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Anlotinib Combined with Chemoradiotherapy Improves Survival in Postoperative Lymph Node Recurrent Esophageal Squamous Cell Carcinoma: A Propensity Score-Matched Real-World Study

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ABSTRACT

Anlotinib, a multitarget tyrosine kinase inhibitor, has demonstrated notable activity against esophageal squamous cell carcinoma (ESCC). This study summarizes real-world outcomes comparing chemoradiotherapy (CRT) combined with anlotinib versus CRT alone in individuals who developed lymph node relapse following curative surgery. Records of patients with nodal recurrence treated with CRT with or without anlotinib between January 2017 and December 2019 were retrospectively reviewed. Tumor response, overall survival (OS), progression-free survival (PFS), and treatment-associated toxicity profiles were examined. Propensity score matching (PSM) was applied to equalize baseline factors. Among 291 patients, 76 received CRT plus anlotinib and 215 underwent CRT alone. After PSM, 68 patients from each group were included. The combination group had higher partial response (58.8% vs 41.2%, $p = 0.04$) and objective response (86.7% vs 61.8%, $p = 0.001$) rates. OS (3-year OS, 42.7% vs 23.5%, $p = 0.008$) and PFS (12-month PFS, 47.1% vs 32.4%, $p = 0.026$) were also superior with anlotinib. Multivariate evaluation confirmed treatment regimen ($p = 0.007$) as an independent OS predictor. Rates of grade 3–4 adverse reactions were not significantly different (39.5% vs 30.7%, $p = 0.162$). Adding anlotinib to CRT yielded better survival without increasing high-grade toxicity in postoperative ESCC patients with lymph node recurrence.

Keywords: Esophageal squamous cell carcinoma, Nodal recurrence, Chemoradiotherapy, Anlotinib, Survival

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Introduction

ESCC remains a major cancer burden in South-East Asia and Africa [1]. China reported roughly 235000 new ESCC diagnoses in 2017, representing 49.6% of all global cases [2]. This disease often behaves aggressively, frequently spreading to regional lymph nodes and involving nearby organs. Despite ongoing advancements in perioperative management and neoadjuvant therapy, postoperative outcomes remain poor because recurrent or metastatic disease is common. Overall, 43–53% of patients eventually develop supraclavicular or regional lymphatic relapse, usually within 10–12 months after surgery [3–6]. Current options for recurrent or metastatic ESCC include chemotherapy, CRT, and immunotherapy. Cisplatin-based CRT, however, still produces unsatisfactory results, with a median OS of 17 months and a 3-year OS of less than 11% [7]. Consequently, identifying more effective strategies is critical.

Angiogenesis plays a pivotal role in tumor maintenance and metastasis. Anti-angiogenic approaches have been beneficial across several malignancies, including hepatocellular carcinoma, NSCLC, and ESCC [8–10]. Anlotinib is an oral multitarget inhibitor affecting VEGFR 1–3, FGFR 1–4, PDGFR α/β, c-Kit, and Ret [11, 12]. Preclinical results indicate that it suppresses proliferation, triggers G2/M arrest, and promotes apoptosis in intrahepatic cholangiocarcinoma lines [13]. In a phase II trial, monotherapy with anlotinib (12 mg daily) extended PFS to 3.02 months compared with 1.41 months in the placebo cohort for advanced/metastatic ESCC [14]. Additional research

shows survival gains when anlotinib is paired with chemotherapy in NSCLC, recurrent glioblastoma, and metastatic osteosarcoma [15–17]. A previous multicenter phase II study noted a median OS of 18.53 months with manageable toxicities when anlotinib plus chemotherapy was used in recurrent or advanced ESCC [18]. Based on such evidence, the 2022 Chinese Society of Clinical Oncology guidelines recommend this combination for first-line or later treatment of metastatic ESCC. While accumulating data support the drug's antitumor potential in many cancers, its integration with CRT in the setting of postoperative lymph node recurrence has not yet been documented.

Therefore, the present study sought to compare survival outcomes and safety between CRT plus anlotinib and CRT alone in patients who developed lymph node recurrence after radical surgical treatment.

Materials and Methods

Patients

Medical files from individuals with recurrent ESCC treated with CRT with or without anlotinib at Huai'an First People's Hospital from January 2017 to December 2019 were reviewed. Inclusion criteria were: primary ESCC treated with R0 resection (with ≥12 months since prior radiotherapy when applicable), Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2, age between 20 and 75 years, recurrence occurring in supraclavicular, mediastinal, or abdominal lymph nodes, and no prior exposure to targeted agents. Exclusion criteria included: esophageal fistula, active upper-GI bleeding, current infection, anastomotic recurrence, distant metastasis, incomplete data, or loss during follow-up. Patients with other cancers or severe dysfunction of cardiac, hepatic, pulmonary, renal, or hematologic systems were also excluded. Postoperative staging followed the 7th UICC TNM classification. Participants were assigned to the CRT-alone group or the CRT plus anlotinib group based on the therapy they actually received.

This study adhered to the Declaration of Helsinki and was approved by the ethics committee of Huai'an First Hospital. All patients provided written consent for treatment and follow-up participation.

Treatments

Radiotherapy

Patients were treated with intensity-modulated techniques, receiving a median total dose of 50.4 Gy (range 50–60 Gy) delivered in 1.8–2.0 Gy fractions each day. Only the disease-bearing regions were irradiated. Gross tumor volume (GTV) was outlined using contrast-enhanced CT, and any lymph node measuring ≥1 cm in short axis or appearing PET-positive was incorporated into the GTV. The 2014 IASLC lymph-node map guided nodal region boundaries [19].

A 0.8-cm circumferential margin and 1.5–2.0-cm cranio-caudal margin produced the clinical target volume (CTV). The final planning target volume (PTV) expanded the CTV by 0.5 cm uniformly.

Chemotherapy

Chemotherapy was administered at the same time as radiotherapy. Most individuals (74.2%, 216/291) received combinations based on cisplatin and docetaxel. Within this group, 87 patients were given docetaxel 25 mg/m² plus cisplatin 25 mg/m² weekly for 5–6 weeks, while 119 patients were provided docetaxel 75 mg/m² on day 1 with cisplatin 25 mg/m² on days 1–3 every 3 weeks for 2 cycles. Participants aged 70 years or older followed an S-1 schedule (70 mg/m² twice daily on days 1–14 and 22–36). Approximately 4–5 weeks after CRT ended, up to four cycles of consolidation chemotherapy using the same regimens were offered to those with adequate performance status.

Anlotinib therapy

CRT combined with anlotinib was recommended for patients demonstrating bulky nodal involvement or unfavorable histopathology. Anlotinib (Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Nanjing, China) was started on the first radiotherapy day and taken once daily in 2-weeks-on/1-week-off cycles. Initial dosing (8 mg, 10 mg, or 12 mg) was individualized based on age, tolerance, and body weight. The same dose was continued after CRT as maintenance therapy until disease progression or a 12-month limit. Interruptions were introduced when grade ≥3 toxicities occurred, and therapy was permanently discontinued in cases of unacceptable adverse

effects or progression. Reported problems included hypertension, hand–foot reactions, proteinuria, liver dysfunction, diarrhea, hemoptysis, and hematemesis.

Assessment of toxicity and response

Acute toxicities were monitored during the entire treatment period and for 3 months afterward. Blood counts and biochemical indicators were checked weekly. CT scans and barium swallow studies were repeated every 2 weeks while CRT was ongoing. During anlotinib maintenance, adverse-event assessments occurred every 3 weeks, following NCI-CTCAE v4.0 grading.

Treatment response was evaluated 4–6 weeks post-CRT using contrast-enhanced CT in accordance with RECIST 1.1 criteria. Complete response (CR) required full disappearance of nodal disease; partial response (PR) required at least a 30% decrease in metastatic lymph-node size. The objective response rate (ORR) corresponded to the combined CR and PR proportions.

Follow-up

In the combined-therapy group, response assessments were repeated once every 3 cycles during maintenance. After completion of all treatment, monitoring occurred every 3–6 months for the first 2 years, then annually. Follow-up tests comprised physical exams, CT imaging, routine blood work, and assessment of hepatic, renal, thyroid, and coagulation function. Information was gathered through medical record review or telephone contact. Study censoring occurred on 31 May 2025.

Statistical analysis

Baseline demographic and clinical variables were summarized descriptively. Between-group differences were analyzed using either the χ^2 test or Fisher's exact test. Propensity score matching (PSM) was applied to equalize patient characteristics, using covariates such as age, sex, ECOG performance status, tumor site, histologic grade, primary tumor stage, previous treatments, recurrence location, largest nodal diameter, chemotherapy plan, and radiation dose. Matching was done 1:1 by nearest-neighbor selection without replacement.

Overall survival (OS) and progression-free survival (PFS) were calculated from the start of CRT until death, radiologic progression/recurrence, or last contact. Kaplan–Meier estimates were used for survival curves. Variables showing $p < 0.05$ in univariate testing were included in the multivariate model. A two-sided $p < 0.05$ was regarded as statistically significant. All analyses, including PSM, were run using SPSS 22.0.

Results and Discussion

Patient and treatment characteristics

During the period January 2017–December 2019, 291 individuals fulfilled the study requirements and were incorporated into the retrospective dataset. Among them, 217 (74.6%) proceeded only with surgical management, while 74 (25.4%) later underwent adjuvant interventions—specifically 28 radiotherapy, 26 chemotherapy, and 20 concurrent chemoradiotherapy (CRT) sessions.

Lymph node recurrence was confirmed predominantly through CT follow-up (245; 84.2%), whereas PET-CT and histological sampling accounted for 28 (9.6%) and 18 (6.2%) cases, respectively. The nodal regions most often involved included station 2R (95; 32.6%), station 7 (77; 26.5%), and the supraclavicular area (71; 24.4%).

Regarding the quantity of involved nodes, 79 patients (27.1%) had a single affected node, 116 (39.9%) had two, 81 (27.8%) had three, and 15 (5.2%) showed involvement of four or more.

The median interval between primary surgery and the identification of recurrent nodal disease was 11 months (range 2–68 months).

Among the total cohort, 76 patients received CRT combined with anlotinib, while 215 underwent CRT alone. Comparative baseline information for both groups appears in **Table 1**. Individuals in the combination arm tended to be younger ($p = 0.026$), had larger primary lesions ($p = 0.007$), and displayed more poorly differentiated tumors ($p = 0.044$).

Furthermore, consolidation chemotherapy was implemented more often among those given anlotinib ($p = 0.004$). No statistically meaningful differences emerged in sex, physical status (ECOG PS), tumor site, initial tumor stage, previous therapeutic history, systemic treatment regimens, or the delivered radiation dose.

Table 1. Baseline patient and treatment profiles prior to and following PSM.

Characteristic	Before Propensity Score Matching			After Propensity Score Matching		
	CRT + Anlotinib (n=76)	CRT (n=215)	p-value	CRT + Anlotinib (n=68)	CRT (n=68)	p-value
Age			0.026			0.483
< 65 years	47 (61.8%)	101 (47.0%)		43 (63.2%)	39 (57.4%)	
≥ 65 years	29 (38.2%)	114 (53.0%)		25 (36.8%)	29 (42.6%)	
Gender			0.755			1.000
Male	60 (78.9%)	166 (77.2%)		54 (79.4%)	54 (79.4%)	
Female	16 (21.1%)	49 (22.8%)		14 (20.6%)	14 (20.6%)	
ECOG Performance Status			0.553			0.602
0	33 (43.4%)	85 (39.5%)		30 (44.1%)	27 (39.7%)	
1–2	43 (56.6%)	130 (60.5%)		38 (55.9%)	41 (60.3%)	
Tumor Location			0.664			0.916
Upper	6 (7.9%)	14 (6.5%)		6 (8.8%)	6 (8.8%)	
Middle	52 (68.4%)	139 (64.7%)		48 (70.6%)	46 (67.6%)	
Lower	18 (23.7%)	62 (28.8%)		14 (20.6%)	16 (23.5%)	
Differentiation			0.044			0.710
Well	6 (7.9%)	10 (4.7%)		3 (4.4%)	4 (5.9%)	
Moderate	50 (65.8%)	172 (80.0%)		45 (66.2%)	48 (70.6%)	
Poor	20 (26.3%)	33 (15.3%)		20 (29.4%)	16 (23.5%)	
Stage of Primary Tumor			0.703			0.720
IB–IIA	28 (36.8%)	74 (34.4%)		25 (36.8%)	23 (33.8%)	
IIB–III	48 (63.2%)	141 (65.6%)		43 (63.2%)	45 (66.2%)	
Previous Treatment			0.689			0.641
Radiotherapy	8 (10.5%)	20 (9.3%)		6 (8.8%)	7 (10.3%)	
Chemotherapy	8 (10.5%)	18 (8.4%)		8 (11.8%)	5 (7.4%)	
Chemoradiotherapy	4 (5.3%)	16 (7.4%)		3 (4.4%)	4 (5.9%)	
Lymph Node Recurrence Site			0.509			0.855
Supraclavicular	11 (14.5%)	37 (17.2%)		10 (14.7%)	10 (14.7%)	
Mediastinal	42 (55.3%)	127 (59.1%)		37 (54.4%)	41 (60.3%)	
Abdominal	6 (7.9%)	19 (8.8%)		5 (7.4%)	5 (7.4%)	
Multiple	17 (22.4%)	32 (14.9%)		16 (23.5%)	12 (17.6%)	
Maximal Lymph Node Diameter			0.007			0.731
< 3 cm	35 (46.1%)	137 (63.7%)		34 (50.0%)	32 (47.1%)	
≥ 3 cm	41 (53.9%)	78 (36.3%)		34 (50.0%)	36 (52.9%)	
Radiation Dose			0.320			0.729
50–50.4 Gy	45 (59.2%)	141 (65.6%)		38 (55.9%)	40 (58.8%)	
> 50.4 Gy	31 (40.8%)	74 (34.4%)		30 (44.1%)	28 (41.2%)	
Concurrent Chemotherapy			0.430			0.679
Docetaxel + cisplatin	59 (77.6%)	157 (73.0%)		52 (76.5%)	54 (79.4%)	

S-1	17 (22.4%)	58 (27.0%)		16 (23.5%)	14 (20.6%)	
Consolidation Chemotherapy			0.004			0.477
Yes	67 (88.2%)	154 (71.6%)		59 (86.8%)	56 (82.4%)	
No	9 (11.8%)	61 (28.4%)		9 (13.2%)	12 (17.6%)	
Nutritional Support			0.455			0.613
Yes	9 (11.8%)	33 (15.3%)		8 (11.8%)	10 (14.7%)	
No	67 (88.2%)	182 (84.7%)		60 (88.2%)	58 (85.3%)	

Abbreviations: PSM, propensity score matching; ECOG PS, Eastern Cooperative Oncology Group performance status; CRT, chemoradiotherapy.

After performing 1:1 propensity matching, 68 subjects remained in each cohort. Post-matching attributes—demographic and tumor-related—showed no significant imbalance (all $p > 0.4$). Among those receiving combined therapy, 63 of 68 (92.6%) began anlotinib at 12 mg, and 66 (97.1%) completed two full cycles concurrent with CRT. The median exposure to anlotinib was 34 weeks (range 2–52 weeks), with 56 patients (82.4%) receiving more than six cycles.

Tumor response

Seven individuals—two treated with anlotinib plus CRT and five treated with CRT alone—could not be evaluated under RECIST 1.1, as death occurred prior to the first assessment. Before matching, nearly all patients reached a radiation dose of at least 50 Gy, specifically 74 (97.4%) in the combination group and 201 (93.5%) in the CRT group. The addition of anlotinib yielded superior outcomes, with a partial response (PR) rate of 58.1% vs 40.5% ($p = 0.009$) and an ORR of 86.5% vs 69.5% ($p = 0.004$) **(Table 2)**.

Table 2. Response evaluation before and following PSM.

Response	**Before Propensity Score Matching**			**After Propensity Score Matching**		
	CRT + Anlotinib (n=74)	CRT (n=210)	p-value	CRT + Anlotinib (n=68)	CRT (n=68)	p-value
Complete Response (CR)	21 (28.4%)	61 (29.0%)	0.913	19 (27.9%)	14 (20.6%)	0.317
Partial Response (PR)	43 (58.1%)	85 (40.5%)	0.009	40 (58.8%)	28 (41.2%)	0.040
Stable Disease (SD)	9 (12.2%)	47 (22.4%)	0.057	9 (13.2%)	19 (27.9%)	0.034
Progressive Disease (PD)	1 (1.4%)	17 (8.1%)	0.077	0	7 (10.3%)	0.020
Objective Response Rate (ORR)	64 (86.5%)	146 (69.5%)	**0.004**	59 (86.7%)	42 (61.8%)	**0.001**

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate.

Following PSM, radiation completion was universal. The PR advantage persisted (58.8% vs 41.2%, $p = 0.04$) alongside a markedly higher ORR (86.7% vs 61.8%, $p = 0.001$) in the anlotinib combination group. A numerically greater proportion of patients achieved CR, though not significantly different (27.9% vs 20.6%, $p = 0.317$).

Overall survival and progression-free survival (before and after PSM)

Prior to matching, progression occurred in 60 of 76 (78.9%) in the combined group and 191 of 215 (88.8%) in the CRT group. Disease relapse was less frequent with anlotinib ($p = 0.016$). The 6-month PFS was 82.9% in the combination arm versus 67.4% in the CRT-only arm, and the 12-month PFS was 44.7% vs 32.1% **(Figure 1a)**.

At the time of outcome evaluation, 58 patients (76.3%) in the anlotinib cohort and 188 (87.4%) from the CRT group had died. Overall survival favored the addition of anlotinib ($p = 0.006$). The 1-year OS rates were 76.3% vs 62.3%, and the 3-year OS rates were 39.5% vs 25.5%, respectively **(Figure 1b)**.

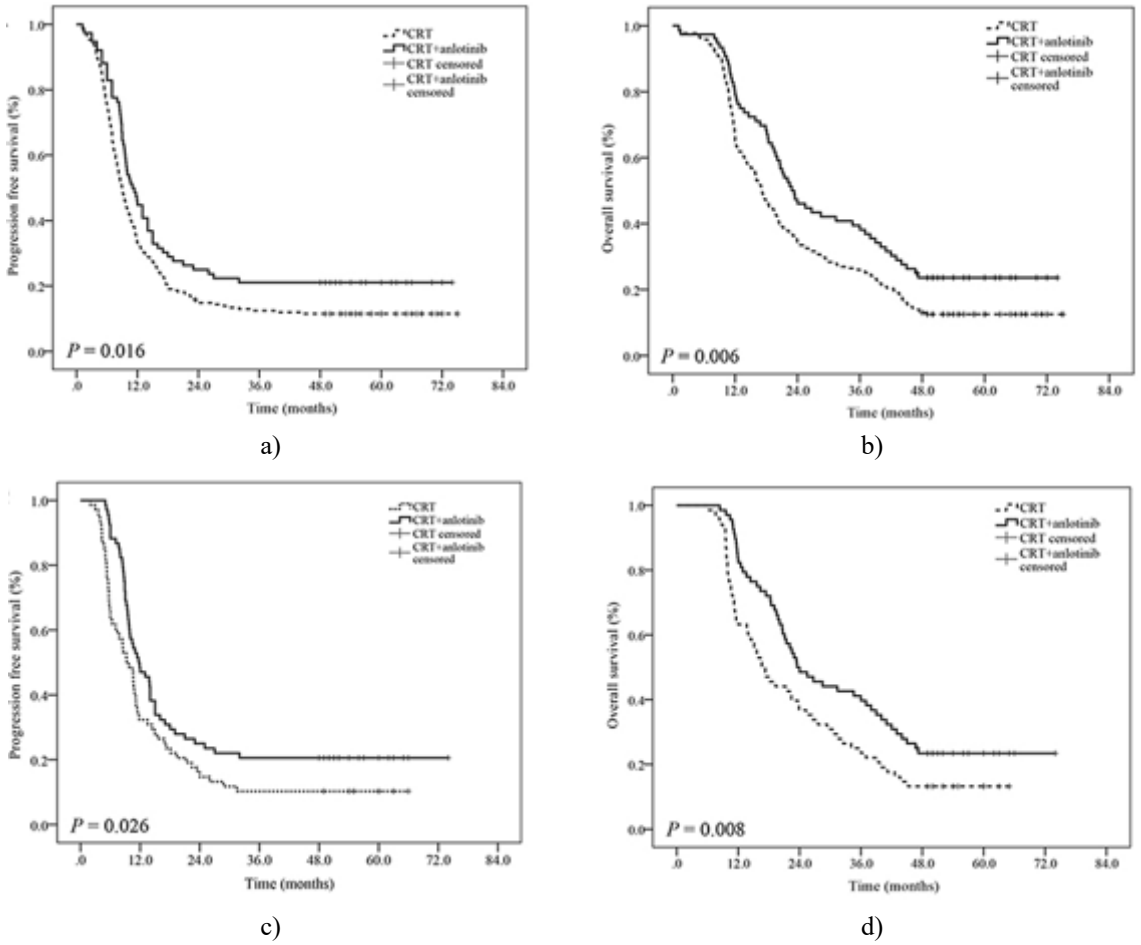

Figure 1. Panels a–d display PFS and OS trends before and after PSM. In both the unmatched and matched datasets, individuals receiving CRT combined with anlotinib maintained superior PFS and OS compared with those treated with CRT alone (all $p < 0.05$).

Following PSM, the differences remained evident: 6-month PFS was 88.2% vs 63.2%, and 12-month PFS was 47.1% vs 32.4% ($p = 0.026$). Likewise, 1-year OS reached 79.4% vs 61.8%, while 3-year OS was 42.7% vs 23.5% ($p = 0.008$) for the combined group **(Figures 1c and 1d)**.

Univariate and multivariate evaluation of factors influencing OS

Potential contributors to OS in the matched sample are detailed in **Table 3**. Several variables showed significant associations on univariate testing, including age ($p = 0.047$), initial tumor stage ($p = 0.043$), extent of nodal recurrence ($p = 0.016$), post-CRT tumor response ($p = 0.039$), and treatment category ($p = 0.009$).

In the multivariate Cox model, three parameters retained significance:

- Number of recurrent lymph nodes (HR 2.023, 95% CI 1.258–3.253, $p = 0.004$)
- Response after CRT (HR 1.771, 95% CI 1.115–2.814, $p = 0.015$)
- Treatment group (HR 0.596, 95% CI 0.408–0.871, $p = 0.007$)

Table 3. Univariate and multivariate Cox results for OS following PSM.

Prognostic Factor	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age						
< 65 years	1 (reference)			1 (reference)		
≥ 65 years	1.471	1.005–2.153	0.047	1.459	0.983–2.165	0.061
Gender						
Male	1 (reference)					

Female	0.830	0.516–1.337	0.444			
ECOG Performance Status						
0	1 (reference)					
1–2	0.912	0.625–1.331	0.634			
Tumor Location						
Upper	1 (reference)					
Middle	0.732	0.378–1.415	0.354			
Lower	0.821	0.394–1.710	0.598			
Differentiation						
Well	1 (reference)					
Moderate	1.026	0.415–2.537	0.956			
Poor	1.393	0.539–3.602	0.493			
Primary Tumor Stage						
IB–IIA	1 (reference)			1 (reference)		
IIB–III	1.516	1.014–2.268	0.043	1.333	0.887–2.002	0.167
Number of Recurrent Lymph Nodes						
Single	1 (reference)			1 (reference)		
Multiple	1.751	1.111–2.760	0.016	2.023	2.258–3.253	0.004
Maximum Lymph Node Diameter						
< 3 cm	1 (reference)					
≥ 3 cm	1.359	0.934–1.977	0.109			
Radiation Dose						
50–50.4 Gy	1 (reference)					
> 50.4 Gy	1.307	0.897–1.904	0.163			
Concurrent Chemotherapy						
Docetaxel + cisplatin	1 (reference)					
S-1	1.151	0.732–1.810	0.541			
Consolidation Chemotherapy						
Yes	1 (reference)					
No	1.471	0.887–2.441	0.135			
Tumor Response After CRT						
Complete Response (CR)	1 (reference)			1 (reference)		
Less than CR	1.573	1.007–2.457	0.039	1.771	1.115–2.814	0.015
Treatment Group						
CRT alone	1 (reference)			1 (reference)		
CRT + Anlotinib	0.609	0.419–0.886	0.009	0.596	0.408–0.871	0.007

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; CRT, chemoradiotherapy; HR, hazard ratio; CI, confidence interval.

Treatment-related toxicity

Grade 3–4 TRAEs occurring in ≥5% of patients are summarized in **Table 4**. In the CRT + anlotinib cohort, higher-grade events included:

- Leukopenia: 23.7% vs 21.9% (p = 0.743)
- Neutropenia: 22.4% vs 20.5% (p = 0.726)
- Anemia: 10.5% vs 8.8% (p = 0.663)
- Nausea/vomiting: 7.9% vs 9.8% (p = 0.629)
- Esophagitis: 7.9% vs 8.4% (p = 0.897)
- Pneumonitis: 3.9% vs 5.1% (p = 0.922)

During CRT, two deaths in the CRT + anlotinib cohort were attributed to pulmonary embolism and gastrointestinal bleeding, while the CRT group experienced five deaths (three from febrile neutropenia, one stroke, and one possible pulmonary embolism).

Table 4. Treatment-related adverse events by group.

Adverse Events (≥ Grade 3)	CRT + Anlotinib (n=76)	CRT alone (n=215)	p-value
Leukopenia	18 (23.7%)	47 (21.9%)	0.743
Neutropenia	17 (22.4%)	44 (20.5%)	0.726
Anemia	8 (10.5%)	19 (8.8%)	0.663
Nausea/Vomiting	6 (7.9%)	21 (9.8%)	0.629
Esophagitis	6 (7.9%)	18 (8.4%)	0.897
Radiation pneumonitis	3 (3.9%)	11 (5.1%)	0.922
Anlotinib-related Adverse Events (Grade 3–4)	**CRT + Anlotinib (n=76)**	**CRT alone (n=215)**	
Hypertension	9 (11.8%)	–	–
Hand-foot syndrome	5 (6.6%)	–	–
Diarrhea	3 (3.9%)	–	–

Notes:
a) TRAEs ≥5% in either arm are listed.
b) Anlotinib-specific events ≥3% in the combination group are included.

Across the full treatment course, 93.4% of patients receiving anlotinib encountered at least one drug-related event, generally grade 1–2. The most common were:

- Hypertension (39; 51.3%)
- Hand-foot syndrome (27; 35.5%)
- Proteinuria (23; 30.3%)
- Hypothyroidism (12; 15.8%)
- Diarrhea (8; 10.5%)

Grade 3–4 rates for these toxicities were 11.8%, 6.6%, and 3.9%, respectively.
A total of six patients required dose reduction to 10 mg (three for hand-foot syndrome, two for diarrhea, one for proteinuria).
No grade 5 events occurred during anlotinib maintenance.
Overall, grade 3–4 TRAEs were somewhat more frequent in the combination group (39.5% vs 30.7%, p = 0.162).
This investigation represents the first reported analysis of CRT combined with anlotinib in individuals experiencing postoperative nodal relapse of ESCC. The findings indicate that adding anlotinib to CRT leads to notable gains in both PFS and OS compared with CRT alone. The toxicity profile was clinically manageable, and no deaths related to anlotinib occurred during maintenance treatment.
After applying PSM, three determinants—nodal burden, CRT response, and treatment strategy—remained significant predictors of OS.
Over the last decade, first-line care for individuals with advanced or metastatic ESCC has typically involved cisplatin given together with either 5-fluorouracil or paclitaxel [20, 21]. Even with these regimens, outcomes remained unsatisfactory: published reports describe ORR values from 9.7% up to 48.6%, and median OS intervals spanning 7–13 months [22–24]. When recurrence occurs only within regional lymph nodes and no distant disease is present, management strategies have included nodal excision, radiotherapy, and combined chemoradiation. Surgical removal of the affected lymph node can improve local tumor control and prolong survival in cases with a single nodal relapse [25], but very few patients are candidates for such procedures. Makino *et al.*, for instance, observed that only 16.7% of those with solitary nodal recurrence were able to undergo surgery [26].
Across earlier investigations evaluating radiotherapy or CRT for postoperative lymph node recurrence in ESCC, the median ORR reported in 10 studies was 75.9% (ranging from 68.8% to 85.0%), and the median 3-year OS was 37.0% (range, 10.5%–56.3%) [7, 27–35]. In one of these analyses, Kawamoto *et al.* tracked 57 patients treated with CRT and documented an ORR of 82.5% together with a 3-year OS of 36.9% after 24 months of median

follow-up.28 Yamashita *et al.* examined 237 cases of recurrent ESCC managed with salvage radiotherapy or CRT and found that CRT offered better overall survival than radiotherapy alone (3-year OS, 39.7% vs 20.8%) [30]. In our investigation, adding anlotinib to CRT yielded longer PFS and OS than CRT by itself. Likewise, the ORR increased from 61.8% to 86.7% with the addition of anlotinib ($p = 0.001$).

Recently, interest has grown in using antiangiogenic agents—either alone or combined with other therapies—for recurrent or advanced ESCC [36–39]. Anlotinib as a single agent has shown an ORR of 8.4% and a median PFS of 3.3 months in previously treated advanced or metastatic disease [40]. Apatinib therapy for chemotherapy-refractory ESCC in the ESO-Shanghai 11 trial achieved an ORR of 7.5% and a median PFS of 3.8 months [37]. In a phase II trial evaluating anlotinib together with paclitaxel and cisplatin as an initial treatment, the regimen resulted in an ORR of 76.1%, a median PFS of 8.38 months with a 12-month PFS of 25.17%, and a median OS of 18.53 months accompanied by a 2-year OS of 37.21% [18]. In comparison, the CRT plus anlotinib arm in our study demonstrated ORR, 12-month PFS, and 3-year OS outcomes of 86.7%, 47.1%, and 42.7%, respectively. The stronger response observed here may reflect cooperative effects between radiotherapy and anlotinib. Supporting this, recent findings indicate that anlotinib can interfere with the repair of radiation-induced DNA double-strand breaks, increase cytosolic dsDNA buildup, and trigger activation of the cGAS/STING pathway, collectively heightening radiosensitivity [41].

Although cytotoxic chemotherapy has historically been the initial approach for advanced or metastatic ESCC, more recent data reveal that combining anti-PD-1 immunotherapy with chemotherapy yields superior survival compared with chemotherapy alone [42–44]. Phase III trials such as ORIENT-15 and JUPITER-06 demonstrated that anti-PD-1 agents (sintilimab or toripalimab) administered with cisplatin plus paclitaxel significantly extended PFS and OS compared with cisplatin plus paclitaxel alone, producing 1-year PFS rates between 27.8% and 38% and 1-year OS rates between 52% and 66% [45, 46]. The therapeutic performance in our cohort exceeded the outcomes documented for sintilimab or toripalimab in these advanced or metastatic ESCC studies.

In the present study, the multivariate evaluation indicated that three variables—the total count of recurrent lymph nodes, the tumor's reaction after CRT, and the assigned treatment arm—functioned as independent determinants of OS. In recent years, multiple groups have attempted to clarify which factors predict outcomes in patients who develop postoperative nodal relapse of ESCC. Prior literature has identified age, radiation exposure, ECOG PS, the number of involved lymph nodes, tumor dimensions, and the specific chemotherapy approach as relevant prognostic indicators [27, 32, 47–49]. Yamashita *et al.* documented that individuals whose largest lymph node measured ≤ 22 mm survived significantly longer than those with a diameter > 22 mm [30]. Nemoto *et al.* noted that both a shorter interval from surgery to recurrence and younger patient age were linked to reduced survival durations [50]. Our findings did not align with these earlier observations. Radiation dose, ECOG PS, and chemotherapy type showed no meaningful relationship with OS. Moreover, in contrast to previous studies, our data indicated worse outcomes among older patients. Distinct treatment strategies, different primary tumor stages, or population heterogeneity may explain these conflicting results.

In our cohort, severe TRAEs (grade 3–4) occurred in 39.5% of those treated with CRT plus anlotinib, a proportion comparable to earlier reports of CRT administered for ESCC nodal recurrence [29, 51]. The most frequently encountered grade 3–4 toxicities—leukopenia, neutropenia, anemia, nausea/vomiting, and esophagitis—were largely attributable to CRT. Adding anlotinib did not result in an overall increase in toxicity apart from several non-hematologic effects. Hypertension, hand–foot syndrome, proteinuria, and diarrhea, all previously recognized reactions to anlotinib, were also observed [52, 53]. Their frequencies were similar to those reported for other anti-vascular targeted drugs [37, 54]. Hemorrhagic events, once described as anlotinib's most severe complication, appeared at lower rates in this study. All TRAEs during CRT were manageable, supporting the safety of combining anlotinib with CRT.

This research has several shortcomings. First, because it was based on a single-center retrospective dataset, selection bias could not be completely eliminated, even with the use of PSM. Second, the study population was relatively small. Additionally, some patients received additional therapies after disease progression, which may have influenced survival outcomes.

Conclusion

Overall, when compared with CRT alone, the CRT plus anlotinib regimen produced notably better response rates and survival in patients with postoperative lymph node recurrence of ESCC. Prospective randomized trials will be necessary to validate these findings.

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