRT can be considered as an alternative option.

Considering postoperative morbidity and reduced quality of life, a large proportion of patients with EC favor non-operative treatment patterns. In our analysis, almost half of the patients chose CRT as their primary treatment, and 17.5% of patients aged >80 years only received RT alone. In the survival analysis, the survival benefit of CRT was only next to the trimodality therapy, and comparable with surgery alone, but remarkably superior to RT or CT alone. CRT has been the standard therapy for patients with locally advanced EC ineligible for surgery, since the Radiation Therapy Oncology Group 85-01 trial (28). However, in clinical practice, due to concerns regarding treatment-related adverse effects, including esophagitis, pneumonitis, and hematologic toxicity, part of elderly EC patients only undergo RT alone (29, 30). Several previous studies have demonstrated that definitive CRT might be considered as both effective and safe in elderly patients with EC, exhibiting similar long-term clinical benefits compared to younger patients (31–33). Our study once again confirmed the superiority of CRT over RT alone among all elderly age groups in a large population. RT alone should be recommended with

TABLE 2 | Univariate Analysis and Multivariate Cox regression analysis of OS in in elderly EC patients with ≥ 70 years.

Variables	Univariate Analysis		Multivariate analysis	
	HR with 95% CI	*p* value	HR with 95%CI	*p* value
Age				
70-74 years	1		1	
75-79 years	1.10 (0.98-1.23)	0.12	1.05 (0.93-1.18)	0.44
80-84 years	1.29 (1.13-1.46)	<0.001	1.07 (0.94-1.22)	0.28
85+ years	1.83 (1.60-2.11)	<0.001	1.29 (1.12-1.50)	0.001
Sex				
Male	1		1	
Female	0.90 (0.81-1.00)	0.05	0.80 (0.71-0.89)	<0.001
Race				
White	1			
Black	1.14 (0.94-1.37)	0.18		
Others	1.04 (0.84-1.29)	0.72		
Pathology				
Adenocarcinoma	1			
Squamous cell	1.03 (0.93-1.13)	0.58		
Grade				
Well (G1)	1		1	
Moderate (G2)	1.12 (0.90-1.39)	0.31	1.31 (1.06-1.63)	0.014
Poorly (G3)	1.31 (1.06-1.63)	0.012	1.50 (1.21-1.85)	<0.001
Undifferentiated (G4)	1.52 (0.90-2.54)	0.12	1.67 (0.99-2.81)	0.052
Unknown	1.19 (0.94-1.50)	0.14	1.17 (0.93-1.48)	0.18
Stage				
II	1		1	
III	1.25 (1.14-1.37)	<0.001	1.06 (0.86-1.31)	0.56
T stage				
T2	1		1	
T3	1.37 (1.23-1.54)	<0.001	1.34 (1.16-1.55)	<0.001
T4a	2.18 (1.81-2.61)	<0.001	1.77 (1.37-2.28)	<0.001
N stage				
N0	1		1	
N1	1.02 (0.92-1.13)	0.68	0.99 (0.84-1.18)	0.96
N2	1.10 (0.94-1.29)	0.24	1.13 (0.89-1.43)	0.32
N3	1.77 (1.31-2.38)	<0.001	1.85 (1.31-2.61)	0.001
Tumor location				
Upper third	1			
Middle third	0.94 (0.78-1.13)	0.52		
Lower third	0.98 (0.83-1.16)	0.81		
Unknown	1.11 (0.89-1.38)	0.37		
Treatment patterns				
Obs	1		1	
Surgery	0.25 (0.20-0.31)	<0.001	0.26 (0.20-0.32)	<0.001
CRT	0.29 (0.25-0.33)	<0.001	0.30 (0.26-0.35)	<0.001
CRT+S	0.17 (0.14-0.21)	<0.001	0.17 (0.14-0.20)	<0.001
RT	0.54 (0.45-0.65)	<0.001	0.54 (0.45-0.64)	<0.001
CT	0.43 (0.33-0.56)	<0.001	0.44 (0.34-0.58)	<0.001
Marital status				
Married	1		1	
Unmarried	1.21 (1.10-1.33)	<0.001	1.12 (1.01-1.24)	0.03
Unknown	1.06 (0.85-1.31)	0.62	0.93 (0.75-1.15)	0.49

caution even in the eldest group (aged >85 years). If patients cannot tolerate doublet CT combined with RT, single-drug oral chemotherapy drugs can be considered, such as S1, Xeloda, and other fluorouracil analogues (12, 34). Notably, a recent randomized phase 3 clinical trial led by our cancer center, confirmed that concurrent CRT with S-1 significantly improved 2-year OS compared with RT alone in older EC patients (35).

Our study has the following strengths. Firstly, our study used a population-based database with a large sample size and long-term follow-up period. Secondly, a comprehensive analysis of primary treatment patterns and wide-ranging subgroup analysis stratified by age, which made the conclusion reliable and stable, were performed in our study. However, our study also has several limitations. Firstly, as with any retrospective study, selection bias and unmeasured confounding variables are inevitable, and the baseline characteristics of patients in different patterns were not well balanced, which reflected real-world treatment choices. Secondly, some information was missing on patient characteristics and treatment process in the SEER database, such as performance status, radiation dose, CT regimens, and comorbidities, which limited the multivariate Cox

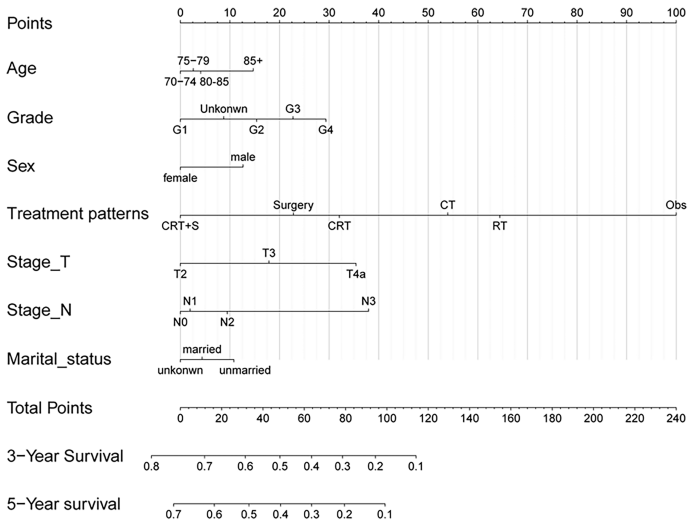

FIGURE 5 | Nomogram for predicting 3- and 5-year probabilities of OS for elderly patients with potentially curable EC. The nomogram summed the points identified on the scale for each variable. The total points projected on the bottom scales indicate the probabilities of 3- and 5-year OS.

regression analysis. Additionally, for study endpoints, data regarding recurrence and metastasis information were unavailable.

Given the natural limitations of retrospective studies, the findings of our study should be interpreted with caution in clinical practice. As described in the limitations of our study, selection bias should be considered. When selecting the optimal treatment pattern for elderly patients with EC, their physical conditions should be comprehensively assessed, including nutritional status, cardiopulmonary function, and associated underlying diseases. If possible, a comprehensive geriatric assessment (CGA) is recommended, which has been increasingly

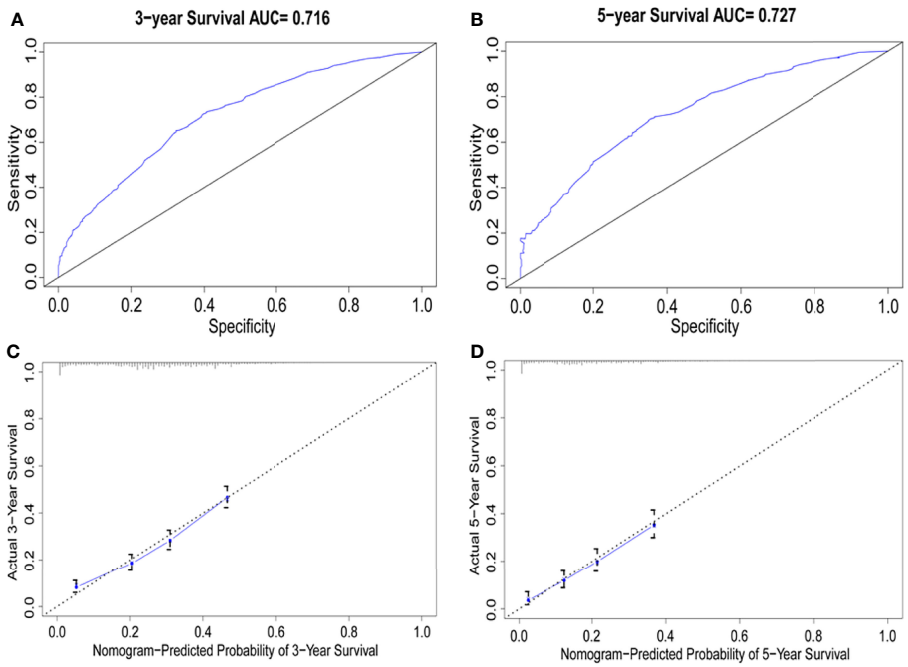

FIGURE 6 | Comparison of the AUCs and Calibration curves for the nomogram. **(A, B)** Area under the curves of the two models to predict overall survival at 3 years **(A)** and 5 years **(B)**, **(C, D)** Calibration curves for the nomogram at 3 years **(C)** and 5 years**(D)**, the x axis represents the nomogram-predicted survival rate, whereas the y axis represents the actual survival rate.

involved in guiding treatment decisions for elderly cancer patients (19). In younger patients with high CGA scores, more aggressive treatment options, such as surgery combined with neoadjuvant CRT, may be considered as the first option. For patients with higher age (aged ≥80 years) or poor general condition or unsuitable for surgery (regardless of medical reasons), CRT was the preferred treatment pattern.

CONCLUSION

In this large sample population-based study, we found that curative-intent treatment patterns can provide survival benefits for elderly patients with EC. Trimodality therapy is associated with longest survival and thus should be considered as the first option, if it is feasible. Subsequently, CRT is remarkably superior to RT or CT alone in elderly patients with EC. For patients intolerable to surgery or aged ≥80 years, definitive CRT should be considered as a preferable selection. Age is not a restrictive condition for treatment options in elderly EC patients, and the optimal treatment strategy should take into account survival benefits and patient preferences in a multidisciplinary setting. Future clinical trials are needed to validate our findings and to reduce the occurrence of complications in the elderly population.

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DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

QW and YY conceived and drafted the study. YY and MC collected and extracted the data. YY, MC, and JX designed the statistical analysis plan and performed the analyses. YY, YJ, and LS interpreted the results and prepared the manuscript. GQ and XD carefully revised the manuscript. All authors commented on drafts of the paper and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.778898/full#supplementary-material

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 0:1–41. doi: 10.3322/caac.21660
2. GBD 2017 Oesophageal Cancer Collaborators. The Global, Regional, and National Burden of Oesophageal Cancer and its Attributable Risk Factors in 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* (2020) 5:582–97. doi: 10.1016/S2468-1253(20)30007-8
3. Bollschweiler E, Plum P, Monig SP, Holscher AH. Current and Future Treatment Options for Esophageal Cancer in the Elderly. *Expert Opin Pharmacother* (2017) 18:1001–10. doi: 10.1080/14656566.2017.1334764
4. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med* (2012) 366:2074–84. doi: 10.1056/NEJMoa1112088
5. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* (2019) 17:855–83. doi: 10.6004/jnccn.2019.0033
6. Farrow NE, Raman V, Jawitz OK, Voigt SL, Tong BC, Harpole DH, et al. Impact of Age on Surgical Outcomes for Locally Advanced Esophageal Cancer. *Ann Thorac Surg* (2021) 111:996–1003. doi: 10.1016/j.athoracsur.2020.06.055
7. Markar SR, Karthikesalingam A, Thrumurthy S, Ho A, Muallem G, Low DE. Systematic Review and Pooled Analysis Assessing the Association Between Elderly Age and Outcome Following Surgical Resection of Esophageal Malignancy. *Dis Esophagus* (2013) 26:250–62. doi: 10.1111/j.1442-2050.2012.01353.x
8. Wakui R, Yamashita H, Okuma K, Kobayashi S, Shiraishi K, Terahara A, et al. Esophageal Cancer: Definitive Chemoradiotherapy for Elderly Patients. *Dis Esophagus* (2010) 23:572–9. doi: 10.1111/j.1442-2050.2010.01062.x
9. Molena D, Stem M, Blackford A, Lidor A. Esophageal Cancer Treatment Is Underutilized Among Elderly Patients in the USA. *J Gastrointest Surg* (2017) 21:126–36. doi: 10.1007/s11605-016-3229-5
10. Koeter M, van Putten M, Verhoeven RHA, Lemmens V, Nieuwenhuijzen GAP. Definitive Chemoradiation or Surgery in Elderly Patients With Potentially Curable Esophageal Cancer in the Netherlands: A Nationwide Population-Based Study on Patterns of Care and Survival. *Acta Oncol* (2018) 57:1192–200. doi: 10.1080/0284186X.2018.1450521
11. Abrams JA, Buono DL, Strauss J, McBride RB, Hershman DL, Neugut AI. Esophagectomy Compared With Chemoradiation for Early Stage Esophageal Cancer in the Elderly. *Cancer* (2009) 115:4924–33. doi: 10.1002/cncr.24536
12. Wang X, Ge X, Wang X, Zhang W, Zhou H, Lin Y, et al. S-1-Based Chemoradiotherapy Followed by Consolidation Chemotherapy With S-1 in Elderly Patients With Esophageal Squamous Cell Carcinoma: A Multicenter Phase II Trial. *Front Oncol* (2020) 10:1499. doi: 10.3389/fonc.2020.01499
13. Smith GL, Smith BD, Buchholz TA, Liao Z, Jeter M, Swisher SG, et al. Patterns of Care and Locoregional Treatment Outcomes in Older Esophageal Cancer Patients: The SEER-Medicare Cohort. *Int J Radiat Oncol Biol Phys* (2009) 74:482–9. doi: 10.1016/j.ijrobp.2008.08.046
14. Luo H, Jiang W, Ma L, Chen P, Fang M, Ding L, et al. Icotinib With Concurrent Radiotherapy vs Radiotherapy Alone in Older Adults With

Unresectable Esophageal Squamous Cell Carcinoma: A Phase II Randomized Clinical Trial. *JAMA Netw Open* (2020) 3:e2019440. doi: 10.1001/jamanetworkopen.2020.19440
15. Moreno AC, Verma V, Hofstetter WL, Lin SH. Patterns of Care and Treatment Outcomes of Elderly Patients With Stage I Esophageal Cancer: Analysis of the National Cancer Data Base. *J Thorac Oncol* (2017) 12:1152–60. doi: 10.1016/j.jtho.2017.04.004
16. Yu JB, Gross CP, Wilson LD, Smith BD. NCI SEER Public-Use Data: Applications and Limitations in Oncology Research. *Oncology (Williston Park)* (2009) 23:288–95.
17. Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavole A, et al. Carboplatin and Weekly Paclitaxel Doublet Chemotherapy Compared With Monotherapy in Elderly Patients With Advanced Non-Small-Cell Lung Cancer: IFCT-0501 Randomised, Phase 3 Trial. *Lancet* (2011) 378:1079–88. doi: 10.1016/S0140-6736(11)60780-0
18. Miller ED, Fisher JL, Haglund KE, Grecula JC, Xu-Welliver M, Bertino EM, et al. The Addition of Chemotherapy to Radiation Therapy Improves Survival in Elderly Patients With Stage III Non-Small Cell Lung Cancer. *J Thorac Oncol* (2018) 13:426–35. doi: 10.1016/j.jtho.2017.11.135
19. Cohen HJ, Feussner JR, Weinberger M, Carnes M, Hamdy RC, Hsieh F, et al. A Controlled Trial of Inpatient and Outpatient Geriatric Evaluation and Management. *N Engl J Med* (2002) 346:905–12. doi: 10.1056/NEJMsa010285
20. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. *J Clin Oncol* (2018) 36:2796–803. doi: 10.1200/JCO.2018.79.1483
21. Harridge SD, Lazarus NR. Physical Activity, Aging, and Physiological Function. *Physiology (Bethesda)* (2017) 32:152–61. doi: 10.1152/physiol.00029.2016
22. Tapias LF, Muniappan A, Wright CD, Gaissert HA, Wain JC, Morse CR, et al. Short and Long-Term Outcomes After Esophagectomy for Cancer in Elderly Patients. *Ann Thorac Surg* (2013) 95:1741–8. doi: 10.1016/j.athoracsur.2013.01.084
23. Lagergren J, Bottai M, Santoni G. Patient Age and Survival After Surgery for Esophageal Cancer. *Ann Surg Oncol* (2021) 28:159–66. doi: 10.1245/s10434-020-08653-w
24. Schlottmann F, Strassle PD, Nayyar A, Herbella FAM, Cairns BA, Patti MG. Postoperative Outcomes of Esophagectomy for Cancer in Elderly Patients. *J Surg Res* (2018) 229:9–14. doi: 10.1016/j.jss.2018.03.050
25. Faiz Z, van Putten M, Verhoeven RHA, van Sandick JW, Nieuwenhuijzen GAP, van der Sangen MJC, et al. Impact of Age and Comorbidity on Choice and Outcome of Two Different Treatment Options for Patients With Potentially Curable Esophageal Cancer. *Ann Surg Oncol* (2019) 26:986–95. doi: 10.1245/s10434-019-07181-6
26. Ruol A, Portale G, Zaninotto G, Cagol M, Cavallin F, Castoro C, et al. Results of Esophagectomy for Esophageal Cancer in Elderly Patients: Age has Little Influence on Outcome and Survival. *J Thorac Cardiovasc Surg* (2007) 133:1186–92. doi: 10.1016/j.jtcvs.2006.12.040
27. Lester SC, Lin SH, Chuong M, Bhooshan N, Liao Z, Arnett AL, et al. A Multi-Institutional Analysis of Trimodality Therapy for Esophageal Cancer in Elderly Patients. *Int J Radiat Oncol Biol Phys* (2017) 98:820–8. doi: 10.1016/j.ijrobp.2017.02.021
28. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of Locally Advanced Esophageal Cancer: Long-Term Follow-Up of a Prospective Randomized Trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* (1999) 281:1623–7. doi: 10.1001/jama.281.17.1623
29. Zhao L, Zhou Y, Pan H, Yin Y, Chai G, Mu Y, et al. Radiotherapy Alone or Concurrent Chemoradiation for Esophageal Squamous Cell Carcinoma in Elderly Patients. *J Cancer* (2017) 8:3242–50. doi: 10.7150/jca.20835
30. Jingu K, Numasaki H, Toh Y, Nemoto K, Uno T, Doki Y, et al. Chemoradiotherapy and Radiotherapy Alone in Patients With Esophageal Cancer Aged 80 Years or Older Based on the Comprehensive Registry of Esophageal Cancer in Japan. *Esophagus* (2020) 17:223–9. doi: 10.1007/s10388-020-00725-w
31. Xu C, Xi M, Moreno A, Shiraishi Y, Hobbs BP, Huang M, et al. Definitive Chemoradiation Therapy for Esophageal Cancer in the Elderly: Clinical Outcomes for Patients Exceeding 80 Years Old. *Int J Radiat Oncol Biol Phys* (2017) 98:811–9. doi: 10.1016/j.ijrobp.2017.02.097
32. Tougeron D, Di Fiore F, Thureau S, Berbera N, Iwanicki-Caron I, Hamidou H, et al. Safety and Outcome of Definitive Chemoradiotherapy in Elderly Patients With Oesophageal Cancer. *Br J Cancer* (2008) 99:1586–92. doi: 10.1038/sj.bjc.6604749
33. Zhang P, Xi M, Zhao L, Shen JX, Li QQ, He LR, et al. Is There a Benefit in Receiving Concurrent Chemoradiotherapy for Elderly Patients With Inoperable Thoracic Esophageal Squamous Cell Carcinoma? *PloS One* (2014) 9:e105270. doi: 10.1371/journal.pone.0105270
34. Huang C, Zhu Y, Li Q, Zhang W, Liu H, Zhang W, et al. Feasibility and Efficiency of Concurrent Chemoradiotherapy With a Single Agent or Double Agents vs Radiotherapy Alone for Elderly Patients With Esophageal Squamous Cell Carcinoma: Experience of Two Centers. *Cancer Med* (2019) 8:28–39. doi: 10.1002/cam4.1788
35. Ji Y, Du X, Zhu W, Yang Y, Ma J, Zhang L, et al. Efficacy of Concurrent Chemoradiotherapy With S-1 vs Radiotherapy Alone for Older Patients With Esophageal Cancer: A Multicenter Randomized Phase 3 Clinical Trial. *JAMA Oncol* (2021) 7:1459–66. doi: 10.1001/jamaoncol.2021.2705

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REVIEW
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PI3K/Akt/mTOR Signaling Pathway: Role in Esophageal Squamous Cell Carcinoma, Regulatory Mechanisms and Opportunities for Targeted Therapy

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Esophageal squamous cell carcinoma (ESCC), is the most common type of esophageal cancer worldwide, mainly occurring in the Asian esophageal cancer belt, including northern China, Iran, and parts of Africa. Phosphatidlinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway is one of the most important cellular signaling pathways, which plays a crucial role in the regulation of cell growth, differentiation, migration, metabolism and proliferation. In addition, mutations in some molecules of PI3K/Akt/mTOR pathway are closely associated with survival and prognosis in ESCC patients. A large number of studies have found that there are many molecules in ESCC that can regulate the PI3K/Akt/mTOR pathway. Overexpression of these molecules often causes aberrant activation of PI3K/Akt/mTOR pathway. Currently, several effective PI3K/Akt/mTOR pathway inhibitors have been developed, which can play anticancer roles either alone or in combination with other inhibitors. This review mainly introduces the general situation of ESCC, the composition and function of PI3K/Akt/mTOR pathway, and regulatory factors that interact with PI3K/Akt/mTOR signaling pathway. Meanwhile, mutations and inhibitors of PI3K/Akt/mTOR pathway in ESCC are also elucidated.

Keywords: PI3K/Akt/mTOR pathway, ESCC, inhibitor, drug resistance, mutation

1 INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer death worldwide. According to statistics, there are more than 604,000 new cases of esophageal cancer diagnosed in 2020, of which about 544,000 died from it. In developed countries, the 5-year survival rate of ESCC is less than 20%, and in many developing countries, the 5-year survival rate is less than 5% (1). Esophageal cancer is mainly

divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), among which ESCC is the most common histological type in the "Asian esophageal carcinoma belt", including Iran, Kazakhstan and northern China. Risk factors for ESCC mainly include gender, race, smoking, alcohol, diet, nutrition and gene alteration, etc. (2).

The phosphatidlinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway is one of the most vital and most frequently altered signaling pathways in organisms. Studies have pointed out that the major components dysregulation of this signaling pathway led to aberrant activation of the downstream pathways, which ultimately promoted occurrence of cancer.

PI3Ks, members of the lipid kinase family, are usually activated by receptor tyrosine kinases (RTK) and G-protein coupled receptors (GPCR). Moreover, phosphatidylinositol (PI) is a membrane phospholipid, which occupies a small proportion in the composition of cell membrane. The inositol ring of PI can be phosphorylated at several sites, especially 4 and 5. These two sites are phosphorylated by various kinases, leading to the formation of PIP2 (phosphatidylinositol 4, 5 -biphosphate) (3). PI3Ks can be divided into three categories, namely class I, class II and class III. The most widely studied class I PI3Ks is a heterodimer, composed of a catalytic subunit (p110) and a regulatory subunit (p85). Class II PI3Ks include PI3K-Cα, PI3K-Cβ and PI3K-Cγ; Class III PI3Ks PIK3C3, also known as vacuolar protein sorting 34 (VPS34). Upon receiving signals from RTKs and GPCRs, the p85 regulatory subunit of PI3K is recruited to the adjacent plasma membrane, where the p110 subunit binds to the p85 subunit to convert the substrate phosphatidylinositol 2 phosphate, PtIns (4, 5)P2(PIP2) into PtIns (3–5)P3(PIP3) for subsequent reactions (4).

Akt is a serine/threonine kinase and a key regulator of the PI3K/Akt/mTOR signaling pathway. There are three subtypes of Akt (Akt1/PKBα, Akt2/PKBβ, and Akt3/PKBγ), which are encoded by different genes and differ greatly in their distribution. PIP3 binds to the N-terminal pH domain of protein kinase B (PKB, Akt) to transfer Akt from the cytoplasm to the cell membrane. Akt is activated by phosphorylation of the threonine phosphorylation site (Thr308) and serine phosphorylation site (Ser473) with the help of phosphoinositide-dependent protein kinase-1 (PDK1) and phosphoinositol-dependent protein kinase-2 (PDK2). Most interestingly, Akt is also activated by mTOR feedback, this activation of Akt is regulated by the mammalian target of rapamycin complex 2 (mTORC2), and it does not require PDK1 participation (5). Phosphatase and tensin homolog deleted on chromosome ten (PTEN) is a classical tumor suppressor involved in the regulation of the PI3K/Akt pathway. Its main function is to hydrolyze PIP3 into PIP2 and prevent Akt activation.

mTOR is a serine/threonine kinase that typically assembled into a variety of complexes, such as mammalian target of rapamycin complex 1(mTORC1) and mammalian target of rapamycin complex 2(mTORC2). In addition to its core protein component, mTOR, mTORC1 also includes raptor (mTOR regulatory related protein), mLST8 (GβL), PRAS40 (proline-rich Akt substrate) and DEPTOR (protein containing the DEP domain).Interestingly, mTORC2 contains the same mTOR, DEPTOR and mLST8 as mTORC1, and it also contains own unique components, PROTOR, rictor and mSIN1. Activated Akt can activate its substrate mTOR through direct and indirect pathways, such as direct phosphorylation of mTOR, or through inactivation of tuberous sclerosis complex 2 (TSC2), and then enhance activation of mTOR (6).

2 MUTATIONS OF PI3K/AKT/MTOR PATHWAY IN ESCC

There are many abnormal mutations in PI3K/Akt/mTOR pathway, such as PIK3CA and Akt subtype mutations, which can activate PI3K/Akt/mTOR pathway and affect the occurrence of ESCC. Among them, mutations in the PIK3CA gene encoding p110α are common in ESCC (3). A study demonstrated that PIK3CA mutations were detected in exon 9 or exon 20 in 46 (21%) of 219 cases of ESCC (7). Moreover, Chang et al. comprehensively analyzed the genomic changes of 94 ESCC tumor samples through whole genome sequencing, and found that the amplification rate of PIK3CA in these samples was 38.3%(36/94). However, both PIK3CA mutation and PIK3CA amplification were present in only 2 samples. Surprisingly, the study also analyzed the mutant spectrum of HNSCC, LUSCC and EAC, and found that the mutations of ESCC were similar to HNSCC and LUSCC, but quite different from EAC. This means that mutations in cancers of the same tissue are largely similar, regardless of whether they are the same organ (8). Wang and his colleagues also showed that this is the case. When they analyzed the epithelial cell genomes of advanced ESCC and EAC, they found that the genomes of ESCC and EAC were different. The mutation rate of PIK3CA in 71 ESCC cases was up to 24%, mainly including amplification, base substitution and short indels. Likewise, PTEN mutation rate could be up to 11%, including truncated mutations, base substitutions and short indels. However, the mutation rate of PIK3CA in EAC was only 10%, and that of PTEN was 4%. It was worth noting that Akt1 was only slightly amplified in EAC (9). Moreover, a study by Zhang et al. found that PIK3CA was the most frequently altered gene in the PI3K/Akt/mTOR pathway, with about 17% mutation rate. Hot spot mutation of PIK3CA (c.1624G> A [p.Glu542Lys] and c. 1633 g & gt; A [P.Glu545lys]) was enriched in ESCC with the characteristics of APOBEC (10). In addition to PIK3CA mutations, single nucleotide polymorphisms (SNPs) of several genes in the Akt signaling pathway are also associated with susceptibility to ESCC. Zhu et al. showed that there were significant gene-gene interactions among the three Akt1 SNPs. Akt1 rs2294750 alone or in combination with two other Akt1 SNPs (rs2494752, rs10138277) can jointly combat ESCC, especially in women and non-alcoholic ESCC patients (11). Michelle A.T et al. identified mutations in Akt1, Akt2, PIK3CA, PTEN, and FRAP1 in 174 resectable adenocarcinoma and 36 squamous cell carcinoma patients. Additionally, this

study demonstrated a significant association between these common genetic variations and clinical outcomes (12). In 1116 patients with ESCC and 1117 non-cancer controls, Zhu et al. found that three SNPs of mTOR were significantly associated with increased risk of ESCC, highlighting the influence of gene-gene and gene-environment interactions (13). Similarly, Hongping Yu et al. identified 8 functional SNPs of mTORC1 that individually or collectively contribute to ESCC risk in 1126 patients with ESCC and 1131 non-cancer controls (14). Yang et al. sequenced the genomes of 24 ESCC specimens and found that the probability of mTOR gene alteration was 25% (6/24). Of the 115 genes detected, only Akt2 and PIK3CA amplification were found, and the frequency of amplification was 4.2% (1/24). These genetic alterations provide potential targets for future therapies of ESCC (15).

3 ROLE OF PI3K/AKT/MTOR SIGNALING PATHWAY IN ESCC

PI3K/Akt/mTOR pathway is essential for the growth and development of ESCC cells. It is involved in multiple stages of cell growth and differentiation, in the meantime, related to many aspects such as cell metastasis, proliferation and apoptosis. In order to understand the specific role of PI3K/Akt/mTOR pathway in ESCC, Lee et al. knocked down mTOR, raptor, rictor and applied mTOR inhibitors respectively. Knocking down raptor and rictor in TE8 cells significantly reduced the proliferation of the cells compared with non-silencing siRNA (16). Rapamycin, an inhibitor of mTOR. It can also inhibit proliferation of ESCC cells, but to a lesser extent than mTOR knockdown. In addition, knockdown of mTOR, raptor, and rictor induced G1 phase cell arrest. Interestingly, both downregulation of raptor or administration of rapamycin induced mild apoptosis. However, downregulation of mTOR and rictor were not associated with apoptosis (16). Hou et al. conducted similar studies and found that siRNA could significantly down-regulate the level of mTOR and its downstream factors, p-p70S6K and p-4E-BP1, promoting their non-phosphorylation (17). Another study showed that siRNA inhibited the expression of Akt in TE-1 and TE-5 cells, leading to a decrease in MDM2 levels. MDM2 has been shown to form a tight complex with wild-type p53. Hence, the function of wild-type p53 can be inhibited by changing the level of MDM2 (18).

In addition to the above effects, the PI3K/Akt/mTOR pathway has been reported to be closely related to the prognosis of ESCC. A study conducted by Wu et al. showed that mTOR, p-mTOR and p70S6K1 were prognostic factors for progression-free survival (PFS). The expression of mTOR, p-mTOR, p70S6K1 and PTEN were associated with lymph node metastasis and late TNM staging of ESCC (19). Another study showed a positive correlation between periostin and mTOR in locally advanced ESCC, which are independent risk factors for overall survival (OS) and PFS in ESCC patients (20). Moreover, Lee et al. demonstrated that p-mTOR/mTOR is inversely proportional to disease-specific survival, meanwhile it is a more powerful prognostic factor for ESCC than p-mTOR (16). Apart from mTOR, PI3Ks has also been reported to affect the prognosis of ESCC. The expression of PI3K was positively correlated with the degree of clinical stage, depth of invasion and differentiation. But PI3K can only be used as a reference for poor prognosis of ESCC, rather than an independent prognostic indicator (21). One study showed that the level of p-Akt was the only independent factor affecting the prognosis of ESCC patients with chemotherapy. The level of p-Akt increased significantly after chemotherapy, while p-mTOR did not change. It was also pointed out that p-Akt was correlated with the depth of tumor invasion before chemotherapy, while it was not correlated with any clinicopathological parameters after chemotherapy (22). However, Shan et al. believed that p-Akt was associated with lymph node metastasis and tumor differentiation degree, and cumulative survival was significantly higher in p-Akt negative patients than in p-Akt positive patients (23). Additionally, a study have showed that both expression level of RNF2 and p-Akt can affect the OS of patients with ESCC, and RNF2 positive/p-Akt-positive ratio was an independent prognostic factor for ESCC (24).

4 MOLECULES REGULATING PI3K/AKT/MTOR PATHWAY IN ESCC

The PI3K/Akt/mTOR pathway is always activated and plays critical roles in the development and progression of ESCC. As shown in **Figure 1**, in ESCC, many molecules can participate in regulating the activity of this pathway, finally facilitating cell proliferation, metastasis and chemoradiosensitivity.

4.1 Molecules Regulating ESCC Proliferation

4.1.1 Positive Regulators of PI3K/Akt/mTOR Pathway on ESCC Proliferation

SDCBP was a crucial promoter of tumor proliferation. Meanwhile, it is also a downstream factor of AURKA. PDZ2 domain of SDCBP can directly bind with EGFR, thereby activating EGFR and PI3K/Akt pathway (25). CDF15, P63 and SOX2 significantly enhanced proliferation of ESCC cells that was mediated, at least in part, through activation of Akt pathway. Notably, overexpression of P63 observably increased the level of p-Akt without affecting Akt (26–28). Moreover, it has been reported that ectopic expression of MAEL promoted tumor cell growth. The mechanism was that MAEL upregulated IL-8 by activating the Akt1/RelA signaling pathway (29). BRE is a stress-responsive gene, and its overexpression significantly promoted the proliferation of ESCC cells. One study indicated that BRE could negatively regulate the expression of PTEN to activate the Akt pathway and promote the occurrence and development of tumors (30). It is interesting to note that TRIM27 was a pro-proliferation factor in ESCC and it could also interact with PTEN to promote poly-ubiquitination. Thus, the activity of PI3K/Akt pathway was increased (31).

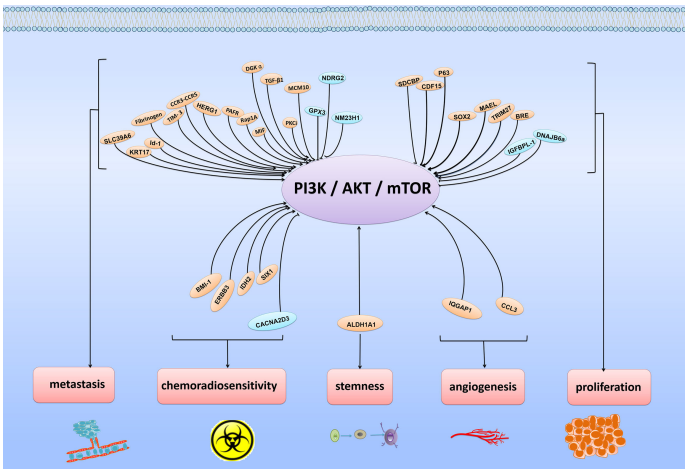

FIGURE 1 | Various regulatory molecules of PI3K/Akt/mTOR signaling pathway and physiological functions of these molecules. The PI3K/Akt/mTOR signaling pathway is usually regulated by various signaling molecules. By targeting major molecules in the PI3K/Akt/mTOR signaling pathway, these molecules play positive or negative roles in regulating cancer proliferation, metastasis, angiogenesis, stemness and chemoradiosensitivity.

4.1.2 Negative Regulators of PI3K/Akt/mTOR Pathway on ESCC Proliferation

In the process of tumor development, there are also many tumor suppressors, which inhibit the proliferation of cells through inactivating PI3K/Akt/mTOR pathway. IGFBPL-1 belonged to IGFBP family and was a tumor suppressor in ESCC. It inhibited proliferation and induced apoptosis in esophageal cancer cells by attenuating PI3K/Akt signaling pathway (32). Additionally, it has been reported that DNAJB6a suppressed ESCC cell proliferation by inhibiting Akt signaling and the activity of functional protein phosphatase 2A (PP2A). It's worth noting that PP2A was required for DNAJB6a to regulate Akt signaling (33).

4.2 Molecules Regulating ESCC Metastasis

4.2.1 Positive Regulators of PI3K/Akt/mTOR Pathway on ESCC Metastasis

Epithelial-mesenchymal transition (EMT), an embryonic program, loosens cell-cell adhesion complexes and enhances cell migration and invasion. In cancer, EMT is associated with tumor initiation, invasion, metastasis, and resistance to treatment (34). Id-1 and HERG1 can regulate EMT, at least in part by activating the PI3K/Akt pathway to promote migration and invasion of ESCC cells. Their mechanisms are that HERG1 participates PI3K/Akt pathway by targeting TXDC5, while Id-1 can directly affect PI3K/Akt pathway (35, 36). Furthermore, we found that many proteins have similar effects. For example, Rap1A and KRT17-induced EMT are driven by the Akt signaling in ESCC. Their overexpression could accelerate cell metastasis by enhancing cell migration and invasion (37, 38). Moreover, TGF-β1 mediated EMT *via* PTEN/PI3K pathway (39). TIM-3 induced EMT is driven by Akt/GSK-3β/snail signaling pathway (40). Additionally, fibrinogen and MIF can mediate EMT *via* p-AKT/p-mTOR and Akt/GSK-3β/β-catenin pathway, respectively (41, 42). In addition to above molecules, there are other molecules that promote metastasis through this pathway, such as SLC39A6, a member of ZRT, IRT-like protein (ZIP) family. At the same time, SLC39A6 is a zinc importer whose roles on promoting migration and invasion of ESCC cells might be related to intracellular zinc accumulation. The underlying mechanism is that SLC39A6 and cellular zinc could active the PI3K/Akt and MAPK/ERK signaling pathways, thus promoting the occurrence and development of ESCC (43). PKCi and PAFR can promote metastasis of esophageal cancer by indirectly regulating the PI3K/Akt pathway. This is because PKCi and PAFR can directly target SKP2 and FAK, thereby affecting the PI3K/Akt signaling pathway (44, 45). On the contrary, MCM10 and CCR3-CCR5 axis induce migration and invasion of ESCC cells through direct regulation of Akt and PI3K/Akt pathways, respectively (46, 47). Not only that, DGKα can also stimulate metastasis of ESCC. The mechanism is that DGKα actives Akt/NF-κB signaling pathway by directly binding with the FERM domain of FAK *via* its catalytic domain. Moreover, DGKα-mediated phosphatidic acid (PA) production can inhibit the activity of CAMP/PTEN and improve the Akt activation (48).

4.2.2 Negative Regulators of PI3K/Akt/mTOR Pathway on ESCC Metastasis

In addition to the above-mentioned molecules that can positively regulate PI3K/Akt/mTOR pathway to promote EMT, there are also some negative regulatory molecules. For instance, upregulation of NDRG2 inhibited Akt/XIAP signaling pathway and the expression of EMT-related proteins, thereby suppressing the migration, invasion and tumor formation of esophageal cancer cells (49). More interestingly, Nm23H1 can also suppress cell invasion and EMT by negatively regulating Akt

activation (50). GPX3 is another negative regulator of FAK/Akt signaling pathway. GPX3 can inhibit expression of MMP9, a substance that contributes to invasion, through deactivating FAK/Akt pathway and suppressing tumor metastasis (51).

4.3 Molecules That Regulate Chemoradiotherapy Sensitivity

Chemotherapy and radiotherapy are two common cancer treatments in ESCC. But they are often limited by intrinsic factors of tumor cells. Some proteins can affect the radioresistance and chemoresistance of tumor cells by regulating the PI3K/Akt/mTOR pathway.

4.3.1 Positive Regulators of PI3K/Akt/mTOR Pathway to Increase Chemoradiotherapy Sensitivity

BMI-1, the core component of PcG, is abnormally expressed in various kinds of cancers, including ESCC. BMI-1 regulated the expression of proteins related to DNA damage repair, such as γH2AX, MDC1 and 53BP1. Moreover, in ESCC,BMI-1 could also involve in the regulation of radiosensitivity. Downregulation of BMI-1 significantly decreased the proportion of G2/M phase cells by inhibiting the PI3K/Akt/mTOR pathway, and reduced the chance of DNA damage repair, and ultimately increased radiosensitivity (52). ERBB3 is a gene that has been reported to be associated with the PI3K/Akt signaling pathway. One study revealed that HOXC10 could directly bind with Ku70 and the promoter region of ERBB3 to facilitate DNA damage repair and upregulate ERBB3 transcription, thereby activating the PI3K/Akt signaling pathway and inducing resistance to chemoradiotherapy (53). Moreover, IC50 value of cisplatin was positively connected with HOXC10 expression, suggesting that HOXC10 was involved in chemotherapy resistance (53). In addition, IDH2 and SIX1 have also been reported to be involved in the regulation of radiosensitivity. The increased radiosensitivity induced by IDH2 knockdown that depends on the decreased phosphorylation of Akt. Likewise, overexpression of SIX1 induced radioresistance through activation of the Akt signaling pathway (54, 55).

4.3.2 Negative Regulators of PI3K/Akt/mTOR Pathway to Induce Chemoradiotherapy Sensitivity

Cisplatin is a well-known chemotherapeutic drug. It has been used to treat numerous cancers such as lung, ovarian, and testicular cancers. However, it also has drug resistance and many undesirable side effects. CACNA2D3 is a gene that is located at 3p29.1 on the short arm of chromosome 3. It has been found to have potential anticancer function in many kinds of tumors. IC50 value of cisplatin was negatively correlated with CACNA2D3 expression in ESCC cells, in the meantime, CACNA2D3 can enhance cisplatin sensitivity by inhibiting the PI3K/Akt pathway (56).

4.4 Other Molecules

Both IQGAP1 and CCL3 could promote angiogenesis in ESCC, and their mechanisms were similar. IQGAP1 facilitated tumor angiogenesis by targeting the VEGF-VEGFR2 signaling pathway mediated *via* Akt and ERK (57). CCL3-CCR5 axis upregulated the level of VEGF-A through activating PI3K/Akt and MEK/ERK signaling pathway, thereby promoting ESCC angiogenesis (47). Moreover, ALDH1A1 is a marker of cancer stem-like cells. One study indicated that overexpression of ALDH1A1 could maintain the cancer stem-like cells characteristics of ESCC and enhance the levels of Akt1, p-Akt (T308), p-Akt(S473) and β-catenin by activating the Akt signal pathway and binding with β-catenin (58).

5 TARGETING THE PI3K/AKT/MTOR PATHWAY IN ESCC THERAPEUTICS

Aberrant activations of the PI3K/Akt/mTOR signaling pathway are common in human cancers, including ESCC. It has been reported that the abnormal activations of this pathway were closely related to the dysregulated expression of PI3K, Akt and mTOR, which lay foundations for targeted therapy. In this review, three types of inhibitors in ESCC will be introduced, namely Akt inhibitors, PI3K inhibitors and mTOR inhibitors (**Figure 2** and **Supplementary Table S1**).

5.1 Akt Inhibitors

Oridonin, a diterpenoid compound extracted from Rabdosia rubescens, has been used to treat a variety of diseases, with cancer being the most notable one. A study conducted by Song et al. found that oridonin can directly interact with Akt1/2, inhibit the activity of Akt1/2 kinase and competitively bind with ATP. Thus, the proliferation of ESCC cells was inhibited, apoptosis and G2/M phase arrest were induced (59). Another compound, triciribine (TCN), was a highly effective radiation sensitizer for ESCC cells *in vitro* and *in vivo*. In ESCC cells and xenograft models, TCN enhanced the radiation sensitivity of ESCC cells by inhibiting hypoxia-induced Akt and HIF-1α expression (60). Xanthohumol is an ATP-competitive Akt kinase inhibitor. It was reported that xanthohumol can induce apoptosis and G1 phase cell arrest. Furthermore, it can suppress phosphorylation of GSK3β, mTOR and ribosomal protein S6, which are downstream targets of Akt, by directly inhibiting Akt 1/2 (61). The scutellarin extracted from scutellaria barbata is another ATP-competitive Akt inhibitor. A recent study has demonstrated that scutellarin can induce G2 cell cycle arrest and show anticancer effects *in vitro* and *in vivo*. Furthermore, it suppressed GSK3-β phosphorylation by directly targeting Akt1 and Akt2 (62). Unlike ATP-competitive inhibitors, allosteric Akt inhibitors including MK-2206 do not cause hyperphosphorylation of Akt at Ser473/Thr308. *In vitro* phenotypic and xenograft mouse models of ESCC, the combination of MK-2206 and BEZ235 was found to be more effective than monotherapy (63, 64).

5.2 PI3K Inhibitors

BEZ235 is an ATP-competitive dual pan-PI3K and mTORC1/mTORC2 inhibitor. Because it can target more than one molecule at the same time, it shows a brighter future in cancer therapy. As mentioned earlier, BEZ235 can be used in combination with MK-2206 to inhibit the progression of

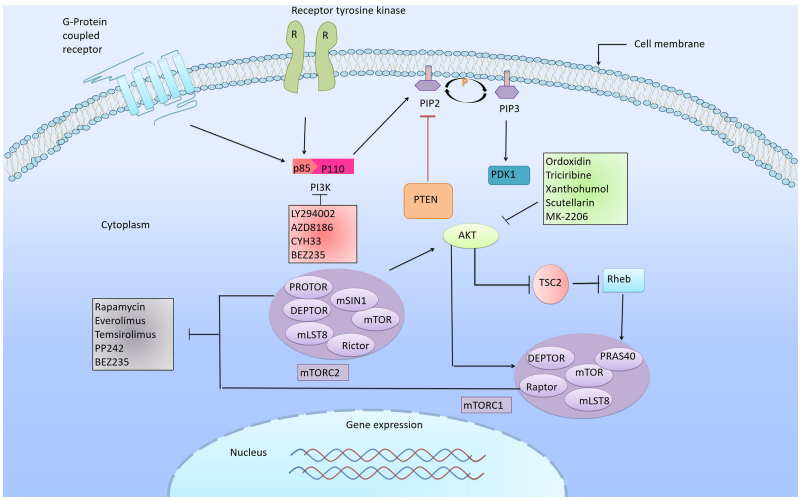

FIGURE 2 | PI3K/Akt/mTOR signaling cascade and its corresponding inhibitors. The PI3K/Akt/mTOR pathway is one of the most frequently altered pathways in cancer, and plays an important role in the regulation of cell growth, differentiation, proliferation, apoptosis and metastasis. Abnormal signal transduction in this pathway is closely related to the progression of cancer. Arrows indicate activation and bars indicate inhibition. The various inhibitors targeting PI3K/Akt/mTOR pathway proven to have inhibitory effects in ESCC.

ESCC. In addition, it also worked in combination with histone deacetylase inhibitor, trichostatin A (TSA). Wu et al. revealed that co-treatment with BEZ235 and TSA improved effects of single drug on cell proliferation, apoptosis and autophagy in ESCC. Moreover, the combination treatment significantly suppressed the phosphorylation of mTOR, Akt, and p70S6K (65). LY294002 is described as the first-generation pan-PI3K inhibitor. Some studies have shown that LY294002 inhibited the proliferation of ESCC cells not only through decreasing the levels of PI3Kp85α, p-Akt (Thr308) and p-p70S6K, but also increasing the expressions of p-Akt (Ser473) and PRAS40 (Thr246) (66). Another study demonstrated that knockdown rictor was capable of inhibiting LY294002-induced Akt compensatory activation, as well as synergically suppressing PI3Kp85α, p-Akt (Thr308) and p-P70S6K. Therefore, the sensitivity of ESCC cells to LY294002 was effectively improved (67). Additionally, AZD8186 is a specific inhibitor of PI3Kβ and PI3Kδ, which was currently in clinical trials and has shown strong anticancer effects. A recent study found that combining DTX and AZD8186, with a disulfide cross-linked micelle (DCM) -based approach, significantly increased the phosphorylation of PI3K and Akt. Meanwhile, the levels of p53, Bax, and Bcl-2 were up-regulated. Thus, the occurrence and development of ESCC can be inhibited *in vivo* and *in vitro* (68). Not only that, CYH33, a novel selective PI3Kα inhibitor, showed a strong inhibitory effect on ESCC. The combination of CYH33 and IR can effectively inhibit tumor growth *in vivo* and *in vitro*. This was because co-treatment with CyH33 and IR further increased the levels of cleaved caspase 3 and γH2AX. Moreover, the quantity of G2/M phase cells were also increased. Hence, accelerating cell apoptosis and DNA damage. Notably, constitutively activated Akt disrupted the synergistic interaction between CyH33 and IR (69, 70)

5.3 mTOR Inhibitors

Rapamycin, an mTORC1 inhibitor, is the first mTOR inhibitor discovered in humans. Rapamycin has been shown to have inhibitory effects on a variety of cancers. It has the flexibility to work either alone or in combination with other drugs. For example, one study has demonstrated that both rapamycin and cisplatin alone can significantly suppress tumor growth, but the combination of them has the strongest anti-cancer effect. At the same time, rapamycin can also inhibit DNA synthesis, thus slowing the progression of cancers (71). It is worth noting that everolimus is an analogue of rapamycin, which has similar chemical properties to rapamycin. In one study, everolimus reduced phosphorylation of p70S6K and 4E-BP1 in TE4 cells with the highest p-mTOR content and TE11 cells with the lowest p-mTOR content. Moreover, in a mouse subcutaneous xenograft model, the combination of everolimus and cisplatin was found to have an additive effect on tumor growth inhibition, similar to rapamycin (72, 73). Temsirolimus is a selective mTOR inhibitor that is essentially a novel analog of rapamycin. In a mouse model of subcutaneous xenograft, temsirolimus has been shown to significantly reduce subcutaneous tumor growth in a dose-dependent manner (74). Moreover, several mTOR kinase inhibitors had inhibitory effects both on mTORC1 and mTORC2, and these drugs were known as dual mTORC1 and mTORC2 inhibitors, such as PP242. One study showed that both PP242 and rapamycin can affect the proliferation and cell cycle arrest of Eca-109 and TE-1 cell lines, but the efficiency of PP242 was higher than rapamycin. Furthermore, compared with rapamycin, PP242 inhibited the phosphorylation of Akt (S473) and p70S6K (T389), while rapamycin acted only on the latter. Additionally, PP242 had a synergistic effect with cisplatin, and PP242 could increase the apoptosis induced by cisplatin (75).

5.4 PI3K/Akt/mTOR Inhibitors and Drug Resistance

ESCC is a kind of cancer with a high degree of malignancy. Although there are many available drugs that can inhibit ESCC, the efficacy, toxicity and prognosis of drugs are not ideal. This is largely due to the existence of multiple resistance mechanisms that reduce the sensitivity of drugs to cancer. How to overcome drug resistance is a difficult point in cancer treatment. Studies have shown that monotherapy can often induce resistance through compensatory activation of downstream molecules. However, simultaneous targeting of multiple targets in the same signaling pathway may overcome this compensation. For example, the above mentioned PI3K inhibitor, LY294002, can inhibit the occurrence and development of ESCC by inhibiting the PI3K/Akt/mTOR/p70S6K signaling pathway. Nevertheless, compensatory activation of Akt Ser473 and PRAS40 at Thr246 might limit the inhibitory effect of LY294002 on ESCC cells, leading to resistance of ESCC to LY294002. In addition, they found that knockdown of rictor inhibited LY294002-induced Akt compensatory activation and reduced its resistance in ESCC cells. Thus, the anti-proliferation, metastasis and clone formation ability of LY294002 were improved (67). The dual mTORC1 and mTORC2 inhibitor PP242 had a similar effect, which was considered to be a sensitizer of cisplatin. In ESCC, PP242 can inhibit mTORC1 and mTORC2 pathways and regulate the constitutive activation of Akt induced by cisplatin, thus enhancing the anti-tumor effect of chemotherapy drug cisplatin. Ultimately, the sensitivity of ESCC cells to cisplatin chemotherapy was enhanced (75). Additionally, Moshe Elkabets et al. observed the levels of EGFR and S6 phosphorylation were increased in BYL719 resistant cells. At the same time, they demonstrated that BYL719, a specific PI3Kα inhibitor, was resistant through activation of mTOR activity (76). The underlying mechanism was as follows: AXL was a membrane-bound receptor tyrosine kinase, which was the most highly expressed gene in genomic analysis of drug-resistant cells. It can activate and phosphorylate EGFR in a ligand-independent manner. Furthermore, it caused the activation of PLCγ and PKC, which in turn led to the activation of mTOR independent of PI3K/Akt. In addition, they demonstrated that the combined inhibition of PI3Kα, EGFR, and PKC was far more effective on ESCC cells than monotherapy (76, 77). Researchers also found the resistance to rapamycin in ESCC patients, the reason is that rapamycin induced a large number of negative feedback loops from p70S6K to PI3K or mTORC2, which significantly activated the PI3K/Akt signaling pathway and weakened the anticancer effect of rapamycin (71, 75). OP16, a derivative of a novel NT-kaurene diterpene isolated from rubescens, significantly inhibited rapamycin-activated PI3K and reversed rapamycin-reduced rictor phosphorylation. Therefore, combined inhibition of PI3K and mTORC2 may be another way to circumvent the rapamycin-induced feedback loop (78).

6 PI3K/AKT/MTOR INHIBITORS IN CLINICAL STUDIES

Multiple PI3K/Akt/mTOR inhibitors have been shown to be effective *in vitro* and *in vivo* in ESCC. However, they are not yet used in clinical practice for ESCC treatment. Here we introduce the PI3K/Akt/mTOR inhibitors which have been under clinical evaluation in other gastrointestinal cancers, including gastric cancer (GC) and colorectal cancer (CRC). A lot of patients have received complete response (CR) or partial response (PR) under the PI3K/Akt/mTOR inhibitors treatment, providing important indications and possibilities for ESCC therapy (**Supplementary Table S2**).

6.1 Akt Inhibitors

Capivasertib (AZD5363) is a novel inhibitor of Akt. AZD5363 in combination with paclitaxel has been utilized in a phase II clinical trial in patients with PIK3CA mutation and PIK3CA amplification in advanced gastric adenocarcinoma.

MK-2206, an allosteric Akt inhibitor, has been tested in several clinical trials and showed good outcomes. These include advanced GC and esophagogastric junction cancers, as well as previously treated metastatic or locally advanced colorectal cancer that cannot be surgically removed. Stable disease (SD) was observed in 20% of GC and esophagogastric junction cancer patients treated with MK-2206, and the rate of radiation PR was 10%. Moreover, MK-2206 can also be used in combination with selumetinib in CRC. However, due to its low efficiency in targeting p-Akt and p-ERK, and high toxicity, these led to various adverse events (AEs), such as acneiform rash, blurred vision, nausea, etc. (79, 80).

GDC-0068 is a selective Akt inhibitor. GDC-0068 combined with paclitaxel was found to improve PFS in the intent-to-treat (ITT) population in metastatic triple-negative breast cancer. The researchers compared the efficacy of GDC-0068 with placebo in combination with 5-fluorouracil, calcium folinolate, and oxaliplatin in advanced metastatic gastric cancer (MGC) and gastroesophageal junction cancer. They observed median PFS of 7.5 months in the placebo group and 6.6 months in the GDC-0068 group. This suggested that GDC-0068 did not improve PFS in GC patients who were not selected or biomarker selected (81).

6.2 PI3K Inhibitors

BKM120 (Buparlisib) is a pan-class I PI3K inhibitor. It has been reported to inhibit the growth of a variety of cancers, particularly in PIK3CA mutant and KRAS wild-type tumor cells. Currently, BKM120 has been tested in phase II clinical trials in CRC patients with PIK3CA-activated mutations. In addition, three clinical trials of BKM120 in combination with mFOLFOX6, panitumumab or irinotecan in patients with metastatic colorectal cancer (MCRC) or advanced CRC have been completed. In a phase I clinical trial, the combination of BKM120 and mFOLFOX6 was shown to have a maximum tolerated dose (MTD) of 40mg/day, significantly lower than the 100mg/day alone. Due to the lack of targeting action of MTD at 40mg/day, the combination is not recommended (82, 83).

BYL719 (Alpelisib) is a selective oral inhibitor of PI3Kα. In the phase II clinical trial of BRAF mutation MCRC, the overall response rate (ORR) and PFS in the combined treatment with BYL719, LGX818, and cetuximab were 18% and 4.2 months, respectively. But this is also accompanied by many AEs such as

fatigue, vomiting, diarrhea, dermatologic AEs (rashes, dermatitis acneiform, dry skin, melanocytic nevus) and hyperglycemia. At present, this study has been completed, but the efficacy of BYL719 still needs further experimental evaluation (84).

PX-866 is a specific PI3K inhibitor. Currently, the clinical trial of PX-866 combined with cetuximab in incurable MCRC has entered the phase I clinical trial and demonstrated stunning anticancer effects. In the 9 patients evaluated for efficacy, both the patients with PR and SD accounted for 44.4% (85).

6.3 mTOR Inhibitors

Temsirolimus (CCI-779) is an inhibitor of mTOR that has been extensively studied in different clinical trials. It is currently approved for the treatment of advanced renal cell carcinoma, but its treatment for CRC is still in clinical trials. The combination of temsirolimus and irinotecan in MCRC patients with KRAS mutations has entered phase II clinical trials and a significant increase in the proportion of patients with SD and reduced tumors was observed (86).

Everolimus has shown strong anticancer activity in many cancers. The safety and efficacy of everolimus plus best supportive care (BSC) in patients with advanced GC has entered phase III clinical trial. They found a tendency to reduce the risk of death with everolimus and found that the estimated median survival with everolimus combined with BSC was 5.4 months, compared with 4.3 months in the placebo group. Moreover, everolimus has often been studied in combination with other drugs, such as bevacizumab, irinotecan, cetuximab, mFOLFOX-6, OSI-906, AV-951 and panitumumab, which have been extensively studied in MCRC, RMCRC, and advanced CRC, while mitomycin C and capecitabine have been primarily studied in GC (87–98).

7 CONCLUSION

The PI3K/Akt/mTOR pathway is one of the most complex regulatory networks in the human body, and the abnormality of main components stimulated the occurrence of cancer. Currently, most studies have focused only on a few common forms of aberrations, such as PIK3CA, PTEN, Akt1, and Akt2. Abnormal changes in these genes have provided potential targets for cancer treatment. Therefore, in order to explore more effective therapeutic approaches, it is necessary to investigate other aberrations about this pathway. At the same time, in order to achieve the desired clinical benefit, we also need to understand the various molecules that regulate the oncogenic function of this pathway. These molecules can directly or indirectly regulate the PI3K/Akt/mTOR pathway through a variety of ways, thereby affecting the proliferation, metastasis, chemoradiotherapy sensitivity and angiogenesis of ESCC.

Several PI3K/Akt/mTOR pathway inhibitors have been investigated to be effective against a variety of cancers, and sufficient clinical data have been obtained. For example, the pan-PI3K inhibitor buparisib (BKM120) has shown antitumor activity in estrogen receptor (ER) positive breast cancer and xenograft tumors, either alone or in combination, and has been studied in phase III clinical trials in breast cancer. Similarly, everolimus has shown a strong antitumor effect in advanced HER2-positive breast cancer and advanced GC, which have also progressed to phase III clinical trials (93, 99). Unfortunately, while many targeted inhibitors of ESCC (such as MK226 and everolimus) have been discovered, no drugs have been approved for clinical use due to severe side effects and drug resistance. Because monotherapy often leads to compensatory activation of other pathways, such as LYZ294002, rapamycin, and cisplatin.LYZ294002 is a pan-PI3K inhibitor that induces compensatory activation of Akt during its inhibitory action, thereby reducing its inhibitory effect. Similarly, BYL719 is a specific PI3K inhibitor that has been shown to have inhibitory effects in head and neck squamous cell carcinoma. BYL719 has also been found to be effective in ESCC but its efficacy is often limited by drug resistance (76). Dual inhibitors can effectively reduce compensatory activations and enhance therapeutic effects. Therefore, in order to overcome this redundant pathway activation, new drugs or multi-drug combinations should be vigorously developed. Therefore, future research should focus on the study of other forms of mutations, the exploration and discovery of new regulatory molecules, and the combination therapy or the development of dual inhibitors to overcome the resistance problems caused by monotherapy.

PI3K/Akt/mTOR pathway is one of the most vital pathway regulating the basic physiological functions of cells. Abnormal activation of this pathway are usually caused by the regulation of its upstream molecules and mutations or amplification of major components (e.g. PIK3CA, Akt1, PTEN, etc.). Although many inhibitors have been shown to be effective in PI3K/Akt/mTOR signaling pathway, clinical studies are still lacking. Moreover, drug resistance has been a persistent problem. The efficacy of a multi-drug combination is superior to that of medication alone in preventing the compensatory activation of other pathways. Therefore, the research focus should be on multi-drug combination therapy and search for multi-inhibitors.

AUTHOR CONTRIBUTIONS

All listed authors made significant and intellectual contribution to this work. XL designs this review. ZD provides guidance. QL wrote the text and collected related data. RD and WL provided assistance on the outline and language. GH is responsible for revising the content of the article. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.852383/full#supplementary-material

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660
2. Enzinger PC, Mayer RJ. Esophageal Cancer. *N Engl J Med* (2003) 349 (23):2241–52. doi: 10.1056/NEJMra035010
3. Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB. Exploiting the PI3K/AKT Pathway for Cancer Drug Discovery. *Nat Rev Drug Discov* (2005) 4(12):988–1004. doi: 10.1038/nrd1902
4. Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in Cancer: Mechanisms and Advances in Clinical Trials. *Mol Cancer* (2019) 18(1):26. doi: 10.1186/s12943-019-0954-x
5. Liu P, Begley M, Michowski W, Inuzuka H, Ginzberg M, Gao D, et al. Cell-Cycle-Regulated Activation of Akt Kinase by Phosphorylation at its Carboxyl Terminus. *Nature* (2014) 508(7497):541–5. doi: 10.1038/nature13079
6. Mossmann D, Park S, Hall MN. mTOR Signalling and Cellular Metabolism are Mutual Determinants in Cancer. *Nat Rev Cancer* (2018) 18(12):744–57. doi: 10.1038/s41568-018-0074-8
7. Shigaki H, Baba Y, Watanabe M, Murata A, Ishimoto T, Iwatsuki M, et al. PIK3CA Mutation Is Associated With a Favorable Prognosis Among Patients With Curatively Resected Esophageal Squamous Cell Carcinoma. *Clin Cancer Res* (2013) 19(9):2451–9. doi: 10.1158/1078-0432.CCR-12-3559
8. Chang J, Tan W, Ling Z, Xi R, Shao M, Chen M, et al. Genomic Analysis of Oesophageal Squamous-Cell Carcinoma Identifies Alcohol Drinking-Related Mutation Signature and Genomic Alterations. *Nat Commun* (2017) 8:15290. doi: 10.1038/ncomms15290
9. Wang K, Johnson A, Ali SM, Klempner SJ, Bekaii-Saab T, Vacirca JL, et al. Comprehensive Genomic Profiling of Advanced Esophageal Squamous Cell Carcinomas and Esophageal Adenocarcinomas Reveals Similarities and Differences. *Oncologist* (2015) 20(10):1132–9. doi: 10.1634/theoncologist.2015-0156
10. Zhang L, Zhou Y, Cheng C, Cui H, Cheng L, Kong P, et al. Genomic Analyses Reveal Mutational Signatures and Frequently Altered Genes in Esophageal Squamous Cell Carcinoma. *Am J Hum Genet* (2020) 107(2):375. doi: 10.1016/j.ajhg.2020.07.008
11. Zhu J, Wang M, He J, Zhu M, Wang JC, Jin L, et al. Polymorphisms in the AKT1 and AKT2 Genes and Oesophageal Squamous Cell Carcinoma Risk in an Eastern Chinese Population. *J Cell Mol Med* (2016) 20(4):666–77. doi: 10.1111/jcmm.12750
12. Hildebrandt MA, Yang H, Hung MC, Izzo JG, Huang M, Lin J, et al. Genetic Variations in the PI3K/PTEN/AKT/mTOR Pathway are Associated With Clinical Outcomes in Esophageal Cancer Patients Treated With Chemoradiotherapy. *J Clin Oncol* (2009) 27(6):857–71. doi: 10.1200/JCO.2008.17.6297
13. Zhu J, Wang M, Zhu M, He J, Wang JC, Jin L, et al. Associations of PI3KR1 and mTOR Polymorphisms With Esophageal Squamous Cell Carcinoma Risk and Gene-Environment Interactions in Eastern Chinese Populations. *Sci Rep* (2015) 5:8250. doi: 10.1038/srep08250
14. Zhu ML, Yu H, Shi TY, He J, Wang MY, Li QX, et al. Polymorphisms in Mtorc1 Genes Modulate Risk of Esophageal Squamous Cell Carcinoma in Eastern Chinese Populations. *J Thorac Oncol* (2013) 8(6):788–95. doi: 10.1097/JTO.0b013e31828916c6
15. Yang JW, Choi YL. Genomic Profiling of Esophageal Squamous Cell Carcinoma (ESCC)-Basis for Precision Medicine. *Pathol Res Pract* (2017) 213(7):836–41. doi: 10.1016/j.prp.2017.02.021
16. Kim SH, Chau GC, Jang YH, Lee SI, Pyo S, Um SH. Clinicopathologic Significance and Function of Mammalian Target of Rapamycin Activation in Esophageal Squamous Cell Carcinoma. *Hum Pathol* (2013) 44(2):226–36. doi: 10.1016/j.humpath.2012.05.011
17. Hou G, Xue L, Lu Z, Fan T, Tian F, Xue Y. An Activated mTOR/P70s6k Signaling Pathway in Esophageal Squamous Cell Carcinoma Cell Lines and Inhibition of the Pathway by Rapamycin and siRNA Against mTOR. *Cancer Lett* (2007) 253(2):236–48. doi: 10.1016/j.canlet.2007.01.026
18. Takahashi K, Miyashita M, Makino H, Akagi I, Orita H, Hagiwara N, et al. Expression of Akt and Mdm2 in Human Esophageal Squamous Cell Carcinoma. *Exp Mol Pathol* (2009) 87(1):42–7. doi: 10.1016/j.yexmp.2008.11.013
19. Wu N, Du Z, Zhu Y, Song Y, Pang L, Chen Z. The Expression and Prognostic Impact of the PI3K/AKT/mTOR Signaling Pathway in Advanced Esophageal Squamous Cell Carcinoma. *Technol Cancer Res Treat* (2018) 17:1533033818758772. doi: 10.1177/1533033818758772
20. Jiang Q, Chen J, Zhang B, Niu J, He Y. Prognostic Significance of Periostin and Mammalian Target of Rapamycin (mTOR) in Locally Advanced Esophageal Squamous Cell Carcinoma. *Med Sci Monit* (2017) 23:3200–8. doi: 10.12659/msm.904992
21. Zhang Y, Liu YP, Du K, Wang H, Wang XL. [Expression and Clinical Significance of PI3K in Esophageal Squamous Cell Carcinoma]. *Zhonghua Zhong Liu Za Zhi* (2011) 33(8):594–8. doi: 10.3760/cma.j.issn.0253-3766.2011.08.009
22. Yoshioka A, Miyata H, Doki Y, Yasuda T, Yamasaki M, Motoori M, et al. The Activation of Akt During Preoperative Chemotherapy for Esophageal Cancer Correlates With Poor Prognosis. *Oncol Rep* (2008) 19(5):1099–107. doi: 10.3892/or.19.5.1099
23. Shan ZZ, Chen PN, Wang F, Wang J, Fan QX. Expression of P-EGFR and P-Akt Protein in Esophageal Squamous Cell Carcinoma and its Prognosis. *Oncol Lett* (2017) 14(3):2859–63. doi: 10.3892/ol.2017.6526
24. Li Q, Li S, Yang X, Zhang X, Song C, Zhu S. Association Between RNF2+P-AKT Expression in Pretreatment Biopsy Specimens, and Poor Survival Following Radiotherapy in Patients With Esophageal Squamous Cell Carcinoma. *Oncol Lett* (2019) 18(4):3734–42. doi: 10.3892/ol.2019.10727
25. Du R, Huang C, Chen H, Liu K, Xiang P, Yao N, et al. SDCBP/MDA-9/Syntenin Phosphorylation by AURKA Promotes Esophageal Squamous Cell Carcinoma Progression Through the EGFR-PI3K-Akt Signaling Pathway. *Oncogene* (2020) 39(31):5405–19. doi: 10.1038/s41388-020-1369-2
26. Urakawa N, Utsunomiya S, Nishio M, Shigeoka M, Takase N, Arai N, et al. GDF15 Derived From Both Tumor-Associated Macrophages and Esophageal Squamous Cell Carcinomas Contributes to Tumor Progression *via* Akt and Erk Pathways. *Lab Invest* (2015) 95(5):491–503. doi: 10.1038/labinvest.2015.36
27. Ye S, Lee KB, Park MH, Lee JS, Kim SM. P63 Regulates Growth of Esophageal Squamous Carcinoma Cells *via* the Akt Signaling Pathway. *Int J Oncol* (2014) 44(6):2153–9. doi: 10.3892/ijo.2014.2374
28. Gen Y, Yasui K, Nishikawa T, Yoshikawa T. SOX2 Promotes Tumor Growth of Esophageal Squamous Cell Carcinoma Through the AKT/mammalian Target of Rapamycin Complex 1 Signaling Pathway. *Cancer Sci* (2013) 104 (7):810–6. doi: 10.1111/cas.12155
29. Li P, Chen X, Qin G, Yue D, Zhang Z, Ping Y, et al. Maelstrom Directs Myeloid-Derived Suppressor Cells to Promote Esophageal Squamous Cell Carcinoma Progression *via* Activation of the Akt1/RelA/IL8 Signaling Pathway. *Cancer Immunol Res* (2018) 6(10):1246–59. doi: 10.1158/2326-6066.CIR-17-0415
30. Jin F, Zhu Y, Chen J, Wang R, Wang Y, Wu Y, et al. BRE Promotes Esophageal Squamous Cell Carcinoma Growth by Activating AKT Signaling. *Front Oncol* (2020) 10:1407:1407. doi: 10.3389/fonc.2020.01407
31. Ma L, Yao N, Chen P, Zhuang Z. TRIM27 Promotes the Development of Esophagus Cancer *via* Regulating PTEN/AKT Signaling Pathway. *Cancer Cell Int* (2019) 19:283. doi: 10.1186/s12935-019-0998-4
32. Liu Y, Zhang M, He T, Yang W, Wang L, Zhang L, et al. Epigenetic Silencing of IGFBPL1 Promotes Esophageal Cancer Growth by Activating PI3K-AKT Signaling. *Clin Epigenet* (2020) 12(1):22. doi: 10.1186/s13148-020-0815-x

33. Yu VZ, Wong VC, Dai W, Ko JM, Lam AK, Chan KW, et al. Nuclear Localization of DNAJB6 Is Associated With Survival of Patients With Esophageal Cancer and Reduces AKT Signaling and Proliferation of Cancer Cells. *Gastroenterology* (2015) 149(7):1825–36.e5. doi: 10.1053/j.gastro.2015.08.025
34. Pastushenko I, Blanpain C. EMT Transition States During Tumor Progression and Metastasis. *Trends Cell Biol* (2019) 29(3):212–26. doi: 10.1016/j.tcb.2018.12.001
35. Li B, Tsao SW, Li YY, Wang X, Ling MT, Wong YC, et al. Id-1 Promotes Tumorigenicity and Metastasis of Human Esophageal Cancer Cells Through Activation of PI3K/AKT Signaling Pathway. *Int J Cancer* (2009) 125 (11):2576–85. doi: 10.1002/ijc.24675
36. Wang H, Yang X, Guo Y, Shui L, Li S, Bai Y, et al. HERG1 Promotes Esophageal Squamous Cell Carcinoma Growth and Metastasis Through TXNDC5 by Activating the PI3K/AKT Pathway. *J Exp Clin Cancer Res* (2019) 38(1):324. doi: 10.1186/s13046-019-1284-y
37. Li Q, Xu A, Chu Y, Chen T, Li H, Yao L, et al. Rap1A Promotes Esophageal Squamous Cell Carcinoma Metastasis Through the AKT Signaling Pathway. *Oncol Rep* (2019) 42(5):1815–24. doi: 10.3892/or.2019.7309
38. Liu Z, Yu S, Ye S, Shen Z, Gao L, Han Z, et al. Keratin 17 Activates AKT Signalling and Induces Epithelial-Mesenchymal Transition in Oesophageal Squamous Cell Carcinoma. *J Proteomics* (2020) 211:103557. doi: 10.1016/j.jprot.2019.103557
39. Zhang HY, Wang ZQ, Li YY, Wang F, Zeng QR, Gao Y, et al. Transforming Growth Factor-Beta1-Induced Epithelial-Mesenchymal Transition in Human Esophageal Squamous Cell Carcinoma *via* the PTEN/PI3K Signaling Pathway. *Oncol Rep* (2014) 32(5):2134–42. doi: 10.3892/or.2014.3453
40. Shan B, Man H, Liu J, Wang L, Zhu T, Ma M, et al. TIM-3 Promotes the Metastasis of Esophageal Squamous Cell Carcinoma by Targeting Epithelial-Mesenchymal Transition *via* the Akt/GSK-3beta/Snail Signaling Pathway. *Oncol Rep* (2016) 36(3):1551–61. doi: 10.3892/or.2016.4938
41. Zhang F, Wang Y, Sun P, Wang ZQ, Wang DS, Zhang DS, et al. Fibrinogen Promotes Malignant Biological Tumor Behavior Involving Epithelial-Mesenchymal Transition *via* the P-AKT/p-mTOR Pathway in Esophageal Squamous Cell Carcinoma. *J Cancer Res Clin Oncol* (2017) 143(12):2413–24. doi: 10.1007/s00432-017-2493-4
42. Liu RM, Sun DN, Jiao YL, Wang P, Zhang J, Wang M, et al. Macrophage Migration Inhibitory Factor Promotes Tumor Aggressiveness of Esophageal Squamous Cell Carcinoma *via* Activation of Akt and Inactivation of GSK3beta. *Cancer Lett* (2018) 412:289–96. doi: 10.1016/j.canlet.2017.10.018
43. Cheng X, Wei L, Huang X, Zheng J, Shao M, Feng T, et al. Solute Carrier Family 39 Member 6 Gene Promotes Aggressiveness of Esophageal Carcinoma Cells by Increasing Intracellular Levels of Zinc, Activating Phosphatidylinositol 3-Kinase Signaling, and Up-Regulating Genes That Regulate Metastasis. *Gastroenterology* (2017) 152(8):1985–97 e12. doi: 10.1053/j.gastro.2017.02.006
44. Liu SG, Wang BS, Jiang YY, Zhang TT, Shi ZZ, Yang Y, et al. Atypical Protein Kinase Ciota (PKCiota) Promotes Metastasis of Esophageal Squamous Cell Carcinoma by Enhancing Resistance to Anoikis *via* PKCiota-SKP2-AKT Pathway. *Mol Cancer Res* (2011) 9(4):390–402. doi: 10.1158/1541-7786.MCR-10-0359
45. Chen J, Lan T, Zhang W, Dong L, Kang N, Zhang S, et al. Platelet-Activating Factor Receptor-Mediated PI3K/AKT Activation Contributes to the Malignant Development of Esophageal Squamous Cell Carcinoma. *Oncogene* (2015) 34(40):5114–27. doi: 10.1038/onc.2014.434
46. Yan J, Du P, Jia Y, Chang Z, Gan S, Xu X, et al. Ablation of MCM10 Using CRISPR/Cas9 Restrains the Growth and Migration of Esophageal Squamous Cell Carcinoma Cells Through Inhibition of Akt Signaling. *Onco Targets Ther* (2018) 11:3323–33. doi: 10.2147/OTT.S157025
47. Kodama T, Koma YI, Arai N, Kido A, Urakawa N, Nishio M, et al. CCL3-CCR5 Axis Contributes to Progression of Esophageal Squamous Cell Carcinoma by Promoting Cell Migration and Invasion *via* Akt and ERK Pathways. *Lab Invest* (2020) 100(9):1140–57. doi: 10.1038/s41374-020-0441-4
48. Chen J, Zhang W, Wang Y, Zhao D, Wu M, Fan J, et al. The Diacylglycerol Kinase Alpha (DGKalpha)/Akt/NF-kappaB Feedforward Loop Promotes Esophageal Squamous Cell Carcinoma (ESCC) Progression *via* FAK-Dependent and FAK-Independent Manner. *Oncogene* (2019) 38(14):2533–50. doi: 10.1038/s41388-018-0604-6
49. Yang CL, Zheng XL, Ye K, Ge H, Sun YN, Lu YF, et al. NDRG2 Suppresses Proliferation, Migration, Invasion and Epithelial-Mesenchymal Transition of Esophageal Cancer Cells Through Regulating the AKT/XIAP Signaling Pathway. *Int J Biochem Cell Biol* (2018) 99:43–51. doi: 10.1016/j.biocel.2018.03.003
50. Kuo KT, Chen CL, Chou TY, Yeh CT, Lee WH, Wang LS. Nm23H1 Mediates Tumor Invasion in Esophageal Squamous Cell Carcinoma by Regulation of CLDN1 Through the AKT Signaling. *Oncogenesis* (2016) 5(7):e239. doi: 10.1038/oncsis.2016.46
51. Zhu X, Wang J, Li L, Deng L, Wang J, Liu L, et al. GPX3 Suppresses Tumor Migration and Invasion *via* the FAK/AKT Pathway in Esophageal Squamous Cell Carcinoma. *Am J Transl Res* (2018) 10(6):1908–20.
52. Yang XX, Ma M, Sang MX, Zhang XY, Liu ZK, Song H, et al. BMI-1 Suppression Increases the Radiosensitivity of Oesophageal Carcinoma *via* the PI3K/Akt Signaling Pathway. *Oncol Rep* (2018) 39(2):667–78. doi: 10.3892/or.2017.6136
53. Suo D, Wang Z, Li L, Chen Q, Zeng T, Liu R, et al. HOXC10 Upregulation Confers Resistance to Chemoradiotherapy in ESCC Tumor Cells and Predicts Poor Prognosis. *Oncogene* (2020) 39(32):5441–54. doi: 10.1038/s41388-020-1375-4
54. Chen X, Zhuo S, Xu W, Chen X, Huang D, Sun X, et al. Isocitrate Dehydrogenase 2 Contributes to Radiation Resistance of Oesophageal Squamous Cell Carcinoma *via* Regulating Mitochondrial Function and ROS/pAKT Signalling. *Br J Cancer* (2020) 123(1):126–36. doi: 10.1038/s41416-020-0852-4
55. He Z, Li G, Tang L, Li Y. SIX1 Overexpression Predicts Poor Prognosis and Induces Radioresistance Through AKT Signaling in Esophageal Squamous Cell Carcinoma. *Onco Targets Ther* (2017) 10:1071–9. doi: 10.2147/OTT.S125330
56. Nie C, Qin X, Li X, Tian B, Zhao Y, Jin Y, et al. CACNA2D3 Enhances the Chemosensitivity of Esophageal Squamous Cell Carcinoma to Cisplatin *via* Inducing Ca(2+)-Mediated Apoptosis and Suppressing PI3K/Akt Pathways. *Front Oncol* (2019) 9:185. doi: 10.3389/fonc.2019.00185
57. Li CH, Sun XJ, Niu SS, Yang CY, Hao YP, Kou JT, et al. Overexpression of IQGAP1 Promotes the Angiogenesis of Esophageal Squamous Cell Carcinoma Through the AKT and ERKmediated VEGFVEGFR2 Signaling Pathway. *Oncol Rep* (2018) 40(3):1795–802. doi: 10.3892/or.2018.6558
58. Wang W, He S, Zhang R, Peng J, Guo D, Zhang J, et al. ALDH1A1 Maintains the Cancer Stem-Like Cells Properties of Esophageal Squamous Cell Carcinoma by Activating the AKT Signal Pathway and Interacting With Beta-Catenin. *BioMed Pharmacother* (2020) 125:109940. doi: 10.1016/j.biopha.2020.109940
59. Song M, Liu X, Liu K, Zhao R, Huang H, Shi Y, et al. Targeting AKT With Oridonin Inhibits Growth of Esophageal Squamous Cell Carcinoma *In Vitro* and Patient-Derived Xenografts *In Vivo*. *Mol Cancer Ther* (2018) 17(7):1540–53. doi: 10.1158/1535-7163.MCT-17-0823
60. Guo Q, He J, Shen F, Zhang W, Yang X, Zhang C, et al. TCN, an AKT Inhibitor, Exhibits Potent Antitumor Activity and Enhances Radiosensitivity in Hypoxic Esophageal Squamous Cell Carcinoma *In Vitro* and *In Vivo*. *Oncol Lett* (2017) 13(2):949–54. doi: 10.3892/ol.2016.5515
61. Liu X, Song M, Wang P, Zhao R, Chen H, Zhang M, et al. Targeted Therapy of the AKT Kinase Inhibits Esophageal Squamous Cell Carcinoma Growth *In Vitro* and *In Vivo*. *Int J Cancer* (2019) 145(4):1007–19. doi: 10.1002/ijc.32285
62. Liu F, Zu X, Xie X, Zhang Y, Liu K, Chen H, et al. Scutellarin Suppresses Patient-Derived Xenograft Tumor Growth by Directly Targeting AKT in Esophageal Squamous Cell Carcinoma. *Cancer Prev Res (Phila)* (2019) 12 (12):849–60. doi: 10.1158/1940-6207.CAPR-19-0244
63. Hirai H, Sootome H, Nakatsuru Y, Miyama K, Taguchi S, Tsujioka K, et al. MK-2206, an Allosteric Akt Inhibitor, Enhances Antitumor Efficacy by Standard Chemotherapeutic Agents or Molecular Targeted Drugs *In Vitro* and *In Vivo*. *Mol Cancer Ther* (2010) 9(7):1956–67. doi: 10.1158/1535-7163.MCT-09-1012
64. Shi N, Yu H, Chen T. Inhibition of Esophageal Cancer Growth Through the Suppression of PI3K/AKT/mTOR Signaling Pathway. *Onco Targets Ther* (2019) 12:7637–47. doi: 10.2147/OTT.S205457
65. Wu N, Zhu Y, Xu X, Zhu Y, Song Y, Pang L, et al. The Anti-Tumor Effects of Dual PI3K/mTOR Inhibitor BEZ235 and Histone Deacetylase Inhibitor Trichostatin A on Inducing Autophagy in Esophageal Squamous Cell Carcinoma. *J Cancer* (2018) 9(6):987–97. doi: 10.7150/jca.22861

66. Brunn GJ, Williams J, Sabers C, Wiederrecht G, Lawrence JCJr., Abraham RT. Direct Inhibition of the Signaling Functions of the Mammalian Target of Rapamycin by the Phosphoinositide 3-Kinase Inhibitors, Wortmannin and LY294002. *EMBO J* (1996) 15(19):5256–67. doi: 10.1002/j.1460-2075.1996.tb00911.x
67. Hou G, Zhao Q, Zhang M, Fan T, Liu M, Shi X, et al. Down-Regulation of Rictor Enhances Cell Sensitivity to PI3K Inhibitor LY294002 by Blocking Mtorc2-Medicated Phosphorylation of Akt/PRAS40 in Esophageal Squamous Cell Carcinoma. *BioMed Pharmacother* (2018) 106:1348–56. doi: 10.1016/j.biopha.2018.07.075
68. Wang XS, Ding XZ, Li XC, He Y, Kong DJ, Zhang L, et al. A Highly Integrated Precision Nanomedicine Strategy to Target Esophageal Squamous Cell Cancer Molecularly and Physically. *Nanomedicine* (2018) 14(7):2103–14. doi: 10.1016/j.nano.2018.06.008
69. Shi JJ, Xing H, Wang YX, Zhang X, Zhan QM, Geng MY, et al. PI3Kalpha Inhibitors Sensitize Esophageal Squamous Cell Carcinoma to Radiation by Abrogating Survival Signals in Tumor Cells and Tumor Microenvironment. *Cancer Lett* (2019) 459:145–55. doi: 10.1016/j.canlet.2019.05.040
70. Xiang HY, Wang X, Chen YH, Zhang X, Tan C, Wang Y, et al. Identification of Methyl (5-(6-((4-(Methylsulfonyl)Piperazin-1-Yl)Methyl)-4-Morpholinopyrrolo[2,1-F][1,2,4]Triazin-2-Yl)-4-(Trifluoromethyl)Pyridin-2-Yl)Carbamate (CYH33) as an Orally Bioavailable, Highly Potent, PI3K Alpha Inhibitor for the Treatment of Advanced Solid Tumors. *Eur J Med Chem* (2021) 209:112913. doi: 10.1016/j.ejmech.2020.112913
71. Hou G, Zhang Q, Wang L, Liu M, Wang J, Xue L. mTOR Inhibitor Rapamycin Alone or Combined With Cisplatin Inhibits Growth of Esophageal Squamous Cell Carcinoma in Nude Mice. *Cancer Lett* (2010) 290(2):248–54. doi: 10.1016/j.canlet.2009.09.015
72. Li SH, Chen CH, Lu HI, Huang WT, Tien WY, Lan YC, et al. Phosphorylated P70s6k Expression is an Independent Prognosticator for Patients With Esophageal Squamous Cell Carcinoma. *Surgery* (2015) 157(3):570–80. doi: 10.1016/j.surg.2014.10.014
73. Hirashima K, Baba Y, Watanabe M, Karashima RI, Sato N, Imamura Y, et al. Aberrant Activation of the mTOR Pathway and Anti-Tumour Effect of Everolimus on Oesophageal Squamous Cell Carcinoma. *Br J Cancer* (2012) 106(5):876–82. doi: 10.1038/bjc.2012.36
74. Nishikawa T, Takaoka M, Ohara T, Tomono Y, Hao H, Bao X, et al. Antiproliferative Effect of a Novel mTOR Inhibitor Temsirolimus Contributes to the Prolonged Survival of Orthotopic Esophageal Cancer-Bearing Mice. *Cancer Biol Ther* (2013) 14(3):230–6. doi: 10.4161/cbt.23294
75. Huang Y, Xi Q, Chen Y, Wang J, Peng P, Xia S, et al. A Dual Mtorc1 and Mtorc2 Inhibitor Shows Antitumor Activity in Esophageal Squamous Cell Carcinoma Cells and Sensitizes Them to Cisplatin. *Anticancer Drugs* (2013) 24(9):889–98. doi: 10.1097/CAD.0b013e328363c64e
76. Elkabets M, Pazarentzos E, Juric D, Sheng Q, Pelossof RA, Brook S, et al. AXL Mediates Resistance to PI3Kalpha Inhibition by Activating the EGFR/PKC/mTOR Axis in Head and Neck and Esophageal Squamous Cell Carcinomas. *Cancer Cell* (2015) 27(4):533–46. doi: 10.1016/j.ccell.2015.03.010
77. Badarni M, Prasad M, Balaban N, Zorea J, Yegodayev KM, Joshua BZ, et al. Repression of AXL Expression by AP-1/JNK Blockage Overcomes Resistance to PI3Ka Therapy. *JCI Insight* (2019) 4(8):e125341. doi: 10.1172/jci.insight.125341
78. Peng KZ, Ke Y, Zhao Q, Tian F, Liu HM, Hou G, et al. OP16, a Novel Ent-Kaurene Diterpenoid, Potentiates the Antitumor Effect of Rapamycin by Inhibiting Rapamycin-Induced Feedback Activation of Akt Signaling in Esophageal Squamous Cell Carcinoma. *Biochem Pharmacol* (2017) 140:16–27. doi: 10.1016/j.bcp.2017.05.013
79. Ramanathan RK, McDonough SL, Kennecke HF, Iqbal S, Baranda JC, Seery TE, et al. Phase 2 Study of MK-2206, an Allosteric Inhibitor of AKT, as Second-Line Therapy for Advanced Gastric and Gastroesophageal Junction Cancer: A SWOG Cooperative Group Trial (S1005). *Cancer* (2015) 121 (13):2193–7. doi: 10.1002/cncr.29363
80. Do K, Speranza G, Bishop R, Khin S, Rubinstein L, Kinders RJ, et al. Biomarker-Driven Phase 2 Study of MK-2206 and Selumetinib (AZD6244, ARRY-142886) in Patients With Colorectal Cancer. *Invest New Drugs* (2015) 33(3):720–8. doi: 10.1007/s10637-015-0212-z
81. Bang YJ, Kang YK, Ng M, Chung HC, Wainberg ZA, Gendreau S, et al. A Phase II, Randomised Study of Mfolfox6 With or Without the Akt Inhibitor Ipatasertib in Patients With Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer. *Eur J Cancer* (2019) 108:17–24. doi: 10.1016/j.ejca.2018.11.017
82. McRee AJ, Sanoff HK, Carlson C, Ivanova A, O'Neil BH. A Phase I Trial of Mfolfox6 Combined With the Oral PI3K Inhibitor BKM120 in Patients With Advanced Refractory Solid Tumors. *Invest New Drugs* (2015) 33(6):1225–31. doi: 10.1007/s10637-015-0298-3
83. Goodwin R, Jonker D, Chen E, Kennecke H, Cabanero M, Tsao MS, et al. A Phase Ib Study of a PI3Kinase Inhibitor BKM120 in Combination With Panitumumab in Patients With KRAS Wild-Type Advanced Colorectal Cancer. *Invest New Drugs* (2020) 38(4):1077–84. doi: 10.1007/s10637-019-00814-3
84. van Geel R, Tabernero J, Elez E, Bendell JC, Spreafico A, Schuler M, et al. A Phase Ib Dose-Escalation Study of Encorafenib and Cetuximab With or Without Alpelisib in Metastatic BRAF-Mutant Colorectal Cancer. *Cancer Discov* (2017) 7(6):610–9. doi: 10.1158/2159-8290.CD-16-0795
85. Bowles DW, Senzer N, Hausman D, Peterson S, Vo A, Walker L, et al. A Multicenter Phase 1 Study of PX-866 and Cetuximab in Patients With Metastatic Colorectal Carcinoma or Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck. *Invest New Drugs* (2014) 32(6):1197–203. doi: 10.1007/s10637-014-0124-3
86. Spindler KL, Sorensen MM, Pallisgaard N, Andersen RF, Havelund BM, Ploen J, et al. Phase II Trial of Temsirolimus Alone and in Combination With Irinotecan for KRAS Mutant Metastatic Colorectal Cancer: Outcome and Results of KRAS Mutational Analysis in Plasma. *Acta Oncol* (2013) 52(5):963–70. doi: 10.3109/0284186X.2013.776175
87. Altomare I, Bendell JC, Bullock KE, Uronis HE, Morse MA, Hsu SD, et al. A Phase II Trial of Bevacizumab Plus Everolimus for Patients With Refractory Metastatic Colorectal Cancer. *Oncologist* (2011) 16(8):1131–7. doi: 10.1634/theoncologist.2011-0078
88. Hecht JR, Reid TR, Garrett CR, Beck JT, Davidson SJ, Mackenzie MJ, et al. Phase I Study of Everolimus, Cetuximab and Irinotecan as Second-Line Therapy in Metastatic Colorectal Cancer. *Anticancer Res* (2015) 35(3):1567–73.
89. Weldon Gilcrease G, Stenehjem DD, Wade ML, Weis J, McGregor K, Whisenant J, et al. Phase I/II Study of Everolimus Combined With mFOLFOX-6 and Bevacizumab for First-Line Treatment of Metastatic Colorectal Cancer. *Invest New Drugs* (2019) 37(3):482–9. doi: 10.1007/s10637-018-0645-2
90. Bendell JC, Jones SF, Hart L, Spigel DR, Lane CM, Earwood C, et al. A Phase Ib Study of Linsitinib (OSI-906), a Dual Inhibitor of IGF-1R and IR Tyrosine Kinase, in Combination With Everolimus as Treatment for Patients With Refractory Metastatic Colorectal Cancer. *Invest New Drugs* (2015) 33(1):187–93. doi: 10.1007/s10637-014-0177-3
91. Wolpin BM, Ng K, Zhu AX, Abrams T, Enzinger PC, McCleary NJ, et al. Multicenter Phase II Study of Tivozanib (AV-951) and Everolimus (RAD001) for Patients With Refractory, Metastatic Colorectal Cancer. *Oncologist* (2013) 18(4):377–8. doi: 10.1634/theoncologist.2012-0378
92. Townsend A, Tebbutt N, Karapetis C, Cooper P, Singhal N, Yeend S, et al. Phase IB/II Study of Second-Line Therapy With Panitumumab, Irinotecan, and Everolimus (PIE) in KRAS Wild-Type Metastatic Colorectal Cancer. *Clin Cancer Res* (2018) 24(16):3838–44. doi: 10.1158/1078-0432.CCR-17-3590
93. Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, et al. Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study. *J Clin Oncol* (2013) 31(31):3935–43. doi: 10.1200/JCO.2012.48.3552
94. Lee SJ, Lee J, Lee J, Park SH, Park JO, Park YS, et al. Phase II Trial of Capecitabine and Everolimus (RAD001) Combination in Refractory Gastric Cancer Patients. *Invest New Drugs* (2013) 31(6):1580–6. doi: 10.1007/s10637-013-0022-0
95. Werner D, Atmaca A, Pauligk C, Pustowka A, Jager E, Al-Batran SE. Phase I Study of Everolimus and Mitomycin C for Patients With Metastatic Esophagogastric Adenocarcinoma. *Cancer Med* (2013) 2(3):325–33. doi: 10.1002/cam4.77
96. Doi T, Muro K, Boku N, Yamada Y, Nishina T, Takiuchi H, et al. Multicenter Phase II Study of Everolimus in Patients With Previously Treated Metastatic Gastric Cancer. *J Clin Oncol* (2010) 28(11):1904–10. doi: 10.1200/JCO.2009.26.2923
97. Shen YC, Li CP, Yen CJ, Hsu C, Lin YL, Lin ZZ, et al. Phase II Multicentered Study of Low-Dose Everolimus Plus Cisplatin and Weekly 24-Hour Infusion

of High-Dose 5-Fluorouracil and Leucovorin as First-Line Treatment for Patients With Advanced Gastric Cancer. *Oncology* (2014) 87(2):104–13. doi: 10.1159/000362671

98. Wainberg ZA, Soares HP, Patel R, DiCarlo B, Park DJ, Liem A, et al. Phase II Trial of Everolimus in Patients With Refractory Metastatic Adenocarcinoma of the Esophagus, Gastroesophageal Junction and Stomach: Possible Role for Predictive Biomarkers. *Cancer Chemother Pharmacol* (2015) 76(1):61–7. doi: 10.1007/s00280-015-2744-5
99. Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K Inhibitors: Lessons Learned From Early Clinical Trials. *Nat Rev Clin Oncol* (2013) 10(3):143–53. doi: 10.1038/nrclinonc.2013.10

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REVIEW
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A Review: PI3K/AKT/mTOR Signaling Pathway and Its Regulated Eukaryotic Translation Initiation Factors May Be a Potential Therapeutic Target in Esophageal Squamous Cell Carcinoma

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Esophageal squamous cell carcinoma (ESCC) is a malignant tumor developing from the esophageal squamous epithelium, and is the most common histological subtype of esophageal cancer (EC). EC ranks 10th in morbidity and sixth in mortality worldwide. The morbidity and mortality rates in China are both higher than the world average. Current treatments of ESCC are surgical treatment, radiotherapy, and chemotherapy. Neoadjuvant chemoradiotherapy plus surgical resection is recommended for advanced patients. However, it does not work in the significant promotion of overall survival (OS) after such therapy. Research on targeted therapy in ESCC mainly focus on EGFR and PD-1, but neither of the targeted drugs can significantly improve the 3-year and 5-year survival rates of disease. Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is an important survival pathway in tumor cells, associated with its aggressive growth and malignant progression. Specifically, proliferation, apoptosis, autophagy, and so on. Related genetic alterations of this pathway have been investigated in ESCC, such as *PI3K*, *AKT* and *mTOR-rpS6K*. Therefore, the PI3K/AKT/mTOR pathway seems to have the capability to serve as research hotspot in the future. Currently, various inhibitors are being tested in cells, animals, and clinical trials, which targeting at different parts of this pathway. In this work, we reviewed the research progress on the PI3K/AKT/mTOR pathway how to influence biological behaviors in ESCC, and discussed the interaction between signals downstream of this pathway, especially eukaryotic translation initiation factors (eIFs) and the development and progression of ESCC, to provide reference for the identification of new therapeutic targets in ESCC.

Keywords: esophageal squamous cell carcinoma (ESCC), PI3K/AKT/mTOR signaling pathway, inhibitors, eukaryotic translation initiation factors (eIFs), therapeutic target

INTRODUCTION

The General Status of Esophageal Carcinoma

In 2020, the incidence and mortality of esophageal carcinoma (EC) ranked tenth and sixth in the world, with about 70% of the cases affection males. According to statistics, in 2020, 544,076 people died due to EC worldwide1]. The incidence in eastern Asia is the highest in the world (1). EC mainly includes ESCC and esophageal adenocarcinoma (EAC). The incidence of ESCC is higher than EAC in Asia (2). Currently, the incidence of ESCC has decreased significantly in Asia (e.g., in China), probably due to the decline in poverty (3), but the mortality rate is still not optimistic.

With the improvement of various examination methods, the detection rate of esophageal squamous dysplasia is increasing, especially in the areas with high incidence of ESCC. Esophageal squamous dysplasia has the potential to develop into ESCC. The two can be regarded as a continuous pathological process (4). The symptoms of EC are very insidious. Early EC is often detected by gastroscopy, CT, or MRI (5). These examinations may reveal ulceration or protuberance on the mucosal esophageal surface, or thickening of the esophageal wall (5). As the lesion progresses, patients might have difficulty swallowing. They can only take half liquid diet or even liquid diet, until they are completely unable to eat and thus significantly lose weight. Some patients even feel chest pain (6).

According to the degree of differentiation of ESCC, three grades can be differentiated: highly, moderately, and poorly (7) (**Figures 1A–C**). Many keratins and intercellular bridges can be seen in a highly differentiated ESCC. The poorly differentiated ESCC does not have keratin pearls and intercellular bridges. These cells are disorderly arranged hierarchy, with higher cellular atypia and nuclear pleomorphism.

Poorly differentiated ESCC and EAC are difficult to distinguish by HE staining alone (7). Immunohistochemistry (IHC) can distinguish them. In poorly differentiated ESCC, markers indicating squamous epithelial differentiation (e.g., CK5/6) (**Figures 1D, E**) are positive and markers indicating glandular epithelial differentiation are negative (e.g., CK7, CK20) (7) (**Figure 1F**). P63 is an indicator that has been shown to be positively expressed in ESCC (8). Some patients can have components of both squamous cell carcinoma and adenocarcinoma, which is termed adenosquamous carcinoma (9).

The Methods and Efficacy of Current Treatments for ESCC

Most ESCC patients are diagnosed at advanced stage. Thus, more attention should be paid to prevention and early diagnosis. If this disease is diagnosed early, endoscopic therapy is possible. This can save the patient's organs and improve the well-being (10, 11). Some scholars suggest that endoscopic ultrasound (EUS) should be performed before treatment to accurately evaluate the condition (it is not recommended for some patients with extreme esophageal stenosis) and guide the therapy. T staging and regional lymph node status are important prognostic factors for ESCC. EUS is a test comparable to PET, accurate for T staging and inexpensive. More importantly, EUS is superior to CT and MRI in the detection of lymph node involvement, with higher sensitivity (10).

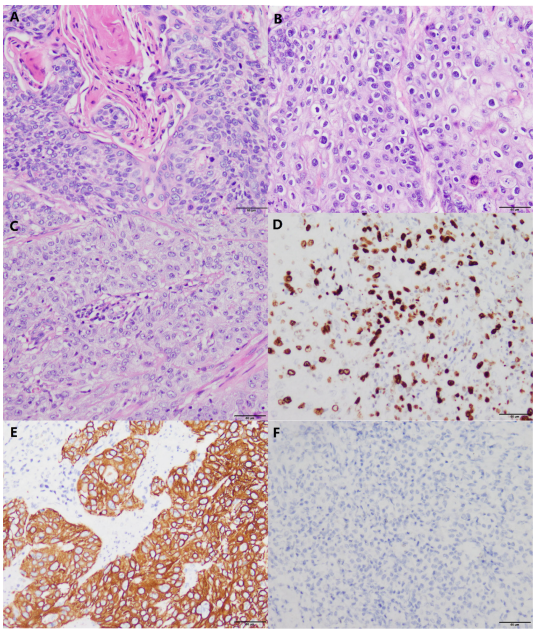

FIGURE 1 | Histomorphology and immunohistochemistry in variably differentiated ESCC (own images, have not been published in elsewhere, the scale bar is 50 μm). **(A)** Highly differentiated ESCC (H&E stain, ×200). **(B)** Moderately differentiated ESCC (H&E stain, ×200). **(C)** Poorly differentiated ESCC (H&E stain, × 200). **(D)** In this case of poorly differentiated ESCC, the positive index of Ki-67 reaches 50% (Envision stain, ×200). **(E)** Poorly differentiated ESCC cells are positive for CK5/6 (Envision stain, ×200). **(F)** Poorly differentiated ESCC cells are negative for CK7 (Envision stain, ×200).

In a randomized controlled trial conducted by Joel Shapiro and colleagues, the addition of neoadjuvant chemoradiotherapy (preoperative chemoradiotherapy) during surgery for patients with resectable EC was found to have an overall survival benefit (12). It was confirmed during the follow-up for a long term. In a phase III clinical trial conducted by Chinese scholars, it was also found that neoadjuvant chemoradiotherapy plus surgery (NCT01216527) improved the survival rate of locally advanced ESCC patients compared with surgery alone, with acceptable and controllable adverse events (13).

Currently, neoadjuvant chemoradiotherapy and esophagectomy are the mainly therapy for ESCC. In a guide to the management of EC, it is suggested that patients with locally advanced ESCC should receive neoadjuvant chemoradiotherapy (14). Multimodal therapy has advantages over performing surgical resection alone. Similarly, patients without metastatic disease should receive esophageal resection after neoadjuvant therapy, if the evaluation of surgery is safe (14).

Japanese scholar Masayuki Watanabe and colleagues found that patients with ESCC received neoadjuvant chemoradiotherapy plus surgical resection, the 3-year survival rate was 29.8% and the 5-year survival rate was 15.0% (15). This data indicates that there is still a large proportion of patients who do not achieve better outcomes. Researchers are still exploring other ways to treat ESCC.

Currently, many researchers are focusing on the treatment of ESCC by molecular targeting. EGFR and PD1 are the hottest targets. It has been demonstrated that EGFR is one of the cancer genes responsible for the common somatic copy number variations (SCNV) in ESCC (16). At the same time, some researchers found abnormally high expression of EGFR in ESCC (17). In a phase II, single-group, multicenter trial conducted in several Chinese hospitals, researchers found that icotinib (an EGFR tyrosine kinase inhibitor, TKI, NCT01855854) exhibited promising activity in advanced ESCC patients whose EGFR was overexpressed or amplified (18). These trial results showed that only a small number of patients respond well to icotinib. So, it can be speculated that ESCC patients may have developed resistance to EGFR-targeted therapy (18). Curtis R Chong and colleagues proposed that the resisting to EGFR-targeted therapy in tumor cells could be relevant to the abnormally activating of PI3K/AKT/mTOR pathway (19).

In the phase III AIO/EORTC clinical trial conducted by M. Moehler and colleagues, they found that the use of panitumumab (an anti-EGFR antibody) combined with cisplatin and 5-fluorouracil did not improve survival compared to unselected advanced ESCC patients who received 5-fluorouracil alone (20). This result supports further studies of serum and tumor biomarkers (20).

Programmed cell death protein 1 (PD-1) is an inhibitory receptor expressed on activated lymphocytes, can connect with the ligands of PD-L1 and PD-L2. And they are favorable to regulating the balance of T cell activation, immune tolerance, and immune-mediated tissue damage (21, 22). Blockading the immune checkpoint has fundamentally improved the treatment of melanoma patients (23). At the same time, many researchers are exploring its efficacy in other cancers (24). A monoclonal antibody targeting PD-1, Nivolumab, could increase tumor antigen-specific T cell proliferation and cytokine secretion *in vitro (*25, 26). It has been approved for the treatment of many other diseases, for example, advanced non-small cell lung cancer and Hodgkin's lymphoma (27, 28). Nivolumab has been approved for ESCC patients who have progressed after chemotherapy in Japan since February 2020 (29). Toshihiro Kudo and colleagues found that Nivolumab is safe and effective in advanced EC patients who are refractory to standard chemotherapy (28). Jiyun Lee and colleagues found that Nivolumab showed some efficacy as second-line therapy for ESCC in a phase III trial, but the improvement of OS was not significant (29). Through analysis, Qu and colleagues found that overexpression of PD-L1 in ESCC might relate to short OS. However, the difference was not statistical significant (P=0.07) (30). Some scholars have also found that the overexpression of PD-L1 in ESCC is related to its disease-free survival (DFS), but it has no correlation with its prognosis (31).

Therefore, the current targeted therapies for EGFR and PD-1 respectively have encountered bottlenecks. The solution is to dig deeper into the molecular mechanisms of ESCC and find other sensitive targets. In the future, combination therapy with multiple molecular-specific targeted drugs may be a good option for the treatment of ESCC.

Environmental Factors and Probably Genetic Mechanisms of ESCC Development

The causes of ESCC are complex. Environmental and genetic factors are contributors for ESCC formation. It is believed that pathogenic genes have an important influence on it.

Previous studies have found that ESCC has a variety of related environmental predisposing factors (32). Such as tobacco (33, 34), alcoholic beverages (35, 36), little or no-intake vegetables and fruits (37, 38), pickled vegetables (39), hot foods (40) and so on. If the body is exposed to these factors for a long time, it may increase the susceptibility of ESCC. Some studies found a genetic link with these exposures for developing ESCC. Chen Wu and colleagues found that there was a gene-environment interaction between alcohol abuse and genetic variation in alcohol metabolic pathways that leads to the development of ESCC. It has been reported that drinkers who carried both the risk alleles of *ADH1B* and *ALDH2* had the highest risk to develop cancer (41).

In ESCC, Yongmei Song and colleagues found genomic alterations in several important pathways (e.g., the RTK-RAS and AKT pathways) and genes (e.g., *PIK3CA*) (42).

De-Chen Lin and colleagues found that the MAPK and PI3K pathways were activated through a variety of mechanisms in ESCC (16). At the same time, several potentially altered genes have been identified in ESCC. Such as *ERBB*, *HDAC*, *PI3K family*, *XPO1*, *FGFR1*, *TP53*, *JAK-STAT3*, and *mTOR-rpS6K* were defined to be recurrent candidate druggable targets (16). These genes have implications for future molecular studies.

The results of a whole-exome sequencing conducted by Genta Sawada and colleagues are consistent with those of De-Chen Lin and colleagues. Their sequencing included 144 Japanese patients with ESCC, including neoplastic and non-neoplastic esophageal tissues (43). In addition, they also found some other gene mutations in many tumor tissues (43). For example, some mutations in genes that regulate cell cycle (*TP53*, *CCND1*, *CDKN2A*, and *FBXW7*) and epigenetic process (*MLL2*, *EP300*, *CREBBP*, and *TET2*). It should be noted that *TP53* plays a role in inhibiting carcinogenesis in organisms (44). The most common genetic change in a variety of human cancers is the mutation of *TP53* (45). According to reports, the mutation rate of *TP53* in ESCC ranges from 60% to 93.1% (16, 43). Many researchers have found that *TP53* is closely related to PI3K/AKT/mTOR pathway, which may be involved in the occurrence and development of tumors (**Figure 2**). Such as, it has been found that *TP53* can negatively regulate PI3K/AKT/mTOR pathway by upregulating related proteins (45). Besides, it was also found that PI3K/AKT/mTOR pathway could negatively affect the expression of *TP53* by upregulating MDM2, which promotes the degradation of p53 (A protein encoded by *TP53*) (44). Mutations were also found in some key genes of signaling pathways, such as NOTCH, WNT (*FAT1*, *YAP1*, and *AJUBA*) and RTK-PI3K (*PIK3CA*, *EGFR*, and *ERBB2*) (43).

At present, abnormal activation of PI3K signaling has been found in ESCC, and genetic mutations of *PI3K*, *AKT* and *mTOR-rpS6K* have been found. The researchers found that *EGFR*,

ERBB2 and *FGFR1* genes were mutated, and their downstream key pathways were PI3K/AKT/mTOR pathway (16, 43). To some extent, the functional realization of the three components depends on PI3K/AKT/mTOR pathway. Therefore, the occurrence and development of ESCC are closely related to the PI3K/AKT/mTOR pathway (**Figure 3**).

At the same time, PI3K/AKT/mTOR pathway has been proved to be an important pathway controlling growth and metabolism in cells, which is an important guarantee for the survival and normal function. Abnormal activation of PI3K/AKT/mTOR pathway has been found in many tumors, and inhibition of this pathway has also achieved certain therapeutic effects for tumors.

PI3K/AKT/mTOR SIGNALING PATHWAY

The PI3K/AKT/mTOR signaling pathway plays an important role in basic functions of cell growth, apoptosis, translation, and cell metabolism (46). There were found abnormal expressions of PI3K/AKT/mTOR signaling pathway in many tumors (47). These evidences suggested that this pathway acting as an essential part in the development of tumors and suggested their potential as new therapeutic targets.

PI3Ks constitute an important enzyme family namely the lipid kinase family. It can be divided into three categories. The class I PI3Ks are heterodimers composed of catalytic subunits and regulatory subunits (48). Class I PI3Ks could be subdivided into class IA and IB enzymes. The class IA consists of three catalytic subunits (p110α, p110β and p110δ) encoded by *PIK3CA*, *PIK3CB* and *PIK3CD* genes, which can be activated by receptor tyrosine kinases (RTKs). While the class IB is composed of p110γ (a catalytic subunit) encoded by *PIK3CG* and activated by G protein-coupled receptors (GPCRs) (49, 50). The regulatory subunits of class IA and IB are also different in structure (51–54). Class II PI3Ks consist of three different subtypes (PI3K-C2α, PI3K-C2β and PI3K-C2γ) (55). Class III PI3Ks are composed of two subunits (Vps34 and Vps15), and could play an important role in the autophagy and phagocytosis pathway of lysosomes (56).

Class I PI3Ks are the research hotspot of PI3K signal transduction. In addition, class IA PI3Ks are widely found in carcinogenic processes. RTK or GPCR activation enrolls class I PI3Ks into the plasma membrane, where p85 (regulatory subunit) -mediated inhibition of p110 is released and p110 directly phosphorylates PIP2 (phosphatidylinositol 4,5-bisphosphate) into PIP3 (phosphatidylinositol 3,4,5-triphosphate) (57). This lipid is similar to the model of second messenger, which activates downstream proteins and participates in cell growth and survival (58). Phosphatase and tensin homolog (PTEN) can dephosphorylate the third site of the PIP3 inositol ring, result in the conversion to PIP2. It is a negative regulatory factor that inhibits the transduction of PI3K signal to pyruvate dehydrogenase kinase 1 (PDK1) (59) (**Figure 3**).

AKT is a serine/threonine kinase and a key downstream signal of PI3K (60). AKT has three subtypes: AKT1, AKT2 and AKT3. Overexpression and phosphorylation of AKT can be found in a variety of cancers (61). Sundaramoorthy Revathidevi and colleagues searched the TCGA data and found that compared with other activation methods such as amplification, overexpression and phosphorylation, the activation of AKT by mutation was rare (60). In many cancers, methylation of its upstream regulators, including PTEN, has been shown to activate AKT (62). Also the activation mutation of *PI3K*, *RAS* can potentially activate *AKT* (63). It is established that PI3K can directly activate mTORC2, and the activated mTORC2 can activate AKT (59) (**Figure 3**).

mTOR signal is one of the key genetic variation targets in cancers, which is often associated with tumor occurrence and progression. The mTOR protein is a serine-threonine kinase of PI3K related family, which is a part of mTORC1 and

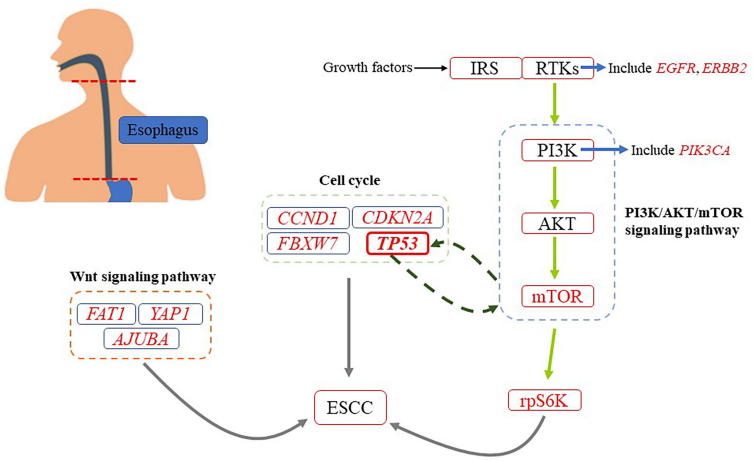

FIGURE 2 | A simplified diagram of genetic changes about ESCC. There are many genetic changes associated with ESCC. It has been found that PI3K/AKT/mTOR pathway is closely related to the occurrence and development of ESCC.

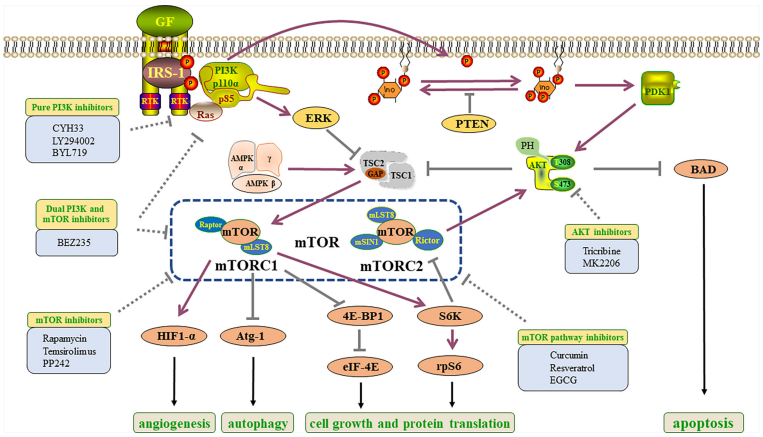

FIGURE 3 | Constituent elements and inhibitors of PI3K/AKT/mTOR pathway in ESCC. Growth factors bind to RTKs to activate the PI3K/AKT/mTOR pathway, which directly and indirectly results in tumorigenesis, the activation of protein translation and angiogenesis, the inhibition of apoptosis and autophagy. GF, growth factors; PI3K, phosphatidylinositol 3-kinase; IRS1, insulin receptor substrate 1; RTK, receptor tyrosine kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; ERK, extracellular signal-related kinase; PIP3, phosphatidylinositol 3,4,5-trisphosphate; TSC, tuberous sclerosis protein; PTEN, phosphatase and tensin homolog; PDK1, pyruvate dehydrogenase lipoamide kinase isozyme 1; AMP,: AMP-activated protein kinase; AKT, protein kinase B; mTORC, mammalian target of rapamycin complex; BAD, Bcl2-related death protein; Raptor, regulatory associated protein of mTOR; HIF1-α, Hypoxia-inducible factor 1-α; mLST8, mammalian lethal with sec-13 protein 8; eIF4E, eukaryotic translation initiation factor 4E; mSIN1, mammalian stress-activated MAPK- interacting protein 1; Rictor, rapamycin insensitive companion of mTOR; Atg-1, autophagy-related protein 1; 4E-BP1, 4E-binding protein 1; S6K, ribosomal S6 kinase; rpS6, ribosomal protein S6.

mTORC2 complexes. These two complexes have different structures and functions (64). The mTORC1 contains regulatory associated protein of mTOR (Raptor), while the mTORC2 contains rapamycin insensitive companion of mTOR (Rictor) (64). Which can explain that mTORC1 is sensitive to rapamycin while mTORC2 is not sensitive to rapamycin treatment. The two both contain mammalian lethal sec-13 protein 8 (mLST8). In addition, mTORC2 contains mammalian stress-activated MAPK-interacting protein 1 (mSIN1; also known as MAPKAP1) (64) (**Figure 3**). The tuberous sclerosis complex (TSC) is a factor that can regulate mTORC1, and it is also one of the convergence points of multiple pathways *in vivo*. TSC is a heterotrimer consisted of TSC1, TSC2 and TBC1D7. At the same time, TSC functions as a GTPase activation protein (GAP) could activate the ras homolog enriched in brain (RHEB), a small GTP enzyme. When AKT is activated, it can mediate TSC2 phosphorylation, inhibit TSC1/2 complex and activate mTORC1 signal (65).

Growth factors, amino acids, and oxygen can activate mTORC1. When it was activated, it can participate in protein, lipid and nucleotide synthesis and autophagy (59). For example, after mTORC1 activation, the phosphorylation of its downstream signal molecule 4E-binding protein 1 (4E-BP1) could be inhibited, thus the eukaryotic translation initiation factor 4E (eIF4E) will be released to participate in protein synthesis (59). Autophagy-related protein 1(Atg-1) is a node in several different signaling pathways regulating autophagy *in vivo*. mTORC1 is one of the upstream signals of Atg-1, and the activation of mTOR signal can inhibit the autophagy induction ability of Atg-1 (66) (**Figure 3**).

mTORC2 is often over-activated in cancer cells, and can promote cell survival and migration through phosphorylation of Akt Ser 47 (67, 68). In addition, mTORC2 can regulate additional physiological functions by phosphorylating different substrates such as glycolytic enzyme pyruvate dehydrogenase kinase 1 (PDHK1), serum and glucocorticoid induced kinase (SGK), protein kinase C ζ (PKC ζ) and so on (59, 69, 70).

The Influence of PI3K/AKT/mTOR Pathway on ESCC Development

Many studies have found that the PI3K/AKT/mTOR pathway is associated with cell proliferation, apoptosis, autophagy, and drug resistance of ESCC. Therefore, therapy targeting PI3K/AKT/mTOR pathway should be a promising therapeutic strategy.

Influence on Cell Proliferation and Apoptosis

The proliferation is inextricably linked with apoptosis, whether in normal cells or in tumor cells (71). Numerous studies have found that mTOR regulates cell growth and division. mTORC1 directly activates the ribosomal protein S6 kinase (p70S6K) and inhibits 4E-BP1, thereby increasing translation. At the same time, to a certain extent, it can regulate cell proliferation by controlling cell cycle. And mTORC2 promotes metabolism mainly by activating AKT2.

Shau-Hsuan Li and colleagues demonstrated overexpression of phosphorylated mTOR, p70S6K, and 4EBP1 in 56% tumor tissues of ESCC patients (72). Survival analysis also found that p-mTOR and p-p70S6K overexpression, Ki-67 index >50% were

associated with poor OS. Among them, the overexpression of p-p70S6K can be considered as an independent prognostic indicator of ESCC. It is confirmed that everolimus (an inhibitor of mTOR) can inhibit the growth of ESCC in both cell lines and transplanted tumor models (72). Before this, Guiqin Hou and colleagues found that rapamycin and siRNA against mTOR can rapidly inhibit the expression of mTOR and phosphorylation of p70S6K and 4EBP1. In addition, inhibition of mTOR can also make cell cycle arrest at G0/G1 phase and induce apoptosis of ESCC cells (73).

In an experiment conducted by Jiarui Yu and colleagues, these scientists explored the effects of Gambogic acid (GA), the mainly active component secreted by Garcinia hanburryi tree, on the ESCC cells (74, 75). It was found that GA could inhibit the proliferation, migration, and invasion of ESCC cells. Meanwhile, GA induced dose-dependent apoptosis in ESCC cells by inhibiting the expression of Bcl2 and up-regulating the expression of apoptosis-related proteins such as Bax and cleaved-caspase3/9 (75). The probably mechanism was that GA can down-regulate the levels of PI3K, p-AKT and p-mTOR, and promote the expression of PTEN in ESCC cells (75).

These experimental data suggest that proliferation and apoptosis are closely related to PI3K/AKT/mTOR pathway in ESCC.

Influence on Cell Autophagy

Autophagy restricts malignant transformation, balances cell metabolism, and maintains cell survival, but autophagy can promote the cells growth and progression of the cancer (66). Many studies have confirmed that autophagy can protect the cancer cells from anticancer therapy by blocking the apoptotic pathway (also called protective autophagy), to keep the cancer cells alive, allowing them to grow and metastasize (76). Some studies have confirmed that autophagy is mainly induced through PI3K/AKT/mTOR signaling pathway (77). If this pathway is blocked, the autophagy will be inhibited, and the apoptosis will be activated. They together enhance the sensitivity of tumor cells to treatment (77). Beclin-1 synergistic with PI3K pathway enhances autophagy vacuole and activates autophagy cascade reaction (78). Microtubule-associated protein light chain 3 (LC3), now widely used as a monitoring autophagy body formed by specific molecular markers (79). Yu and colleagues found that enhanced autophagy was associated with cisplatin resistance in ESCC cell lines (80). O'Donovan and colleagues found that in drug-resistant ESCC cells, LC3-II levels were significantly increased after treatment with 5-fluorouracil (81). However, inhibition of autophagy induction by siRNA targeting Beclin1 and ATG7 significantly enhanced the effect of 5-fluorouracil (81). These studies suggest that in ESCC cells, autophagy acts as a protective mechanism to promote cell survival during antitumor therapy, leading to therapeutic resistance. In addition, Le Yu and colleagues found that autophagy inhibition can enhance the sensitivity of ESCC cells to cisplatin *in vivo* (80). Chi Lu and colleagues reported that ionizing radiation activates autophagy in ESCC cell lines. In addition, they found that inhibiting autophagy can enhance apoptosis and cell cycle arrest *in vitro* induced by radiation (82). Yan Cai and colleagues found that chloroquine inhibited the growth and proliferation of ESCC cell EC109, and this was mediated by regulating autophagy (83).

THE RELATED INHIBITORS TO PI3K/AKT/MTOR PATHWAY OF ESCC

Pure PI3K Inhibitors

According to selectivity, pure PI3K inhibitors can be divided into two types: pan PI3K inhibitors and selective isoform PI3K inhibitors (84). CYH33 is a novel selective inhibitor of PI3Kα with a unique structure. Jia-jie Shi and colleagues reported that CYH33 combined with radiotherapy can synergistically inhibit the proliferation of ESCC (85). Clinical trial of CYH33 in the treatment of advanced ESCC(NCT03544905) is currently under way (**Table 1**). LY294002 was identified as a generic PI3K inhibitor. Guiqin Hou and colleagues found that LY294002 could inhibit proliferation of ESCC cells through PI3K/AKT/mTOR/p70S6K signaling pathway. However, LY294002 triggered AKT (Ser473)/PRAS40 (Thr246) feedback activation mediated by mTORC2 in Eca109 and Ec9706 cells. This may lead to limited therapeutic effect of LY294002 on ESCC (86). Therefore, the role of a single PI3K inhibitor is limited. Further experiments by Guiqin Hou and colleagues highlighted that shRNA inhibition of Rictor could reduce phosphorylation of AKTSer473 and Thr308 sites, and counteract activation of AKT (Ser473)/PRAS40 (Thr246) induced by LY294002, which significantly improved the sensitivity of ESCC cells to LY294002 *in vitro* and *in vivo* (86). BYL719 is a PI3Kα inhibitor. Moshe Elkabets and colleagues found that AXL is involved in ESCC resistance to BYL719 (87). The mechanism of drug resistance may be that AP-1 transcription factors c-JUN and c-FOS regulate the overexpression of AXL (88). The combination of BYL719-SP600125 (blocking JNK signaling pathway) has achieved certain results *in vitro* and *in vivo* (88). For PI3K inhibitor, the application of PI3K inhibitor combined with other drugs should be a hot spot in the future. However, the result of a completed clinical trial of combined drug use was not satisfactory. Combined application of LJM716(HER3 targeting antibody) and BYL719 (NCT01822613) in ESCC patients, the tumor did not shrink as expected.

AKT Inhibitors

Few Akt inhibitors are currently used in clinical trials. Tricribine (TCN), an Akt inhibitor, significantly inhibited p-Akt, HIF-1α, and VEGF expression *in vitro* and *in vivo*, enhancing the radiosensitivity of ESCC *in vitro* and *in vivo* (89). ESCC has been proved to have a close relationship with PI3K/AKT/mTOR. The phosphorylation at Thr308 and at Ser473 is both necessary for full AKT activation. MK-2206 is an oral inhibitor targeting on all three AKT subtypes. Ni Shi and colleagues found that in ESCC cells, the phosphorylation level of AKT at Ser473 only slightly decreased upon treatment with MK2206 (**Table 1**) (90). The effect of MK2206 alone in the mouse model of ESCC was also not ideal. However, in a clinical trial conducted by Timothy

A. Yap and colleagues, it was found that MK-2206 has a certain therapeutic effect on solid tumors such as lung and colorectal cancer (91). The underlying molecular changes in ESCC may be more complex. For example, when MK2206 is used alone, the up or downstream targets of AKT may be activated to affect drug action. Subsequent experiments by Nishi and colleagues found that MK2206 combined with BEZ235 (a co-inhibitor of PI3K and mTOR) enhanced the inhibiting of proliferation in ESCC cells, both *in vivo* and *in vitro*.

mTOR Inhibitors

The mTOR inhibitors are divided into three generations (92). Current researches are mainly focused on the first and second generations.

The First Generation of mTOR Inhibitors

Rapamycin and its analogues are the first generation of mTOR inhibitors. Through allosteric mechanism, they can partially inhibit the activity of mTORC1 and slow down the proliferation of cancer cells (93). Guiqin Hou and colleagues reported that rapamycin could induce apoptosis in ESCC cells. In addition, rapamycin was found to inhibit tumor growth in human ESCC cell line EC9706 in nude mice. Its inhibitory effect was stronger than that of cisplatin used alone. But the combination of rapamycin and cisplatin was the strongest (94). Temsirolimus (CCI-779, TriceITM) is one of these analogues. Toshio Nishikawa and colleagues found that in some ESCC cell lines (such as TE-1, TE-8, and TE-10), the level of mTOR phosphorylation was increased, accompanied by the upregulation of hypoxia-inducible factor-1α (HIF-1α). Temsirolimus significantly inhibited the activation of mTOR and its downstream effector proteins, resulting in decreased proliferation of ESCC cells. Finally, *in vitro*, temsirolimus significantly reduced the size of subcutaneous tumors in nude mice and effectively extended the survival of mice with esophageal carcinoma *in situ* (the cell used for this experiment was TE-8) (95).

At the same time, the first generation of mTOR inhibitors only had little effect on the phosphorylation of 4E-BP1 (96).These inhibitors do not inhibit the activity of mTORC2, so the direct activation of AKT by mTORC2 is not affected. And the negative feedback loop formed after suppressing mTORC1 can activate the PI3K/AKT signal (93). This may be the cause of inhibitor resistance. Now some studies have found that some tumors are resistant to these inhibitors. For example, T Fujishita and colleagues found that everolimus (a rapamycin analogue) had little effect on blocking tumor invasion when used in the later phase of locally aggressive intestinal adenocarcinoma (cis-Apc/Smad4 mice model). But inhibiting mTOR and EGFR or MEK at the same time may be more effective in treating colon cancer (97). As such, the molecular in tumors are more complex than expected, and combination of drugs seems to be a more meaningful route.

Clinical trials with rapamycin and its analogues related to ESCC have not been carried out. Still some researchers have also had limited success in treating a small number of rare cancers with monotherapy, including mantle cell lymphoma and pancreatic neuroendocrine tumors (98, 99).

The Second Generation of mTOR Inhibitors

The second generation mTOR inhibitors are some small molecule ATP competitive inhibitors. They can target mTOR or both mTOR and PI3K. Several categories according to the chemical structure exist (92). The pyrazolopyrimidine class is one of them. PP242 is a typical example of a pyrazolopyrimidine. The inhibitory effect of PP242 was stronger than that of rapamycin, and PP242 could inhibit the activities of mTORC1 and mTORC2.

Yu Huang and colleagues examined the antitumor effect of PP242 in ESCC cell lines include Eca-109 and TE-1 (100). As expected, they found that PP242 can weaken the activities of both mTORC1 and mTORC2 signaling in ESCC, stronger than rapamycin. PP242 could inhibit 4E-BP1 phosphorylation and abrogate PI3K/AKT feedback activation relying on mTORC1 (100). It seems that the anti-tumor effect of the second generation of inhibitors should be far more obvious than that of the first generation. In ESCC cells, Yu Huang and colleagues found PP242 can effectively inhibit the proliferation, induce apoptosis, and arrest cell cycle (100).

PP242 is not tested in currently ongoing clinical trials. TAK-228 (derived from PP242) was well tolerated as a single agent and showed initial therapeutic activity in hematological malignancies (NCT01118689) (101).

Dual PI3K and mTOR Inhibitors

Regarding second generation mTOR inhibitors, some compounds were found to target both PI3K and mTOR (92). BEZ235 is one of them. Ning Wu and colleagues found the activity of p-AKT, p-mTOR, and p-p70S6K can be reduced significantly by BEZ235 in ESCC cells include Eca-109 and TE-1. This inhibitory effect can induce autophagy and apoptosis of human ESCC cells (102). At the same time, they found that BEZ235 combined with Trichostatin A(histone deacetylase inhibitor) had better tumor inhibition effect than single drug (102).Clinical trials of dual PI3K and mTOR inhibitors have not been conducted in the ESCC. But the clinical trials of BEZ235 in other tumors are ongoing. In a clinical trial, the dual PI3K and mTOR inhibitor, PF-05212384 was found to have manageable safety and antitumor activity. This trial provides support for further clinical studies in patients with advanced solid malignancies (NCT 00940498) (103).

mTOR Pathway Inhibitors

Some natural polyphenols extracted from plants, such as curcumin and resveratrol, have been confirmed to inhibit mTOR signaling pathway directly or indirectly in certain tumors (92). Researchers have also explored the role of these extracts in ESCC (104, 105).

Curcumin is a polyphenolic compound extracted from turmeric roots. It is safe, non-toxic, and has anti-tumor effects in the human body (106). Many studies have shown that curcumin and PI3K/AKT/mTOR signaling pathway are closely related. Lian Deng and colleagues found that curcumin combined with docetaxel can induce apoptosis and autophagy in ESCC cells, which may be based on the PI3K/AKT/mTOR signaling pathway (104).

Resveratrol is rich in grapes, red wine, and peanuts (107). It is a plant defensin that has specific cytotoxicity for multiple carcinoma cells (such as melanoma and breast cancer), with certain treatment potential (108, 109). Qishan Tang and colleagues has confirmed that resveratrol can induce cell cycle arrest at the sub-G1 phase and result in subsequent apoptosis, in a dose-dependent manner (110). They also confirmed that resveratrol can inactivate the mTOR signal (110).

Epigallocatechin-3-gallate (EGCG), a primary tea polyphenol, has been shown to inhibit the growth of certain human cancer cells (111). The mechanisms of inhibiting tumor are antioxidation, inhibiting cell proliferation and angiogenesis, as well as increasing cancer apoptosis (111). Yao-Kuang Wang and colleagues has confirmed that EGCG can inhibit the proliferation and colony formation of arecoline-induced ESCC cells by inhibiting AKT and ERK1/2 pathway (105). Exactly, an important downstream signal of AKT and ERK1/2 is mTOR. A clinical trial on EGCG (NCT05039983) in ESCC is currently ongoing in China.

These natural compounds can inhibit the growth of ESCC cells and are inseparable from mTOR signal.

eIFS AND PI3K/AKT/mTOR PATHWAY

PI3K/AKT/mTOR Pathway Can Regulate eIFs to Influence the Translation

Translation is an important and complicated process of gene expression in eukaryotes. Translation mainly includes four processes: initiation, elongation, termination, and ribosome recycling (112). The regulation of translation mainly takes place at initiation phase and which is the rate limiting phase of protein synthesis (113). The regulators of translation initiation are the eIFs. The activation of RTKs, MAPK and PI3K/AKT signaling pathways could be stimulated by some signals which promoting tumorigenesis (114). These pathways play an important role in the regulating of eIF functions (115). Both MAPK and PI3K/AKT pathways regulate the functions of eIFs *via* mTOR. Therefore, mTOR plays a leading role in the regulation of eIF functions (115, 116). Their mis-regulation usually causes abnormal translation, synthesizes aberrant proteins, finally leading to tumorigenesis (117–120).

Overview on the Role of eIFs in Translation Initiation

The initiation process of translation begins with the formation of the 43S pre-initiation complex (121). The 43S initiation complex consists of 40S ribosomal subunit, eIF2–GTP–Met-tRNAiMet, eIF1, eIF1a and eIF3 (121, 122). The 43S initiation complex can then be guided by the eIF4F complex to bind with mRNA. The eIF4F complex is a heterotrimer composed of eIF4A, eIF4E and eIF4G subunits (123). The mRNA was scanned by 43S initiation complex. With the assistance of eIF1, the tRNA anticodon ring correctly binds to the start codon AUG on the mRNA (121). eIF4A has helicase activity. eIF4E binds to the mRNA's cap structure. It is usually bonded with 4E-BP1. Once 4E-BP1 was phosphorylated, the eIF4E could be released. The role of eIF4G is to link mRNA with ribosomes (123, 124). eIF3 acts more like a scaffold, links other eIFs with 40S ribosomal subunit (125). When the complex encounters the correct AUG start codon, eIF2 will be hydrolyzed, and other eIFs will be released. At the last stage of translation initiation, eIF2 is in an inactive GDP binding state, the GTP bound to eIF5B is hydrolyzed, and these translation factors are separated from the ribosome (122, 126). In addition, eIF6, which has not yet been mentioned, is the first eIF associated with the 60S subunit that modulates translation in response to extracellular signals (127, 128).

eIFs-Potential Therapeutic Targets in Tumors

Moreover, some researchers found that changes in the expression of certain translation promoters (primarily increased expression) were associated with the development of specific tumors (129–131). For example, eIF1A is a small 17kDa promoter and highly conserved in all eukaryotes. Somatic mutations in the N-terminal tail (NTT) of eIF1A have been found to be associated with uveal melanoma, thyroid cancer, and ovarian cancer (132–134). Urmila Sehrawat and colleagues found that eIF1A could regulate different mRNAs differently in mammalian cells (135). The eIF1A NTT mutants enhanced the scanning of the 5 'UTR-containing cell cycle genes, possibly affecting the cell cycle and promoting cell proliferation (135). eIF3H is one of the central subunits of eIF3 complex. It has been observed that eIF3H is often amplified in breast and prostate cancer together with proto-oncogene Myc (136, 137). Researchers have found the amplification of eIF3H gene in colorectal cancer and non-small cell lung cancer (NSCLC) through genome-wide analyses and fluorescent *in situ* hybridization (FISH) (117, 138, 139). In addition, the expression level of eIF3H is positively correlated with the poor differentiation and invasive growth of prostate cancer (117, 137).

In ESCC, there are also some limited studies on eIFs. For example, Ting Liu and colleagues found that eIF4E increased significantly in clinical ESCC tissues and ESCC cell lines, and its expression level was associated with lymph node metastasis, TNM period, and ESCC's overall and disease-free survival (140). After using the shRNA knockout eIF4E, it was found that the induced cytotoxicity by cisplatin has increased in the ESCC cell lines, and the chemosensitivity to cisplatin in xenograft tumor models also has increased (140). Hong Yang and colleagues found that excessive expression of eIF5A2 in ESCC cells resulted in increased chemoresistance to 5-fluorouracil, docetaxel, and taxol. Conversely, the shRNAs of eIF5A2 could increase the sensitivity of tumors to these chemotherapeutic drugs. It was found that in patients who underwent taxane-based chemotherapy after esophagectomy, eIF5A2 overexpression was associated with poor total survival rate (P <0.05) (141). Therefore, targeting eIF4E or eIF5A2 may be a feasible method of improving ESCC chemotherapy sensitivity. However, eIFs in ESCC still require more researches.

These previous examples reveal eIFs may be a promising target for future tumor treatment. At present, there are some inhibitors of eIFs in preclinical and clinical trials (**Table 2**). Ribavirin is an antiviral drug approved by the Food and Drug

Administration (FDA) for hepatitis C, which can also treat syncytial virus infection and viral hemorrhagic fever (144–146). Importantly, ribavirin has been extensively documented as an inhibitor of eIF4E (147–149).

JingJin and colleagues found an overexpression of eIF4E in most ovarian cancer patients. In addition, the eIF4E function is critical for the growth and survival of tumors (150). eIF4E inhibition was found to be achieved at clinically achievable doses of ribavirin. Inhibition of eIF4E by ribavirin may be a potential therapeutic approach to improve clinical management of ovarian cancer (150). Sakibul Huq and colleagues found that ribavirin enhanced radiosensitivity in nasopharyngeal carcinoma (NPC). At the same time, it can inhibit the expression of various proteins which are all overexpressed in NPC and correlated with poor prognosis, also can inhibit the mTOR/eIF4E axis (151). These studies indicate that ribavirin is a potential targeted drug for tumor therapy.

Several clinical trials related to ribavirin are underway, such as oropharynx squamous cell cancer (NCT01721525), acute myeloid leukemia (NCT01056523), melanoma (NCT00897312).

CONCLUSIONS AND DISCUSSIONS

ESCC is a complex disease, the external predisposing factors and genetic mutations both have an important impact on oncogenesis and tumor progression. So, we should focus on the prevention, warning high-risk individuals away from alcohol, cigarettes, and so on. At the same time, we should pay attention to the screening of disease and improve the early diagnostic rate. Once ESCC patients could be diagnosed in the early stage, their prognosis and living quality will be improved significantly.

From the global cancer report, the incidence and mortality rate of ESCC are currently ranked tenth and sixth (1). This data shows that the current situation of ESCC is not optimistic. At present, neoadjuvant chemoradiotherapy and esophagectomy are the mainstream treatment methods of ESCC. Many researchers focus on treating ESCC by targeted therapy (EGFR or PD-1). There are currently a variety of related drugs used for clinical, and some ESCC patients respond particularly well to them. Still the increase of patients' overall five-year survival rate has no statistical significance (18, 31).

In all results of ESCC gene testing conducted by several research groups, the abnormal expression of PI3K/AKT/mTOR and its related pathways have been found. In this article, we discussed how the PI3K/AKT/mTOR pathway affects the growth, proliferation, and autophagy of ESCC. It is also discussed that inhibitors in different parts of PI3K/AKT/mTOR pathway can affect the growth and biological behavior of ESCC (**Table 1**). Additionally, the eIFs regulated by PI3K/AKT/mTOR pathway, also has an important influence on the occurrence and development of tumors. Through the discussion, it was found that the PI3K/AKT/mTOR pathway and eIFs could be the future therapeutic target of ESCC.

Still, it should not be ignored that there are only few relevant studies on the application of PI3K/AKT/mTOR pathway inhibitors in ESCC. Most studies have used a single inhibitor and with limited efficacy. At present, there are few studies on the combination of multiple inhibitors with different targets in ESCC ongoing. It may be

TABLE 1 | The researches about inhibitors of PI3K/AKT/mTOR pathway in ESCC.

Classification	Drug	Target	Administration	Latest researches in ESCC	Trial Number
PI3K inhibitors	Rigosertib	PI3K	Oral, parenteral	Clinical trials	NCT01807546
	LY294002	PI3K	Suggest not to use in clinical	Pre-clinical	/
	BYL719	PI3Kα	Oral	Clinical trials	NCT01822613
	CYH33	PI3Kα	Oral	Clinical trials	NCT03544905
AKT inhibitors	MK2206	AKT	Oral	Pre-clinical	/
	Tricribine	AKT	Parenteral	Pre-clinical	/
mTOR inhibitors	Rapamycin	mTORC1	Oral	Pre-clinical*	/
	Temsirolimus	mTORC1	Parenteral	Pre-clinical*	/
	PP242	mTORC1/2	Parenteral	Pre-clinical	/
Dual PI3K and mTOR inhibitors	BEZ235	PI3K, mTORC1/2	Oral	Pre-clinical	/
mTOR pathway inhibitors	Curcumin	mTOR pathway	Oral	Pre-clinical	/
	Resveratrol	mTOR pathway	Oral	Pre-clinical	/
	EGCG	AKT, ERK1/2, mTOR pathway	Oral	Clinical trials	NCT05039983

**FDA approved.*

TABLE 2 | The inhibitors of eIFs in tumor and the specific tumor types that can be inhibited in clinical trials.

Classification	Target	Administration	Development	Tumor type	Trial Number
4EGI-1	eIF4F	Not published	Pre-clinical	/	/
Ribavirin	eIF4E	Oral, parenteral	Clinical trials*	Acute Myeloid Leukemia (142)	NCT01056523
ISIS 183750	eIF4E	Parenteral	Clinical trials	Colorectal Cancer (143)	NCT01675128
LY2275796	eIF4E	Parenteral	Clinical trials	/	/
eFT226	eIF4A1	Parenteral	Clinical trials	/	/

**FDA approved.*

that researchers have not yet paid attention to the potential therapeutic effects of PI3K/AKT/mTOR pathway and its regulated eIFs in ESCC. It also could be that new drugs are being developed slowly and in fewer varieties. But why the effectiveness of a single inhibitor is limited?

The researchers found that the activation of multiple pathways is the main cause of drug resistance in tumor cells (115). Such as, Jessie Villanueva and colleagues found that melanoma cells show enhanced activation of PI3K signaling after treatment with BRAF inhibitors, leading to drug resistance of tumor cells (152). In ESCC, some researchers found the resistance of tumor cells to EGFR-targeted therapy might be related to the abnormal activation of PI3K/AKT/mTOR pathway (19). Thus, the growth of tumors carrying oncogenes that activate multiple pathways does not depend on a single signaling pathway.

The PI3K/AKT/mTOR pathway and its regulated eIFs have been proved to be a key pathway involved in growth. And many other pathways in the body are inseparable from it. Therefore, the future treatment of ESCC must be related tightly with the PI3K/AKT/mTOR pathway and its regulated eIFs. Simultaneous suppression of multiple targets of this pathway may be a future research focus. One hypothesis: it may be focused more on the co-inhibition of PI3K/AKT/mTOR pathway and eIFs.

In this context, multiple components of several oncogenic signaling pathways and eIFs participated in mRNA translation have been identified as biomarkers with potential diagnostic, therapeutic and prognostic value. Therefore, anti-tumor agents targeting the core elements of protein synthesis and related signaling pathways can get over intratumor heterogeneity and represent as novel promising anticancer drugs.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71:209–49. doi: 10.3322/caac.21660
2. Yang HX, Hou X, Liu QW, Zhang LJ, Liu JG, Lin P, et al. Tumor Location Does Not Impact Long-Term Survival in Patients With Operable Thoracic Esophageal Squamous Cell Carcinoma in China. *Ann Thorac Surg* (2012) 93:1861–6. doi: 10.1016/j.athoracsur.2012.03.002
3. Akhtar S, Sheikh AA, Qureshi HU. Chewing Areca Nut, Betel Quid, Oral Snuff, Cigarette Smoking and the Risk of Oesophageal Squamous-Cell Carcinoma in South Asians: A Multicentre Case-Control Study. *Eur J Cancer* (2012) 48:655–61. doi: 10.1016/j.ejca.2011.06.008
4. Taylor PR, Abnet CC, Dawsey SM. Squamous Dysplasia–The Precursor Lesion for Esophageal Squamous Cell Carcinoma. *Cancer Epidemiol Biomark Prev* (2013) 22:540–52. doi: 10.1158/1055-9965.Epi-12-1347
5. Oda I, Abe S, Kusano C, Suzuki H, Nonaka S, Yoshinaga S, et al. Correlation Between Endoscopic Macroscopic Type and Invasion Depth for Early Esophagogastric Junction Adenocarcinomas. *Gastric Cancer* (2011) 14:22–7. doi: 10.1007/s10120-011-0001-0
6. Takubo K, Sasajima K, Yamashita K, Tanaka Y, Fujita K. Prognostic Significance of Intramural Metastasis in Patients With Esophageal Carcinoma. *Cancer* (1990) 65:1816–9. doi: 10.1002/1097-0142(19900415)65:8<1816::aid-cncr2820650825>3.0.co;2-l
7. DiMaio MA, Kwok S, Montgomery KD, Lowe AW, Pai RK. Immunohistochemical Panel for Distinguishing Esophageal Adenocarcinoma From Squamous Cell Carcinoma: A Combination of P63, Cytokeratin 5/6, MUC5AC, and Anterior Gradient Homolog 2 Allows Optimal Subtyping. *Hum Pathol* (2012) 43:1799–807. doi: 10.1016/j.humpath.2012.03.019
8. Hara T, Kijima H, Yamamoto S, Kenmochi T, Kise Y, Tanaka H, et al. Ubiquitous P63 Expression in Human Esophageal Squamous Cell Carcinoma. *Int J Mol Med* (2004) 14:169–73. doi: 10.3892/ijmm.14.2.169
9. Zhang HD, Chen CG, Gao YY, Ma Z, Tang P, Duan XF, et al. Primary Esophageal Adenosquamous Carcinoma: A Retrospective Analysis of 24 Cases. *Dis Esophagus* (2014) 27:783–9. doi: 10.1111/dote.12153
10. Luo LN, He LJ, Gao XY, Huang XX, Shan HB, Luo GY, et al. Endoscopic Ultrasound for Preoperative Esophageal Squamous Cell Carcinoma: A Meta-Analysis. *PloS One* (2016) 11:e0158373. doi: 10.1371/journal.pone.0158373
11. Probst A, Aust D, Märkl B, Anthuber M, Messmann H. Early Esophageal Cancer in Europe: Endoscopic Treatment by Endoscopic Submucosal Dissection. *Endoscopy* (2015) 47:113–21. doi: 10.1055/s-0034-1391086
12. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant Chemoradiotherapy Plus Surgery Versus Surgery Alone for Oesophageal or Junctional Cancer (CROSS): Long-Term Results of a Randomised Controlled Trial. *Lancet Oncol* (2015) 16:1090–8. doi: 10.1016/s1470-2045(15)00040-6
13. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. *J Clin Oncol* (2018) 36:2796–803. doi: 10.1200/jco.2018.79.1483
14. Little AG, Lerut AE, Harpole DH, Hofstetter WL, Mitchell JD, Altorki NK, et al. The Society of Thoracic Surgeons Practice Guidelines on the Role of Multimodality Treatment for Cancer of the Esophagus and Gastroesophageal Junction. *Ann Thorac Surg* (2014) 98:1880–5. doi: 10.1016/j.athoracsur.2014.07.069
15. Watanabe M, Mine S, Nishida K, Yamada K, Shigaki H, Matsumoto A, et al. Salvage Esophagectomy After Definitive Chemoradiotherapy for Patients With Esophageal Squamous Cell Carcinoma: Who Really Benefits From This High-Risk Surgery? *Ann Surg Oncol* (2015) 22:4438–44. doi: 10.1245/s10434-015-4556-6
16. Lin DC, Hao JJ, Nagata Y, Xu L, Shang L, Meng X, et al. Genomic and Molecular Characterization of Esophageal Squamous Cell Carcinoma. *Nat Genet* (2014) 46:467–73. doi: 10.1038/ng.2935

17. Jiang D, Li X, Wang H, Shi Y, Xu C, Lu S, et al. The Prognostic Value of EGFR Overexpression and Amplification in Esophageal Squamous Cell Carcinoma. *BMC Cancer* (2015) 15:377. doi: 10.1186/s12885-015-1393-8
18. Huang J, Fan Q, Lu P, Ying J, Ma C, Liu W, et al. Icotinib in Patients With Pretreated Advanced Esophageal Squamous Cell Carcinoma With EGFR Overexpression or EGFR Gene Amplification: A Single-Arm, Multicenter Phase 2 Study. *J Thorac Oncol* (2016) 11:910–7. doi: 10.1016/j.jtho.2016.02.020
19. Chong CR, Janne PA. The Quest to Overcome Resistance to EGFR-Targeted Therapies in Cancer. *Nat Med* (2013) 19:1389–400. doi: 10.1038/nm.3388
20. Moehler M, Maderer A, Thuss-Patience PC, Brenner B, Meiler J, Ettrich TJ, et al. Cisplatin and 5-Fluorouracil With or Without Epidermal Growth Factor Receptor Inhibition Panitumumab for Patients With Non-Resectable, Advanced or Metastatic Oesophageal Squamous Cell Cancer: A Prospective, Open-Label, Randomised Phase III AIO/EORTC Trial (POWER). *Ann Oncol* (2020) 31:228–35. doi: 10.1016/j.annonc.2019.10.018
21. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The Function of Programmed Cell Death 1 and Its Ligands in Regulating Autoimmunity and Infection. *Nat Immunol* (2007) 8:239–45. doi: 10.1038/ni1443
22. Okazaki T, Honjo T. PD-1 and PD-1 Ligands: From Discovery to Clinical Application. *Int Immunol* (2007) 19:813–24. doi: 10.1093/intimm/dxm057
23. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab Plus Dacarbazine for Previously Untreated Metastatic Melanoma. *N Engl J Med* (2011) 364:2517–26. doi: 10.1056/NEJMoa1104621
24. Raufi AG, Klempner SJ. Immunotherapy for Advanced Gastric and Esophageal Cancer: Preclinical Rationale and Ongoing Clinical Investigations. *J Gastrointest Oncol* (2015) 6:561–9. doi: 10.3978/j.issn.2078-6891.2015.037
25. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. *N Engl J Med* (2012) 366:2443–54. doi: 10.1056/NEJMoa1200690
26. Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, et al. Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. *J Clin Oncol* (2015) 33:4015–22. doi: 10.1200/jco.2015.62.3397
27. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. *J Clin Oncol* (2010) 28:3167–75. doi: 10.1200/jco.2009.26.7609
28. Kudo T, Hamamoto Y, Kato K, Ura T, Kojima T, Tsushima T, et al. Nivolumab Treatment for Oesophageal Squamous-Cell Carcinoma: An Open-Label, Multicentre, Phase 2 Trial. *Lancet Oncol* (2017) 18:631–9. doi: 10.1016/s1470-2045(17)30181-x
29. Lee J, Kim B, Jung HA, La Choi Y, Sun JM. Nivolumab for Esophageal Squamous Cell Carcinoma and the Predictive Role of PD-L1 or CD8 Expression in Its Therapeutic Effect. *Cancer Immunol Immunother* (2021) 70:1203–11. doi: 10.1007/s00262-020-02766-7
30. Qu HX, Zhao LP, Zhan SH, Geng CX, Xu L, Xin YN, et al. Clinicopathological and Prognostic Significance of Programmed Cell Death Ligand 1 (PD-L1) Expression in Patients With Esophageal Squamous Cell Carcinoma: A Meta-Analysis. *J Thorac Dis* (2016) 8:3197–204. doi: 10.21037/jtd.2016.11.01
31. Rong L, Liu Y, Hui Z, Zhao Z, Zhang Y, Wang B, et al. PD-L1 Expression and its Clinicopathological Correlation in Advanced Esophageal Squamous Cell Carcinoma in a Chinese Population. *Diagn Pathol* (2019) 14:6. doi: 10.1186/s13000-019-0778-4
32. Abnet CC, Arnold M, Wei WQ. Epidemiology of Esophageal Squamous Cell Carcinoma. *Gastroenterology* (2018) 154:360–73. doi: 10.1053/j.gastro.2017.08.023
33. Zendehdel K, Nyrén O, Luo J, Dickman PW, Boffetta P, Englund A, et al. Risk of Gastroesophageal Cancer Among Smokers and Users of Scandinavian Moist Snuff. *Int J Cancer* (2008) 122:1095–9. doi: 10.1002/ijc.23076
34. Ishiguro S, Sasazuki S, Inoue M, Kurahashi N, Iwasaki M, Tsugane S. Effect of Alcohol Consumption, Cigarette Smoking and Flushing Response on Esophageal Cancer Risk: A Population-Based Cohort Study (JPHC Study). *Cancer Lett* (2009) 275:240–6. doi: 10.1016/j.canlet.2008.10.020
35. Liu Y, Chen H, Sun Z, Chen X. Molecular Mechanisms of Ethanol-Associated Oro-Esophageal Squamous Cell Carcinoma. *Cancer Lett* (2015) 361:164–73. doi: 10.1016/j.canlet.2015.03.006
36. Nieminen MT, Novak-Frazer L, Collins R, Dawsey SP, Dawsey SM, Abnet CC, et al. Alcohol and Acetaldehyde in African Fermented Milk Mursik–a Possible Etiologic Factor for High Incidence of Esophageal Cancer in Western Kenya. *Cancer Epidemiol Biomark Prev* (2013) 22:69–75. doi: 10.1158/1055-9965.EPI-12-0908
37. Jeurnink SM, Büchner FL, Bueno-de-Mesquita HB, Siersema PD, Boshuizen HC, Numans ME, et al. Variety in Vegetable and Fruit Consumption and the Risk of Gastric and Esophageal Cancer in the European Prospective Investigation Into Cancer and Nutrition. *Int J Cancer* (2012) 131:E963–73. doi: 10.1002/ijc.27517
38. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, et al. Population Attributable Risks of Esophageal and Gastric Cancers. *JNCI J Natl Cancer Inst* (2003) 95:1404–13. doi: 10.1093/jnci/djg047
39. Islami F, Ren J-S, Taylor PR, Kamangar F. Pickled Vegetables and the Risk of Oesophageal Cancer: A Meta-Analysis. *Br J Cancer* (2009) 101:1641–7. doi: 10.1038/sj.bjc.6605372
40. Munishi MO, Hanisch R, Mapunda O, Ndyetabura T, Ndaro A, Schüz J, et al. Africa's Oesophageal Cancer Corridor: Do Hot Beverages Contribute? *Cancer Causes Control* (2015) 26:1477–86. doi: 10.1007/s10552-015-0646-9
41. Wu C, Kraft P, Zhai K, Chang J, Wang Z, Li Y, et al. Genome-Wide Association Analyses of Esophageal Squamous Cell Carcinoma in Chinese Identify Multiple Susceptibility Loci and Gene-Environment Interactions. *Nat Genet* (2012) 44:1090–7. doi: 10.1038/ng.2411
42. Song Y, Li L, Ou Y, Gao Z, Li E, Li X, et al. Identification of Genomic Alterations in Oesophageal Squamous Cell Cancer. *Nature* (2014) 509:91–5. doi: 10.1038/nature13176
43. Sawada G, Niida A, Uchi R, Hirata H, Shimamura T, Suzuki Y, et al. Genomic Landscape of Esophageal Squamous Cell Carcinoma in a Japanese Population. *Gastroenterology* (2016) 150:1171–82. doi: 10.1053/j.gastro.2016.01.035
44. Vousden KH, Prives C. Blinded by the Light: The Growing Complexity of P53. *Cell* (2009) 137:413–31. doi: 10.1016/j.cell.2009.04.037
45. Ekshyyan O, Anandharaj A, Nathan CA. Dual PI3K/mTOR Inhibitors: Does P53 Modulate Response? *Clin Cancer Res* (2013) 19:3719–21. doi: 10.1158/1078-0432.Ccr-13-1291
46. Fresno Vara JA, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt Signalling Pathway and Cancer. *Cancer Treat Rev* (2004) 30:193–204. doi: 10.1016/j.ctrv.2003.07.007
47. Fruman DA, Rommel C. PI3K and Cancer: Lessons, Challenges and Opportunities. *Nat Rev Drug Discov* (2014) 13:140–56. doi: 10.1038/nrd4204
48. Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR Signaling in Cancer. *Front Oncol* (2014) 4:64. doi: 10.3389/fonc.2014.00064
49. Fruman DA, Meyers RE, Cantley LC. Phosphoinositide Kinases. *Annu Rev Biochem* (1998) 67:481–507. doi: 10.1146/annurev.biochem.67.1.481
50. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in Cancer: Divergent Roles of Isoforms, Modes of Activation and Therapeutic Targeting. *Nat Rev Cancer* (2014) 15:7–24. doi: 10.1038/nrc3860
51. Ciraolo E, Gulluni F, Hirsch E. Methods to Measure the Enzymatic Activity of PI3Ks. *Methods Enzymol* (2014) 543:115–40. doi: 10.1016/B978-0-12-801329-8.00006-4
52. Suire S, Coadwell J, Ferguson GJ, Davidson K, Hawkins P, Stephens L. P84, a New Gbetagamma-Activated Regulatory Subunit of the Type IB Phosphoinositide 3-Kinase P110gamma. *Curr Biol* (2005) 15:566–70. doi: 10.1016/j.cub.2005.02.020
53. Vadas O, Burke JE, Zhang X, Berndt A, Williams RL. Structural Basis for Activation and Inhibition of Class I Phosphoinositide 3-Kinases. *Sci Signaling* (2011) 4:re2. doi: 10.1126/scisignal.2002165
54. Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, Bilanges B. The Emerging Mechanisms of Isoform-Specific PI3K Signalling. *Nat Rev Mol Cell Biol* (2010) 11:329–41. doi: 10.1038/nrm2882
55. Wang H, Lo WT, Vujicic Zagar A, Gulluni F, Lehmann M, Scapozza L, et al. Autoregulation of Class II Alpha PI3K Activity by Its Lipid-Binding PX-C2 Domain Module. *Mol Cell* (2018) 71:343–51.e344. doi: 10.1016/j.molcel.2018.06.042

56. Rostislavleva K, Soler N, Ohashi Y, Zhang L, Pardon E, Burke JE, et al. Structure and Flexibility of the Endosomal Vps34 Complex Reveals the Basis of Its Function on Membranes. *Science* (2015) 350:aac7365. doi: 10.1126/science.aac7365
57. Alzahrani AS. PI3K/Akt/mTOR Inhibitors in Cancer: At the Bench and Bedside. *Semin Cancer Biol* (2019) 59:125–32. doi: 10.1016/j.semcancer.2019.07.009
58. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. *Cell* (2017) 170:605–35. doi: 10.1016/j.cell.2017.07.029
59. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. *Cell* (2017) 169:361–71. doi: 10.1016/j.cell.2017.03.035
60. Revathidevi S, Munirajan AK. Akt in Cancer: Mediator and More. *Semin Cancer Biol* (2019) 59:80–91. doi: 10.1016/j.semcancer.2019.06.002
61. Hay N. The Akt-mTOR Tango and its Relevance to Cancer. *Cancer Cell* (2005) 8:179–83. doi: 10.1016/j.ccr.2005.08.008
62. Nakakido M, Deng Z, Suzuki T, Dohmae N, Nakamura Y, Hamamoto R. Dysregulation of AKT Pathway by SMYD2-Mediated Lysine Methylation on PTEN. *Neoplasia* (2015) 17:367–73. doi: 10.1016/j.neo.2015.03.002
63. Downward J. Targeting RAS Signalling Pathways in Cancer Therapy. *Nat Rev Cancer* (2003) 3:11–22. doi: 10.1038/nrc969
64. Mossmann D, Park S, Hall MN. mTOR Signalling and Cellular Metabolism are Mutual Determinants in Cancer. *Nat Rev Cancer* (2018) 18:744–57. doi: 10.1038/s41568-018-0074-8
65. Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and Regulation of Akt/PKB by the rictor-mTOR Complex. *Science* (2005) 307:1098–101. doi: 10.1126/science.1106148
66. Scott RC, Juhász G, Neufeld TP. Direct Induction of Autophagy by Atg1 Inhibits Cell Growth and Induces Apoptotic Cell Death. *Curr Biol* (2007) 17:1–11. doi: 10.1016/j.cub.2006.10.053
67. Tanaka K, Babic I, Nathanson D, Akhavan D, Guo D, Gini B, et al. Oncogenic EGFR Signaling Activates an Mtorc2-NF-κb Pathway That Promotes Chemotherapy Resistance. *Cancer Discov* (2011) 1:524–38. doi: 10.1158/2159-8290.Cd-11-0124
68. Xu K, Chen G, Li X, Wu X, Chang Z, Xu J, et al. MFN2 Suppresses Cancer Progression Through Inhibition of Mtorc2/Akt Signaling. *Sci Rep* (2017) 7:41718. doi: 10.1038/srep41718
69. Zhang F, Zhang X, Li M, Chen P, Zhang B, Guo H, et al. mTOR Complex Component Rictor Interacts With PKCzeta and Regulates Cancer Cell Metastasis. *Cancer Res* (2010) 70:9360–70. doi: 10.1158/0008-5472.Can-10-0207
70. Zhang J, Jia L, Liu T, Yip YL, Tang WC, Lin W, et al. Mtorc2-Mediated PDHE1α Nuclear Translocation Links EBV-LMP1 Reprogrammed Glucose Metabolism to Cancer Metastasis in Nasopharyngeal Carcinoma. *Oncogene* (2019) 38:4669–84. doi: 10.1038/s41388-019-0749-y
71. Guo M, Hay BA. Cell Proliferation and Apoptosis. *Curr Opin Cell Biol* (1999) 11:745–52. doi: 10.1016/S0955-0674(99)00046-0
72. Li SH, Chen CH, Lu HI, Huang WT, Tien WY, Lan YC, et al. Phosphorylated P70s6k Expression Is an Independent Prognosticator for Patients With Esophageal Squamous Cell Carcinoma. *Surgery* (2015) 157:570–80. doi: 10.1016/j.surg.2014.10.014
73. Hou G, Xue L, Lu Z, Fan T, Tian F, Xue Y. An Activated mTOR/P70s6k Signaling Pathway in Esophageal Squamous Cell Carcinoma Cell Lines and Inhibition of the Pathway by Rapamycin and siRNA Against mTOR. *Cancer Lett* (2007) 253:236–48. doi: 10.1016/j.canlet.2007.01.026
74. Zhang HZ, Kasibhatla S, Wang Y, Herich J, Guastella J, Tseng B, et al. Discovery, Characterization and SAR of Gambogic Acid as a Potent Apoptosis Inducer by a HTS Assay. *Bioorg Med Chem* (2004) 12:309–17. doi: 10.1016/j.bmc.2003.11.013
75. Yu J, Wang W, Yao W, Yang Z, Gao P, Liu M, et al. Gambogic Acid Affects ESCC Progression Through Regulation of PI3K/AKT/mTOR Signal Pathway. *J Cancer* (2020) 11:5568–77. doi: 10.7150/jca.41115
76. Xu Z, Han X, Ou D, Liu T, Li Z, Jiang G, et al. Targeting PI3K/AKT/mTOR-Mediated Autophagy for Tumor Therapy. *Appl Microbiol Biotechnol* (2020) 104:575–87. doi: 10.1007/s00253-019-10257-8
77. Kondo Y, Kanzawa T, Sawaya R, Kondo S. The Role of Autophagy in Cancer Development and Response to Therapy. *Nat Rev Cancer* (2005) 5:726–34. doi: 10.1038/nrc1692
78. Han T, Guo M, Gan M, Yu B, Tian X, Wang JB. TRIM59 Regulates Autophagy Through Modulating Both the Transcription and the Ubiquitination of BECN1. *Autophagy* (2018) 14:2035–48. doi: 10.1080/15548627.2018.1491493
79. Yoshioka A, Miyata H, Doki Y, Yamasaki M, Sohma I, Gotoh K, et al. LC3, an Autophagosome Marker, Is Highly Expressed in Gastrointestinal Cancers. *Int J Oncol* (2008) 33:461–8. doi: 10.3892/ijo_00000028
80. Yu L, Gu C, Zhong D, Shi L, Kong Y, Zhou Z, et al. Induction of Autophagy Counteracts the Anticancer Effect of Cisplatin in Human Esophageal Cancer Cells With Acquired Drug Resistance. *Cancer Lett* (2014) 355:34–45. doi: 10.1016/j.canlet.2014.09.020
81. O'Donovan TR, O'Sullivan GC, McKenna SL. Induction of Autophagy by Drug-Resistant Esophageal Cancer Cells Promotes Their Survival and Recovery Following Treatment With Chemotherapeutics. *Autophagy* (2011) 7:509–24. doi: 10.4161/auto.7.6.15066
82. Lu C, Xie C. Radiation-Induced Autophagy Promotes Esophageal Squamous Cell Carcinoma Cell Survival Via the LKB1 Pathway. *Oncol Rep* (2016) 35:3559–65. doi: 10.3892/or.2016.4753
83. Cai Y, Cai J, Ma Q, Xu Y, Zou J, Xu L, et al. Chloroquine Affects Autophagy to Achieve an Anticancer Effect in EC109 Esophageal Carcinoma Cells. *Vitro Oncol Lett* (2018) 15:1143–8. doi: 10.3892/ol.2017.7415
84. Elmenier FM, Lasheen DS, Abouzid KAM. Phosphatidylinositol 3 Kinase (PI3K) Inhibitors as New Weapon to Combat Cancer. *Eur J Med Chem* (2019) 183:111718. doi: 10.1016/j.ejmech.2019.111718
85. Shi JJ, Xing H, Wang YX, Zhang X, Zhan QM, Geng MY, et al. PI3Kalpha Inhibitors Sensitize Esophageal Squamous Cell Carcinoma to Radiation by Abrogating Survival Signals in Tumor Cells and Tumor Microenvironment. *Cancer Lett* (2019) 459:145–55. doi: 10.1016/j.canlet.2019.05.040
86. Hou G, Zhao Q, Zhang M, Fan T, Liu M, Shi X, et al. Down-Regulation of Rictor Enhances Cell Sensitivity to PI3K Inhibitor LY294002 by Blocking Mtorc2-Medicated Phosphorylation of Akt/PRAS40 in Esophageal Squamous Cell Carcinoma. *BioMed Pharmacother* (2018) 106:1348–56. doi: 10.1016/j.biopha.2018.07.075
87. Elkabets M, Pazarentzos E, Juric D, Sheng Q, Pelossof RA, Brook S, et al. AXL Mediates Resistance to PI3Kalpha Inhibition by Activating the EGFR/PKC/mTOR Axis in Head and Neck and Esophageal Squamous Cell Carcinomas. *Cancer Cell* (2015) 27:533–46. doi: 10.1016/j.ccell.2015.03.010
88. Badarni M, Prasad M, Balaban N, Zorea J, Yegodayev KM, Joshua BZ, et al. Repression of AXL Expression by AP-1/JNK Blockage Overcomes Resistance to PI3Ka Therapy. *JCI Insight* (2019). doi: 10.1172/jci.insight.125341
89. Guo Q, He J, Shen F, Zhang W, Yang X, Zhang C, et al. TCN, an AKT Inhibitor, Exhibits Potent Antitumor Activity and Enhances Radiosensitivity in Hypoxic Esophageal Squamous Cell Carcinoma. *Vitro Vivo Oncol Lett* (2017) 13:949–54. doi: 10.3892/ol.2016.5515
90. Shi N, Yu H, Chen T. Inhibition of Esophageal Cancer Growth Through the Suppression of PI3K/AKT/mTOR Signaling Pathway. *Onco Targets Ther* (2019) 12:7637–47. doi: 10.2147/OTT.S205457
91. Yap TA, Yan L, Patnaik A, Fearen I, Olmos D, Papadopoulos K, et al. First-In-Man Clinical Trial of the Oral Pan-AKT Inhibitor MK-2206 in Patients With Advanced Solid Tumors. *J Clin Oncol* (2011) 29:4688–95. doi: 10.1200/JCO.2011.35.5263
92. Xu T, Sun D, Chen Y, Ouyang L. Targeting mTOR for Fighting Diseases: A Revisited Review of mTOR Inhibitors. *Eur J Med Chem* (2020) 199:112391. doi: 10.1016/j.ejmech.2020.112391
93. Guertin DA, Sabatini DM. The Pharmacology of mTOR Inhibition. *Sci Signal* (2009) 2:pe24. doi: 10.1126/scisignal.267pe24
94. Hou G, Zhang Q, Wang L, Liu M, Wang J, Xue L. mTOR Inhibitor Rapamycin Alone or Combined With Cisplatin Inhibits Growth of Esophageal Squamous Cell Carcinoma in Nude Mice. *Cancer Lett* (2010) 290:248–54. doi: 10.1016/j.canlet.2009.09.015
95. Nishikawa T, Takaoka M, Ohara T, Tomono Y, Hao H, Bao X, et al. Antiproliferative Effect of a Novel mTOR Inhibitor Temsirolimus Contributes to the Prolonged Survival of Orthotopic Esophageal Cancer-Bearing Mice. *Cancer Biol Ther* (2013) 14:230–6. doi: 10.4161/cbt.23294
96. Choo AY, Yoon S-O, Kim SG, Roux PP, Blenis J. Rapamycin Differentially Inhibits S6Ks and 4E-BP1 to Mediate Cell-Type-Specific Repression of

mRNA Translation. *Proc Natl Acad Sci USA* (2008) 105:17414–9. doi: 10.1073/pnas.0809136105
97. Fujishita T, Kojima Y, Kajino-Sakamoto R, Taketo MM, Aoki M. Tumor Microenvironment Confers mTOR Inhibitor Resistance in Invasive Intestinal Adenocarcinoma. *Oncogene* (2017) 36:6480–9. doi: 10.1038/onc.2017.242
98. Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, et al. Phase III Study to Evaluate Temsirolimus Compared With Investigator's Choice Therapy for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma. *J Clin Oncol* (2009) 27:3822–9. doi: 10.1200/JCO.2008.20.7977
99. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Cutsem EV, et al. Everolimus for Advanced Pancreatic Neuroendocrine Tumors. *N Engl J Med* (2011) 364:514–23. doi: 10.1056/NEJMoa1009290
100. Huang Y, Xi Q, Chen Y, Wang J, Peng P, Xia S, et al. A Dual Mtorc1 and Mtorc2 Inhibitor Shows Antitumor Activity in Esophageal Squamous Cell Carcinoma Cells and Sensitizes Them to Cisplatin. *Anti-Cancer Drugs* (2013) 24:889–98. doi: 10.1097/CAD.0b013e328363c64e
101. Ghobrial IM, Siegel DS, Vij R, Berdeja JG, Richardson PG, Neuwirth R, et al. TAK-228 (Formerly MLN0128), an Investigational Oral Dual TORC1/2 Inhibitor: A Phase I Dose Escalation Study in Patients With Relapsed or Refractory Multiple Myeloma, non-Hodgkin Lymphoma, or Waldenstrom's Macroglobulinemia. *Am J Hematol* (2016) 91:400–5. doi: 10.1002/ajh.24300
102. Wu N, Zhu Y, Xu X, Zhu Y, Song Y, Pang L, et al. The Anti-Tumor Effects of Dual PI3K/mTOR Inhibitor BEZ235 and Histone Deacetylase Inhibitor Trichostatin A on Inducing Autophagy in Esophageal Squamous Cell Carcinoma. *J Cancer* (2018) 9:987–97. doi: 10.7150/jca.22861
103. Shapiro GI, Bell-McGuinn KM, Molina JR, Bendell J, Spicer J, Kwak EL, et al. First-In-Human Study of PF-05212384 (PKI-587), a Small-Molecule, Intravenous, Dual Inhibitor of PI3K and mTOR in Patients With Advanced Cancer. *Clin Cancer Res* (2015) 21:1888–95. doi: 10.1158/1078-0432.CCR-14-1306
104. Deng L, Wu X, Zhu X, Yu Z, Liu Z, Wang J, et al. Combination Effect of Curcumin With Docetaxel on the PI3K/AKT/mTOR Pathway to Induce Autophagy and Apoptosis in Esophageal Squamous Cell Carcinoma. *Am J Transl Res* (2021) 13:57–72.
105. Wang YK, Chen WC, Lai YH, Chen YH, Wu MT, Kuo CT, et al. Influence of Tea Consumption on the Development of Second Esophageal Neoplasm in Patients With Head and Neck Cancer. *Cancers (Basel)* (2019). doi: 10.3390/cancers11030387
106. Shen CY, Jiang JG, Yang L, Wang DW, Zhu W. Anti-Ageing Active Ingredients From Herbs and Nutraceuticals Used in Traditional Chinese Medicine: Pharmacological Mechanisms and Implications for Drug Discovery. *Br J Pharmacol* (2017) 174:1395–425. doi: 10.1111/bph.13631
107. Foroozesh M, Primrose G, Guo Z, Bell LC, Alworth WL, Guengerich FP. Aryl Acetylenes as Mechanism-Based Inhibitors of Cytochrome P450-Dependent Monooxygenase Enzymes. *Chem Res Toxicol* (1997) 10:91–102. doi: 10.1021/tx960064g
108. Fuggetta MP, D'Atri S, Lanzilli G, Tricarico M, Cannavo E, Zambruno G, et al. *In Vitro* Antitumour Activity of Resveratrol in Human Melanoma Cells Sensitive or Resistant to Temozolomide. *Melanoma Res* (2004) 14:189–96. doi: 10.1097/01.cmr.0000130007.54508.b2
109. Osman AM, Bayoumi HM, Al-Harthi SE, Damanhouri ZA, Elshal MF. Modulation of Doxorubicin Cytotoxicity by Resveratrol in a Human Breast Cancer Cell Line. *Cancer Cell Int* (2012) 12:47. doi: 10.1186/1475-2867-12-47
110. Tang Q, Li G, Wei X, Zhang J, Chiu JF, Hasenmayer D, et al. Resveratrol-Induced Apoptosis is Enhanced by Inhibition of Autophagy in Esophageal Squamous Cell Carcinoma. *Cancer Lett* (2013) 336:325–37. doi: 10.1016/j.canlet.2013.03.023
111. Yang CS, Wang H. Cancer Preventive Activities of Tea Catechins. *Molecules* (2016). doi: 10.3390/molecules21121679
112. Hershey JW, Sonenberg N, Mathews MB. Principles of Translational Control: An Overview. *Cold Spring Harb Perspect Biol* (2012). doi: 10.1101/cshperspect.a011528
113. Verma M, Choi J, Cottrell KA, Lavagnino Z, Thomas EN, Pavlovic-Djuranovic S, et al. A Short Translational Ramp Determines the Efficiency of Protein Synthesis. *Nat Commun* (2019) 10:5774. doi: 10.1038/s41467-019-13810-1
114. Ali MU, Ur Rahman MS, Jia Z, Jiang C. Eukaryotic Translation Initiation Factors and Cancer. *Tumour Biol* (2017) 39:1010428317709805. doi: 10.1177/1010428317709805
115. Chen K, Yang J, Li J, Wang X, Chen Y, Huang S, et al. Eif4b is a Convergent Target and Critical Effector of Oncogenic Pim and PI3K/Akt/mTOR Signaling Pathways in Abl Transformants. *Oncotarget* (2016) 7:10073–89. doi: 10.18632/oncotarget.7164
116. Golob-Schwarzl N, Krassnig S, Toeglhofer AM, Park YN, Gogg-Kamerer M, Vierlinger K, et al. New Liver Cancer Biomarkers: PI3K/AKT/mTOR Pathway Members and Eukaryotic Translation Initiation Factors. *Eur J Cancer* (2017) 83:56–70. doi: 10.1016/j.ejca.2017.06.003
117. Hao P, Yu J, Ward R, Liu Y, Hao Q, An S, et al. Eukaryotic Translation Initiation Factors as Promising Targets in Cancer Therapy. *Cell Commun Signal* (2020) 18:175. doi: 10.1186/s12964-020-00607-9
118. Silvera D, Formenti SC, Schneider RJ. Translational Control in Cancer. *Nat Rev Cancer* (2010) 10:254–66. doi: 10.1038/nrc2824
119. Smolle E, Taucher V, Pichler M, Petru E, Lax S, Haybaeck J. Targeting Signaling Pathways in Epithelial Ovarian Cancer. *Int J Mol Sci* (2013) 14:9536–55. doi: 10.3390/ijms14059536
120. Golob-Schwarzl N, Wodlej C, Kleinegger F, Gogg-Kamerer M, Birkl-Toeglhofer AM, Petzold J, et al. Eukaryotic Translation Initiation Factor 6 Overexpression Plays a Major Role in the Translational Control of Gallbladder Cancer. *J Cancer Res Clin Oncol* (2019) 145:2699–711. doi: 10.1007/s00432-019-03030-x
121. Jackson RJ, Hellen CU, Pestova TV. The Mechanism of Eukaryotic Translation Initiation and Principles of its Regulation. *Nat Rev Mol Cell Biol* (2010) 11:113–27. doi: 10.1038/nrm2838
122. Spilka R, Ernst C, Mehta AK, Haybaeck J. Eukaryotic Translation Initiation Factors in Cancer Development and Progression. *Cancer Lett* (2013) 340:9–21. doi: 10.1016/j.canlet.2013.06.019
123. Walsh D, Perez C, Notary J, Mohr I. Regulation of the Translation Initiation Factor Eif4f by Multiple Mechanisms in Human Cytomegalovirus-Infected Cells. *J Virol* (2005) 79:8057–64. doi: 10.1128/jvi.79.13.8057-8064.2005
124. Marintchev A, Edmonds KA, Marintcheva B, Hendrickson E, Oberer M, Suzuki C, et al. Topology and Regulation of the Human Eif4a/4G/4H Helicase Complex in Translation Initiation. *Cell* (2009) 136:447–60. doi: 10.1016/j.cell.2009.01.014
125. Masutani M, Sonenberg N, Yokoyama S, Imataka H. Reconstitution Reveals the Functional Core of Mammalian Eif3. *EMBO J* (2007) 26:3373–83. doi: 10.1038/sj.emboj.7601765
126. Pöyry TA, Kaminski A, Jackson RJ. What Determines Whether Mammalian Ribosomes Resume Scanning After Translation of a Short Upstream Open Reading Frame? *Genes Dev* (2004) 18:62–75. doi: 10.1101/gad.276504
127. Gandin V, Miluzio A, Barbieri AM, Beugnet A, Kiyokawa H, Marchisio PC, et al. Eukaryotic Initiation Factor 6 is Rate-Limiting in Translation, Growth and Transformation. *Nature* (2008) 455:684–8. doi: 10.1038/nature07267
128. Golob-Schwarzl N, Schweiger C, Koller C, Krassnig S, Gogg-Kamerer M, Gantenbein N, et al. Separation of Low and High Grade Colon and Rectum Carcinoma by Eukaryotic Translation Initiation Factors 1, 5 and 6. *Oncotarget* (2017) 8:101224–43. doi: 10.18632/oncotarget.20642
129. Smolle MA, Czapiewski P, Lapinska-Szumczyk S, Majewska H, Supernat A, Zaczek A, et al. The Prognostic Significance of Eukaryotic Translation Initiation Factors (eIFs) in Endometrial Cancer. *Int J Mol Sci* (2019) 20. doi: 10.3390/ijms20246169
130. Skofler C, Kleinegger F, Krassnig S, Birkl-Toeglhofer AM, Singer G, Till H, et al. Eukaryotic Translation Initiation Factor 4ai: A Potential Novel Target in Neuroblastoma. *Cells* (2021) 10. doi: 10.3390/cells10020301
131. Krassnig S, Wohlrab C, Golob-Schwarzl N, Raicht A, Schatz C, Birkl-Toeglhofer AM, et al. A Profound Basic Characterization of eIFs in Gliomas: Identifying Eif3i and 4H as Potential Novel Target Candidates in Glioma Therapy. *Cancers* (2021) 13. doi: 10.3390/cancers13061482
132. Ewens KG, Kanetsky PA, Richards-Yutz J, Purrazzella J, Shields CL, Ganguly T, et al. Chromosome 3 Status Combined With BAP1 and EIF1AX Mutation Profiles Are Associated With Metastasis in Uveal Melanoma. *Invest Ophthalmol Vis Sci* (2014) 55:5160–7. doi: 10.1167/iovs.14-14550
133. Karunamurthy A, Panebianco F, J.Hsiao S, Vorhauer J, Nikiforova MN, Chiosea S, et al. Prevalence and Phenotypic Correlations of EIF1AX

Mutations in Thyroid Nodules. *Endocr Relat Cancer* (2016) 23:295–301. doi: 10.1530/erc-16-0043
134. Etemadmoghadam D, Azar WJ, Lei Y, Moujaber T, Garsed DW, Kennedy CJ, et al. EIF1AX and NRAS Mutations Co-Occur and Cooperate in Low-Grade Serous Ovarian Carcinomas. *Cancer Res* (2017) 77:4268–78. doi: 10.1158/0008-5472.Can-16-2224
135. Sehrawat U, Koning F, Ashkenazi S, Stelzer G, Leshkowitz D, Dikstein R. Cancer-Associated Eukaryotic Translation Initiation Factor 1a Mutants Impair Rps3 and Rps10 Binding and Enhance Scanning of Cell Cycle Genes. *Mol Cell Biol* (2019). doi: 10.1128/MCB.00441-18
136. Zhang L, Smit-McBride Z, Pan X, Rheinhardt J, Hershey JW. An Oncogenic Role for the Phosphorylated H-Subunit of Human Translation Initiation Factor Eif3. *J Biol Chem* (2008) 283:24047–60. doi: 10.1074/jbc.M800956200
137. Nupponen NN, Porkka K, Kakkola L, Tanner M, Persson K, Borg A, et al. Amplification and Overexpression of P40 Subunit of Eukaryotic Translation Initiation Factor 3 in Breast and Prostate Cancer. *Am J Pathol* (1999) 154:1777–83. doi: 10.1016/s0002-9440(10)65433-8
138. Choe J, Lin S, Zhang W, Liu Q, Wang L, Ramirez-Moya J, et al. mRNA Circularization by METTL3-Eif3h Enhances Translation and Promotes Oncogenesis. *Nature* (2018) 561:556–60. doi: 10.1038/s41586-018-0538-8
139. Golob-Schwarzl N, Puchas P, Gogg-Kamerer M, Weichert W, GÖPpert B, Haybaeck J. New Pancreatic Cancer Biomarkers Eif1, Eif2d, Eif3c and Eif6 Play a Major Role in Translational Control in Ductal Adenocarcinoma. *Anticancer Res* (2020) 40:3109–18. doi: 10.21873/anticanres.14292
140. Liu T, Li R, Zhao H, Deng J, Long Y, Shuai MT, et al. Eif4e Promotes Tumorigenesis and Modulates Chemosensitivity to Cisplatin in Esophageal Squamous Cell Carcinoma. *Oncotarget* (2016) 7:66851–64. doi: 10.18632/oncotarget.11694
141. Yang H, Li XD, Zhou Y, Ban X, Zeng TT, Li L, et al. Stemness and Chemotherapeutic Drug Resistance Induced by EIF5A2 Overexpression in Esophageal Squamous Cell Carcinoma. *Oncotarget* (2015) 6:26079–89. doi: 10.18632/oncotarget.4581
142. Assouline S, Culjkovic-Kraljacic B, Bergeron J, Caplan S, Cocolakis E, Lambert C, et al. A Phase I Trial of Ribavirin and Low-Dose Cytarabine for the Treatment of Relapsed and Refractory Acute Myeloid Leukemia With Elevated Eif4e. *Haematologica* (2015) 100:e7–9. doi: 10.3324/haematol.2014.111245
143. Duffy AG, Makarova-Rusher OV, Ulahannan SV, Rahma OE, Fioravanti S, Walker M, et al. Modulation of Tumor Eif4e by Antisense Inhibition: A Phase I/II Translational Clinical Trial of ISIS 183750-an Antisense Oligonucleotide Against Eif4e-in Combination With Irinotecan in Solid Tumors and Irinotecan-Refractory Colorectal Cancer. *Int J Cancer* (2016) 139:1648–57. doi: 10.1002/ijc.30199
144. Casaos J, Gorelick NL, Huq S, Choi J, Xia Y, Serra R, et al. The Use of Ribavirin as an Anticancer Therapeutic: Will It Go Viral? *Mol Cancer Ther* (2019) 18:1185–94. doi: 10.1158/1535-7163.Mct-18-0666
145. Liu WL, Su WC, Cheng CW, Hwang LH, Wang CC, Chen HL, et al. Ribavirin Up-Regulates the Activity of Double-Stranded RNA-Activated Protein Kinase and Enhances the Action of Interferon-Alpha Against Hepatitis C Virus. *J Infect Dis* (2007) 196:425–34. doi: 10.1086/518894
146. Crotty S, Cameron C, Andino R. Ribavirin's Antiviral Mechanism of Action: Lethal Mutagenesis? *J Mol Med (Berl)* (2002) 80:86–95. doi: 10.1007/s00109-001-0308-0
147. Loustaud-Ratti V, Debette-Gratien M, Jacques J, Alain S, Marquet P, Sautereau D, et al. Ribavirin: Past, Present and Future. *World J Hepatol* (2016) 8:123–30. doi: 10.4254/wjh.v8.i2.123
148. Tan K, Culjkovic B, Amri A, Borden KL. Ribavirin Targets Eif4e Dependent Akt Survival Signaling. *Biochem Biophys Res Commun* (2008) 375:341–5. doi: 10.1016/j.bbrc.2008.07.163
149. Chen J, Xu X, Chen J. Clinically Relevant Concentration of Anti-Viral Drug Ribavirin Selectively Targets Pediatric Osteosarcoma and Increases Chemosensitivity. *Biochem Biophys Res Commun* (2018) 506:604–10. doi: 10.1016/j.bbrc.2018.10.124
150. Jin J, Xiang W, Wu S, Wang M, Xiao M, Deng A. Targeting Eif4e Signaling With Ribavirin as a Sensitizing Strategy for Ovarian Cancer. *Biochem Biophys Res Commun* (2019) 510:580–6. doi: 10.1016/j.bbrc.2019.01.117
151. Huq S, Casaos J, Serra R, Peters M, Xia Y, Ding AS, et al. Repurposing the FDA-Approved Antiviral Drug Ribavirin as Targeted Therapy for Nasopharyngeal Carcinoma. *Mol Cancer Ther* (2020) 19:1797–808. doi: 10.1158/1535-7163.MCT-19-0572
152. Villanueva J, Vultur A, Lee JT, Somasundaram R, Fukunaga-Kalabis M, Cipolla AK, et al. Acquired Resistance to BRAF Inhibitors Mediated by a RAF Kinase Switch in Melanoma can be Overcome by Cotargeting MEK and IGF-1r/PI3K. *Cancer Cell* (2010) 18:683–95. doi: 10.1016/j.ccr.2010.11.023

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Predictive Value of Endoscopic Observations and Biopsy After Neoadjuvant Chemoradiotherapy in Assessing the Pathologic Complete Response of Patients With Esophageal Squamous Cell Carcinoma

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Introduction: No standard method has been defined to evaluate the therapeutic response of esophageal cancer to neoadjuvant chemoradiotherapy (CRT). This study aimed to determine the predictive value of endoscopic evaluation and biopsy after CRT in predicting the complete pathological response to neoadjuvant CRT in patients with esophageal squamous cell carcinoma (SCC).

Materials and Method: This prospective, descriptive study was conducted on patients with stage II and III esophageal SCC who could undergo esophagectomy. Patients underwent neoadjuvant CRT. Four to six weeks after the end of treatment, re-endoscopy was performed and a biopsy was taken in the presence of a tumor lesion. In the absence of a tumor lesion, the marked site of the esophagus was removed as a blind biopsy. Gastrologist observations during endoscopy and the result of the pathological examination of an endoscopic biopsy were recorded. The patient underwent esophagectomy. The pathology obtained from endoscopic biopsy was compared with the pathology response obtained from esophagectomy.

Results: Sixty-nine patients were included in the study, of which 32 underwent esophagectomy. In an endoscopic examination after CRT, 28 patients had macroscopic tumor remnants and 4 patients did not. Pathological examination of the samples obtained from endoscopy showed no tumor remnants in 10 patients (31.3%), and in 22 patients (68.7%), living tumor remnants were seen in the biopsy specimen. Pathologic evaluation of the samples obtained by surgical resection showed that in 13 patients, there were no viable carcinomas in the esophagus or lymph nodes removed, and the rate of pathologic complete response was 40.6. Sensitivity, specificity,

positive predictive, and negative predictive values of endoscopic observations were 94.7, 23, 64.2, and 75%, respectively. Preoperative biopsy sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 68.4, 30.7, 59, and 40%, respectively.

Conclusion: Considering the negative and positive predictive values of endoscopic observations and biopsy after neoadjuvant CRT, it seems that these two methods alone are not suitable for assessing the pathologic complete response after neoadjuvant treatment.

Keywords: Esophageal squamous cell carcinoma, endoscopic biopsy, neoadjuvant chemoradiotherapy, predictive value, neoadjuvant treatment

INTRODUCTION

Malignancies are one of the most common causes of death in developing and developed countries, accounting for a large portion of the annual health system expenditures in these countries. Meanwhile, esophageal cancer does not have a significant prevalence worldwide, but due to its regional prevalence pattern, it is still highly prevalent in areas such as the north and northeast of Iran. It is the second most common cancer in Iranian men and the third among Iranian women (1, 2). Despite advances in the diagnosis and treatment of esophageal cancer and the relative reduction in mortality due to them, this cancer is still considered one of the most lethal (3).

The standard treatment for esophageal cancer in patients with curative intent is esophagectomy. However, methods such as tumor removal by endoscopy, neoadjuvant, or definitive CRT are used depending on the condition of the patient. In most cases, staging is performed before starting treatment to select the appropriate treatment using endoscopic ultrasonography with CT scan. Neoadjuvant CRT in patients with operable esophageal cancer in stages IIB and III has significantly increased the survival of patients and is the recommended treatment (4, 5).

Although esophagectomy is a difficult operation with many complications, currently the only way to evaluate the response of an esophageal tumor to neoadjuvant treatment is to examine the samples from esophagectomy and lymphadenectomy (6), and a standard method for evaluating the therapeutic response of esophageal tumors to preoperative CRT in patients has not been defined before surgery. In the presence of a reliable method for evaluating the therapeutic response, this heavy surgery could be avoided. In numerous studies, various combinations of fluorodeoxy glucose positron emission tomography (FDG-PET) scan, computed tomography (CT) scan, endoscopy, and esophagography in cohorts of 60–280 patients have found a physician-assessed clinical response to have an accuracy of between 46 and 79% and an NPV of between 31 and 74% (7–9). From these, FDG-PET scan was more accurate and the reduction in FDG uptake in the tumor site was associated with pathologic complete response (10), but this method is expensive and has some limitations too. This study determined the predictive value of endoscopic evaluation and biopsy after DRT in predicting the complete pathological response to neoadjuvant CRT in patients with esophageal SCC.

MATERIALS AND METHODS

This prospective descriptive study was conducted in the radiation oncology department of Imam Reza Hospital and Omid Hospital, affiliated with Mashhad University of Medical Sciences during 2017 and 2018. Inclusion criteria included patients with stage II and III esophageal SCC whose disease was confirmed by endoscopic biopsy and tissue examination by a pathologist, and whose clinical condition (in terms of comorbidities) allowed esophagectomy. The exclusion criteria were the presence of distant metastasis, failure to complete the treatment protocol by patients, failure to perform esophagectomy for any reason after completing the course of CRT, and dissatisfaction with participating in the study. During primary endoscopy, the location of the tumor for future interventions was determined using anatomical criteria. Patients underwent thoracic and abdominal CT scans to stage the disease. Following written consent, patients received weekly carboplatin (AUC = 2) and paclitaxel (50 mg/m^2) chemotherapy for five weeks, followed by 28 sessions of radiotherapy with a final dose of 5,040 centigray (cGY) and 180 cGY/fraction. Four to six weeks after the end of CRT, endoscopy was performed again and a biopsy was taken from tumor. In the absence of a tumor lesion, the esophageal marked site was removed as a blind biopsy. Gastrologist observations and the result of the pathological examination of endoscopic biopsy were recorded. Then the patient was referred for surgery, and after esophagectomy, the sample was sent for pathology, and finally, the pathology results obtained from endoscopic biopsy were compared with the pathology results obtained from esophagectomy. Data were entered into the SPSS 21 software and descriptive statistics such as mean, standard deviation, frequency, percentage, sensitivity and specificity, positive and negative predictive value, positive and negative probability, and preoperative biopsy accuracy in predicting postoperative pathology response were reported.

RESULTS

Sixty-nine patients were enrolled in the study, of whom 32 underwent esophagectomy after neoadjuvant CRT. In the 32 patients who underwent surgery, the median age was 65.5 years. Other patient characteristics are listed in **Table 1**.

Endoscopic observations after neoadjuvant CRT showed macroscopic remnants of the tumor in 28 patients (87.5%), and 4 patients (12.5%) had no macroscopic remnants. Pathological examination of endoscopic biopsy after neoadjuvant treatment showed that in 10 patients (31.3%), there was no viable tumor. In 22 patients (68.7%), tumor remnants were seen in the biopsy specimen. Evaluation of the samples obtained from surgical resection showed that in 13 patients, there were no tumor remains in the esophagus or lymph nodes removed, so the rate of pathologic complete response was 40.6. Of the 19 patients with tumor remnants, 13 (40.6%) reported T + (three were yT1, seven were yT2, and three were yT3) and six were yT0 N^+. Also, in the lymph node evaluation, the results showed that 10 patients (31.3%) had yN1.

The results of the diagnostic accuracy of endoscopic observations after CRT showed that the frequency of true positive, false positive, true negative, and false negative macroscopic findings in this study were 18, 10, 3, and 1, respectively. **Table 2** shows the frequency of positive and negative material from macroscopic findings in preoperative endoscopy in predicting the true pathological response of the tumor. As shown in the table, the sensitivity and specificity of endoscopic macroscopic findings after CRT in predicting tumor pathology response after esophagectomy are 94.7 and 23%, respectively. Also, the PPV (cancer remaining in esophagectomy sample) and NPV (no cancer remaining in esophagectomy sample) in predicting pathologic complete response are 64.2 and 75%, respectively. Overall, the accuracy of endoscopic macroscopic findings after CRT in predicting the pathologic complete response after esophagectomy is 65.6%.

TABLE 1 | Background characteristics of the subjects at the beginning of the study.

Variable	Percent (Number)
Gender	
Male	53 (17)
Female	47 (15)
Tumor site	
Middle esophagus	47 (15)
Lower esophagus	53 (17)
Tumor grade	
I	25 (8)
II	62.5 (25)
III	12.5 (4)
Duration of CRT	
5 Weeks	43.8 (14)
6 Weeks	40.6 (13)
7 weeks	15.6 (5)
Radiation dose	
50 or 50.4 Gy	59.4 (19)
Higher dose	40.6 (13)

CRT, Chemoradiotherapy; Gy,Gray.

TABLE 2 | Frequency of true positive, false positive, true negative, and false negative macroscopic findings during endoscopy.

Surgical results			
	Positive	**Negative**	**Total**
Positive	18	10	28
Negative	1	3	4
Total	19	13	32

Macroscopic Findings

Examination of the diagnostic accuracy of biopsy during endoscopy after CRT showed that the frequency of true positive, false positive, true negative, and false negative microscopic findings in biopsy specimens were 13, 9, 4, and 6, respectively (**Table 3**). The sensitivity and specificity of endoscopic biopsy findings after CRT in predicting pathological response after esophagectomy were 68.4 and 30.7%, respectively. Also, the positive and negative predictive values of this method in predicting the pathologic complete response are 59 and 40%, respectively. Overall, the accuracy of microscopic findings from endoscopic biopsy after CRT in predicting the pathologic complete response after esophagectomy is 53.1%.

DISCUSSION

In this study, we sought to answer the question of whether it is possible to rely on endoscopic and biopsy findings after neoadjuvant CRT to ensure the response of esophageal SCC, follow up the patients based on these findings, and not recommend surgery. Numerous studies have been conducted in this field. For example, in a study by Yang et al., 183 patients with locally advanced esophageal and gastroesophageal junction carcinoma who underwent neoadjuvant therapy and then surgery were retrospectively evaluated. Of these patients, 65 cases underwent esophageal biopsy after CRT, which reported remaining cancer cells in the biopsy specimen of 20% (13 patients), and in 52 patients, no remnants of cancer cells were reported. Examining the relationship between esophageal biopsy results after CRT and residual tumor status in esophagectomy specimens, the results showed that there was no significant difference in cancer residual status in esophagectomy specimens between patients with positive biopsy and patients with negative biopsy. The PPV of esophageal biopsy after CRT was 92.3% and the NPV was 23.1%. The sensitivity of endoscopic biopsy after neoadjuvant treatment was 23.1% and its specificity was 92.3%. This study concluded that endoscopic biopsy after neoadjuvant therapy is a specific but not sensitive method for predicting post-esophagectomy cancer remnants (11).

TABLE 3 | Frequency of true positive, false positive, true negative, and false negative of microscopic.

Microscopic findings Surgical results	Positive	Negative	Total
Positive	13	9	22
Negative	6	4	10
Total	19	13	32

Schneider et al. studied the response of esophageal cancer to neoadjuvant CRT by endoscopy, biopsy, and endoscopic ultrasonography. Ninety-one patients were evaluated. The results of re-biopsy evaluation after neoadjuvant CRT showed that 69.7% had no evidence of tumor cells (negative result) and 30.3% had tumor cells (positive result) in at least one sample. The evaluation of response by re-biopsy had a sensitivity of 36.4%, specificity of 100%, PPV of 100%, NPV of 23.9%, and accuracy of 47% in predicting histopathological response. This study concludes that the use of endoscopy and re-biopsy is not accurate enough to predict the histopathological regression after neoadjuvant CRT (12).

In their study, Sarkaria et al. examined 443 patients with esophageal cancer from 1996 to 2007. These patients received neoadjuvant CRT and then underwent esophagectomy. From these, 221 patients underwent endoscopy and 156 patients underwent endoscopic biopsy after neoadjuvant treatment. Of the 156 patients who underwent biopsy, 75.6% were negative and 24.4% were positive for malignancy. Patients who had a positive biopsy result after neoadjuvant treatment had more macroscopic remnants of endoscopy than patients with a negative biopsy. The results of this study showed that patients with a negative biopsy result were more likely to have a pathologic complete response. The sensitivity of endoscopic biopsy after CRT in predicting the pathologic complete response was 30.8% and its specificity was 94.9%. The positive and negative predictive values of this method were 94.7 and 31.4%, respectively. This study concludes that a negative endoscopic biopsy is not a useful predictor of the pathologic complete response following CRT, lymph node status, and survival (13).

In a study by Miyata et al. on the prognostic value of endoscopic biopsy findings after induction therapy with or without surgery for esophageal cancer, 169 patients who underwent endoscopic biopsy following induction CRT were evaluated. Of these, 123 underwent neoadjuvant CRT and then surgery. The study of the relationship between endoscopic biopsy after neoadjuvant CRT with pathologic outcome and survival showed that the biopsy result was negative in 50% of cases (61 out of 123 patients). Sensitivity, specificity, PPV, and NPV of endoscopic biopsy following neoadjuvant CRT in predicting pathologic complete response were 58.9, 78.6, 90.3, and 36.1%, respectively (14).

The findings of this study showed that the accuracy of endoscopic and biopsy findings after CRT in examining the tumor response to neoadjuvant treatment was more than 50%. Positive results of these methods on tumor remnants are more reliable than negative results. Because the response rate to neoadjuvant therapy in the involved lymph nodes in these evaluations cannot be assessed, the sensitivity, specificity, positive, and negative predictive values of these studies alone are unreliable and there is a need for additional studies. **Table 4** compares the results of this study with those mentioned in the study of endoscopic biopsy after neoadjuvant treatment. This study is the first evaluation in northeastern Iran with the aim of finding a diagnostic method to predict the response of esophageal cancer to neoadjuvant therapies other than esophagectomy. This study is limited to patients with esophageal SCC, so generalizing its results to patients with esophageal adenocarcinoma is limited. Another limitation of this study is the small sample size, the main reason being the lack of referral of patients for esophagectomy after CRT.

TABLE 4 | Comparison of microscopic findings value of endoscopic biopsy after CRT in several studies.

Study	Patient Number	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
Yang	65	92.3	23.1	23.1	92.3
Schneider	91	100	23.9	36.4	100
Sarkaria	156	94.7	31.4	30.8	94.9
Miyata	123	90.3	36.1	58.9	78.6
Our Study	32	59	40	68.4	30.7

CONCLUSION

The NPV of endoscopic observations and biopsy after neoadjuvant CRT is 75 and 40%, respectively, and the PPV of these two methods is about 64 and 59%, respectively. So, these two methods alone are inappropriate tools for assessing the pathologic complete response after neoadjuvant treatment of esophageal SCC.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Mashhad University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: ATK. Data curation: SJ and RG. Funding acquisition: ATK. Investigation: RG. Methodology: AET. Project administration: ATK. Resources: ATK. Software: SJ. Supervision: ATK. Validation: AET. Visualization: MJM. Roles/Writing original draft: SJ and AET. Writing—review & editing: ATK and AET. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REFERENCES

1. Radmard AR. Five Common Cancers in Iran. *Arch Iranian Med* (2010) 13 (2):143–6.
2. Sadjadi A, Marjani H, Semnani S, Nasseri-Moghaddam S. Esophageal Cancer in Iran: A Review. *Middle East J Cancer* (2010) 1(1):5–14. doi: 10.1016/s0093-7754(01)90086-7
3. Castro C, Bosetti C, Malvezzi M, Bertuccio P, Levi F, Negri E, et al. Patterns and Trends in Esophageal Cancer Mortality and Incidence in Europe (1980–2011) and Predictions to 2015. *Ann Oncol* (2014) 25(1):283–90. doi: 10.1093/annonc/mdt486
4. Kidane B, Coughlin S, Vogt K, Malthaner R. Preoperative Chemotherapy for Resectable Thoracic Esophageal Cancer. *Cochrane Library* (2015) 2015(5): CD001556. doi: 10.1002/14651858.CD001556.pub3
5. Nemati S, Hadji M, Seifi P, Shirkhoda M, Rajabpour MV, Rajaei N, et al. Improvement in the Survival of Esophageal Cancer Patients at Cancer Institute of Iran After Implementation of the Neo-Adjuvant Chemo-Radiation: Retrospective Cohort Study. *Middle East J Cancer* (2021) 84185:1205. doi: 10.30476/MEJC.2021.84185.1205
6. Bollschweiler E, Holscher AH, Metzger R. Histologic Tumor Type and the Rate of Complete Response After Neoadjuvant Therapy for Esophageal Cancer. *Future Oncol* (2010) 6(1):25–35. doi: 10.2217/fon.09.133
7. Kim MK, Ryu JS, Kim SB, Ahn JH, Kim SY, Song HY, et al. Value of Complete Metabolic Response by 18F-Fluorodeoxyglucose-Positron Emission Tomography in Oesophageal Cancer for Prediction of Pathologic Response and Survival After Preoperative Chemoradiotherapy. *Eur J Cancer* (2007) 43:1385–91. doi: 10.1016/j.ejca.2007.04.001
8. Cheedella NKS, Suzuki A, Xiao L, Hofstetter WL, Maru DM, Taketa T, et al. Association Between Clinical Complete Response and Pathological Complete Response After Preoperative Chemoradiation in Patients With Gastroesophageal Cancer: Analysis in a Large Cohort. *Ann Oncol* (2013) 24:1262–6. doi: 10.1093/annonc/mds617
9. Liu S-L, Xi M, Yang H, Yang YD, Wu YJ, Zhao L, et al. Is There a Correlation Between Clinical Complete Response and Pathological Complete Response After Neoadjuvant Chemoradiotherapy for Esophageal Squamous Cell Cancer? *Ann Surg Oncol* (2016) 23:273–81. doi: 10.1245/s10434-015-4764-0
10. Brücher BL, Weber W, Bauer M, Fink U, Avril N, Stein HJ, et al. Neoadjuvant Therapy of Esophageal Squamous Cell Carcinoma: Response Evaluation by Positron Emission Tomography. *Ann Surge* (2001) 233(3):300. doi: 10.1097/00000658-200103000-00002
11. Yang Q, Cleary K, Yao J, Swisher S, Roth J, Lynch P, et al. Significance of Post-Chemoradiation Biopsy in Predicting Residual Esophageal Carcinoma in the Surgical Specimen. *Dis Esophagus* (2004) 17(1):38–43. doi: 10.1111/j.1442-2050.2004.00355.x
12. Schneider PM, Metzger R, Schaefer H, Baumgarten F, Vallbohmer D, Brabender J, et al. Response Evaluation by Endoscopy, Rebiopsy, and Endoscopic Ultrasound Does Not Accurately Predict Histopathologic Regression After Neoadjuvant Chemoradiation for Esophageal Cancer. *Ann Surge* (2008) 248(6):902–8. doi: 10.1097/SLA.0b013e31818f3afb
13. Sarkaria IS, Rizk NP, Bains MS, Tang LH, Ilson DH, Minsky BI, et al. Post-Treatment Endoscopic Biopsy is a Poor-Predictor of Pathologic Response in Patients Undergoing Chemoradiation Therapy for Esophageal Cancer. *Ann Surge* (2009) 249(5):764–7. doi: 10.1097/SLA.0b013e3181a38e9e
14. Miyata H, Yamasaki M, Takiguchi S, Nakajima K, Fujiwara Y, Konishi K, et al. Prognostic Value of Endoscopic Biopsy Findings After Induction Chemoradiotherapy With and Without Surgery for Esophageal Cancer. *Ann Surge* (2011) 253(2):279–84. doi: 10.1097/SLA.0b013e318206824f

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Local Ablative Treatment Improves Survival in ESCC Patients With Specific Metastases, 2010–2016: A Population-Based SEER Analysis

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Background: We aimed to explore the role of local ablative treatment (LAT) in metastatic esophageal squamous cell cancer (ESCC) patients who received chemotherapy and identify patients who will most likely benefit.

Methods: We analyzed data of metastatic ESCC patients from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2016. The chi-square test was used to evaluate the unadjusted clinicopathological categorical variables between the two groups. Univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors of overall survival. Propensity score matching (PSM) was used to adjust the differences between the two groups.

Results: Overall, 720 metastatic ESCC patients treated with chemotherapy were analyzed in this study; 63.2% of patients (n = 455) received LAT, including radiotherapy (n = 444), primary site surgery (n = 12), or lymph node dissection (n = 27). Gender (HR = 1.220, 95% CI: 1.024–1.453, p = 0.026), bone metastases (HR = 1.559, 95% CI: 1.292–1.882, p < 0.001), and liver metastases (HR = 1.457, 95% CI: 1.237–1.716, p < 0.001) were independent prognostic factors in the entire population. However, LAT was not an independent prognostic factor. Further subgroup analyses showed that LAT improved OS from 8.0 months to 10.0 months in patients with metastases other than bone/liver (HR = 0.759, 95% CI: 0.600–0.961, p = 0.022). LAT was not a prognostic factor in patients with bone/liver metastases (HR = 0.995, 95% CI: 0.799–1.239, p = 0.961). After PSM, the median OS was 8.0 months (95% CI: 7.2–8.8 months) and patients who received LAT had a better OS than patients without LAT (HR = 0.796, 95% CI: 0.653–0.968, p = 0.023). Patients with metastases other than bone/liver could benefit from LAT compared with those with bone/liver metastases.

Conclusions: Our study indicated that metastatic ESCC patients with metastases other than bone/liver could derive additional benefit from LAT with systemic chemotherapy.

Keywords: esophageal squamous cell cancer, local ablative treatment, chemotherapy, metastases, radiotherapy, surgery, prognosis, SEER

INTRODUCTION

Esophageal cancer (EC) is the seventh most frequent cancer and had 544,076 estimated new cases of cancer deaths worldwide in 2020, according to the GLOBOCAN database (1). Esophageal squamous cell cancer (ESCC) accounts for more than 90% of EC in Asia and is closely associated with having hot food or water and alcohol consumption (2). About 20.0% of patients present with stage IV at the time of diagnosis (3). Chemotherapy was the standard treatment before the appearance of novel systemic therapy, such as immunotherapy and target therapies (4–6). However, response rates to chemotherapy alone ranged from 20% to 40%, and the median survival time was only approximately 8 months (7). So far, clinical trials have reported that immune checkpoint inhibitors, like programmed death ligand-1 (PD-L1) inhibitors or programmed death (PD-1) inhibitors, could prolong the median progression-free survival (PFS) time and even median overall survival (OS) time in advanced ESCC patients compared with chemotherapy (8–13).

However, local therapy is not a typical first-line treatment for metastatic ESCC patients. The common distant metastatic sites include lung, liver, bone, brain, adrenal glands, or distant lymph nodes (14). Many metastases are suitable for radiation, surgery, or other local therapies. Previous studies reported that local ablative therapy (LAT) to the primary tumor or metastatic sites could relieve the symptoms of obstructions, subsequent malnutrition, chronic bleeding, or pains in metastatic ESCC patients (12, 15, 16). We wonder if the addition of LAT to chemotherapy could improve the survival time of metastatic ESCC patients.

An observational cohort study used data from the National Cancer Database to assess the efficacy of radiotherapy in metastatic EC patients. In this study, 12,683 patients treated with chemotherapy were analyzed, and 3/4 of them were adenocarcinomas. Radiotherapy was performed directly at the primary tumor, and the results showed that definitive dose radiotherapy (≥50.4 Gy) improved median OS compared to chemotherapy alone [11.3 months vs. 8.3 months; hazard ratio (HR) = 0.72, 95% confidence interval (CI): 0.70–0.74, $p < 0.001$] (17). Another retrospective study investigated 461 stage IV ESCC patients with oligometastases (≤3 metastases). Among them, 265 patients were treated with chemotherapy alone, and 196 patients received concurrent chemoradiotherapy (CRT) for all metastases. Patients with concurrent CRT had a superior median PFS (8.7 months vs. 7.3 months, $p = 0.002$) and a trend toward better median OS (16.8 months vs. 14.8 months, $p = 0.056$) compared to those receiving chemotherapy alone (18). The latest retrospective study analyzed 126 advanced ESCC patients and found that CRT provided survival benefit to patients with distant metastasis. The CRT group had a greater median PFS (9.9 months vs. 4.0 months, $p = 0.0032$) and longer median OS (12.9 months vs. 9.3 months, $p = 0.029$) (19).

As for surgery, a retrospective investigation analyzed 96 stage IV EC patients treated with neoadjuvant chemotherapy followed by CRT, with or without surgery. Patients who had surgery had a more satisfying disease-free survival (DFS) (14.6 months vs. 5.9 months, $p = 0.021$) and a better median OS [NR (not reached) vs. 20 months, $p = 0.001$] (20). Meanwhile, another retrospective research included 34 advanced ESCC patients with concurrent CRT and reported that the addition of surgery improved median survival time (MST) from 5.0 months to 11.0 months (HR = 3.857, 95% CI: 1.142–13.024, $p = 0.030$) (21).

Hence, aggressive LAT added to palliative chemotherapy may improve prognosis in metastatic ESCC patients. However, previous studies are almost retrospective studies with a limited number of enrolled patients. Our study analyzed the large-scale population from the SEER database to clarify the potential benefit of LAT and identify other prognostic factors in metastatic ESCC. Patients who will most likely benefit were also uncertain. We further studied the difference in patients with different metastatic sites to identify the patients who benefit most from LAT. Results support clinicians to select the most appropriate treatment and recommend aggressive LAT to proper patients.

MATERIALS AND METHODS

Patient Selection

SEER Stat software (SEER*Stat, v8.3.8) was used to search the data from the Surveillance, Epidemiology, and End Results (SEER) database of metastatic ESCC patients between 2010 and 2016. The inclusion criteria were as follows: (1) adults aged 18 years or older; (2) a pathological diagnosis of primary ESCC according to positive histology; (3) American Joint Committee on Cancer (AJCC) (7th Edition) TNM (tumor, node, metastasis) stage IV; (4) received chemotherapy; (5) complete chemotherapy, radiotherapy, and surgery information; and (6) a record of cancer-related death and OS. The following data were extracted: year of diagnosis, age, gender, race, AJCC (7th Edition) TNM stage, metastases at diagnosis, treatment (including chemotherapy, radiotherapy, and surgery), OS, and LAT (radiotherapy or surgery).

Statistical Methods

SPSS 25.0 (SPSS Inc., USA) was used for statistical analysis. OS time was defined as the time of diagnosis to the date of death or last follow-up. The chi-square test was conducted to analyze the difference in baseline characteristics between every two groups. The Cox proportional hazard regression was used for univariate and multivariate analysis to identify potential prognostic factors. Factors with $p < 0.05$ in univariate analysis were included in the multivariate analysis. The estimated HR and 95% CI were calculated. Propensity score matching (PSM) was used to account for differences in patient characteristics among the two groups. The Kaplan–Meier method was used to create survival curves, calculate the median survival time, and compare prognosis between groups with the log-rank p test. p-values of <0.05 indicate statistical significance.

RESULTS

Patient Characteristics

We identified 720 metastatic ESCC patients treated with chemotherapy. The baseline characteristics are listed in

Table 1. Patients were diagnosed between 2010 and 2015. A total of 139 patients were diagnosed in 2010, 114 patients were diagnosed in 2011, 111 patients were diagnosed in 2012, 124 patients were diagnosed in 2013, 109 patients were diagnosed in 2014, and 123 patients were diagnosed in 2015. The median age at diagnosis of the entire population was 64 years (range: 39–93 years), and most patients (83.1%) were younger than 70 years old. Male was the main gender type (73.6%), and principal patients were white (59.9%). A total of 427 (59.3%) patients were T1–2, and 506 (70.3%) patients had positive lymph nodes. All patients were stage IV (M1) at the time of diagnosis. Lung metastases were the most common, followed by liver metastases and bone metastases (n = 277, 233, and 145, respectively). Of these, only 18 patients had brain metastases. Other metastases and the metastases numbers of each patient were not provided.

Of this population, 63.2% of patients (n = 455) received LAT, including radiotherapy (n = 444), primary site surgery (n = 12), or lymph node dissection (n = 27). There were no significant differences in the distributions of diagnosis year, age, gender, race, bone metastases, and lung metastases between the two groups ($p > 0.05$ for all). However, T stage ($p < 0.001$), N stage ($p = 0.039$), brain metastases ($p = 0.005$), and liver metastases ($p < 0.001$) were associated with LAT usage (**Table 1**). Thus, patients with T3–4, N+, brain metastases, and without liver metastases are more inclined to receive LAT.

TABLE 1 | The correlation between clinical parameters and LAT use.

		LAT (n = 455)	Non-LAT (n = 265)	*P*
Year of diagnosis				
2010	139 (19.3%)	92	47	0.148
2011	114 (15.8%)	75	39	
2012	111 (15.4%)	67	44	
2013	124 (17.3%)	67	57	
2014	109 (15.1%)	68	41	
2015	123 (17.1%)	86	37	
Age				
Median (range)	64 (39–93)	63 (39–93)	64 (39–91)	
<70	598 (83.1%)	378	220	0.984
≥70	122 (16.9%)	77	45	
Gender				
Male	530 (73.6%)	335	195	0.990
Female	190 (26.4%)	120	70	
Race				
White	431 (59.9%)	273	158	0.217
Black	201 (27.9%)	120	81	
Others	88 (12.2%)	62	26	
T				
T1–2	427 (59.3)	249	178	<0.001
T3–4	293 (40.7)	206	82	
N				
N0	214 (29.7%)	123	91	0.039
N+	506 (70.3%)	332	174	
Metastases at diagnosis				
Bone metastases	145 (20.1%)	96	49	0.400
No bone metastases	575 (79.9%)	359	216	
Brain metastases	18 (2.5%)	17	1	0.005
No brain metastases	702 (97.5%)	438	264	
Liver metastases	233 (32.4%)	104	129	<0.001
No liver metastases	487 (67.6%)	351	136	
Lung metastases	277 (38.5%)	179	98	0.530
No lung metastases	443 (61.5%)	276	167	

Univariate and Multivariate Analyses in Entire Population

Results of univariate analysis in the entire population are shown in **Figure 1A**. Univariate analysis specified that gender ($p = 0.008$), bone metastases ($p < 0.001$), liver metastases ($p < 0.001$), and LAT ($p = 0.005$) were associated with OS in metastatic ESCC patients receiving chemotherapy. The multivariate analysis identified that gender (HR = 1.220, 95% CI: 1.024–1.453, $p = 0.026$), bone metastases (HR = 1.559, 95% CI: 1.292–1.882, $p < 0.001$), and liver metastases (HR = 1.457, 95% CI: 1.237–1.716, $p < 0.001$) were independent prognostic factors in the entire population. However, LAT was not an independent prognostic factor.

Univariate and Multivariate Analyses in Patients With Different Metastatic Sites

To further clarify the role of LAT, we divided patients into two groups according to the existence of bone or liver metastases at diagnosis. A total of 336 patients had bone/liver metastases, and 384 patients had metastases other than bone/liver. The clinical characteristics are compared in **Table 2**.

There were no significant differences in the distributions of diagnosis year, race, and brain metastases between the two groups ($p > 0.05$ for all). Patients with bone/liver metastases were more likely to be male ($p = 0.013$), with T1–2 ($p < 0.001$), N0 ($p = 0.047$), without lung metastases ($p = 0.005$), and had less chance to receive LAT ($p < 0.001$) compared with patients with other metastases (**Table 2**).

Univariate analysis of subgroup with bone/liver metastases revealed that T stage (HR = 0.784, 95% CI: 0.622–0.989, $p = 0.040$) was the only prognostic factor, and LAT was not associated with OS (HR = 0.995, 95% CI: 0.799–1.239, $p = 0.961$) (**Figure 1B**). However, univariate analysis of the subgroup with metastases other than bone/liver metastases observed that LAT was a significant prognostic factor (HR = 0.759, 95% CI: 0.599–0.961, $p = 0.022$) (**Figure 1C**). The multivariate analysis further indicated that LAT improved OS in patients with metastases other than bone/liver metastases (HR = 0.759, 95% CI: 0.600–0.961, $p = 0.022$).

Survival Outcomes in the Matched Patients

As age, gender, race, T stage, N stage, and metastatic site were important factors according to the multivariate analyses, we further made a PSM with these factors between the "LAT" group and the "non-LAT group". After PSM, each group had 215 patients and the two groups were well balanced ($p > 0.05$ for all) (**Table 3**).

The Kaplan–Meier survival curve showed that the median OS was 8.0 months (95% CI: 7.2–8.8 months) in all the patients after PSM. The OS of LAT and non-LAT groups had a significant difference [8.0 months (95% CI: 6.7–9.3 months) vs. 8.0 months (95% CI: 7.0–8.0 months), $p = 0.017$] (**Figure 2A**). Cox proportional hazard regression analysis found that patients

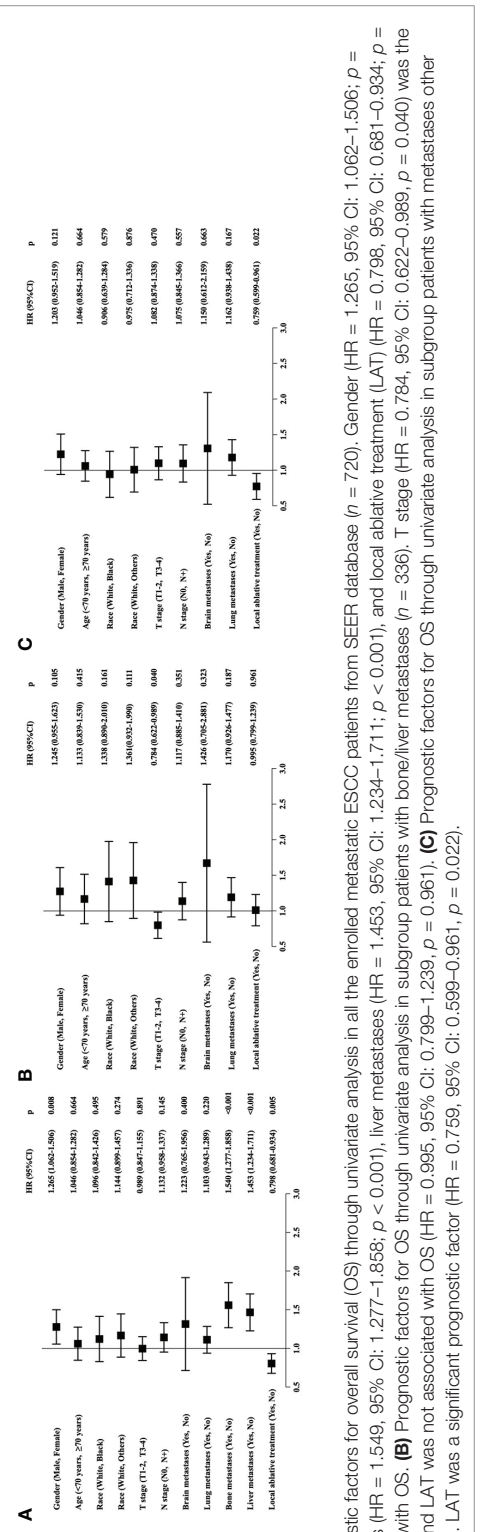

FIGURE 1 | **(A)** Prognostic factors for overall survival (OS) through univariate analysis in all the enrolled metastatic ESCC patients from SEER database (n = 720). Gender (HR = 1.265, 95% CI: 1.062–1.506; p = 0.008), bone metastases (HR = 1.549, 95% CI: 1.277–1.858; p < 0.001), liver metastases (HR = 1.453, 95% CI: 1.234–1.711; p < 0.001), and local ablative treatment (LAT) (HR = 0.798, 95% CI: 0.681–0.934; p = 0.005) were associated with OS. **(B)** Prognostic factors for OS through univariate analysis in subgroup patients with bone/liver metastases (n = 336). T stage (HR = 0.784, 95% CI: 0.622–0.989, p = 0.040) was the only prognostic factor, and LAT was not associated with OS (HR = 0.995, 95% CI: 0.799–1.239, p = 0.961). **(C)** Prognostic factors for OS through univariate analysis in subgroup patients with metastases other than bone/liver (n = 384). LAT was a significant prognostic factor (HR = 0.759, 95% CI: 0.599–0.961, p = 0.022).

TABLE 2 | The clinical parameters between groups with bone/liver metastases or other metastases.

		With bone/liver metastases (n = 336)	With metastases other than bone/liver (n = 384)	P
Year of diagnosis				0.338
2010	139	53	86	
2011	114	58	56	
2012	111	55	56	
2013	124	61	63	
2014	109	50	59	
2015	123	59	64	
Age				
Median (range)	64 (39–93)	59 (39–91)	61 (41–93)	
<70	598	283	315	0.433
≥70	122	53	69	
Gender				
Male	530	262	268	0.013
Female	190	74	116	
Race				
White	431	208	223	0.179
Black	201	95	106	
Others	88	33	55	
T				
T1–2	427	223	204	<0.001
T3–4	293	113	180	
N				
N0	214	112	102	0.047
N+	506	224	282	
Metastases at diagnosis				
Brain metastases	18	8	10	0.848
No brain metastases	702	328	374	
Lung metastases	277	111	166	0.005
No lung metastases	443	225	218	
LAT	455	178	277	<0.001
Non-LAT	265	158	107	

who received LAT had a better OS than patients without LAT (HR = 0.796, 95% CI: 0.653–0.968, p = 0.023).

Survival Outcomes in Patients With Different Metastases

To clarify the different role of LAT in patients with different metastatic sites, we further made a PSM according to age, gender, race, T stage, and N stage between the groups "with bone/liver metastases" and "with metastases other than bone/liver". After PSM, data from 594 patients were available for analysis, and characteristics including age, gender, race, T stage, N stage, brain metastases, and lung metastases (p > 0.05 for all) were well balanced between the two groups (**Table 4**).

For the 297 patients with bone/liver metastases, the median OS was 6.0 months (95% CI: 5.1–6.9 months), and the LAT and non-LAT groups had no significant difference (p = 0.903) (**Figure 2B**). Patients with metastases other than bone/liver had a better median OS of 9.0 months (95% CI: 8.0–10.0 months), and patients with LAT improved median OS from 8.0 months to 10.0 months compared with non-LAT patients

TABLE 3 | The clinical parameters of matched LAT and non-LAT groups.

		LAT (*n* = 215)	Non-LAT (*n* = 215)	*P*
Age				
Median (range)	64 (39–91)	64 (41–88)	64 (39–91)	
<70	352	176	176	1.000
≥70	78	39	39	
Gender				
Male	328	166	162	0.650
Female	102	49	53	
Race				
White	272	139	133	0.335
Black	108	48	60	
Others	50	28	22	
T				
T1–2	308	157	151	0.521
T3–4	122	58	64	
N				
N0	126	64	62	0.832
N+	304	151	153	
Metastases at diagnosis				
Bone metastases	87	42	45	0.719
No bone metastases	343	173	170	
Brain metastases	2	1	1	1.000
No brain metastases	428	214	214	
Liver metastases	201	99	102	0.772
No liver metastases	229	116	113	
Lung metastases	151	73	78	0.613
No lung metastases	279	142	137	

($p = 0.010$) (**Figure 2C**). These results also supported the findings of our univariate and multivariate analyses.

DISCUSSION

Metastatic ESCC patients had a poor prognosis, and the 5-year survival rate was no more than 5% (7). LAT to the primary or metastatic sites may be suitable choices that not only relieve symptoms to improve life quality but also prolong the survival time in metastatic ESCC patients (18–21). However, previous studies were mostly retrospective studies with a limited number of patients. Up to now, conclusive results are lacking to affirm the advantages of LAT in metastatic ESCC patients.

Based on the large-scale population from the SEER database, our study calculated a median OS of 8.0 months in metastatic ESCC patients, and patients who received LAT had a superior OS to non-LAT patients (HR = 0.796, 95% CI: 0.653–0.968, $p = 0.023$). Compared with the largest previous study, the multicenter 3JECROG Survey, the median OS in our studies was much lower. The 3JECROG Survey summarized 3,977 ESCC patients who received chemotherapy and definitive radiotherapy at the primary tumor between 2002 and 2018 from nine institutions in China (3); 23.3% of patients ($n = 928$) were stage IV ESCC patients (according to the 6th TNM staging system), and the median OS of stage IVA and IVB patients was 17.2 months (95% CI: 15.0–19.3 months), and 16.6 months (95% CI: 14.7–18.5 months), respectively (3). No difference in OS was observed between stage IVA and stage IVB patients ($p = 0.12$) (3). Furthermore, the survival of patients who received

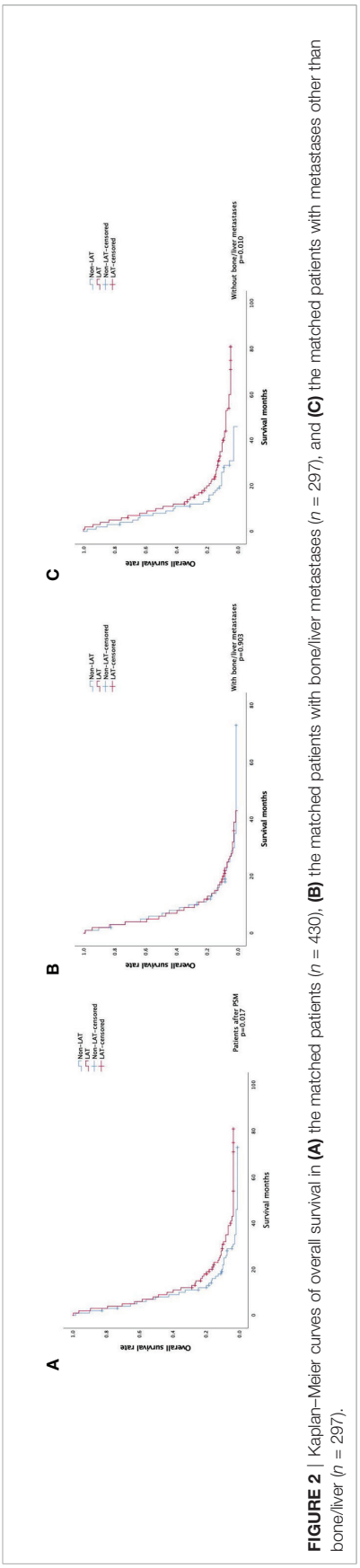

FIGURE 2 | Kaplan–Meier curves of overall survival in **(A)** the matched patients ($n = 430$), **(B)** the matched patients with bone/liver metastases ($n = 297$), and **(C)** the matched patients with metastases other than bone/liver ($n = 297$).

TABLE 4 | The clinical parameters of matched groups with different metastases.

		With bone/liver metastases (*n* = 297)	With metastases other than bone/liver (*n* = 297)	*P*
Age				
Median (range)	64 (39–93)	63 (39–91)	65 (41–93)	
<70	500	251	249	0.822
≥70	94	46	48	
Gender				
Male	452	231	221	0.336
Female	142	66	76	
Race				
White	259	182	177	0.313
Black	161	84	77	
Others	74	31	43	
T				
T1–2	365	184	181	0.800
T3–4	229	113	116	
N				
N0	164	75	89	0.199
N+	430	222	208	
Metastases at diagnosis				
Brain metastases	15	6	9	0.433
No brain metastases	579	291	288	
Lung metastases	214	99	115	0.171
No lung metastases	380	198	182	

concurrent CRT was better than that of patients who received sequential CRT (OS: 23.5 months vs. 17.6 months, $p < 0.001$) (3). Multivariate analysis in the concurrent CRT group found that patients receiving higher radiation dose (≥60 Gy) had a greater OS than those patients receiving low-dose radiotherapy (<50 Gy) (PFS: HR = 0.81, 95% CI: 0.68–0.98, $p = 0.025$; OS: HR = 0.77, 95% CI: 0.63–0.94, $p = 0.009$) (3).

Our study was different from the 3JECROG Survey. First, there were differences in the enrolled population: (1) We used the 7th TNM staging system instead of the 6th staging system in our study, and all the enrolled patients were M1. (2) Patients of the 3JECROG Survey were all Chinese and our study was based on an American database. Second, there were differences in multimodality treatment: (1) For the 3JECROG Survey, all patients received definitive radiotherapy at the primary site. However, radiation sites and doses were not provided in our study. Patients probably received radiotherapy for metastases or primary sites. (2) Some patients in our study received an operation of the primary site or lymph nodes, and the surgery may be very different from standard surgery. (3) Chemotherapy agents were heterogeneous in both studies and may affect the OS results.

The radiation dose of palliative intent for metastatic EC reportedly ranges from 30 to 50 Gy (21–23). However, a higher radiation dose with a definitive aim appears to produce better survival outcomes in metastatic EC patients. The impact of radiation dose was evaluated in another study consisting of 12,683 patients: 57% were treated with chemotherapy alone, 24% were treated with chemotherapy plus palliative dose radiotherapy, and 19% were treated with chemotherapy plus definitive dose radiotherapy (17). Radiotherapy was performed directed to the primary site, and the definitive dose of radiotherapy (≥50.4 Gy) improved median OS compared to those receiving chemotherapy alone (11.3 months vs. 8.3 months; HR = 0.72, 95% CI: 0.70–0.74, $p < 0.001$). However, palliative dose only slightly improved median OS from 8.3 months to 7.5 months (HR = 1.10, 95% CI: 1.07–1.13, $p < 0.001$) (17). The prognostic value of radiotherapy may be influenced by the radiation dose (definitive vs. palliative), sites (primary site vs. metastases; partial vs. all), and sequence (concurrent or sequential with chemotherapy), which need further randomized controlled clinical trials (RCTs) to answer this question.

The strength of our study is that we analyzed data from the SEER database, including a large number of metastatic ESCC patients, demonstrating continuous treatment and survival data for 6 years. LAT was applied in 63.2% of patients ($n = 455$), including radiotherapy ($n = 444$), primary site surgery ($n = 12$), or lymph node dissection ($n = 27$). It reveals the clinician's choice of LAT for metastatic ESCC patients in the real world. Univariate and multivariate analyses of the entire population demonstrated that gender (HR = 1.220, 95% CI: 1.024–1.453, $p = 0.026$), bone metastases (HR = 1.559, 95% CI: 1.292–1.882, $p < 0.001$), and liver metastases (HR = 1.457, 95% CI: 1.237-1.716, $p < 0.001$) were independent prognostic factors.

Moreover, our study is the first to identify the effect of metastatic sites on the benefit of LAT in metastatic ESCC patients. LAT could improve median OS from 8.0 months to 10.0 months in patients with metastases other than bone/liver (HR = 0.759, 95% CI = 0.600–0.961, $p = 0.022$) and has no sense in patients with bone/liver metastases ($p = 0.903$). Another retrospective study of 198 stage IV ESCC patients reported that the CRT group had a longer median OS (14.0 months vs. 11.0 months, $p = 0.007$) than the chemotherapy group (74.5% versus 45.3%, $p = 0.001$). Multivariate analysis identified CRT (CRT vs. chemotherapy: HR = 0.626, 95% CI: 0.437–0.898, $p = 0.013$) and solitary metastasis (solitary vs. multiple metastasis: HR = 0.621, 95% CI: 0.426–0.905, $p = 0.037$) as independent factors for better OS in this study (24). The number of metastases may also be a prognostic factor, but it was not provided from the SEER database in our study. However, the different roles of LAT in ESCC patients with different metastatic sites had not been reported before. Based on our study, metastatic sites may help predict the survival time of patients and determine whether to use LAT or not.

Based on our study, LAT could improve OS in patients with metastases other than bone/liver. However, the prognosis of metastatic ESCC patients remains poor with LAT. Now, PD-1/PD-L1 inhibitors have emerged as a therapeutic option in advanced or metastatic patients. Previous studies reported that radiotherapy could enhance the anti-tumor immunity, break the resistance to immunotherapy, and induce a synergistic effect with PD-1/PD-L1 inhibitors in various cancers (25–27). The ATTRACTION-3 (8), KEYNOTE-181 (9), ESCORT (10), and ESCORT-1st (28) trials have led to remarkable changes in ESCC patients with the introduction of PD-1/PD-L1 inhibitors. So far, the combination of chemotherapy and pembrolizumab was approved as first-line treatment in metastatic ESCC patients by the National Comprehensive Cancer Network

(NCCN). Meanwhile, pembrolizumab or nivolumab alone was preferred as second-line or subsequent therapy. However, very few studies evaluated the efficacy of combining radiotherapy with PD-1/PD-L1 inhibitors in metastatic EC patients. A phase Ib trial, NCT03222440, evaluated concurrent camrelizumab and radiotherapy (60 Gy/30 fr) as first-line therapy in 20 ESCC patients and observed two (11.1%) patients with complete response (CR), 13 (72.2%) with a partial response (PR), and three (16.7%) with a stable disease (SD) (29). More phase III RCTs are needed to further calculate the role of radiotherapy in immunotherapy.

It is worthy to note that our study had potential limitations. First, because of the deficiency of the SEER database, we were incapable of obtaining detailed data, especially the specifics on treatment (chemotherapy regimens, surgery progress, radiation site, dose and sequence, and the time of using LAT). Second, bias was inevitable because the SEER database does not mention possible prognostic factors, such as patient performance status, alcohol drinking history, smoking history, blood inflammatory factors, associated gene expression, and prior treatments. Finally, another limitation of this study is that our findings are not for those with adenocarcinomas or those with early-stage and locally advanced ESCC patients.

In conclusion, our study suggests that male, metastatic ESCC patients with bone/liver metastases may have poorer survival outcomes, and patients with metastases other than bone/liver could derive additional benefits from LAT with systemic chemotherapy. Our study support aggressive LAT in metastatic ESCC patients with metastases other than bone/liver. Due to the lack of convincing results, we recommend aggressive LAT usage be further tested in large-scale RCTs to define patients who will most likely benefit and evaluate the treatment-associated adverse events.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HY and LY designed the study. HG improved study design and supervised this study with HY and LY. HY, KW, YL, and SL collected the data and drafted the manuscript. HY, KW and HG performed the statistical analysis. HG reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. *CA Cancer J Clin* (2020) 70(1):7–30. doi: 10.3322/caac.21590
2. Zhang Y. Epidemiology of Esophageal Cancer. *World J Gastroenterol* (2013) 19(34):5598–606. doi: 10.3748/wjg.v19.i34.5598
3. Li C, Wang X, Wang L, Chen J, Zhang W, Pang Q, et al. Clinical Practice and Outcome of Radiotherapy for Advanced Esophageal Squamous Cell Carcinoma Between 2002 and 2018 in China: The Multi-Center 3JECROG Survey. *Acta Oncol (Stockholm Sweden)* (2021) 60(5):627–34. doi: 10.1080/0284186X.2021.1902564
4. Kakeji Y, Oshikiri T, Takiguchi G, Kanaji S, Matsuda T, Nakamura T, et al. Multimodality Approaches to Control Esophageal Cancer: Development of Chemoradiotherapy, Chemotherapy, and Immunotherapy. *Esophagus* (2021) 18(1):25–32. doi: 10.1007/s10388-020-00782-1
5. Fatehi Hassanabad A, Chehade R, Breadner D, Raphael J. Esophageal Carcinoma: Towards Targeted Therapies. *Cell Oncol (Dordr)* (2020) 43 (2):195–209. doi: 10.1007/s13402-019-00488-2
6. vL HW. Is Chemotherapy for Advanced or Metastatic Oesophageal Squamous Cell Carcinoma No Longer Needed? *Lancet Oncol* (2020) 21 (6):743–5. doi: 10.1016/S1470-2045(20)30182-0
7. Tanaka T, Fujita H, Matono S, Nagano T, Nishimura K, Murata K, et al. Outcomes of Multimodality Therapy for Stage IVB Esophageal Cancer With Distant Organ Metastasis (M1-Org). *Dis Esophagus* (2010) 23(8):646–51. doi: 10.1111/j.1442-2050.2010.01069.x
8. Kato K, Cho BC, Takahashi M, Okada M, Lin CY, Chin K, et al. Nivolumab Versus Chemotherapy in Patients With Advanced Oesophageal Squamous Cell Carcinoma Refractory or Intolerant to Previous Chemotherapy (ATTRACTION-3): A Multicentre, Randomised, Open-Label, Phase 3 Trial. *Lancet Oncol* (2019) 20 (11):1506–17. doi: 10.1016/S1470-2045(19)30626-6
9. Kojima T, Shah MA, Muro K, Francois E, Adenis A, Hsu CH, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. *J Clin Oncol* (2020) 38 (35):4138–48. doi: 10.1200/JCO.20.01888
10. Huang J, Xu J, Chen Y, Zhuang W, Zhang Y, Chen Z, et al. Camrelizumab Versus Investigator's Choice of Chemotherapy as Second-Line Therapy for Advanced or Metastatic Oesophageal Squamous Cell Carcinoma (ESCORT): A Multicentre, Randomised, Open-Label, Phase 3 Study. *Lancet Oncol* (2020) 21(6):832–42. doi: 10.1016/S1470-2045(20)30110-8
11. Zhang B, Qi L, Wang X, Xu J, Liu Y, Mu L, et al. Phase II Clinical Trial Using Camrelizumab Combined With Apatinib and Chemotherapy as the First-Line Treatment of Advanced Esophageal Squamous Cell Carcinoma. *Cancer Commun (Lond)* (2020) 40(12):711–20. doi: 10.1002/cac2.12119
12. van Rossum PSN, Mohammad NH, Vleggaar FP, van Hillegersberg R. Treatment for Unresectable or Metastatic Oesophageal Cancer: Current Evidence and Trends. *Nat Rev Gastroenterol Hepatol* (2018) 15(4):235–49. doi: 10.1038/nrgastro.2017.162
13. Yang H, Wang K, Wang T, Li M, Li B, Li S, et al. The Combination Options and Predictive Biomarkers of PD-1/PD-L1 Inhibitors in Esophageal Cancer. *Front Oncol* (2020) 10:300. doi: 10.3389/fonc.2020.00300
14. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* (2019) 17 (7):855–83. doi: 10.6004/jnccn.2019.0033

15. Levy A, Wagner AD, Chargari C, Moehler M, Verheij M, Durand-Labrunie J, et al. Palliation of Dysphagia in Metastatic Oesogastric Cancers: An International Multidisciplinary Position. *Eur J Cancer* (2020) 135:103–12. doi: 10.1016/j.ejca.2020.04.032
16. Kawamoto T, Nihei K, Sasai K, Karasawa K. Palliative Radiotherapy and Chemoradiotherapy in Stage IVA/B Esophageal Cancer Patients With Dysphagia. *Int J Clin Oncol* (2018) 23(6):1076–83. doi: 10.1007/s10147-018-1324-1
17. Guttmann DM, Mitra N, Bekelman J, Metz JM, Plastaras J, Feng W, et al. Improved Overall Survival With Aggressive Primary Tumor Radiotherapy for Patients With Metastatic Esophageal Cancer. *J Thorac Oncol* (2017) 12 (7):1131–42. doi: 10.1016/j.jtho.2017.03.026
18. Chen Y, Cheng X, Song H, Wu AJ, Ku GY, Lee P, et al. Outcomes of Concurrent Chemoradiotherapy Versus Chemotherapy Alone for Esophageal Squamous Cell Cancer Patients Presenting With Oligometastases. *J Thorac Dis* (2019) 11(4):1536–45. doi: 10.21037/jtd.2019.03.10
19. Li LQ, Fu QG, Zhao WD, Wang YD, Meng WW, Su TS. Chemoradiotherapy Versus Chemotherapy Alone for Advanced Esophageal Squamous Cell Carcinoma: The Role of Definitive Radiotherapy for Primary Tumor in the Metastatic Setting. *Front Oncol* (2022) 12:824206. doi: 10.3389/fonc.2022.824206
20. Wang J, Suri JS, Allen PK, Liao Z, Komaki R, Ho L, et al. Factors Predictive of Improved Outcomes With Multimodality Local Therapy After Palliative Chemotherapy for Stage IV Esophageal Cancer. *Am J Clin Oncol* (2016) 39 (3):228–35. doi: 10.1097/COC.0000000000000066
21. Sakaguchi M, Maebayashi T, Aizawa T, Ishibashi N, Saito T. Clinical Results of Multimodality Therapy for Esophageal Cancer With Distant Metastasis. *J Thorac Dis* (2018) 10(3):1500–10. doi: 10.21037/jtd.2018.03.45
22. Hayter CR H-WC, Paszat L, Youssef YM, Shelley WE, Schulze K. A Prospective Trial of Short-Course Radiotherapy Plus Chemotherapy for Palliation of Dysphagia From Advanced Esophageal Cancer. *Radiother Oncol* (2000) 56(3):329–33. doi: 10.1016/s0167-8140(00)00225-5
23. Burmeister BH, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, et al. Is Concurrent Radiation Therapy Required in Patients Receiving Preoperative Chemotherapy for Adenocarcinoma of the Oesophagus? A Randomised Phase II Trial. *Eur J Cancer* (2011) 47(3):354–60. doi: 10.1016/j.ejca.2010.09.009
24. Lyu J, Li T, Wang Q, Li F, Diao P, Liu L, et al. Outcomes of Concurrent Chemoradiotherapy Versus Chemotherapy Alone for Stage IV Esophageal Squamous Cell Carcinoma: A Retrospective Controlled Study. *Radiat Oncol* (2018) 13(1):233. doi: 10.1186/s13014-018-1183-y
25. He M, Yang T, Wang Y, Wang M, Chen X, Ding D, et al. Immune Checkpoint Inhibitor-Based Strategies for Synergistic Cancer Therapy. *Adv Healthc Mater* (2021) 10(9):e2002104. doi: 10.1002/adhm.202002104
26. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and Immunotherapy: A Beneficial Liaison? *Nat Rev Clin Oncol* (2017) 14 (6):365–79. doi: 10.1038/nrclinonc.2016.211
27. Ko EC, Raben D, Formenti SC. The Integration of Radiotherapy With Immunotherapy for the Treatment of Non-Small Cell Lung Cancer. *Clin Cancer Res* (2018) 24(23):5792–806. doi: 10.1158/1078-0432.CCR-17-3620
28. Luo H, Lu J, Bai Y, Mao T, Wang J, Fan Q, et al. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial. *JAMA* (2021) 326 (10):916–25. doi: 10.1001/jama.2021.12836
29. Doi T, Piha-Paul SA, Jalal SI, Saraf S, Lunceford J, Koshiji M, et al. Safety and Antitumor Activity of the Anti-Programmed Death-1 Antibody Pembrolizumab in Patients With Advanced Esophageal Carcinoma. *J Clin Oncol* (2018) 36(1):61–7. doi: 10.1200/JCO.2017.74.9846

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