

Pathological response and serum VEGF changes during chemoradiotherapy for esophageal carcinoma

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Abstract

The aim of this study was to observe pathological response and change in serum vascular endothelial growth factor (VEGF) in esophageal carcinoma (EC) during chemoradiotherapy (CRT).

Eighty-nine patients diagnosed with EC were treated with radiotherapy at the Department of Radiotherapy of the Second People's Hospital of Changzhou between May 2008 and December 2014, including 65 patients with CRT. Gastroscopy and pathological examination were conducted 4 weeks afterwards. The pathological responses were classified as complete response (CR) and non-CR. Serum samples were collected from the patients before radiotherapy, during week 4 of radiotherapy, and 1 week after radiotherapy. The VEGF changes were classified as increase, stable, and decrease.

The median overall survival (OS) and median progression-free survival (PFS) in the pathological CR group was significantly longer than that of the non-CR group ($P < .001$). The 1-, 3-, and 5-year OS rates in the non-CR group were lower than that in the CR group ($P < .05$). Moreover, the 1-, 3-, and 5-year PFS rates in the non-CR group were lower than that in the CR group ($P < .05$). VEGF serum level was decreased during and after radiotherapy compared with pre-radiotherapy, and the differences were statistically significant ($P < .05$). The 1-, 3-, and 5-year OS rates in the increased group were lower than that in the decreasing group ($P < .05$). Moreover, the 1-, 3-, and 5-year PFS rates in the increasing group were lower than that in the decreasing group ($P < .05$). Pathological response ($P < .05$), serum VEGF trend ($P < .05$), and tumor-node-metastasis stage ($P < .05$) in response to CRT were factors that influenced patient prognosis.

Pathological response and serum VEGF change during CRT can predict prognosis of nonsurgical patients with EC. Monitoring these changes is of significance in individualized treatment.

Abbreviations: 3D = 3-dimensional, CR = complete response, CRT = chemoradiotherapy, CT = computed tomography, CTV = Clinical target volume, EC = esophageal carcinoma, ECOG = Eastern Cooperative Oncology Group, ESCC = esophageal squamous cell carcinoma, GTV = gross tumor volume, OS = overall survival, PFS = progression-free survival, PTV = planning target volume, TNM = tumor-node-metastasis, VEGF = vascular endothelial growth factor.

Keywords: chemoradiotherapy, esophageal carcinoma, pathological response, prognosis, vascular endothelial growth factor

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All study participants, or their legal guardian, provided informed written consent before study enrollment.

All the data were available upon appropriate request.

Few studies have evaluated the pathological response in tumor tissues and the changes in serum vascular endothelial growth factor (VEGF) level in patients with esophageal carcinoma (EC) receiving radiotherapy or chemoradiotherapy (CRT). Tumor tissue pathological response and changes in serum VEGF level during treatment can predict the prognosis of EC patients receiving CRT. Hence, monitoring these changes during treatment is important to perform and evaluate individualized therapy in clinical practice.

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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1. Introduction

Surgery-based comprehensive therapy is the main treatment strategy for thoracic esophageal carcinoma (EC). However, >60% of patients are not suitable for surgery because they are diagnosed at an advanced stage.^[1] The survival rate in patients with chemoradiotherapy (CRT) is close to that in patients who undergo surgery.^[2,3] CRT is recognized as a standard nonsurgical therapy for EC by the US National Comprehensive Carcinoma Network and by the Esophageal Carcinoma Treatment Guidelines of Japan. Evaluation of the efficacy and prognosis of CRT in EC is of clinical importance to identify individualized therapy.

According to the pathological characteristics in the EC tissues after neoadjuvant therapy, Ou et al^[4] classified the pathological responses into mild, moderate, and intensive, and found that the 5-year overall survival (OS) rates in these 3 groups were 21.1%, 46.4%, and 60.7%, respectively. This observation suggests that the pathological response was associated with OS, that is, a stronger pathological response led to better prognosis, and vice versa. Cheng et al^[5] analyzed the pathological response to neoadjuvant therapy in 79 EC patients, and found that pathological CR was an independent prognostic factor.

Vascular endothelial growth factor (VEGF), mainly secreted by vascular endothelial cells, is a mitogenic factor that specifically promotes division of endothelial cells, enhances permeability of blood capillaries, and induces endothelial cell migration and angiogenesis, and it is positively correlated with microvascular density. VEGF is normally expressed in vascular endothelial cells, esophageal mucosal cells, and macrophages, and can also be expressed in tumor cells and endothelial cells inside the tumor, and detected in serum and exudates.^[6] VEGF is expressed at a low level in normal tissues to maintain vascular density and permeability for transportation of nutrients.^[7] In contrast, VEGF is highly expressed in tumors,^[8] especially in vascular-dependent malignant tumors such as EC, as its growth demands nutrient supply by blood vessels. Angiogenesis is a complicated and multistep process, in which VEGF plays the most important role among all the angiogenic factors and participates in the whole process. VEGF is an independent prognostic factor of EC, as it plays a crucial role in recurrence and metastasis.^[9–11] Serum VEGF level is closely associated with tumor load, depth of infiltration, and lymphatic metastasis, and is higher in patients with a larger tumor size and more lymph node metastasis.^[12] The secretion of VEGF is decreased along with the reduction in tumor load as a result of radiotherapy, and serum VEGF level declines accordingly.^[12] Recently, expression of VEGF was found to be associated with tumor angiogenesis, lymphatic metastasis, and survival in EC,^[13,14] and it is an independent prognostic factor for EC.

In this study, we evaluated the pathological responses in the tumor tissues and the changes in serum VEGF level in the nonsurgical EC patients who received CRT, to study the relationship between these 2 factors and treatment efficacy and patient prognosis. Our study provides additional information for individualized therapy and for further improvement of efficacy of CRT.

2. Materials and methods

2.1. Patients

We included 89 patients with EC (squamous cell carcinoma) treated with radiotherapy or CRT in the Department of Radiotherapy at the Second People's Hospital of Changzhou

between January 2008 and May 2016. The inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; no treatment before enrollment; age ≤ 80 years; denied history of surgical treatment or with contraindications for surgery; absence of esophageal perforation; without severe hepatic, renal, and cardiopulmonary dysfunction; and no severe cachexia. Patients in pregnancy or lactation, with other malignancies, or those with inadequate follow-up data were excluded. The study was approved by the Ethics Committee of the Second People's Hospital of Changzhou Affiliated to Nanjing Medical University.

2.2. Treatment

All patients underwent computed tomography (CT) simulation in the supine position, with CT images obtained at 3 mm thickness throughout the entire neck and thorax. Treatment plans were generated with a 3-dimensional (3D) planning system (ADAC-Pinnacle 3; Philips Healthcare, Amsterdam, Netherlands, version 9.3). Irradiation was delivered with 6 MV photon energy through 3D conformal radiotherapy or intensity-modulated irradiation therapy. Gross tumor volume (GTV) was defined as any visible primary tumor on 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 GTV and 3 cm of proximal and distal normal esophagus without lateral margins. Planning target volume (PTV) was determined by adding a 1 cm margin around the CTV. Radical prescription dose was 60 to 66 Gy/30 to 33 fractions/6.0 to 6.6 weeks. PTV prescription dose was 50 Gy/25 fractions/5 weeks. The maximal dose for the spinal cord was < 45 Gy, and the mean dose for the lung should not surpass 13 Gy. The pulmonary V20 (volume of the whole lung receiving ≥ 20 Gy) and cardiac V50 (volume of the whole heart receiving ≥ 50 Gy) should be $< 28\%$ and $< 45\%$, respectively. In total, 65 cases received chemotherapy with liposomal paclitaxel (LUYE Pharma, Nanjing, China) at a dose of 135 mg/m² given by intravenous infusion on the first day and cisplatin (Nuoxin; Hansoh Pharmaceutical, Jiangsu, China) at a dose of 20 mg/m² daily given by intravenous infusion from day 2 to day 5. Two cycles of chemotherapy were carried out concurrently with radiotherapy. After radiotherapy, 2 cycles (21–28 days for each cycle) of maintenance chemotherapy were administered.

2.3. Pathological examination

Gastroscopy was performed at week 4 after radiotherapy to collect tumor biopsies. The pathological responses to radiation were classified into 3 types based on the pathological features in the tumor tissues.^[4] Non-CR responses were presence of tumor cells, slight degeneration of tumor cells, reduced number of mitotic cells, mild infiltration of inflammatory cells, and angiogenesis. CR responses were disappearance of the majority of tumor cells, degeneration of residual tumor cells, often surrounded by granulation tissue, and plenty of infiltrated inflammatory cells.

2.4. Detection of serum VEGF level

Blood was collected from the patients before, at week 4 of, and 1 week after radiotherapy. Two milliliters of peripheral venous

blood was collected, mixed, and centrifuged for 10 minutes at 3000 rpm with a centrifugal radius of 10 cm. The serum was kept at -70°C for further tests. Serum samples from 30 healthy subjects were collected and represented the VEGF healthy controls. VEGF was detected using a double-antibody sandwich avidin-biotin complex ELISA (ABC-ELISA VEGF kit, Zhongjin Life Sciences, Inc., Shanghai, China).

2.5. Treatment toxicity evaluation and follow-up

Radiation and chemotherapy toxicity was classified according to RTOG and CTC toxicity criteria, respectively. The highest score noted was recorded as the patient's toxicity grade. After CRT, the patients were followed up every 3 months for the first 2 years and every 6 months thereafter. Each visit included history taking, physical examination, complete peripheral blood tests, electrocardiography, abdominal ultrasound, esophageal barium radiography, and chest CT. The efficacy was evaluated on the basis of OS and progression-free survival (PFS).

2.6. Statistical analysis

Statistical analysis was performed using SPSS Statistics 19.0 (IBM Corp., Armonk, NY), and the measurement data were expressed as mean \pm standard deviation. Comparison of the rates between multiple groups and correlation analysis of the categorical data were performed using the χ^2 test. The OS and PFS rates were calculated using the Kaplan–Meier method, and the statistical significance was tested with the log-rank test. Cox proportional hazard model was used to analyze the prognosis of multiple prognostic factors. For the 2-tailed tests, $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

Eight patients were not willing to undergo gastroscopy and 3 were lost to follow-up. The remaining patients were followed up for 12 to 91 months until December 31, 2015. Fifty-four patients died during follow-up, with 8 deaths unrelated to tumor recurrence, metastasis, or treatment complications. The overall 1- and 3-year OS rates were 70.8% (63/89) and 33.3% (26/78), respectively; 1- and 3-year PFS rates were 61.8% (55/89) and 28.2% (22/78), respectively; and median OS and PFS were 20.5 and 15.7 months, respectively. Table 1 summarizes the clinical profiles of the patients.

3.2. Tolerance and toxicity

All 89 patients tolerated CRT well and completed treatment without interruption. Esophageal grade 1, 2, 3, and 4 toxicity rates were 66%, 29%, 5%, and 0%, respectively. Eight patients were not willing to undergo gastroscopy, and all other patients tolerated gastroscopy without severe complications. Grade 1, 2, 3, and 4 lung toxicity rates were 54%, 5%, 2%, and 0%, respectively. Grade 1, 2, 3, and 4 blood toxicity rates were 11%, 45%, 28%, and 8%, respectively.

3.3. Relationship between pathological response in EC tissue and patient prognosis

Gastroscopy was performed at week 4 to collect tumor biopsies. The pathological responses were classified into non-CR (22 cases)

Table 1
Patients' characteristics.

Clinical parameter	n	Percentage
Sex		
Male	62	69.7
Female	27	30.3
Age, y		
<60	18	20.2
≥ 60	71	79.8
Pathological type		
Squamous cell carcinoma	86	96.7
Adenosquamous carcinoma and adenocarcinoma	3	3.3
Tumor location		
Upper thoracic	22	24.7
Middle thoracic	40	44.9
Lower thoracic	27	30.3
Tumor type		
Medullary	84	94.4
Ulcerative	5	5.6
T stage		
T ₁ + T ₂	17	19.1
T ₃	55	61.8
T ₄	17	19.1
N stage		
N ₀	17	19.1
N ₁ + N ₂	72	80.9
TNM stage		
I	8	9.0
II	64	71.9
III	17	19.1

TNM = tumor-node-metastasis.

and CR (67 cases). The OS and PFS rates in these 2 groups are summarized in Table 2. The OS curves are shown in Fig. 1 and the PFS curves in Fig. 2.

3.4. Effects of CRT on serum VEGF level in EC patients

The average serum VEGF levels in the 89 EC patients before, during, and after radiotherapy were 109.6 ± 33.7 , 101.2 ± 24.3 , and 99.5 ± 22.9 ng/L, respectively. These values were all higher than those in the healthy subjects, which were all 79.6 ± 39.2 ng/L, and the differences were significant ($P < .05$ for all the comparisons). The serum VEGF level was reduced during and after radiotherapy as compared to before radiotherapy ($P < .05$ for both comparisons). The OS and PFS rates in these 3 groups are listed in Table 3. The OS curves of these subgroups are illustrated in Fig. 3 and the PFS curves in Fig. 4.

3.5. The relationship between pathological reaction and serum VEGF level before radiotherapy and the changes of serum VEGF in radiotherapy

The serum VEGF levels of pathological CR and non-CR patients were 108.9 ± 33.9 and 111.9 ± 33 ng/L before radiotherapy, respectively, and there was no statistical difference between the 2 groups ($t = 0.362$, $P = .718$). There was no correlation between pathological changes and VEGF changes ($r_s = 0.091$, $P = .396$).

3.6. Analysis of prognostic factors

Kaplan–Meier estimates of OS and PFS for the entire cohort are summarized in Table 4. The univariate analysis showed that the

Table 2
Pathological responses according to sex, age, tumor location, tumor type, T stage, N stage, and TNM stage.

Clinical parameter	n	Pathological response		P
		Non-CR	CR	
Sex				1.000
Male	62	15	47	
Female	27	7	20	
Age, y				.368
<60	18	6	12	
≥60	71	16	55	
Tumor location				.703
Upper thoracic	22	7	15	
Middle thoracic	40	9	31	
Lower thoracic	27	6	21	
Tumor type				.594
Medullary	84	20	64	
Ulcerative	5	2	3	
T stage				<.001
T ₁ +T ₂	17	2	15	
T ₃	55	9	46	
T ₄	17	11	6	
N stage				.755
N ₀	17	5	12	
N ₁ +N ₂	72	17	55	
TNM stage				<.001
I	8	1	7	
II	64	10	54	
III	17	11	6	
Therapeutic method				.103
Radiotherapy	24	9	15	
CRT	65	13	52	

CR=complete response, CRT=chemoradiotherapy, TNM=tumor-node-metastasis.

patient's age, sex, pathological type, Karnofsky Performance Score, tumor type, and treatment method (radiotherapy or CRT) did not exert any significant effect on OS ($\chi^2=0.022-2.762$, $P=.097-.881$), whereas T stage, N stage, tumor-node-metastasis (TNM) stage, pathological response, and VEGF trend did influence survival ($\chi^2=7.20-26.155$, $P=.097-.881$). The beneficial factors for OS and PFS were identified in multivariate analysis (Table 5). The multivariate analysis revealed that TNM stage,

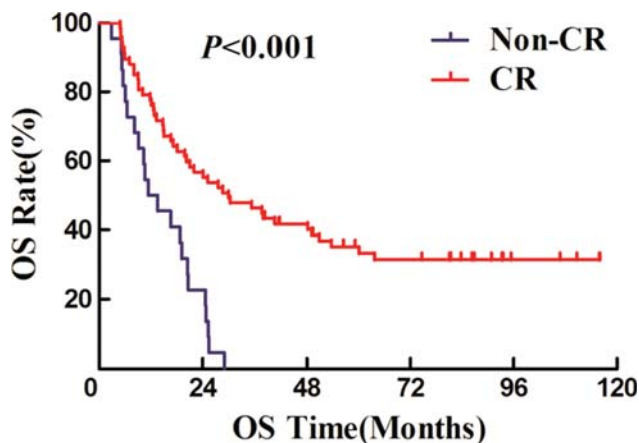


Figure 1. Comparison of OS in subgroups of pathological response. CR=complete response, EC=esophageal cancer, OS=overall survival.

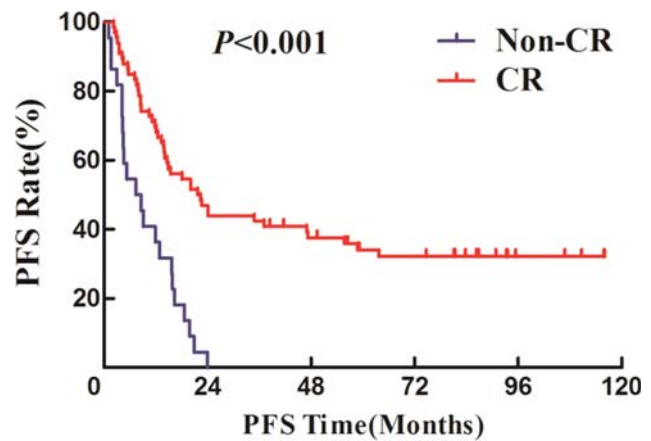


Figure 2. Comparison of PFS in subgroups of pathological response. CR=complete response, EC=esophageal cancer, OS=overall survival.

pathological response, and VEGF trend were factors that influenced prognosis ($\chi^2=4.316-8.289$, $P=.004-.038$).

4. Discussion

Surgery is the primary therapeutic strategy for EC. However, it is not suitable for patients who were diagnosed at an advanced stage or had other underlying diseases, or when the patient

Table 3
VEGF trends according to sex, age, tumor location, tumor type, T stage, N stage, and TNM stage.

Clinical parameter	n	VEGF trends			P
		Increased	Stable	Decreased	
Sex					.078
Male	62	13	33	16	
Female	27	3	10	14	
Age, y					1.000
<60	18	3	9	6	
≥60	71	13	34	24	
Tumor location					.710
Upper thoracic	22	3	10	9	
Middle thoracic	40	6	20	14	
Lower thoracic	27	7	13	7	
Tumor type					.117
Medullary	84	16	42	26	
Ulcerative	5	0	1	4	
T stage					.718
T ₁ +T ₂	17	2	7	8	
T ₃	55	10	27	18	
T ₄	17	4	9	4	
N stage					.824
N ₀	17	4	8	5	
N ₁ +N ₂	72	12	35	25	
TNM stage					.791
I	8	1	3	4	
II	64	11	31	22	
III	17	4	9	4	
Therapeutic method					.661
Radiotherapy	24	4	10	10	
CRT	65	12	33	20	

CRT=chemoradiotherapy, TNM=tumor-node-metastasis, VEGF=vascular endothelial growth factor.

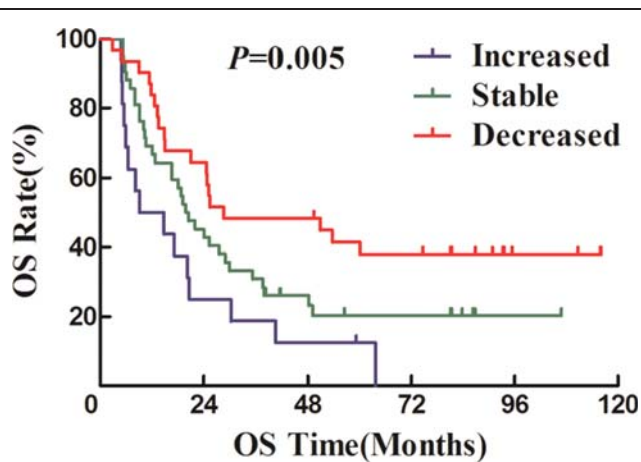


Figure 3. Comparison of OS in various VEGF changes among EC patients. EC=esophageal cancer, OS=overall survival, VEGF=vascular endothelial growth factor.

refuses surgery, and CRT becomes the main therapeutic alternative. Thus, assessment of CRT in nonsurgical EC patients is of clinical importance.

Several studies have reported that neoadjuvant therapy could guarantee a greater response in tumor tissue such as a better long-term survival.^[4,5,15] In a study by Tahara et al,^[16] EC patients received radical radiotherapy, and gastroscopy-guided pathological examination was performed 1 month later. The pathological responses were classified as CR (58%, 80/139) and non-CR (42%, 59/139), 3- and 5-year OS rates in the CR group were 55% and 46%, respectively, while 3- and 5-year OS rates in the non-CR group were 11% and 6%, respectively. The OS in the CR group was significantly higher than that in the non-CR group. CR criteria were as follows: complete disappearance of tumor; complete disappearance of ulcerative and necrotic tissues; and tumor cells not detected by biopsy. Our study adopted the pathological criteria previously reported by Ou et al,^[4] and the pathological response in the CR group was similar to that in the CR group in the study by Tahara et al.^[16] In our study, the CR rate was 46.1%, which was lower than the CR rate (58%) in the

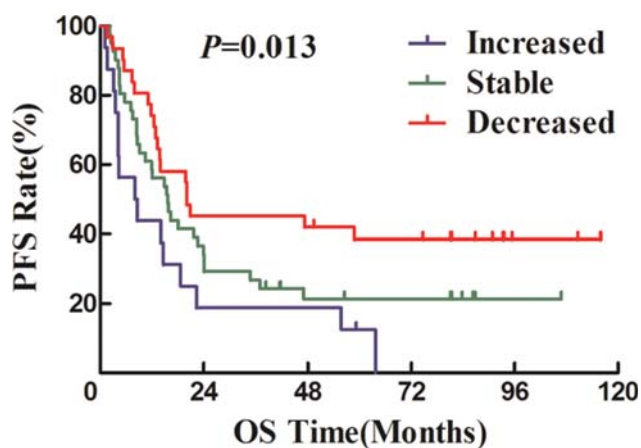


Figure 4. Comparison of PFS in various VEGF changes among EC patients. EC=esophageal cancer, PFS=progression-free survival, VEGF=vascular endothelial growth factor.

study by Tahara et al.^[16] This is probably related to the different times of biopsy. In the present study, gastroscopic biopsy was performed during the course of radiotherapy (40 Gy/20 times), whereas Tahara et al^[16] performed biopsy 1 month after radiotherapy (60 Gy/30 times). Our group previously studied the relationship between pathological response to CRT and prognosis in 46 EC patients. No significant difference was observed in the OS rate or the survival time between these 3 groups.^[11] In the present study, the OS rate and the OS time in the non-CR group were lower than in the CR groups, which was consistent with the findings by Tahara et al.^[16] PFS and LC rate in the non-CR group were also lower than the CR groups.

In this study, the overall VEGF serum level was reduced in all the patients during and after chemotherapy compared with before therapy. However, the relationship between pre-therapy serum VEGF level and patient’s prognosis in our study was not the same as in previous studies. Rades et al^[17] discussed the impact of VEGF on the prognosis of late-stage focal EC, and proposed that pre-therapy serum VEGF level is negatively correlated with prognosis. Cheng et al^[5] examined VEGF level in EC patients before and after preoperative radiotherapy, and found that pre-radiation serum VEGF level was negatively correlated with PFS but not with OS. In our previous study, we did not detect a correlation between pre-radiation serum VEGF level and patient prognosis.^[11] Unlike most studies, after evaluation of pre-radiotherapy serum VEGF level in 44 patients, Yoon et al^[11] proposed a positive correlation between a high level of pre-radiotherapy VEGF and post-CRT CR. In the present study, the pre-radiotherapy serum VEGF level was not significantly correlated with OS or PFS, and the results are consistent with our previous study.^[11] Kimura et al^[18] found that a high pre-therapy serum VEGF level increased the recurrence rate of EC. However, in the present study, serum VEGF level was not correlated with LC rate. In our previous work, we discovered that the VEGF trend in response to radiotherapy was associated with radiosensitivity and prognosis, and the short-term efficacy was worse in the VEGF-increasing group compared with the VEGF-declining group, but the OS was not significantly different between these 2 groups. In the present study, 1- and 3-year OS rate, 3-year PFS rate, OS, and PFS in the VEGF-increasing group were all significantly worse than those in the VEGF-declining group. However, the difference in 1-year PFS rate was not significant, probably due to the small sample size. Among the patients with a better prognosis, serum VEGF levels during and after therapy were decreased compared with the pre-therapy level, whereas the VEGF level increased in those with a worse prognosis. It seems that VEGF expression was upregulated in response to radiotherapy, suggesting that it is a self-protection and pro-survival mechanism in the endothelial cells to reduce radiation-induced cytotoxicity and radioresistance enhancement.

In a study by Cheng et al,^[5] the pre-radiotherapy serum VEGF level and VEGF trend during radiotherapy were not associated with pathological response. Consistent with the findings by Cheng et al,^[5] we found that the pre-radiotherapy serum VEGF level did not significantly change among the patients with different pathological responses, nor did the VEGF trend. There was no correlation between pathological response and VEGF trend. In the CR group, the VEGF level significantly declined during radiotherapy compared with pre-therapy, suggesting that the patients with a rapid decline in VEGF may have been more sensitive to radiation. This observation is consistent with a previous study by Yu et al.^[11]

Table 4**Univariate results for overall survival and progression-free survival of prognostic factors in patients of esophageal cancer.**

Clinical parameter	n	OS rate (%)				χ^2	P	PFS rate (%)				χ^2	P
		Median OS, mo	1 y	3 y	5 y			Median PFS, mo	1 y	3 y	5 y		
Gender						0.699	.403					0.555	.456
Male	62	19.9	67.7	43.5	23.5			14.9	57.4	31.1	22.0		
Female	27	25.2	77.8	37.0	33.3			20.1	70.4	33.3	33.3		
Age, y						1.801	.180					1.278	.258
<60	18	12.8	61.1	16.7	16.7			11.9	50.0	16.7	16.7		
≥60	71	24.1	73.2	39.4	28.9			15.9	64.3	34.3	28.0		
Tumor location						4.948	.084					2.842	.241
Upper thoracic	22	25.5	86.4	40.9	31.8			19.9	61.9	33.3	30.3		
Middle thoracic	40	20.7	65.0	45.0	34.7			14.9	60.0	40.0	31.9		
Lower thoracic	27	18.1	66.7	14.8	9.9			14.7	63.0	14.8	9.9		
Tumor type						0.000	.989					0.004	.953
Medullary	84	20.7	70.2	35.7	26.8			15.5	60.2	31.3	26.1		
Ulcerative	5	25.5	80.0	20.0	20.0			20.9	80.0	20.0	20.0		
T stage						30.146	<.001					32.968	<.001
T ₁ + T ₂	17	53.7	100.0	58.8	47.1			47.2	88.2	52.9	47.1		
T ₃	55	24.1	76.4	38.2	28.5			18.1	66.7	33.3	26.9		
T ₄	17	8.2	23.3	0.0	0.0			4.5	17.6	0.0	0.0		
N stage						4.805	.028					4.899	.027
N ₀	17	63.7	76.5	58.8	46.3			63.7	76.5	58.8	46.3		
N ₁ + N ₂	72	19.9	69.4	29.2	20.1			14.0	57.7	23.9	19.2		
TNM stage						30.190	<.001					33.630	<.001
I	8	63.7	100.0	75.0	50.0			63.7	100.0	75.0	50.0		
II	64	22.0	79.7	39.1	29.1			16.4	68.3	33.3	28.0		
III	17	8.2	23.5	0.0	0.0			8.2	23.5	0.0	0.0		
Therapeutic method						0.403	.525					0.536	.465
Radiotherapy	24	16.6	58.3	29.2	0.0			11.8	45.8	29.2	0.0		
Chemoradiotherapy	65	22.0	75.4	36.9	25.8			26.4	67.2	31.3	24.6		
Pathological responses						19.945	<.001					22.085	<.001
CR	67	30.0	77.6	46.3	35.2			30.0	69.7	40.9	34.3		
Non-CR	22	11.4	50.0	0.0	0.0			11.4	50.0	0.0	0.0		
VEGF trends						10.426	.005					9.015	.011
VEGF increased	16	9.2	50.0	18.8	12.5			8.0	43.8	12.5	12.5		
VEGF stable	43	19.9	67.4	30.2	19.9			15.5	57.1	26.2	19.9		
VEGF decreased	30	28.7	86.7	50.0	42.9			20.1	76.7	46.7	42.9		

CR = complete response, OS = overall survival, PFS = progression-free survival, TNM = tumor-node-metastasis, VEGF = vascular endothelial growth factor.

The multivariate analysis indicated that TNM stage, pathological response, and serum VEGF trend are prognostic factors of nonsurgical EC patients. A higher recurrence rate in patients with a non-CR was observed, suggesting that more-intensive local treatment should be considered. Anti-angiogenic agents such as thalidomide can increase radiosensitivity in EC cells and reduce VEGF expression in EC patients with a rising VEGF level in response to radiotherapy, therefore enhancing the therapeutic efficacy and improving prognosis.^[19,20]

In conclusion, the pathological response to radiotherapy and VEGF trend are both closely associated with CRT efficacy and prognosis in nonsurgical EC patients. Our study has identified potential radiosensitivity indicators for prognosis in EC, which may be important for the adjustment of therapeutic plans and guidance for individualized therapy.

5. Article highlights

5.1. Background

ESCC is the predominant histological subtype of esophageal cancer in China. Radiotherapy is the main treatment for

advanced esophageal cancer. Although radiotherapy technology has made great progress, the 5-year survival rate is still only 10% to 39%. Few studies have investigated the pathological responses in the tumor tissues and the changes in VEGF serum level in EC patients receiving radiotherapy or CRT. We studied the impacts of these 2 factors on the prognosis of the patients with confirmed ESCC using data from the Department of Radiotherapy at the Second People's Hospital of Changzhou.

5.2. Research frontiers

The main reason for the poor efficacy of radiotherapy for esophageal cancer may be the existence of radiation-resistant cells in esophageal cancer tissues. Anti-angiogenesis therapy is an effective way to overcome esophageal hypoxia and improve radiotherapy sensitivity of esophageal cancer cells. Among the many factors regulating angiogenesis, VEGF is most closely related to radiotherapy sensitivity of esophageal cancer. The expression of VEGF in esophageal cancer tissues is negatively correlated with radiosensitivity.

Table 5
Multivariate analysis of OS and PFS as prognostic factors in EC.

Clinical parameter	RR	95% CI	P
OS			
Sex			
Male vs female	1.033	0.572–1.745	.915
Age			
<60 vs ≥60 y	1.054	0.561–1.983	.869
Tumor location			
Upper vs middle	0.607	0.322–1.145	.123
Upper vs lower	0.488	0.230–1.036	.062
TNM stage			
I vs II	0.391	0.167–0.917	.031
I vs III	0.120	0.033–0.430	.001
Therapeutic method			
RT vs CRT	1.286	0.671–2.465	.448
Pathological responses			
CR vs non-CR	0.463	0.224–0.958	.038
VEGF trends			
Increased vs stable	1.566	0.841–2.916	.157
Increased vs decreased	2.722	1.293–5.731	.008
PFS			
Sex			
Male vs female	1.018	0.559–1.855	.953
Age			
<60 vs ≥60 y	1.140	0.627–2.074	.667
Tumor location			
Upper vs middle	0.687	0.375–1.261	.225
Upper vs lower	0.548	0.250–1.202	.133
TNM stage			
I vs II	0.331	0.142–0.774	.011
I vs III	0.110	0.031–0.382	.001
Therapeutic method			
RT vs CRT	1.233	0.643–2.361	.528
Pathological responses			
CR vs non-CR	0.443	0.219–0.898	.024
VEGF trends			
Increased vs stable	1.574	0.834–2.969	.162
Increased vs decreased	2.408	1.129–5.137	.023

EC=esophageal carcinoma, CR=complete response, CRT=chemoradiotherapy, OS=overall survival, VEGF=vascular endothelial growth factor.

5.3. Innovations and breakthroughs

This is one of the largest studies on the pathological response and change in serum VEGF, and explores their correlation with the prognosis of nonsurgical patients with EC treated with CRT. It showed that the expression of VEGF in the blood of patients with esophageal cancer was closely related to the efficacy and prognosis of radiotherapy. It can be seen that anti-angiogenic drugs targeting VEGF enhance the sensitivity of esophageal cancer to radiotherapy.

5.4. Applications

The pathological response of tumor tissue and the changes in serum VEGF in the course of radiotherapy and chemotherapy can predict therapeutic efficacy in patients with esophageal cancer. The pathological response and changes in VEGF during treatment are important in guiding individualized treatment, which can benefit patients with esophageal cancer.

Author contributions

Sun SP, Wang J, and Yu JP designed the research; Wang JL, Ni XC, and Sun ZQ performed the research; Sun W and Nie B analyzed the data; Wang JL and Wang J wrote the paper.

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