

## Clinical trial of thalidomide combined with radiotherapy in patients with esophageal cancer

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### Abstract

**AIM:** To investigate the short-term efficacy and tolerability of radiotherapy plus thalidomide in patients with esophageal cancer (EC).

**METHODS:** Serum samples from 86 EC patients were collected before, during, and after radiotherapy, and the vascular endothelial growth factor (VEGF) level was examined by ELISA. According to the change in serum VEGF level during radiotherapy, the patients were divided into two groups: in the drug group, VEGF level was increased or remained unchanged, and thalidomide was administered up to the end of radiotherapy; in the non-drug group, VEGF level was decreased and radiotherapy was given alone. Thirty healthy volunteers served as controls. The efficacy and safety of radiotherapy plus thalidomide therapy were investigated.

**RESULTS:** The 86 EC patients had a significantly

higher level of VEGF compared with the 30 healthy controls before radiotherapy ( $P < 0.01$ ), and the VEGF level was significantly correlated with primary tumor size, lymph node metastasis, histopathologic type, and clinical stage ( $P < 0.01$ ). Of 83 evaluable cases, VEGF level was significantly decreased after radiotherapy in 32 patients in the drug group ( $P < 0.05$ ), with an effective rate of 71.88%. The incidence of dizziness and/or burnout in the drug group and non-drug group was 62.50% and 15.69%, respectively ( $P = 0.000$ ), and the incidence of somnolence was 12.50% and 0%, respectively ( $P = 0.019$ ). No significant differences were observed.

**CONCLUSION:** Thalidomide can down-regulate serum VEGF level in EC patients, and combined with radiotherapy may improve treatment outcome. Thalidomide was well tolerated by EC patients.

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**Key words:** Thalidomide; Radiotherapy; Esophageal cancer; Vascular endothelial growth factor

**Core tip:** Vascular endothelial growth factor (VEGF)-based individualized radiotherapy for esophageal cancer (EC) was achieved in this clinical study. EC patients undergoing radiation treatment may receive different protocols: thalidomide combined with radiation or radiation alone, according to their VEGF level. This study was designed to set appropriate radiotherapy regimens for different patients, improve sensitivity, and decrease resistance in radiation oncology.

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## INTRODUCTION

In 1971, Folkman proposed that tumor growth is angiogenesis-dependent, which resulted in a new concept for the control of tumor growth. Previous studies also demonstrated that, of all the angiogenesis-related factors, vascular endothelial growth factor (VEGF) is the most important. Many researchers have reported that VEGF is an independent prognostic factor of esophageal cancer (EC) that plays a decisive role in the recurrence and metastasis of EC<sup>[1-4]</sup>. Moreover, research has indicated a negative relationship between VEGF expression in tumor tissue and radiosensitivity; tumors with high VEGF expression have poor sensitivity to radiotherapy, and thus predict a poor prognosis<sup>[5-8]</sup>. Given these findings, radiotherapy combined with an anti-VEGF-mediated anti-angiogenesis protocol is expected to cast new light on EC treatment.

Thalidomide<sup>[9-13]</sup> was marketed as a non-prescription sedative in Europe in 1956, and was withdrawn from the market in the early 1960s due to strong teratogenic effects. Surprisingly, in the 1990s, thalidomide was reported to be effective in the treatment of AIDS complications, multiple myeloma, and other tumors, which was largely attributable to its anti-neoangiogenic effect. Therefore, in 1998 thalidomide was again approved by the FDA for the treatment of tumors. Subsequent studies confirmed that thalidomide could inhibit VEGF and basic fibroblast growth factor (bFGF) secretion, and had immunoregulatory, anti-tumor proliferation, and metastasis effects<sup>[14-17]</sup>.

In the present study we used thalidomide to down-regulate VEGF expression in EC patients receiving radiotherapy, with the intention of improving the radiotherapy outcome of EC patients. From July 2009, we divided EC patients receiving radiotherapy into two groups according to the change in serum VEGF levels. Patients with increased or unchanged VEGF levels during radiotherapy were also given thalidomide. The efficacy, side effects (SE), and toxicity of the combination therapy were determined.

## MATERIALS AND METHODS

### Eligibility and baseline parameters

Between July 2009 and March 2011, 86 patients with pathologically-confirmed EC with no prior treatment were enrolled in this study, including those classified as having early esophageal carcinoma that had rejected surgical therapy for underlying diseases or other personal reasons. The clinical baseline evaluation on admission included general and baseline investigations. General investigations included a complete medical history, physical examination, routine blood examination, blood biochemistry, routine urine examination, routine stool examination, abdominal Doppler ultrasound, and an electrocardiogram (ECG). Baseline investigations included chest computed tomography (CT), upper gastroenterography, and serum VEGF level. The 86 patients included 62 males and 24 females, with a median age of 66.4 years (range, 40-86 years). Ac-

cording to the CT staging strategy for EC proposed by Kienle *et al.*<sup>[18]</sup>, 15 cases were at stage I, 45 at stage II, 9 at stage III, and 17 at stage IV. Histopathologic typing identified squamous cell carcinoma in 81 cases, adenocarcinoma in 3 cases, and small cell carcinoma in 2 cases. X-ray pathologic typing showed marrow type in 76 cases, massive type in 5, ulcer type in 3, and narrow type in 2. The blood specimens from 30 healthy volunteers (including 18 males and 12 females, with a median age of 33.3 years and a range of 26-45 years) were used as controls. An increase or decrease in VEGF of 10% compared with the VEGF level before radiotherapy was deemed clinically significant. The study was approved by the Institutional Review Board (IRB) of the Second People's Hospital of Changzhou. All patients were well-informed of the possible treatment side effects, toxicities, and complications, and informed consent was obtained from each patient.

### Radiotherapy

The patients were placed in the supine position, with both hands on their head and fixed using a mold immobilizing technique. Twenty patients received conventional X-ray simulation and three-field radiotherapy; one anterior (width 6 cm) and two posterior (width 4.5-5.5 cm), with both upper and lower margins being 3-5 cm. Forty-seven patients received CT simulation and three-dimensional conformal radiation therapy (3DCRT). The gross target volume (GTV) consisted of thickened esophagus wall according to CT (the results of esophagography and esophagoscopy were also considered) and enlarged lymph nodes with a diameter  $\geq 1$  cm. Clinical target volume (CTV) covered the GTV + 2.5-3.0 cm of the craniocaudal margin + 0.5-0.8 cm of the transverse and anteroposterior margin + the corresponding lymphatic drainage region. A 0.5 cm isotropic margin was added to the CTV to make up the planning target volume (PTV). This ensured that the prescribed dose covered 95% of the PTV, with the maximum dose for spinal cord  $< 45$  Gy and for both lung  $V_{20} < 30\%$ . 1.8-2.0 Gy/fraction, 5 fractions a week, with a total dose of 60-72 Gy, were delivered to all patients by a 6-MV-X-ray linear accelerator.

### VEGF determination

Peripheral venous blood samples were obtained within one week before, during (3-4 wk), and within one week after radiotherapy. The samples (2 mL for each) were well mixed and centrifuged (4 °C, 3000 r/min, radius was 10 cm) for 10 min, and the obtained sera were stored at -70 °C until use. Serum VEGF level was determined by enzyme-linked immunosorbent assay (ELISA) (Purchased from 4A Biotech Co., Ltd, Beijing).

### Administration of thalidomide

Serum VEGF level was determined in EC patients 3-4 wk after the initiation of radiotherapy, and patients with increased or unchanged VEGF levels compared with levels before radiotherapy were also given thalidomide. In the first week, thalidomide was given at 100 mg/d before

**Table 1 Relationship between pre-radiotherapy serum vascular endothelial growth factor level and clinical characteristics of esophageal cancer patients**

Variable	Cases	VEGF (ng/L)	t (F)	P value
Sex			1.11	> 0.05
Male	62	120.78 ± 44.72		
Female	24	135.92 ± 61.00		
Age, yr			0.89	> 0.05
< 55	71	126.96 ± 51.37		
≥ 55	15	115.73 ± 42.47		
Lesion site			0.40	> 0.05
Cervical and upper thoracic segment	22	131.00 ± 59.42		
Middle thoracic segment	36	119.50 ± 36.04		
Lower thoracic segment	28	127.36 ± 57.71		
Histopathologic type			3.40	< 0.01
Squamous cell carcinoma	81	122.26 ± 45.91		
Adenocarcinoma	3	196.67 ± 115.14		
Small cell carcinoma	2	128.50 ± 19.09		
X-ray pathologic types			0.47	> 0.05
Marrow	76	126.89 ± 52.3		
Massive	5	120.40 ± 14.00		
Ulcer	3	94.67 ± 23.07		
Narrow	2	110.00 ± 31.11		
Primary foci			4.55	< 0.01
T1 + T2	29	99.66 ± 22.64		
T3 + T4	57	137.89 ± 54.95		
Lymph node metastasis			7.50	< 0.01
N0	30	89.80 ± 12.80		
N1-2	56	144.50 ± 51.69		
Distant metastasis			1.02	> 0.05
M0	65	128.15 ± 49.71		
M1	21	115.23 ± 50.36		
Clinical stage			2.52	< 0.01
I + II	60	115.08 ± 39.76		
III + IV	26	149.40 ± 63.20		

Vascular endothelial growth factor (VEGF) level in 86 esophageal cancer (EC) cases was significantly correlated with primary tumor size, lymph node metastasis, histopathologic type, and clinical stage of EC ( $P < 0.01$ ), but was not correlated with lesion site, distant metastasis, X-ray pathologic type, gender, or age ( $P > 0.05$ ).

sleep; if no side effects were observed, 200 mg/d was started from the next week up to the end of radiotherapy.

### Evaluation of short-term effect

Esophageal barium examination was performed in the fourth week and at the end of radiotherapy in all patients. The short-term effect was assessed according to the criteria of the International Union Against Cancer (UICC). Complete response (CR): mass shadow disappeared, mucosa returned to normal or became coarse, barium agent passed smoothly, no or slight rigidity of the esophagus, and no or slight stenosis. Partial response (PR): no obvious distortion or ulceration, tumor volume reduced by more than 50%, barium agent passed fairly smoothly, border not so smooth (with a little filling-defect or crater), or a smooth border, but with obvious stenosis. Minor response (MR): broadened lumen, improved distortion, and ulceration and tumor volume reduced by less than 50%. No change (NC): obvious filling-defect or crater, aggravated stenosis, no noticeable tumor volume

reduction or volume increase (by less than 25%). CR and PR were considered to demonstrate effective treatment, while MR and NC denoted ineffective treatment.

### Statistical analysis

All data were analyzed by SAS 9.0. Mean values for measurement data were presented as mean ± SD, differences in measurement data and enumeration data were compared using analysis of variance and  $\chi^2$  test, respectively. A  $P$  value less than 0.05 was considered statistically significant.

## RESULTS

### Relationship between pre-radiotherapy VEGF level and clinical characteristics of EC patients

The mean pre-radiotherapy serum VEGF level in the 86 EC patients was  $125.00 \pm 49.89$  ng/L, which was significantly higher than that in the 30 healthy controls ( $79.63 \pm 39.17$  ng/L,  $P < 0.01$ ). The pre-radiotherapy serum VEGF level in the 86 EC patients was significantly correlated with primary tumor size, lymph node metastasis, histopathologic type, and clinical stage, but was not correlated with lesion site, distant metastasis, X-ray pathologic types, gender, or age (Table 1).

### Dynamic changes in VEGF level

Serum VEGF levels were determined in all 86 EC patients before radiotherapy. Radiotherapy was discontinued in 3 cases due to intolerable complications. Of the remaining 83 evaluable EC cases, VEGF levels were significantly increased in 32 cases during radiotherapy ( $P < 0.01$ ); these patients were given thalidomide with radiotherapy (drug group), and their VEGF levels were significantly decreased at the end of treatment compared with those during radiotherapy ( $P < 0.05$ ). The other 51 patients, whose VEGF levels were significantly decreased during radiotherapy compared with before radiotherapy ( $P < 0.01$ ), received radiotherapy as initially planned (non-drug group); the VEGF levels in these patients were not significantly different during and after radiotherapy ( $P > 0.05$ ) (Table 2).

### Short-term response

The response rate (CR + PR) was 71.88% for 32 patients in the drug group and 78.43% for 51 patients in the non-drug group (Table 3).

### Side effects

The incidence of dizziness and/or burnout in the drug and non-drug groups was 62.50% and 15.69%, respectively ( $P = 0.000$ ), and the incidence of somnolence was 12.50% and 0%, respectively ( $P = 0.019$ ). These differences were significant. In the drug and non-drug groups, the incidence of grade III-IV esophagitis was 12.50% and 11.76% ( $P = 0.812$ ), grade III-IV leukocyte decrease was 6.25% and 9.80% ( $P = 0.864$ ), grade III-IV platelet decrease was 3.13% and 5.88% ( $P = 0.961$ ), and grade III-IV

**Table 2** Dynamic changes in vascular endothelial growth factor levels in 83 evaluable esophageal cancer patients

Group	<i>n</i>	Before radiotherapy	During radiotherapy	After radiotherapy
Drug group	32	98.56 ± 28.74	122.69 ± 43.03 <sup>d</sup>	109.53 ± 32.48 <sup>b</sup>
Non-drug group	51	141.76 ± 53.78	100.94 ± 22.61 <sup>c</sup>	100.31 ± 23.45

<sup>b</sup>*P* < 0.01 *vs* during radiotherapy (drug group); <sup>d</sup>*P* < 0.01 *vs* before radiotherapy (drug group); <sup>c</sup>*P* < 0.01 *vs* before radiotherapy (non-drug group).

nausea and vomiting was 9.38% and 27.45%, respectively (*P* = 0.089). Anaphylaxis was not observed in the two groups (*P* = 1.000) (Table 4). All patients tolerated the side effects, and there were no withdrawals due to them.

## DISCUSSION

EC is one of the most common malignant tumors in China, and radiotherapy is currently the main treatment for EC. However, the efficacy of radiotherapy has not improved over the past 30 years, with the 5-year survival rate being 15%-39%<sup>[19]</sup>. Improvements in treatment efficacy and patient compliance, and a reduction in recurrence, metastasis, and side effects are still the focus of EC studies.

Tumor growth is neo-angiogenesis-dependent, and VEGF has been demonstrated to be an independent prognostic factor for EC, and plays a key role in the recurrence and metastasis of EC. It has been reported that a high expression of VEGF may indicate poor radio-sensitivity and prognosis of tumors. Recent research has confirmed that thalidomide can inhibit VEGF secretion, tumor proliferation, and metastasis. In 1999, thalidomide was first reported by Singhal *et al*<sup>[14]</sup> in the treatment of refractory multiple myeloma, which yielded a clinical remission rate of 32%. Thalidomide was subsequently found to have definite effects on several malignant hematological tumors. Thalidomide, as an angiogenesis inhibitor, has become an important choice in the comprehensive treatment of solid tumors<sup>[20-22]</sup>.

Reports on the relationship between thalidomide and radiosensitivity of esophageal tumors are very rare. Between 2009 and 2010, we explored the relationship between thalidomide and the radiosensitivity of esophageal carcinoma cells, and found that thalidomide enhanced the radiosensitivity of esophageal carcinoma cells both *in vitro* and *in vivo*, probably by down-regulating VEGF expression in esophageal carcinoma cells<sup>[23,24]</sup>. In addition, our previous clinical research also demonstrated that the response rate to radiotherapy was 61.90% in EC patients, with increased VEGF level during radiotherapy and 90.25% in those with decreased VEGF level, suggesting that patients with increased VEGF were resistant to radiotherapy. Therefore, the dynamic variation in serum VEGF plays a key role in predicting the radiosensitivity of EC patients. In the present study, we found that the

**Table 3** Response rate of 83 evaluable esophageal cancer patients *n* (%)

Group	<i>n</i>	CR	PR	MR	NC
Drug group	32	10 (31.25)	13 (40.63)	7 (21.87)	2 (6.25)
Non-drug group	51	26 (50.98)	14 (27.45)	7 (13.73)	4 (7.84)

CR: Complete response; MR: Minor response; PR: Partial response; NC: No change.

**Table 4** Side effects in 83 evaluable esophageal cancer cases

Side effects	Group		$\chi^2$	<i>P</i> value
	Drug group	Non-drug group		
Dizziness or burnout	20	8	19.28	0.000
Somnolence	4	0	-	0.019
Grade III-IV esophagitis	4	6	0.06	0.812
Grade III-IV leukocyte decrease	2	5	0.03	0.864
Grade III-IV platelet decrease	1	3	0.02	0.961
Grade III-IV nausea and vomiting	3	14	2.913	0.089
Anaphylaxis	0	0	-	1.000

pre-radiotherapy VEGF level in 86 EC cases was significantly higher than that in the healthy controls, and was correlated with primary tumor size, lymph node metastasis, histopathologic type, and clinical stage of EC, and was not correlated with lesion site, distant metastasis, X-ray pathologic type, gender, or age. These results indicated that high VEGF levels help to maintain hypertonic status, and can increase tumor vessel permeability, thus exerting a significant influence on the invasion and metastasis of EC cells. These findings suggest that VEGF is a key indicator for evaluating biological behavior and predicting the prognosis of EC. In this study, VEGF level was significantly increased in 32 EC patients during radiotherapy, and when thalidomide was given concurrently with radiotherapy, this resulted in a significantly decreased VEGF level at the end of treatment; 32 patients had a response rate (CR + PR) of 71.88%. These results indicate that thalidomide may improve the radiosensitivity of EC patients with high VEGF expression by down-regulating the VEGF level and improving the outcome of radiotherapy.

Teratogenesis is the main side effect of thalidomide, and other frequent side effects include central nervous system symptoms such as dizziness, burnout, and somnolence, followed by peripheral neuropathy; venous thromboembolism (VTE) is the most severe side effect<sup>[25]</sup>. Neither VTE nor other severe side effects were observed in the 32 EC patients who received thalidomide in this study; only dizziness, burnout and/or somnolence were observed, which were tolerable after expectant treatment. It has been reported that the side effects of thalidomide are dose-related, and 90% of patients could tolerate a dose of 400 mg/d with few severe side effects;



the adverse reactions of thalidomide were alleviated or disappeared in most patients following dose reduction or drug discontinuation<sup>[26]</sup>.

Generally, EC patients have different degrees of psychological disorders, such as depression, anxiety, and dysphoria, resulting in insomnia, decreased quality of life, and in some cases radiotherapy has to be withdrawn. Thalidomide has been shown to have a satisfactory sedative effect, and in this study we noted that EC patients who received thalidomide had a better sleep and diet pattern, and their quality of life and treatment compliance were greatly improved. All patients in the drug group received radiotherapy up to the end of the treatment period without interruption. We also found that thalidomide could achieve a satisfactory sedative effect in advanced EC patients with persistent insomnia. Wijermans *et al*<sup>[27]</sup> and Tassinari *et al*<sup>[28]</sup> also demonstrated that thalidomide, as a TNF- $\alpha$  inhibitor, improved the quality of life of EC patients.

Currently available anti-angiogenesis drugs include Avastin and endostatin; however, they are very expensive and most patients cannot afford them, which greatly limits the clinical application of anti-angiogenesis therapy. In comparison, thalidomide has the advantages of low price, oral administration, and fewer side effects, making it an affordable agent for anti-angiogenesis-based target therapy.

These findings indicate that thalidomide has the potential to down-regulate serum VEGF in EC patients during radiotherapy, and the combination of thalidomide and radiotherapy can not only increase the response rate of EC patients to radiotherapy, but also improve their quality of life and treatment compliance. Considering the relatively small sample size of the present study, we plan to conduct a clinical randomized controlled trial with a larger sample size to further investigate the efficacy, side effects, and influence on long-term survival of this combined therapy, with the hope of providing a new treatment strategy for EC patients.

## COMMENTS

### Background

Angiogenesis is essential for tumor growth, invasion, metastasis, and relapse, and the pro-angiogenic vascular endothelial growth factor (VEGF) is a key factor. Esophageal cancer (EC) tumors which overexpress VEGF may indicate lymph node metastasis and poor prognosis, and VEGF has been shown to be an independent prognostic factor. A VEGF-targeted antiangiogenic agent combined with radiation may be a novel strategy for EC patients.

### Research frontiers

VEGF has been demonstrated to be a target for anti-angiogenesis therapy, but few reports on thalidomide as a radiation-sensitizing agent are available, and its influence on VEGF regulation remains undetermined.

### Innovations and breakthroughs

In this study, the authors found that the determination of VEGF level in EC patients can indicate whether a patient would benefit from radiation treatment.

### Applications

VEGF variation during radiotherapy has significance in predicting prognosis.

### Terminology

Thalidomide is a potential radiation-sensitizing agent which may cooperate with

radiation to down-regulate VEGF and enhance radiosensitivity in EC patients.

### Peer review

This study mainly focused on VEGF change in EC patients during radiation treatment under thalidomide intervention, as well as its influence on the patients' response and tolerance to radiotherapy.

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