Thalidomide combined with chemo-radiotherapy for treating esophageal cancer: A randomized controlled study

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Abstract. The aim of the present study was to investigate the efficiency and safety of a combination of thalidomide and chemo-radiotherapy (CRT) for treating esophageal cancer (EC). Eligible patients received two cycles of chemotherapy using paclitaxel liposome and cisplatin concurrently with three-dimensional radiotherapy. Following radiotherapy, two cycles of maintenance chemotherapy were performed. Patients with elevation of vascular endothelial growth factor (VEGF) during radiotherapy were randomly divided into: i) a test group (n=31), who received a combination of CRT and thalidomide; and ii) a control group (n=30), who received CRT only. Patients with locally advanced EC in the test group demonstrated a significantly improved 3-year overall survival (OS) rate, progression-free survival (PFS) rate, local control and median PFS time compared with the control group (P<0.05). Multivariate analysis indicated that Tumor-Node-Metastasis (TNM) stage was associated with the OS time, while TNM stage and the residence of cancer cells following radiotherapy were associated with PFS time. The present data indicate that thalidomide contributes to an improvement of prognosis for patients with locally advanced EC with elevated serum VEGF levels during radiotherapy. In addition, the toxicities induced by thalidomide were demonstrated to be tolerable.

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Abbreviations: EC, esophageal cancer; CRT, chemo-radiotherapy; VEGF, vascular endothelial growth factor; OS, overall survival; PFS, progression-free survival; LC, local control; CR, complete response; PR, partial response

Key words: esophageal cancer, chemo-radiotherapy, thalidomide, vascular endothelial growth factor, prognosis

Introduction

Esophageal cancer (EC), a common malignancy of the digestive tract, is one of the leading causes for cancer-associated mortality worldwide (1). Surgery is not recommended for EC as the majority of patients (60%) present with advanced EC upon diagnosis (2). Therefore, radiotherapy-based combined modality is considered a major treatment option for EC. Unfortunately, a large percentage of patients with EC (60-70%) exhibit a poor response following non-surgical treatment, including local recurrence and/or distal metastasis, with a 5-year survival rate of only 20-40% (3,4).

Thalidomide, initially used as a sedative, has been reported to be effective for the management of vomiting and nausea in pregnancy; however, its application is hindered as it can induce congenital disabilities in neonates (5). In 2006, thalidomide was approved by Food and Drug Administration for treating newly diagnosed multiple myeloma as it demonstrated anti-tumor activity in refractory multiple myeloma possibly by inhibiting angiogenesis (6). In addition, thalidomide has been considered as a treatment option for solid tumors due to its anti-angiogenesis effects (7). It has been demonstrated that EC cells exhibit increased sensitivity to a combination of radio-therapy and thalidomide (8-10). Our previous study revealed that a variation of serum vascular endothelial growth factor (VEGF) could predict the prognosis of patients with EC during chemo-radiotherapy (CRT). Additionally, the overall survival (OS) and progression-free survival (PFS) time in patients with elevated serum VEGF levels were significantly lower compared with patients with a decreased serum VEGF level (11). In a retrospective analysis, Yu *et al* (12) reported radiotherapy combined with thalidomide triggered a down-regulation of VEGF expression, but it caused no OS extension. The present study evaluated patients with EC with a poor prognosis, who exhibited elevated serum VEGF level during radiotherapy, with the aim of comparing the treatment efficiency, prognosis

and side-effects between CRT and a combination of CRT and thalidomide.

Materials and methods

Clinical data. A total of 215 patients (male: 152; female: 63, age: 40-87 years, median age: 66.3±9.9 years) diagnosed with esophageal squamous carcinoma, who were admitted to the Department of Radiotherapy, the Affiliated Changzhou No. 2 People's Hospital, Nanjing Medical University (Changzhou, China) between February 2011 and December 2015, were enrolled in the present study. The inclusion criteria were as follows: i) An Eastern Cooperative Oncology Group performance status score of 0 or 1; ii) received no treatment previously; iii) age ≤75 years; iv) denied surgical treatment or with contraindications of surgery; v) lesion size ≤10 cm; vi) absence of esophageal perforation; vii) no severe hepatic, renal and cardiopulmonary disease; viii) no severe cachexia; ix) Karnofsky performance score (KPS) (13) ≥80; and iix) a survival time of >3 months from the time of diagnosis. Pregnant patients, patients who were breast-feeding and patients with any other malignancy were excluded from the study. VEGF elevation was defined as an elevation of serum VEGF of ≥16.2 ng/l during radiation compared with that before radiation. The value of 16.2 ng/l was defined according to the two-fold of the standard (8.1 ng/l). The number of patients with increased, stable or decreased VEGF during radiotherapy was 61, 88 and 66, respectively. Patients with elevated VEGF during radiotherapy (n=61) were randomly divided into: i) a test group (n=31), who received a combination of CRT and thalidomide; and ii) a control group (n=30), who received CRT only. The criteria for the EC staging were based on the guidelines proposed by the 7th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) staging system (14). Written informed consent was obtained from each patient. The study protocols were approved by the Ethics Committee of the Second People's Hospital of Changzhou Affiliated to Nanjing Medical University (Nanjing, China). This clinical trial was registered in the United States Trial Registry (ID: NCT01551641).

Treatment regimen. CT simulation was performed in all patients in the supine position. CT images were obtained at a 5-mm thickness throughout the entire neck and thorax. Treatment plans were generated with a three-dimensional planning system (ADAC-Pinnacle 3; Philips Medical Systems, Inc.; version 9.3). Irradiation was delivered with 6-MV photon energy through three-dimensional conformal radiotherapy or intensity modulated irradiation therapy. Gross tumor volume (GTV) was defined as any visible primary tumor on the CT or esophageal barium study, as well as metastatic lymph nodes. Metastatic nodes were identified based on the following radiographic criteria: Nodes ≥1 cm in the shortest axis in the intra-abdominal and/or intrathoracic regions and nodes beside the recurrent nerve with the shortest axis of ≥0.5 cm. Clinical target volume (CTV) was defined as the GTV plus 3 cm of proximal and distal normal esophagus without lateral margins. Planning target volume was termed by adding a 1-cm margin around the CTV. For radiotherapy, patients were treated 5 days per week (1.8-2.0 Gy) with a total dose of 50-70 Gy. The maximal dose for the spinal cord was <45 Gy and the mean dose for the lung was ≤13 Gy. The volume of the whole lung receiving ≥20 Gy and volume of the whole heart receiving ≥50 Gy was <28 and 45%, respectively. The regimen of chemotherapy consisted of paclitaxel (Lvye Pharma, www.luyesike.com, Nanjing, China; d1, 135 mg/m^2) and cisplatin (Jiangsu Hanson Pharmaceutical Co., Ltd., Lianyungang, China; d2-5, 20 mg/m^2). Two cycles of chemotherapy were performed concurrently with the radiotherapy. Following radiotherapy, two cycles (21-28 days for each cycle) of maintenance chemotherapy were performed. In the test group, the patients received thalidomide with an initial dose of 200 mg/day and then the dose was increased to 300 mg/day in the absence of moderate or severe side-effects within 1 week.

Determination of VEGF. Peripheral blood (2 ml) was collected before, during weeks 2-4 of radiotherapy and 1 week after radiotherapy. Blood samples were centrifuged at 999 x g at 4˚C for 10 min and the serum was stored at -70˚C for further analyses. The level of VEGF was determined using a commercial ELISA kit for VEGF (cat. no., 69-50044; http://www.mskbio.com/search.aspx?word=VEGF; International Capital Corporation Limited, Beijing, China), according to the manufacturer's protocol.

Evaluation of treatment efficiency and side-effects. The efficiency was evaluated by a barium esophagogram and thoracic computed tomography (CT) scan 1 month after radiotherapy. The primary lesions in the esophagus were evaluated by barium esophagogram. Treatment efficiency of the lymph node metastasizing lesions was evaluated based on the response evaluation criteria in solid tumors (2.1) guidelines (15). The side-effects of radiotherapy were evaluated using the guidelines proposed by the Radiation Therapy Oncology Group (16). The side-effects of chemotherapy and thalidomide were evaluated using the toxicity criteria by the World Health Organization (12). Hemoglobin: Grade 0 ≥11.0 g/l; grade 1, 9.5-11.0 g/l; grade 2, 7.5-9.5 g/l; grade 3, 5.0-7.5 g/l; grade 3, <5.0 g/l. White blood cell: Grade 0 ≥4.0x10^9/l; grade 1, 3.0-4.0x10^9/l; grade 2, 2.0-3.0x10^9/l; grade 3, 1.0-2.0x10^9/l; grade 4, <1.0x10^9/l. Platelet: Grade 0 ≥100.0x10^9/l; grade 1, 75.0-100.0x10^9/l; grade 2, 50.0-75.0x10^9/l; grade 3, 25.0-75.0x10^9/l; grade 4, <25.0x10^9/l.

Follow-up. Follow-up was performed every 3 months among those with a survival of <2 years and every 6 months for those with a survival >2 years, according to the National Comprehensive Cancer Network guidelines (17). Data collection in the follow-up included case history, physical examinations, laboratory tests, electrocardiogram, abdominal ultrasound examination, and a barium esophagogram and thoracic CT scan. The OS time, PFS time and local control (LC; no recurrence in the primary lesion and local lymph node metastasis after radiotherapy) were used to evaluate the prognosis.

Statistical analysis. The primary endpoint was PFS and the secondary endpoints were the OS and LC. SPSS 19.0 software

Table I. Comparison of the characteristics of patients with esophageal cancer in the control and test groups.

Characteristic	n	Control group (n=25)	Test group (n=26)	P-value
Sex				0.499[a]
Male	40	21	19	
Female	11	4	7	
Age, years				0.843[b]
41-59	17	8	9	
60-75	34	17	17	
Site of tumor				0.318[a]
Chest, upper	10	7	3	
Chest, middle segment	21	10	11	
Chest, lower	20	8	12	
Type of cancer				0.977[a]
Medullary type	49	24	25	
Ulcer type	2	1	1	
T stage				0.090[a]
T1	2	2	0	
T2	7	2	5	
T3	36	20	16	
T4	6	1	5	
N stage				0.169[a]
N0	11	6	5	
N1	36	19	17	
N2	4	0	4	
TNM stage				0.343[a]
I	6	3	3	
II	39	21	18	
III	6	1	5	

[a]Analysis was performed with Fisher's exact test. [b]Analysis was performed with χ^2 test. TNM, Tumor-Node-Metastasis.

(IBM Corp., Armonk, NY, USA) was used for the data analysis. Measurement data are presented as the mean ± standard deviation. χ^2 test or Fisher's exact test were used for the comparison of grouped data. Mann-Whitney rank sum test was performed for the comparison of ranked data in two groups. Univariate analysis was performed using the Kaplan-Meier method and a log rank test. Multivariate analysis was performed using the Cox proportional hazards model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 3 patients in the present study were recommended to receive other treatment options due to the presence of distal metastasis during radiotherapy. One case terminated the radiotherapy due to radiation pneumonitis, one case was transferred to another department due to presence of gallstones and one case denied subsequent therapy due to a high fever. In total, 2 patients denied the four-cycle chemotherapy. In addition, 2 patients completed the study but were lost during follow-up. Therefore, a total of 51 cases were included in the analysis (test group, 26; control group, 25). The characteristics or these patients are presented in Table I. No statistical differences were identified in the characteristics at the baseline level between the test group and control group ($P>0.05$).

Side-effects evaluation. The patients demonstrated no significant cardiac side-effects following radiotherapy. No statistical differences were revealed in the radiotherapy-associated esophageal injury and lung injury between the two groups ($P>0.05$; Table II). The present study also evaluated chemotherapy-associated adverse events, including blood count, vomiting, liver function, peripheral nerve injury, constipation and muscular pain. The data indicated no statistical differences between the two groups for these factors ($P>0.05$; Table III). The major side-effects for thalidomide included hypersomnia (n=3, 5 and 3 for mild, moderate and severe, respectively). No cardiovascular system issues, including deep vein thrombosis, hypotension and bradycardia, were recorded.

Treatment response. In the test group, 16 patients demonstrated a complete response (CR) and 8 exhibited a partial response

Table II. Toxicity of radiotherapy in the lung and esophagus.

	Esophageal injury, %			Lung injury, %		
Group	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Control (n=25)	32.0	60.0	8.0	44.0	48.0	8.0
Test (n=26)	42.3	46.2	11.5	53.8	34.6	11.5
Z-value		-0.485			-0.481	
P-value		0.628			0.631	

Analysis was performed with Mann-Whitney rank sum test.

Table III. Comparison of chemotherapy-associated toxicities.

		Toxicities, %						
Variable	Group	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Z-value	P-value
Hemoglobin	Control (n=25)	76.0	24.0	0.0	0.0	0.0	-0.237	0.813
	Test (n=26)	73.1	26.9	0.0	0.0	0.0		
White blood cell	Control (n=25)	0.0	56.0	36.0	4.0	4.0	-0.368	0.713
	Test (n=26)	0.0	61.5	30.8	3.8	3.8		
Platelet	Control (n=25)	64.0	28.0	8.0	0.0	0.0	-0.261	0.794
	Test (n=26)	69.2	19.2	11.5	0.0	0.0		
Nausea and vomiting	Control (n=25)	48.0	40.0	12.0	0.0	0.0	-0.738	0.461
	Test (n=26)	57.7	34.6	7.7	0.0	0.0		
Liver function	Control (n=25)	96.0	4.0	0.0	0.0	0.0	-0.555	0.579
	Test (n=26)	92.3	7.7	0.0	0.0	0.0		
Peripheral nerve disease	Control (n=25)	56.0	44.0	0.0	0.0	0.0	-0.153	0.878
	Test (n=26)	53.8	46.2	0.0	0.0	0.0		
Constipation	Control (n=25)	44.0	40.0	12.0	4.0	0.0	-0.041	0.968
	Test (n=26)	50.0	23.1	23.1	3.8	0.0		
Muscular pain	Control (n=25)	72.0	28.0	0.0	0.0	0.0	-1.466	0.143
	Test (n=26)	88.5	11.5	0.0	0.0	0.0		

Analysis was performed with Mann-Whitney rank sum test.

Table IV. Comparison of the total effectiveness rates.

Group	CR, %	PR, %	SD, %
Test (n=26)	61.5	30.8	7.7
Control (n=25)	60.0	32.0	8.0
Z-value		-0.109	
P-value		0.913	

Analysis was performed with Mann-Whitney rank sum test; CR, complete response; PR, partial response; SD, stable disease.

(PR). In the control group, 15 demonstrated a CR and 8 exhibited a PR. The total treatment effective rate demonstrated no statistical differences between the two groups (92.3 vs. 92.0%; P>0.05; Table IV).

Prognosis analysis. In all cases, the 1-year and 3-year OS rates were 70.6 and 22.5%, respectively. The 1-year and 3-year PFS rates were 56.9 and 22.0%, respectively. In addition, the 1-year and 3-year LC rates were 81.0 and 52.6%, respectively. The comparison of these data between the test and control group was shown in Table V. For the 9 patients with cancer recurrence, the median time to recurrence was 7.5 months [95% confidence interval (CI), 1.3-13.7 months], and the median OS and PFS times were 20.6 months (95% CI, 15.1-26.2 months) and 17.0 months (95% CI, 8.8-25.2 months), respectively. The median OS time in the test group was 36.8 months (95% CI, 14.0-59.5 months), while that for the control group was 17.0 months (95% CI, 8.8-25.8 months), respectively (P=0.104; Fig. 1A). The median PFS time in the test group was 36.2 months (95% CI, 13.2-58.8 months), while that in the control group was 13.9 months (95% CI, 3.7-24.0 months), respectively (P=0.063; Fig. 1B).

Table V. Comparison of the OS, PFS and LC rates for patients with esophageal cancer.

	1-yr OS		3-yr OS		1-yr PFS		3-yr PFS		1-yr LC		3-yr LC	
VEGF type	Survival	Dead	Survival	Dead	Progression free	Progression	Progression free	Progression	No local recurrence	Local recurrence	No local recurrence	Local recurrence
Test group	19	7	7	12	16	10	7	12	19	2	4	7
Control group	17	8	2	19	13	12	2	20	15	6	9	2
χ^2 value	0.158		-		0.473		-		-		-	
P-value	0.764[a]		0.060[b]		0.577[a]		0.057[b]		0.238[b]		0.070[b]	

[a]Analysis was performed with χ^2 test. [b]Analysis was performed with Fisher's exact test. OS, overall survival; PFS, progression-free survival; LC, local control.

Table VI. Comparison of the OS, PFS and LC rates for patients with locally advanced esophageal cancer.

	1-year OS		3-year OS		1-year PFS		3-year PFS		1-year LC		3-year LC	
Group	Survival	Died	Survival	Died	PFS	Progression	PFS	Progression	No local recurrence	Local recurrence	No local recurrence	Local recurrence
Test	16	7	5	11	13	10	5	11	16	2	5	2
Control	14	8	0	19	10	12	0	22	12	6	1	8
χ^2-value	0.178		-		-		-		-		-	
P-value	0.758		0.013[a]		0.556		0.012[a]		0.228		0.041[a]	

Analysis was performed with Fisher's exact test. OS, overall survival; PFS, progression-free survival; LC, local control. [a]P<0.05.

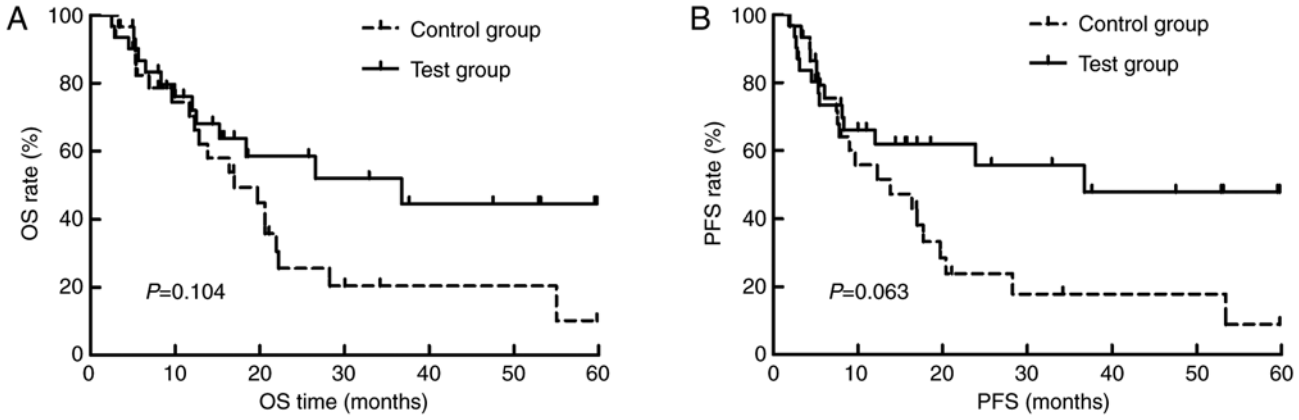

Figure 1. OS and PFS time analysis of all patients with EC. Comparison of the (A) OS and (B) PFS time of patients with EC in the test and control groups. OS, overall survival; PFS, progression-free survival; EC, esophageal cancer.

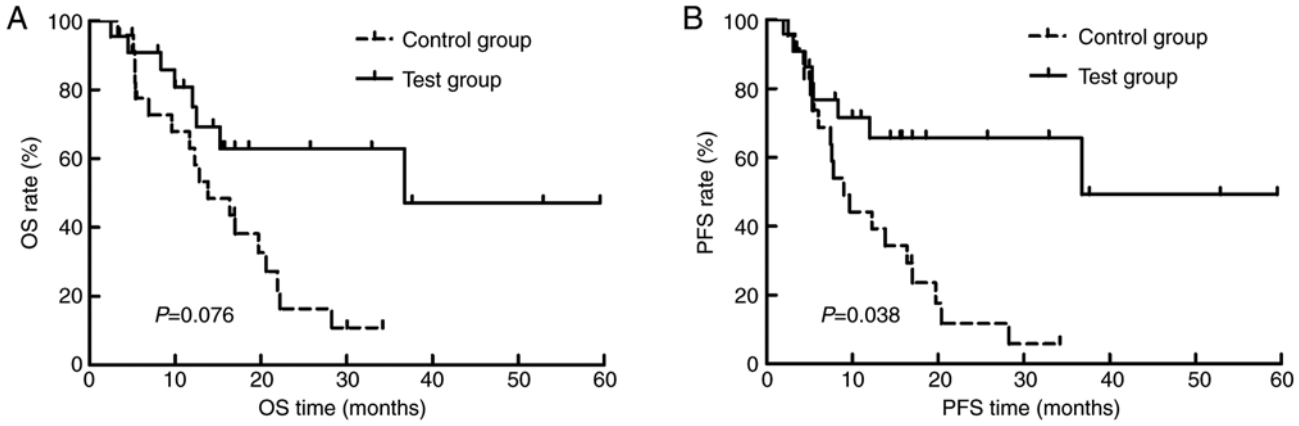

Figure 2. OS and PFS time analysis of patients with locally advanced EC. Comparison of the (A) OS and (B) PFS time of patients with locally advanced EC in the test and control groups. OS, overall survival; PFS, progression-free survival; EC, esophageal cancer.

Prognosis analysis in locally advanced patients. Among the 61 cases, 55 were confirmed with locally advanced EC (test group, n=23; control group, n=22). Locally advanced EC referred to primary lesions of ≥T3 or positive for lymph nodes. Table VI summarizes the OS, PFS and LC rates in the test and control groups of patients with locally advanced EC. The 3-year OS, PFS and LC rates in the test group were higher than that of the control. The median OS times in the test and control groups were 36.8 months (95% CI, 21.2-46.3 months) and 16.4 months (95% CI, 10.5-22.3 months), respectively (P=0.076; Fig. 2A). The median PFS time was 36.8 months (95% CI, 20.2-47.3 months) in the test group, while that for the control group was 9.7 months (95% CI, 3.6-15.9 months), respectively (P=0.038; Fig. 2B).

Effects of thalidomide on the change of serum VEGF. The changes of VEGF level were classified as decrease, stable or increase compared with the level during radiotherapy. Compared with the control group, statistical differences were identified in the changes of VEGF between the test group and control group (P<0.05; Table VII).

Associations between VEGF changes and prognosis. Subsequently, the associations between VEGF changes and the OS, PFS and LC rates for patients with EC were evaluated. Patients with increased VEGF following radiotherapy all died within 1 year. A significant increase was identified in the 1-year OS, 1-year PFS, 1-year LC and 3-year LC rates for patients with stable or decreased VEGF compared with those with an increase of VEGF (P<0.05; Table VIII).

Analysis of prognostic factors. Univariate analysis revealed that the OS time was not associated with sex, age, site and type of tumors, KPS, pre-treatment cancer length, tumor diameter, N stage, radiotherapy dose, administration of thalidomide or the presence of residual cancer after radiotherapy (Table IX). However, T stage (P=0.028) and TNM stage (P=0.024) were identified to be significantly associated with OS time (Table IX). Cox multivariate analysis demonstrated that compared with stage I patients, the risk of mortality increased in stage II [relative risk (RR), 5.613; 95% CI, 1.161-27.127; P<0.05] and III patients (RR, 8.097; 95% CI, 1.312-49.972; P<0.05) after adjusting for age, sex and administration of thalidomide (Table X). For the PFS time, univariate analysis revealed age, sex, site and type of tumor, KPS, pre-treatment tumor length, tumor diameter, N stage, dose of radiotherapy and administration of thalidomide were not significant associated. By contrast, the presence of residual cancer cell after radiotherapy

Table VII. Changes of VEGF in control and test groups post-radiotherapy compared with during radiotherapy.

Group	Decreased VEGF, %	Stable VEGF, %	Elevated VEGF, %
Test (n=26)	53.8	38.5	7.7
Control (n=25)	16.0	64.0	20.0
Z-value		-2.745	
P-value		0.006[a]	

Analysis was performed with Mann-Whitney rank sum test; VEGF, vascular endothelial growth factor. [a]P<0.05.

(P=0.006), T stage (P=0.025) and TNM stage (P=0.019) were identified to be associated with PFS time (Table XI). Cox multivariate analysis demonstrated that compared with stage I patients, the risk of disease progression increased in stage II (RR, 4.190; 95% CI, 0.630-27.853; P<0.05) and III patients (RR, 5.693; 95% CI, 1.117-29.025; P<0.05) after adjusting for age, sex and administration of thalidomide (Table XII). Compared with those with CR following radiotherapy, patients with the presence of residue EC cells demonstrated a significant increase in disease progression after radiotherapy (RR, 1.910; 95% CI, 1.246-2.930; P<0.05; Table XII).

Discussion

Surgery is not recommended for the majority of patients who present with advanced EC upon diagnosis. In a previous study, CRT demonstrated a comparable efficiency to surgery for patients with EC (18). Therefore, concurrent CRT is recommended by the National Cancer Institute Network as a standard treatment option for EC (18). The present study compared the treatment efficiency, prognosis and side-effects between CRT and a combination of CRT and thalidomide.

VEGF, a mitogen-activated factor secreted by vascular endothelial cells, serves important roles in several biological processes, including differentiation of endothelial cells, elevation of capillary permeability, endothelial cell migration and angiogenesis (19). VEGF has been identified to be expressed in vascular endothelial cells, esophageal endothelial cells and mononuclear macrophages. In addition, it is expressed in several types of malignant cell including cancer cells and tumor vascular endothelial cell. Furthermore, it has been detected in serum and exudate (20). Generally, the expression of VEGF in the normal tissues was relatively low, as it could only maintain vascular density and basic osmosis, which contributed to the nutrition delivery (21). The expression of VEGF in cancer tissues is markedly higher compared with normal tissues as the growth of cancer depends on the transport of nutrients mediated by blood vessels (11). VEGF has been reported to serve a pivotal role in vascularization (11). In addition, VEGF is considered as an independent prognosis factor and is closely associated with the recurrence and metastasis of cancer (22). Serum VEGF has been reported to be closely associated with tumor load, infiltration and lymph node metastasis. The expression of VEGF was identified to

Table VIII. Comparison of the OS, PFS, and LC for patients of the test group with various changes of VEGF.

	1-year OS		3-year OS		1-year PFS		3-year PFS		1-year LC		3-year LC	
VEGF change	Survival	Died	Survival	Died	PFS	Progression	PFS	Progression	No local recurrence	Local recurrence	No local recurrence	Local recurrence
Decrease	13	1	6	4	12	2	6	4	6	0	6	6
Stable	6	4	1	6	10	4	1	6	3	0	1	0
Elevated	0	2	0	2	0	2	0	2	0	2	0	2
P-value	0.013[a]		0. 110		0.006[a]		0.110		0.005[a]		0.028[a]	

Analysis was performed with Fisher's exact test. OS, overall survival; PFS, progression-free survival; LC, local control; VEGF, vascular endothelial growth factor. [a]P<0.05.

Table IX. Univariate analysis of the overall survival rate of patients with esophageal cancer.

Variable	β-value	Standard error	Wald-value	RR	95% CI	P-value
Sex	0.261	0.429	0.371	1.298	0.560-3.009	0.543
Age	-0.025	0.027	0.897	0.975	0.926-1.027	0.343
KPS	0.038	0.038	0.991	1.039	0.964-1.121	0.320
Lesion position	-0.132	0.248	0.286	0.876	0.539-1.423	0.593
Lesion type	0.421	0.749	0.315	1.523	0.351-6.606	0.574
T stage	0.710	0.324	4.808	2.033	1.078-3.834	0.028[a]
N stage	0.670	0.345	3.779	1.955	0.994-3.844	0.052
TNM stage	0.634	0.282	5.066	1.885	1.085-3.275	0.024[a]
Cancer length before treatment	0.134	0.088	2.358	1.144	0.964-1.358	0.125
Lesion diameter	0.033	0.197	0.027	1.033	0.702-1.520	0.868
Residual cancer cells after radiotherapy	0.365	0.194	3.541	1.441	0.985-2.109	0.060
Radiotherapy dose	-0.058	0.035	2.774	0.944	0.882-1.010	0.096
Thalidomide	-0.575	0.359	2.568	0.562	0.278-1.137	0.109

KPS, Karnofsky performance score; TNM, Tumor-Node-Metastasis; CI, confidence interval; RR, relative risk. [a]P<0.05.

Table X. Cox multivariate analysis of the overall survival rate of patients with esophageal cancer.

Variable	RR	95% CI	P-value
Sex			
Male	1.000	-	
Female	0.745	0.311-1.785	0.509
Age	1.006	0.952-1.063	0.838
TNM stage			
Stage I	1.000	-	
Stage II	5.613	1.161-27.127	0.032[a]
Stage III	8.097	1.312-49.972	0.024[a]
Thalidomide			
No	1.000	-	
Yes	0.523	0.248-1.101	0.088

TNM, Tumor-Node-Metastasis; CI, confidence interval; RR, relative risk. [a]P<0.05.

be significantly higher in patients with a large tumor volume and lymph node metastasis compared with those with a small tumor volume and the absence of lymph node metastasis (22). Our previous study (19) demonstrated that VEGF level is associated with the sensitivity to radiotherapy and prognosis of chemo-radiotherapy, and the treatment efficiency in patients with downregulated VEGF was higher compared with those with an increased level of VEGF. In patients with EC with a satisfactory prognosis, the VEGF level during radiotherapy was demonstrated to be decreased compared with the baseline level. The elevation of VEGF induced by radiotherapy may be associated with the self-protection of cancer cells to encounter the toxicity of radiotherapy.

Thalidomide was initially utilized for the management of lepra reactions and was then demonstrated to be effective for attenuating vomiting and nausea in early gestation. However, the application of thalidomide is limited as it causes congenital defects in neonates (10,12). Since then, studies involving thalidomide predominantly focused on the immune system, anti-inflammation and anti-angiogenesis. In 1999, Singhal *et al* (23) reported that thalidomide exhibited antitumor activity in refractory multiple myeloma with a CR rate of 32%. Subsequently, thalidomide has been demonstrated to be effective for the treatment of various types pf hematologic neoplasm (24-26). Thalidomide has been regarded as a treatment option for solid tumors (27) and the majority of studies have been focused on anti-angiogenesis, chemotherapy sensitivity and attenuation of the chemotherapy-associated side-effects (28,29). To the best of our knowledge, no previous studies have investigated the efficiency of thalidomide for concomitant therapy with CRT. Previously, thalidomide has been reported to increase the radiotherapy sensitivity of EC cells (30). Our previous study (22) demonstrated that a combination of thalidomide and radiotherapy could trigger a downregulation of VEGF, specifically patients receiving thalidomide demonstrated satisfactory tolerance to radiotherapy.

In the present study, patients with EC with an elevated VEGF level were randomly divided into the test group and control group to investigate the effects of thalidomide on VEGF and prognosis. The data revealed that the short-term treatment efficiency was similar between the two groups, and the 1-year and 3-year OS, PFS and LC rates, and median OS and PFS times demonstrated no statistical differences. The stratified analysis revealed that the patients with locally advanced EC in the test group exhibited significantly higher 3-year OS, PFS and LC rates and median PFS time compared with the control group, which indicates that a combination of thalidomide and chemo-radiotherapy contributes to the prognosis of patients

Table XI. Univariate analysis of the progression-free survival rate of patients with esophageal cancer.

Variable	β-value	Standard error	Wald-value	RR	95% CI	P-value
Sex	-0.312	0.427	0.534	0.732	0.317-1.691	0.465
Age	-0.042	0.026	2.580	0.959	0.911-1.009	0.108
KPS	0.048	0.038	1.572	1.049	0.973-1.131	0.210
Lesion position	-0.069	0.242	0.082	0.933	0.581-1.499	0.774
Lesion type	0.184	0.742	0.061	1.202	0.281-5.146	0.804
T stage	0.727	0.325	5.022	2.070	1.096-3.910	0.025[a]
N stage	0.706	0.360	3.849	2.027	1.001-4.105	0.050
TNM stage	0.658	0.282	5.468	1.932	1.112-3.354	0.019[a]
Cancer length before treatment	0.155	0.090	2.997	1.168	0.980-1.393	0.083
Lesion diameter	0.198	0.195	1.028	1.219	0.831-1.787	0.311
Residual cancer cells after radiotherapy	0.535	0.194	7.627	1.707	1.168-2.495	0.006[a]
Radiotherapy dose	-.045	0.036	1.608	0.956	0.891-1.025	0.205
Thalidomide	-.652	0.357	3.340	0.521	0.259-1.048	0.068

KPS, Karnofsky performance score; TNM, Tumor-Node-Metastasis; CI, confidence interval; RR, relative risk. [a]P<0.05.

Table XII. Cox multivariate analysis of the progression-free survival rate of patients with esophageal cancer.

Variable	RR	95% CI	P-value
Sex			
Male	1.000	-	
Female	0.853	0.346-2.108	0.731
Age	0.962	0.909-1.018	0.178
TNM stage			
Stage I	1.000	-	
Stage II	4.190	0.630-27.853	0.138
Stage III	5.693	1.117-29.025	0.036[a]
Thalidomide			
No	1.000	-	
Yes	0.473	0.221-1.014	0.054
Residual cancer cells after radiotherapy	1.910	1.246-2.930	0.003[a]

TNM, Tumor-Node-Metastasis; CI, confidence interval; RR, relative risk. [a]P<0.05.

with locally advanced EC with elevated VEGF. Compared with the control group, the post-treatment VEGF level demonstrated a significant decrease in the test group. This indicates that thalidomide contributes to the decrease of serum VEGF level in patients with EC with elevated VEGF during the concurrent CRT. Furthermore, the OS, PFS and LC rates for patients with decreased VEGF following administration of thalidomide were higher compared with those with increased VEGF, which indicates that the benefits of thalidomide may be associated with the inhibition of VEGF in cancer tissues. Additionally, multivariate analysis demonstrated that TNM stage was significantly associated with OS time, while the presence of residual cancer cells and TNM stage were significantly associated with the PFS time following radiotherapy.

There were certain limitations of the present study. Firstly, the sample size was too small. To improve this, more data from a larger number of patients should be included in future studies. In addition, no significant differences were identified in the 1-year OS and PFS rates for the patients with locally advanced EC between the two groups. This may be due to the small sample size. Furthermore, the present study only focused on the side-effects, treatment efficiency and prognosis of thalidomide combined with CRT. Therefore, potential mechanisms should be investigated in future studies.

In conclusion, the current study demonstrated that thalidomide contributes to an improvement of prognosis for patients with locally advanced EC with elevated serum VEGF during radiotherapy. Furthermore, the toxicities observed were tolerable. It was concluded that the benefits of thalidomide in clinical practice may be associated with the inhibition of VEGF in cancer cells.

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Availability of data and materials

The raw data were available upon appropriate requests.

Authors' contributions

JW was responsible for data collection and analysis, as well as manuscript writing. JY, JLW, XN, ZS and WS were responsible for data collection and analysis. SS and YL designed the study and revised the manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from each patient. The study protocols were approved by the Ethics Committee of the Second People's Hospital of Changzhou Affiliated to Nanjing Medical University (Nanjing, China). This clinical trial was registered in the United States Trial Registry (ID: NCT01551641).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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