Oncology and Translational Medicine
DOI 10.1007/s10330-018-0256-6

February 2018, Vol. 4, No. 1, P1–P5

ORIGINAL ARTICLE

Predictive value of serum levels of transforming growth factor beta 1 for the short-term effects of radiotherapy and chemotherapy in patients with esophageal cancer

Fei Gao[1] (✉), Lin Jia[1], Jianjun Han[1], Jisheng Wang[2], Yun Wang[1]

1 Department of Oncology, The Third Hospital of Mianyang, Sichuan Mental Health Center, Mianyang 621000, China
2 Department of Pharmacy, The Third Hospital of Mianyang, Sichuan Mental Health Center, Mianyang 621000, China

Abstract

Objective To investigate variation in levels of transforming growth factor beta 1 (TGF-β1) before and after radiotherapy in patients with esophageal cancer in order to evaluate the predictive value of TGF-β1 for the effects of radiotherapy

Methods A total of 140 patients with esophageal squamous carcinoma undergoing radical radiation therapy in the Department of Oncology from March 2015 to December 2017 were enrolled. The patients were divided into the effective (115 cases) and ineffective (25 cases) groups according to World Health Organization (WHO) criteria for the evaluation of solid tumors (2009 RECIST standard). TGF-β1 levels were measured in all patients by using enzyme-linked immunosorbent assay (ELISA). Multiple-factor analysis of the predictive value of the treatment efficacy was performed by Cox regression analysis.

Results After radiotherapy, 36, 79, and 25 cases experienced complete response (CR), partial response (PR), and no response (NR), respectively, with a total effective rate of 82.14%. The TGF-β1 level was significantly lower in the effective group than that in the ineffective group ($P < 0.05$) and covariance analysis revealed significantly reduced TGF-β1 level in esophageal cancer patients following radiotherapy. The multi-factor Cox regression model revealed that the predictive value of TGF-β1 for the effect of radiotherapy was largest, with a hazard ratio [HR] of 1.955 ($P = 0.002$), followed by exposure dose, with (HR = 1.367; $P = 0.035$).

Conclusion Serum TGF-β1 level can serve as a predictor for the short-term effects of radiotherapy in patients with esophageal cancer.

Received: 7 February 2018
Revised: 14 February 2018
Accepted: 23 February 2018

Key words: transforming growth factor-β; esophagus cancer; radiotherapy; short-term efficacy; prediction

Esophageal cancer is one of the most common malignant tumors of the digestive tract in China, and the high incidence area of esophageal cancer in Mianyang area indicates that it has become one of the major tumors harmful to human health [1]. In addition to surgical treatment, most patients choose radiotherapy and chemotherapy, while radiotherapy alone is an option for frail elderly patients with poor tolerance. Although radical radiotherapy is administered to patients with esophageal cancer, the clinical efficacy remains unsatisfactory because of many factors, including radiation dose, individual differences, site, and adverse reactions. Therefore, it is necessary to identify indicators that can effectively monitor and evaluate the effect of radiotherapy in cancer patients. Transforming growth factor-β1 (TGF-β1) is a multipotent biological effect factor. Studies have shown that TGF-β1 plays an important role in tumor occurrence and development [2–3]. There is a correlation between serum levels of TGF-β1 in patients with esophageal cancer and both the stage of cancer and the curative effect of surgery [4]. However, there are few studies on changes in serum TGF-β1 level and their relationship between the

✉ Corresponding to: Fei Gao. Email: 6221252@qq.com
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effect of radiotherapy in patients with esophageal cancer and chemotherapy. Therefore, this study investigated changes in TGF-β1 levels in patients with esophageal cancer before and after radiotherapy and chemotherapy and evaluated the predictive value of TGF-β1 level for radiotherapy effect, in order to explore the evaluation value of TGF-β1 in clinical efficacy and prognosis. The report is as follows.

Materials and methods

Research subjects

A total of 140 patients with esophageal squamous cell carcinoma who received radical radiotherapy from March 2015 to December 2017 in our Department of Onoclogy were selected, including 78 male patients and 62 female patients, aged 43–82 years, with an average age of 56.21 + 9.26 years. All patients were pathologically diagnosed as having esophageal squamous cell carcinoma. Stage II was the main clinical stage of the tumor. The main clinical stages of the tumor were stage II (26 cases), stage III (68 cases), and stage IV (46 cases). The regional lymph node metastasis in the left gastric artery of supraclavicular and epigastric was mainly observed in patients with stage IV, but not in viscera. The lesions were located in the cervical segment (n = 8), upper thoracic segment (n = 29), middle segment (n = 55), lower segment (n = 42) and multiple segments (n = 6). All patients were aware of the contents of the study, refused surgery, and signed an informed consent for this medical research.

Treatment programs

All 140 patients were affixed with thermoplastic elastomer and underwent scanning and positioning in a computed tomography (CT) simulator. The scanning range was from C2-L4, the interval thickness and the layer thickness were both 3 mm, and CT images were input through LAN (treatment planning system). All patients were treated with image-guided intensity-modulated conformal radiotherapy (IGRT). The clinical target gross target volume (GTV) and gross involved volume (GTVnd) were determined using the Varian IX linear accelerator Eclipse 10.0 planning system of the CT visual-positive lesions and lymph nodes; the subclinical target CTV (GTV up and down 3 cm, tube circumferential 0.6 cm); the lymphatic drainage area of CTVln, including the upper chest neck, supraclavicular and upper mediastinum, specifically for the C6–3 cm edge lesions, irradiation of carcinoma of the lower thoracic esophagus for wild thoracic entrance to include all the mediastinum, left gastric artery and cardiac region, plan target PTV CTV put 0.5 cm. All patients were treated with the final target area of the radiotherapy PTV, in which the clinical target volume (CTV) of PTV. The spinal cord was avoided during the placement. The planned dose for the PTV included the 90% isodose curve range and tried to ensure the lowest possible irradiation lung doses, using a total of 30–32 fractionated irradiation doses of 1.85–2.1 Gy each. The median total dose of irradiation was GTV/GTVnd 58–64 Gy, with 38 patients receiving < 60 Gy, 82 patients receiving 60–64 Gy, 20 patients receiving > 65 Gy. The CTV was 56–60 Gy and the CTVln was 45–50.4 Gy. CBCT validation was performed twice weekly.

Measurement of serum TGF-β1 levels

Venous whole blood (2–3 mL) was collected from all patients 1 day before and 6 months after radiotherapy. After centrifugation at 5 000 rpm for 3 min, the supernatant removed in order to measure the level of TGF-β1 by ELISA according to the manufacturer's protocol.

Efficacy evaluation criteria

The short-term curative effect of esophageal cancer after radiotherapy was evaluated with reference to the 2009 RECIST criterion [5]. The short-term curative effects after radiotherapy were divided into complete response (CR), partial response (PR), and no response (NR). The sum of the former two was the total effective rate; that is, CR and PR patients were considered the effective group while NR patients were considered the ineffective group.

Statistical analysis

All data in this study were analyzed using IBM SPSS Statistics for Windows, version 20.0. T-tests were used to compare the measurement data between groups (mean and standard deviation [± SD]), while covariance analysis was used to compare TGF-β1 levels before and after radiotherapy between the two groups. Counts data were expressed as rates or composition ratios and compared between groups by chi-square tests. The single-factor analysis of the effect factors was performed by log-rank analysis and Cox regression analysis models were used for multifactor analysis. P < 0.05 were considered statistically significant.

Results

Therapeutic effect in patients after radiotherapy

After radiotherapy, CR, PR, and NR occurred in 36, 79, and 25 cases, respectively. The total effective rate was 82.14%. The results were shown in Table 1. The CR and PR patients were included in the effective treatment group, while the NR patients comprised the ineffective treatment group.

Table 1 Therapeutic effect after PTV radiotherapy in patients with esophageal carcinoma

Efficacy	CR	PR	NR
Number of examples	36	79	25
Percentage (%)	25.71	56.43	17.86

Comparisons of the basic conditions of patients with different curative effects

There was no significant difference in age, sex, and overall distribution of tumor sites between the effective and ineffective treatment groups; however, there were significant differences in clinical staging and irradiation dose ($P < 0.05$). As shown in Table 2, patients in the ineffective group had higher stages of disease than those in the effective group and the overall distribution of radiation doses in the effective group was higher than that in the ineffective group.

Changes in serum levels of TGF-β1 in patients before and after radiotherapy

There was a significant difference in TGF-β1 level before radiotherapy between the two groups, in which the level in the effective group was significantly lower than that in the ineffective group ($P < 0.05$) (Fig. 1). Therefore, covariance analysis was used to investigate the effect of radiotherapy on the TGF-β1 level. The results are shown in Table 3. From the calibration model in the table, $P < 0.001$ indicates the existence of factors that affect the level of TGF-β1. Further examination of the level of TGF-β1 before radiotherapy according to therapeutic group showed a $P > 0.05$ for the difference in level before radiotherapy in the therapeutic group $P< 0.05$, which showed that the therapeutic group had statistical significance to the level of TGF-β1 during the course of radiotherapy. The interaction between the efficacy group and TGF-β1 level before radiotherapy had a $P > 0.05$, indicating that there was no interaction between the treatment efficacy and the TGF-β1 level before radiotherapy. In other words, the TGF-β1 level before and after radiotherapy after radiotherapy did not vary with the efficacy of the different groups, indicating that the basic conditions of covariance have been met. After chemotherapy, the TGF-β1 levels in the effective group remained significantly lower than the levels in the ineffective Group ($P < 0.05$). Analysis of covariance showed that radiotherapy can significantly reduce the level of TGF-β1 in esophageal cancer patients. After the covariance analysis, that radiotherapy could significantly reduce the level of TGF-β1 in patients with esophageal cancer.

Single factor analysis of prognosis of radiotherapy for esophageal carcinoma

The present study performed single factor analysis of the indicators that may predict the efficacy of radiotherapy for esophageal cancer. The results showed that the clinical stage, radiation dose, and TGF-β1 level could predict the effect of radiotherapy to different extents, with HR values of 1.568, 1.684, and 1.236, respectively (Table 4).

Multivariate analysis of the prognosis of radiotherapy for esophageal carcinoma

In order to further clarify the predictive value of the above indicators for radiotherapy and chemotherapy, factors with $P < 0.1$ in the factor analysis were incorporated into the multiple Cox regression analysis model. The results are shown in Table 5. This analysis revealed the highest predictive value of radiotherapy

Table 2 Comparisons of the basic conditions of patients with different curative effects

	Effective group (115 cases)	Ineffective group (25 cases)	t/χ^2	P
Age (years)	56.32 ± 11.06	57.41 ± 12.33	0.675	0.510
Gender (male / female)	68 / 47	10 / 15	3.046	0.081
Tumor site				
Cervical segment	5	3		
Upper thoracic segment	21	8		
Middle chest segment	46	9	8.326	0.075
Lower thoracic segment	39	3		
Multiple segment	4	2		
Clinical stage				
II	24	2		
III	60	8	10.376	0.005
IV	31	15		
Irradiation dose (Gy)				
< 60	25	13		
60–65	75	7	12.48	0.002
> 65	15	5		

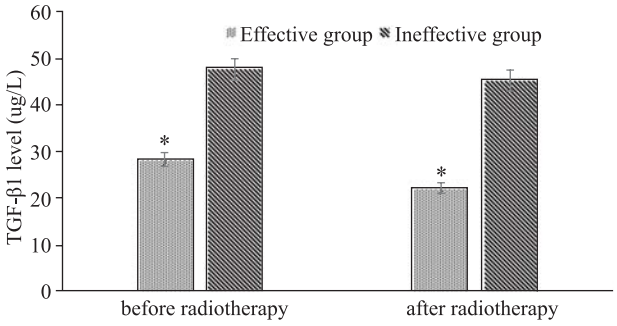

Fig. 1 Levels of TGF-β1 in two groups of patients before and after radiotherapy (* $P < 0.05$ compared to an ineffective group)

Table 3 Covariance analysis of the effect of radiotherapy on the level of TGF-β1 in patients' serum

Project	Degree of freedom	*F*	*P* value
Correction model	3	602.351	< 0.001
Constant term	1	53.271	< 0.001
Level of TGF-β1 before radiotherapy	1	0.135	0.714
Curative effect group	1	5.153	0.025
Therapeutic group	1	0.094	0.759
TGF-β1 level before therapy			

Table 4 Single factor analysis of prognosis of radiotherapy for esophageal carcinoma

Indicators	HR	95%CI	*P* value
Age	0.765	0.329–1.236	0.125
Gender	0.428	0.127–0.965	0.548
Tumor site	0.649	0.225–1.138	0.262
Clinical stage	1.568	0.716–2.949	0.003
TGF-β1 level	1.684	0.961–2.675	0.015
Irradiation dose	1.236	0.423–2.182	0.021

effect for TGF-β1 level (HR = 1.955, $P = 0.002$), followed by irradiation dose (HR = 1.367, $P = 0.035$).

Discussion

Surgery remains the preferred treatment for esophageal cancer; however, there is a risk of traumatic stress and complications with surgery, especially in patients with advanced and senile cancer. As a result, radiotherapy or concurrent radiotherapy and chemotherapy has become the first choice for patients with advanced esophageal cancer. Simultaneous radiotherapy and chemotherapy can significantly inhibit tumor tissue growth and reduce recurrence and metastasis in esophageal cancer patients, thus effectively improving their survival rate [6–8]. However, the side effects of concurrent radiotherapy and chemotherapy are also relatively significant, with adverse

Table 5 Multivariate analysis of the prognosis of radiotherapy for esophageal carcinoma

Indicators	HR	95%CI	*P* value
Clinical stage	0.892	0.210-1.561	0.062
TGF-β1	1.955	0.982-3.053	0.002
Irradiation dose	1.367	0.845-2.572	0.035

effects in patients with poor tolerance often leading to chemotherapy failure or termination. Therefore, the efficacy of radiotherapy and chemotherapy remains controversial. Several studies have reported no significant difference in the short-term curative effect of patients between radiotherapy alone and concurrent radiotherapy and chemotherapy [5, 9]. Moreover, it can also reduce the side effects of chemotherapy. This study also showed that the total effectiveness rate for all cancer patients after radiotherapy was 82.14%, lower than the 91.6% mentioned above. This difference may be related to the smaller number of cases in the present study. In addition, COX multiple factor regression analysis revealed that the TGF-β1 level and the irradiation dose may have a predictive value for the curative effect in patients with esophageal cancer.

A number of studies have identified many factors that influence the curative effect and prognosis of esophageal cancer, including the clinical TNM stage of the tumor, which has been used as an independent index to predict the curative effect and prognosis of radiotherapy. Pan *et al* [10] and Liu [11] showed that the prognosis of esophageal carcinoma can be predicted by N stage, T stage, and N stage [5]. Luo *et al* [5] reported that clinical stage was a predictor of the prognosis of esophageal cancer in univariate analysis. However, after multiple regression analysis, the HR was <1 and the difference was not significant, which is consistent with our findings. In addition to the clinical staging of the tumor, tumor location and radiation dose can also affect the prognosis and efficacy of esophageal cancer [12–13]. However, in the present study, the tumor site was not an independent predictor of radiotherapy efficacy; this difference may be due to differences in the study subjects and research methods. Consistent with the findings reported by Ohshima [13], the present study also found irradiation dose to be an independent predictor of radiotherapy, but we also observed through multifactor Cox regression analysis the predictive value of TGF-β1 level for the short-term curative effect after radiotherapy. The HR value was 1.955; thus, serum levels of TGF-β1 are an important index to predict the efficacy of radiotherapy. TGF-β1 is also involved in the development and development of cancer in addition to infectious diseases. Tang [4] and colleagues explored the relationship between serum levels of beta 1 and

esophageal cancer, observing significantly higher levels in patients with esophageal cancer compared to those in the control group. The tumor cells may secrete high levels of TGF-β1, which promotes malignant cell proliferation through the regulation of the tumor microenvironment to promote remodeling infiltration, tumor progression, and metastasis [14–15]. Therefore, with high levels of tumor TGF-β1 malignant low level high and due to the high concentration of TGF-β1 formed by local immune suppression and extracellular matrix remodeling on tumor cell survival favorable microenvironment which makes this type of tumor response to treatment with low concentration of TGF-β1 tumors not sensitive. As the results of the present study showed, TGF-β1 levels were significantly higher in the invalid group than those in the effective group before radiotherapy, which reflected the high level of immune TGF-beta in patients with one malignant tumor microenvironment in the inhibitory state and the therapeutic effect was lower than the low level of TGF-β1 of patients, and we with the same covariance the analysis also showed that effective serum TGF-β1 changes were significantly higher than the invalid group after radiotherapy, indicating the sensitivity of microenvironment remodeling effective group of patients with low level of TGF-β1 in the radiotherapy larger, most of the tumor cells were killed after radiotherapy, resulting in the reduction of the source of TGF-β1. Therefore, serum levels of TGF-β1 in patients with esophageal cancer can be used as an important auxiliary detection index for the short-term efficacy of radiotherapy.

The results of the present study showed that TGF-β1 plays a key role in beta 1 in the occurrence and development of malignant tumors. Serum levels of TGF-β1 can be used to predict the short-term efficacy of radiotherapy, including the clinical curative effect, as well as the prognosis of esophageal carcinoma patients undergoing radiotherapy.

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DOI 10.1007/s10330-018-0256-6
Cite this article as: Fei G, Jia J, Han JJ, *et al*. Predictive value of serum levels of transforming growth factor beta 1 for the short-term effects of radiotherapy and chemotherapy in patients with esophageal cancer. Oncol Transl Med, 2018, 4: 1–5.