Original Article

Serum VEGF during chemo-radiotherapy and its clinical significance in esophageal squamous cell carcinoma

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Background: Many studies have focused on the relationship between dynamic changes in serum vascular endothelial growth factor (VEGF) and the prognosis of esophageal cancer (EC) patients undergoing chemo-radiotherapy (CRT). Few studies have reported the appropriate time-point for the measurement of VEGF during radiotherapy. In this study, we aimed to identify the appropriate time-point for VEGF measurement during radiotherapy among EC patients.

Methods: Serum VEGF in 76 EC patients was determined before, during (per 10 Gy) and after radiotherapy. The levels were categorized into three groups depending on the VEGF changes: increased, stable and decreased.

Results: The 1-year overall survival (OS) and progression-free survival (PFS) rates of the patients were 55.7% and 51.4%, respectively, with median OS of 15.8 months [95% confidence interval (CI): 10.4–21.2 months] and 12.5 months (95% CI: 7.6–17.5 months), respectively. There were 13 cases of recurrence within 2 years post-treatment. The 1-yr OS rates of the patients with increased, stable and decreased VEGF were 31.6%, 60.0% and 71.4%, respectively (P=0.034). Significant differences were noticed in the 1-yr PFS rates among those with increased, stable and decreased VEGF (P=0.039). The 1-yr local control (LC) rates showed no significant differences (P=0.306). Compared to those before radiotherapy, the serum VEGF levels of 19 patients were found to be increased at approximately 20–30 Gy during radiotherapy or post-radiotherapy. VEGF decreases were noticed in 21 cases at 20–30 Gy during radiotherapy.

Conclusions: Serum VEGF changes could be used to predict the prognosis of EC patients undergoing CRT. It is appropriate to determine serum VEGF at 20–30 Gy during radiotherapy and post-radiotherapy among EC patients.

Keywords: Esophageal cancer (EC); radiotherapy; vascular endothelial growth factor (VEGF); prognosis

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Introduction

Esophageal squamous cell carcinoma (ESCC), a malignant tumor of the digestive system (1,2), accounts for approximately 80% of all esophageal cancer (EC) cases worldwide. More than 60% of patients with EC cannot undergo surgical treatment because they are diagnosed at advanced stages (3). Recently, chemo-radiotherapy (CRT) has been commonly used for the treatment of patients with EC (4). Unfortunately, a majority of EC patients (approximately 60–70%) show poor response after treatment due to local recurrence and/or metastasis with a 5-yr survival rate of 20–42.5% (5-7).

Vascular endothelial growth factor (VEGF), an independent prognostic factor for EC, plays an important role in recurrence and metastasis (8). Our previous studies indicated that increased VEGF in EC correlated with poor prognosis in those receiving radiotherapy. Meanwhile, decreased VEGF levels during/post radiotherapy were associated with satisfactory responses (3,9). Antiangiogenic drugs (e.g., thalidomide) combined with radiotherapy reduced VEGF levels in patients with EC and may improve the prognosis (10). In clinical practice, the alternation of serum VEGF in patients undergoing radiotherapy is usually reflected in the comparison between serum VEGF in the fourth week during radiotherapy or post-radiotherapy and the level determined pre-radiotherapy. However, few studies have been focused on whether the timing of serum VEGF determination is appropriate, as well as whether it reflects VEGF changes in a timely manner.

In the present study, serum VEGF was determined before, during (per 10 Gy) and after radiotherapy. Changes in serum VEGF levels were analyzed, and the correlation between serum VEGF changes and prognosis was explored.

Methods

Clinical data

A total of 76 patients [male: 57, female: 19; Karnofsky (KPS) score: ≥80; age: 44–86 y, median age: 67 y] with ESCC treated for the first time in the Department of radiotherapy of Changzhou No. 2 People's Hospital between March 2012 and November 2014 were included in this study. Among these patients, 2 had lesions in cervical segments, 17 had lesions in the upper thoracic portion, 27 had lesions in the mid-thoracic portion, and 30 had lesions in the lower thoracic portion. The pathological types were medullary type (n=71), ulcerative type (n=2) and mushroom type (n=3). According to the AJCC esophageal cancer staging system (the 7th Edition) (11), 2 were T_1 stage, 4 were T_2 stage, 58 were T_3 stage, 12 were T_4 stage, 10 were N_0 stage, 59 were N_1 stage, 7 were N_2 stage, 2 were TNM I stage, 64 were TNM II stage and 10 were TNM III stage. Thirty healthy individuals (male: 18, female: 12, age: 26–45 y, average: 33.3 y) were selected as controls. Written informed consent was obtained from each patient. The study protocols were approved by the Ethical Committee of Changzhou No. 2 People's Hospital (No. 2012-S002-01).

Treatment

Patients received CT simulation in the supine position, and CT images were obtained at 5-mm thickness throughout the entire neck and thorax. Treatment plans were generated using a three-dimensional planning system (Pinnacle 3, version 9.3). Radiation was given with 6-MV photon energy using a three-dimensional conformal technique. The gross tumor volume (GTV) included primary tumor (GTVp) and metastatic lymph nodes (GTVn). Clinical target volume (CTV) consisted of GTVp plus 3–5 cm of proximal and distal normal esophagus without lateral margins and GTVn. Planning target volume (PTV) was determined by adding a 1-cm margin around the CTV. Conventional dose fractionation was used to ensure PTV with a radiation dose of 60–66 Gy (30–33 fractions/6–6.6 weeks). Twenty-three patients received single radiotherapy. Fifty-three patients received concurrent chemotherapy (1–2 cycles) using a regimen including paclitaxel (Lvye Pharma, Nanjing, China; d1, 135 mg/m^2) and cisplatin (Hanson Pharma, Lianyungang, China; d2–5, 20 mg/m^2). Patients received maintenance chemotherapy (1–3 cycles, 21–28 days for each cycle) after radiotherapy.

Measurement of serum VEGF

Peripheral venous blood was collected to determine serum VEGF using a commercial ELISA kit (Pierce Biotech, Rockford, IL, USA), according to the manufacturer's instructions. Blood sample collection was performed one week before radiotherapy, as well as during (per 10 Gy) and after radiotherapy. Blood samples (2 mL) were centrifuged at 3,000 r/min for 10 min. The obtained sera were stored at −70 ℃ until use.

Table 1 Comparison of serum VEGF at different time points with the normal control

Time point	Serum VEGF (ng/L)	D-value	SD	T value	P
1 week before RT	101.7±22.4	21.8	6.190	3.526	0.001
10 Gy	97.3±17.2	17.4	5.650	3.089	0.003
20 Gy	96.9±20.2	17.2	5.939	2.910	0.004
30 Gy	95.2±17.9	15.4	5.758	2.681	0.009
40 Gy	92.3±19.2	12.8	5.840	2.193	0.031
50 Gy	91.9±18.3	12.1	5.749	2.114	0.037
1 week after RT	93.8±19.2	13.9	5.864	2.379	0.019

The serum VEGF for normal control was 79.6±39.2 ng/L. VEGF, vascular endothelial growth factor; RT, radiotherapy.

Follow-up

The primary lesions in the esophagus were evaluated by barium enema. Treatment efficiency of the lymph node metastatic lesions was evaluated based on the response evaluation criteria in the solid tumors (RECIST 1.1) guidelines (12). Follow-up was carried out every 3 months among those with an overall survival (OS) of 2 y and every 6 months among those with an OS of >2 y. For each visit, data collection including case history, physical examination, complete peripheral blood tests, electrocardiography, ultrasonic examination of the abdomen, esophageal barium radiography and chest CT were performed. Outcomes included OS, progression-free survival (PFS) and local control (LC).

Statistical analysis

All data were analyzed by SPSS 19.0 (SPSS version19.0, Inc., Chicago, IL, USA). The measurement data were presented as the mean ± standard deviation (SD). The Chi-square test was used to compare several groups. Variance analysis was used to compare the means among the multi-group measurement data. The same index measured at various time points was included in the one-way ANOVA with repeated measures. The determination was performed at least in triplicate. Prognosis analysis was carried out using the Kaplan-Meier method and the Log Rank test. Multivariate analysis was performed using the Cox proportional hazards model. $P<0.05$ was considered statistically significant.

Results

Results of follow-up and survival

All 76 patients completed the therapy. Six patients dropped out from the group due to absence of serum VEGF drawn on time. All patients were followed-up for 12–47 months until December 31, 2015. During follow-up, 48 patients died. The 1-yr OS rate and 1-yr PFS rates were 55.7% and 51.4%, respectively. The median OS and PFS were 15.8 months (95% CI: 10.4–21.2 months) and 12.5 months (95% CI: 7.6–17.5 months), respectively. Thirteen patients showed recurrence within 2 years, and the median recurrence time was 7.7 months (95% CI: 4.9–10.4 months).

Effects of CRT on serum VEGF level

The levels of serum VEGF before, during (10–50 Gy) and after treatment were 101.7±22.4, 97.3±17.2, 96.9±20.2, 95.2±17.9, 92.3±19.2, 91.9±18.3 and 93.8±19.2 ng/L. Compared with the normal control, serum VEGF was substantially higher during and after radiotherapy ($P<0.05$, *Table 1*). The standard deviation (SD) of serum VEGF was 8.1 ng/L, and 2 SD was 16.2 ng/L. VEGF with an increase or decrease of 2 SD compared to the baseline level was defined as increased or decreased, respectively. A VEGF change of less than 2 SD was defined as stable. The patient numbers with increased, stable or decreased VEGF were 19, 30 and 21, respectively. One-way ANOVA with repeated measures indicated that the serum VEGF during radiotherapy showed significant decreases compared with those of baseline levels that showed gradual decreases from week 1 to week 5 during radiotherapy ($F_{time}=6.806$, $P<0.05$; $F_{group}=5.783$, $P<0.05$; $F_{time\times group}=12.004$, $P<0.001$, *Table 2*).

Correlation between serum VEGF change and EC prognosis

Pre-radiotherapy serum VEGF showed no correlations with

Table 2 Effects of radiotherapy on changes of serum VEGF (ng/L)

Group	1 week before RT	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy	Post-RT
Increase	89.1±18.6	92.6±16.4	99.4±22.7	101.9±22.4	97.5±25.4	97.8±23.4	100.9±24.5
Stable	96.0±16.1	93.5±15.7	93.1±16.1	92.7±15.9	91.8±16.7	91.9±15.5	93.0±15.8
Decrease	113.13±22.9	102.4±18.5	98.0±21.3	95.1±16.9	89.7±16.4	87.9±16.4	89.4±17.6

F_{time} =6.806, P<0.05; F_{groups} =5.783, P<0.05; $F_{time\times groups}$ =12.004, P<0.001. VEGF, vascular endothelial growth factor; RT, radiotherapy.

Table 3 The VEGF trends with different gender, age, tumor location, tumor type, T stage, N stage and TNM stage

Clinical parameter	N	VEGF trends			P
		Increased	Stable	Decreased	
Gender					0.093
Male	53	17	19	17	
Female	17	2	11	4	
Age(years)					0.262
<60	11	1	7	3	
≥60	59	18	23	18	
Tumor location					0.704
Upper thoracic	15	5	6	4	
Middle thoracic	25	5	10	10	
Lower thoracic	30	9	14	7	
Tumor type					0.463
Medullary	67	19	29	19	
Mushroom	3	0	1	2	
T stage					0.434
T_1	2	0	1	1	
T_2	4	1	2	1	
T_3	60	18	23	19	
T_4	4	0	4	0	
N stage					0.201
N_0	8	0	2	6	
N_1	55	16	24	15	
N_2	7	3	4	0	
TNM stage					0.144
I	2	0	0	2	
II	59	16	24	19	
III	9	3	6	0	

VEGF, vascular endothelial growth factor.

OS (r= –0.033, P=0.789) or PFS (r= –0.056, P=0.645). The VEGF changes (increased, stable or decreased) in patients with different gender, ages, tumor locations, tumor types, T stages, N stages, TNM stages and treatment regimens are shown in *Table 3*. Among the patients with increased VEGF, serum VEGF increased from 10 to 50 Gy during the

Table 4 Increase of VEGF at different time points in each patient

Case	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy	Post-radiotherapy
Increase 1	–	–	↑	↑	–	↑
Increase 2	–	↑	↑	–	↑	↑
Increase 3	–	↑	–	–	–	–
Increase 4	–	–	↑	↑	↑	–
Increase 5	–	↑	–	↑	–	↑
Increase 6	–	↑	↑	–	–	–
Increase 7	–	↑	–	–	–	–
Increase 8	–	↑	↑	–	–	↑
Increase 9	–	–	↑	–	–	–
Increase 10	–	↑	↑	–	–	↑
Increase 11	–	↑	–	–	–	↑
Increase 12	–	↑	↑	–	–	–
Increase 13	–	–	↑	–	–	↑
Increase 14	–	↑	–	–	↑	↑
Increase 15	–	–	↑	↑	↑	–
Increase 16	↑	↑	–	–	–	–
Increase 17	–	↑	–	–	–	↑
Increase 18	–	↑	↑	–	–	–
Increase 19	–	–	↑	↑	–	↑

↑ , Increase of VEGF; –, stable VEGF. VEGF, vascular endothelial growth factor.

radiotherapy in 1, 13, 12, 5 and 4 patients, respectively. Ten patients showed decreased serum VEGF post-radiotherapy. Patients with increased VEGF at 10, 40 and 50 Gy also showed increases at 20, 30 Gy and post-radiotherapy (*Table 4*). Among the patients with decreased VEGF, decreases were observed per 10 Gy during radiotherapy and post-radiotherapy in 3, 16, 13, 7, 4 and 4 patients, respectively. Cases with decreased VEGF at 10, 40, 50 Gy and post-radiotherapy also showed decreases at 20, 30 Gy (*Table 5*). The 1-yr OS rate, 1-yr PFS rate and 1-yr LC rate of patients are shown in *Table 6*. Comparison of the OS and PFS are shown in *Figures 1* and *2*, respectively.

Prognostic factor analysis

Univariate analysis showed that age, gender, tumor sites and types showed no substantial effects on survival time, while tumor length before and after radiotherapy, tumor diameter, T stage, N stage, TNM stage and VEGF levels had substantial effects on survival time (*Table 7*). Multivariate analysis showed that TNM stages, VEGF levels, and tumor length after the radiotherapy were prognostic factors for patients (*Table 8*).

Discussion

VEGF, an important cytokine secreted by vascular endothelial cells (VSCs), specifically promotes endothelial cell division and increases capillary permeability (13). In normal cells such as VSCs, esophageal mucosal cells and macrophages, VEGF is involved in vascular density and basic capillary permeability (14,15). In cancer tissues, VEGF is over-expressed and is essential for tumor progression and metastasis (16-18). Studies showed that VEGF was over-expressed in several tumors including ESCC, and high VEGF expression in ESCC was related with progression (19) and/or poor prognosis (13,19-23). Serum VEGF level was positively correlated with tumor load, depth of invasion and

Table 5 Decrease of VEGF at different time points in each patient

Case	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy	Post-radiotherapy
Decrease 1	↓	↓	–	–	–	–
Decrease 2	–	↓	–	–	–	↓
Decrease 3	–	↓	–	–	↓	↓
Decrease 4	–	↓	↓	–	–	–
Decrease 5	–	–	↓	↓	–	–
Decrease 6	–	↓	–	↓	–	–
Decrease 7	–	↓	↓	–	–	–
Decrease 8	–	↓	↓	–	–	–
Decrease 9	↓	–	↓	–	–	–
Decrease 10	–	–	↓	↓	–	–
Decrease 11	–	↓	–	–	↓	–
Decrease 12	–	↓	↓	–	–	–
Decrease 13	–	↓	–	–	↓	–
Decrease 14	–	–	↓	–	↓	–
Decrease 15	–	↓	↓	–	–	↓
Decrease 16	↓	↓	–	↓	–	↓
Decrease 17	–	↓	–	↓	–	–
Decrease 18	–	↓	↓	–	–	–
Decrease 19	–	↓	↓	–	–	–
Decrease 20	–	↓	↓	↓	–	–
Decrease 21	–	–	↓	↓	–	–

↓ , Decrease of VEGF; –, stable VEGF. VEGF, vascular endothelial growth factor.

Table 6 Relationship between the changes in post-radiotherapy serum VEGF and the 1-year OS, PFS and LC rates in EC patients

Change in VEGF	N	1-yr OS rate (%)	1-yr PFS rate (%)	1-yr LC rate (%)
Increase	19	31.6	26.3	89.5
Stable	30	60.0	60.0	73.3
Decrease	21	71.4	61.9	85.7
χ^2 value		6.811	6.602	–
P value		0.034	0.039	0.306

–, Fisher exact test. VEGF, vascular endothelial growth factor; OS, overall survival; EC, esophageal cancer; PFS, progression-free survival.

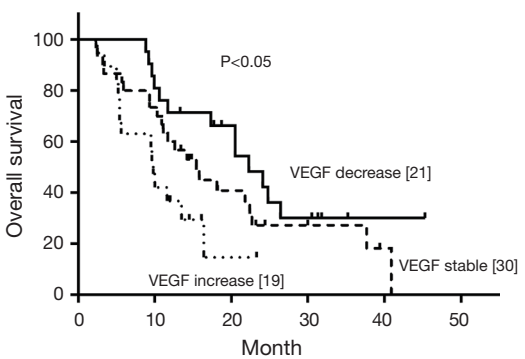

Figure 1 Comparison of OS in various VEGF changes among EC patients. VEGF, vascular endothelial growth factor; OS, overall survival; EC, esophageal cancer.

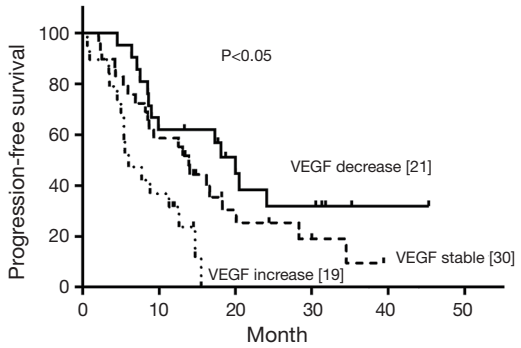

Figure 2 Comparison of PFS in various VEGF changes among EC patients. VEGF, vascular endothelial growth factor; EC, esophageal cancer; PFS, progression-free survival.

lymph node metastasis (20-22).

Our previous study suggested that VEGF levels in patients undergoing CRT were related to radiosensitivity and prognosis (3). Serum VEGF showed significant decreases during radiotherapy in patients with good prognosis, while levels showed significant increases during radiotherapy in those with poor prognosis. This outcome may be related to the self-protection of cancer cells against vascular toxicities induced by irradiation. In the present study, the clinical value of VEGF for patients undergoing CRT was evaluated, showing that high expression levels of VEGF were associated with poor prognosis and OS.

VEGF expression in tumor tissues is closely related

Table 7 Univariate analysis of prognostic factors of OS in EC patients

Clinical parameter	B	SE	Wald	df	P	RR (95% CI)
Gender	0.102	0.325	0.098	1	0.754	1.107 (0.585–2.096)
Age	–0.563	0.357	2.482	1	0.115	0.570 (0.283–1.147)
Tumor location	–	–	0.233	2	0.890	–
Middle thoracic	–0.133	0.374	0.126	1	0.723	0.875 (0.420–1.824)
Lower thoracic	–0.145	0.328	0.194	1	0.659	0.865 (0.455–1.646)
Tumor type	–0.651	0.605	1.161	1	0.281	0.521 (0.159–1.705)
Pre-treatment tumor length	0.431	0.133	10.508	1	0.001	1.538 (1.186–1.996)
Pre-treatment tumor diameter	0.376	0.163	5.309	1	0.021	1.457 (1.058–2.006)
Tumor length at week four	0.277	0.184	2.255	1	0.133	1.319 (0.919–1.894)
Post-treatment residual tumor length	0.653	0.143	20.814	1	0.000	1.922 (1.452–2.545)
TNM stage	1.923	0.415	21.488	1	0.000	6.839 (3.034–15.419)
T stage	0.967	0.425	5.188	1	0.023	2.630 (1.144–6.044)
N stage	0.994	0.461	4.653	1	0.031	2.702 (1.095–6.665)
Treatment methods	–0.330	0.303	1.188	1	0.276	0.719 (0.397–1.302)
VEGF changes	–0.419	0.168	6.256	1	0.012	0.657 (0.473–0.913)

VEGF, vascular endothelial growth factor; OS, overall survival; EC, esophageal cancer.

Table 8 Multivariate analysis of prognostic factors of OS in EC patients

Clinical parameter	B	SE	Wald	P	RR (95% CI)
Post-treatment residual tumor length	0.597	0.168	12.664	<0.001	1.817 (1.308–2.525)
TNM stage	1.957	0.707	7.665	0.006	7.081 (1.771–28.305)
VEGF changes	–0.445	0.184	5.842	0.016	0.641 (0.447–0.919)

VEGF, vascular endothelial growth factor; OS, overall survival; EC, esophageal cancer.

with radiotherapy sensitivity, manifested by higher serum VEGF levels in those with poor radiosensitivity (24). To date, several studies have been conducted to investigate the relationship between pre-radiotherapy serum VEGF level and prognosis, however, the results remain controversial. For example, Rades *et al.* showed that pre-radiotherapy VEGF levels were negatively correlated with the prognosis in local advanced ESCC (25). Our previous study showed that pre-radiotherapy serum VEGF levels had no correlation with prognosis (3). Cheng *et al.* (26) found that pre-radiotherapy VEGF levels were negatively correlated with PFS and had no correlation with OS. Yoon *et al.* (27) reported that high VEGF levels before radiotherapy were positively correlated with complete response after radiotherapy. Our data showed that pre-radiotherapy serum VEGF levels showed no correlation with OS or PFS. Pre-radiotherapy VEGF levels had no correlation with LC rate.

The combination of anti-angiogenic agent(s) and radiotherapy contributed to the decrease in VEGF, possibly being promising for the treatment of cancer patients with VEGF increases (28-32). The prognosis of patients with decreased serum VEGF during the radiotherapy showed more satisfactory responses than those without. For these patients, anti-angiogenic therapy caused no additional benefits (10). To date, there remains no consensus regarding the selection of patients with increased VEGF level during radiotherapy, as well as the appropriate time for the administration of anti-angiogenic agent(s) over time. In our study, VEGF levels were determined before, after, and every 10 Gy during radiotherapy, demonstrating that the VEGF increased at 20 and 30 Gy during radiotherapy and post-radiotherapy. Patients with decreased VEGF showed decreased VEGF at 20 and 30 Gy during radiotherapy. Thus, 20 and 30 Gy during radiotherapy or post-radiotherapy may be the suitable time for determination of VEGF levels based on our data. Future studies are needed to confirm this aspect.

In conclusion, changes in VEGF levels were associated with prognosis in ESCC receiving CRT. VEGF levels during radiotherapy may serve as a factor for evaluating radiosensitivity and prognosis. Doses of 20 and 30 Gy during radiotherapy or post-radiotherapy may be the suitable times for the determination of VEGF levels. Our study provided a theoretical basis for the management of ESCC in clinical practice.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.08.32). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocols were approved by the Ethical Committee of Changzhou No. 2 People's Hospital (No. 2012-S002-01) and written informed consent was obtained from all patients.

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