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Original Research

Expression of miR-93-5p in patients with esophageal carcinoma and its relationship with the curative effect and prognosis of radiotherapy

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Abstract: This study aimed to investigate the expression of miR-93-5p in esophageal carcinoma-patients and its relationship with the curative effect and prognosis of radiotherapy. 102 patients with esophageal carcinoma treated in Yiwu Central Hospital from May 2013 to July 2015 were considered as the experimental group, and 89 healthy people for physical examination during the same period were selected as the control group. The expression of miR-93-5p in the serum of the two groups was compared. Based on the mean expression of miR-93-5p in serum, esophageal carcinoma patients were divided into high expression and low expression groups. Then the relationship between clinical-pathological characteristics and the expression of miR-93-5p was analyzed. The curative effect of radiotherapy in patients with esophageal carcinoma was evaluated, and the relationship between the expression of miR-93-5p, the curative effect of radiotherapy and the 3-year survival rate in patients with esophageal carcinoma was analyzed. The expression of miR-93-5p in the serum of the experimental group was significantly higher than that of the control group (P< 0.05); there was a significant correlation between the expression of miR-93-5p and pathological stage (P< 0.05). The expression of miR-93-5p in the effective radiotherapy group was significantly lower than that in the ineffective radiotherapy group (P< 0.05). ROC curve showed that the sensitivity and specificity of miR-93-5p in predicting radiotherapy response of esophageal carcinoma were 88.57 and 64.69% respectively, AUC was 0.864 (95%CI:0.791~0.936), P< 0.001; the 3-year survival rate of low expression group was significantly higher than that of high expression group (P< 0.05). In Conclusion, the expression of miR-93-5p was high in esophageal carcinoma patients, and the higher the expression, the worse the curative effect of radiotherapy and the worse the prognosis, which may be a new predictor of radiotherapy effect and prognosis in patients with esophageal carcinoma.

Key words: miR-93-5p; Esophageal carcinoma; Radiotherapy.

Introduction

As a common malignant tumor of the digestive tract in the clinic, esophageal cancer has become more and more common in recent years with the change of living habits and social environment, which is a serious threat to human life and health (1-7). For patients with esophageal carcinoma, the early symptoms are not obvious. About half of the patients are diagnosed within an advanced stage and lose the chance of surgery (8-12). Radiotherapy is the main treatment for patients with advanced esophageal carcinoma, and most of the patients need to receive radiotherapy. But after conventional radiotherapy, the number of patients dying from recurrence can be as high as 70%-80% (13, 14). Therefore, for patients with advanced esophageal carcinoma, to explore a biomarker with high sensitivity and specificity for predicting the therapeutic effect of radiotherapy is an urgency to be solved at present (13-16).

microRNA (miRNA) as a key factor in the occurrence and development of malignant tumors, is a kind of highly conservative non-coding single-stranded RNA. Many kinds of miRNAs have been proved to be biomarkers for predicting the therapeutic efficacy of malignant tumors (16, 18). miR-21, for example, has been shown to have an important clinical value in predicting the prognosis of esophageal carcinoma (19). miR-93-5p, a member of the miR-106b-25 family, has been found to be involved in the carcinogenesis progression of colorectal cancer (20) and lung cancer (21). In addition, some studies (22) explored the expression of microRNA-93-5p in colorectal cancer, indicating that its expression is closely related to the poor prognosis of colorectal cancer.

However, there has been no research on the prediction of the radiotherapy effect of miR-93-5p in esophageal cancer patients at present. In order to find a new biomarker for predicting the curative effect of radiotherapy in patients with esophageal cancer, we investigated the expression of miR-93-5p in patients with esophageal cancer and its relationship with the curative effect of radiotherapy.

Materials and Methods

General materials

102 patients with esophageal cancer treated in Yiwu Central Hospital from May 2013 to July 2015 were considered as the experimental group (54 male patients and 48 female patients). The mean age of all patients was (55.73 ±8.65) years old, of which 69 patients were in the III stage and 33 in the IV stage. 89 healthy people

Table 1. General Information of studied cases in this research [n (%)].

Factor	Experimental Group n=102	Control Group n=89	t/χ^2	*P*
Sex			0.030	0.862
Male	54(52.94)	46(51.69)		
Female	48(47.06)	43(48.31)		
Age (years)			0.009	0.923
≤55	50(49.02)	43(48.31)		
>55	52(50.98)	46(51.69)		
BMI(kg/m^2)			0.024	0.878
≤ 22	55(53.92)	47(52.81)		
>22	47(46.08)	42(47.19)		
Marital Status			0.081	0.776
Married	94(92.16)	81(91.01)		
Unmarried	8(7.84)	8(8.99)		
Pathological Type			-	-
Squamous Cell Carcinoma	41(40.20)	-		
Adenocarcinoma	27(26.47)	-		
Small Cell Carcinoma	34(33.33)	-		
Pathological Stage			-	-
Stage III	69(67.65)	-		
Stage IV	33(32.35)	-		
Focus Location			-	-
Upper Thoracic Segment	33(32.35)	-		
Middle Thoracic Segment	30(29.41)	-		
Lower Thoracic Segment	39(38.24)	-		

who came to Yiwu Central Hospital through the same period were selected as the control group. There was no significant difference for sex, age and BMI between the two groups (P> 0.05), which is comparable (Table 1).

Inclusion and exclusion criteria

Inclusion criteria: Patients with esophageal cancer diagnosed pathologically who cannot receive standard concurrent radiotherapy and chemotherapy but can only undergo radical radiotherapy; Patients with expected survival longer than 3 months.

Exclusion criteria: Patients with other malignant tumors; patients with symptomatic or uncontrollable brain metastasis; patients with cognitive or communication impairments; patients with liver and kidney dysfunction; patients with poor compliance.

All patients and their families agreed to participate in the experiment and signed a conscious consent. The test has been approved by the Ethics Committee of Yiwu Central Hospital.

Experimental materials and reagents

Quantitative real-time PCR instrument (BioRad Inc., America), G-9 UV spectrophotometer (Rangqi Instrument Technology Co., Ltd., Shanghai), XSP-L130 biological microscope (Puqian Optical Instruments Co., Ltd., Shanghai), Trizol reagent (Applide Invitrogen Inc., America), cDNA reverse transcription kit (Invitrogen Inc., America). All primer sequences were produced and designed by Bioengineering Co., Ltd., Shanghai.

Treatment method

All patients took barium sulfate orally before chemotherapy and then took the supine position. Spiral CT was used to locate the tumors and to delineate the focus and metastatic lymph node regions of the patients. The left and right edges of the delineated target area were increased by 1.5 cm and the upper and lower edges were increased by 4.0 cm for radiotherapy. The single-dose was 2 Gy (once a day, 5 times a week). The total radiation dose was about 60~66Gy.

Detection of miR-93-5p expression in serum by RT-PCR

When all the subjects were admitted to the hospital, a 3-mL sample of fasting venous blood was collected from each subject and centrifuged at 3000r/min. The serum was taken after centrifuging for detection. The total RNA was extracted by adding Trizol reagent to the serum. Then the purity and concentration of RNA were detected by UV spectrophotometer. OD260/280 ranged from 1.7 to 2.1. The 5-μg total RNA of each sample was then reverse transcribed to cDNA in strict accordance with the manufacturer's instructions. The sequence of primers is shown in Table 2. The reaction parameters: 37 ℃ for 15 min, 42 ℃ for 42 min and 70 ℃ for 5 min. PCR amplification was carried out using post-transcriptional cDNA. The amplification conditions are as fol-

Table 2. Relative primers sequence that was used in this experiment.

Factor	Upstream Primer	Downstream Primer
miR-93-5p	5'-ACACTCCAGCTGGGTCCTGTACT- GAGCTGCCC-3'	5'-CTCAACTGGTGTCGT-GGA-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

lows: pre-denatured at 95 ℃ for 5min, denatured at 95 ℃ for the 30s, then circulated 40 times at 65 ℃ (15s/time). PCR instrument was used for real-time fluorescence quantitative PCR detection. The experiment was repeated three times.

Evaluation criteria

The expression of miR-93-5p in the serum of the two groups was compared. According to the mean expression of miR-93-5p in serum, esophageal cancer patients were divided into high expression and low expression groups. Then the relationship between the expression of miR-93-5p and clinical pathological characteristics was analyzed. The curative effect of radiotherapy in patients with esophageal cancer was evaluated and divided into complete remission, partial remission, stability and progress according to the curative effect of radiotherapy. Total remission +partial remission = effective radiotherapy, no progress+ progress = ineffective. The relationship between the expression of miR-93-5p in serum and the curative effect of radiotherapy was analyzed. The relationship between the expression of miR-93-5p in serum and 3-year survival rate in patients with esophageal carcinoma was analyzed.

Statistical Methods

The SPSS18.0(Boyi Zhixun Information Technology Co., Ltd., Beijing, China) software was used to statistically analyze the collected data, the chi-square test was used for counting data, the measured data were expressed as the mean ± standard deviation, the t-test was used for comparison between the two groups, GraphPad Prism 6 was used to plot the data. Kaplan-Meier was used for survival analysis. A value of $P < 0.05$ was considered as indicating a statistically significant difference between the two groups.

Results

Comparison of the expression of miR-93-5p in serum between the two groups

The expression of miR-93-5p in the serum of the experimental group was (7.381 ±2.265), and that of the control group was (1.026 ±0.119). The expression of miR-93-5p in the serum of the experimental group was significantly higher than that of the control group ($P< 0.05$) (Figure 1).

Relationship between the expression of miR-93-5p in serum and clinical pathological features in patients with esophageal cancer

According to the mean expression of miR-93-5p in serum, esophageal cancer patients were divided into high expression group (49 patients, > 7.381) and low expression group (53 patients, ≤ 7.381). Then the relationship between the expression of miR-93-5p and clinical-pathological features was analyzed. There was no significant correlation among the expression of miR-93-5p, sex, age, pathological type and tumor location in patients with esophageal cancer, but there was a significant correlation between the expression of miR-93-5p and clinical-pathological stage ($P < 0.05$) (Table 3).

Relationship between the miR-93-5p expression in serum of patients with esophageal cancer and the therapeutic effect of radiotherapy

After evaluating the efficacy of radiotherapy, the

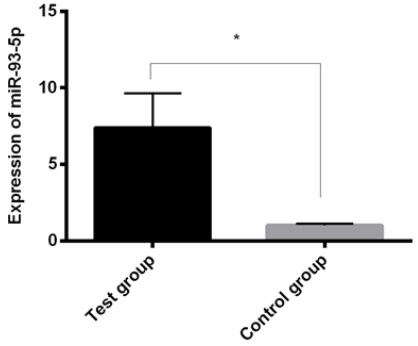

Figure 1. Comparison of the Expression of miR-93-5p in Serum between the Two Groups. The results of RT-PCR showed that the expression of miR-93-5p in the serum of the experimental group was significantly higher than that of the control group ($P < 0.05$). Note: * indicates that $P < 0.05$.

Table 3. Relationship between miR-93-5p and different clinical-pathological features in ovarian cancer.

Clinical Pathological Parameters	n	High Expression Group n=49	Low Expression Group n=53	X^2	P
Sex				0.001	0.981
Male	54	26(53.06)	28(52.83)		
Female	48	23(46.94)	25(47.17)		
Age (years)				0.005	0.994
≤55	50	24(48.98)	26(49.06)		
>55	52	25(51.02)	27(50.94)		
Pathological Type				0.100	0.951
Squamous Cell Carcinoma	41	19(38.78)	22(41.51)		
Adenocarcinoma	27	13(26.53)	14(26.42)		
Small Cell Carcinoma	34	17(34.69)	17(32.08)		
Pathological Stage				11.07	0.001
Stage III	69	41(83.67)	28(52.83)		
Stage IV	33	8(16.33)	25(47.17)		
Focus Location				0.275	0.871
Upper Thoracic Segment	33	15(30.61)	18(33.96)		
Middle Thoracic Segment	30	14(28.57)	16(30.19)		
Lower Thoracic Segment	39	20(40.82)	19(35.85)		

patients were divided into an effective radiotherapy group (67 patients) and an ineffective radiotherapy group (35 patients). The expression of miR-93-5p in patients of effective radiotherapy group (6.21±1.33) was significantly lower than that in patients of ineffective radiotherapy group (8.33±1.46), the difference was statistically significant (P< 0.05). ROC curve showed that the sensitivity and specificity of miR-93-5p in predicting radiotherapy response of esophageal carcinoma were 88.57% and 64.69% respectively, AUC was 0.864 (95%CI:0.791~0.936), P< 0.001 (Figures 2 and 3).

Survival analysis of high and low expression groups of miR-93-5p

The 3-year survival rate of low expression group (54.72%(29/53)) was significantly higher than that of the high expression group [22.45% (11/49)], the difference was statistically significant (P< 0.05). See Figure 4 for details.

Discussion

As a very important regulatory factor in a gene network, the miRNA expression is closely related to tumorigenesis (23, 24). In recent years, it has been shown that miRNA has important clinical significance in diagnosis, curative effect and prognosis prediction of esophageal carcinoma (25). And More and more attention has been paid to miRNA and tumor radiosensitivity. For example, some studies have examined miR-451 in patients with non-small cell lung cancer with different radiotherapy effects and suggested that miR-451 may enhance the radiotherapy sensitivity of tumor cells (26). As a member of the miR-93 family, miR-93-5p has been reported to promote the G1 / S stage transformation and proliferation of tumor cells (27, 28). In order to find a new biomarker for predicting the curative effect of radiotherapy in patients with esophageal cancer, the expression of miR-93-5p in patients with esophageal cancer and its relationship with the curative effect and prognosis of patients with esophageal cancer were investigated.

Firstly, we studied the expression of miR-93-5p in the serum of patients with advanced esophageal cancer. The results showed that the expression of miR-93-5p in the serum of the experimental group was significantly higher than that of the control group (P< 0.05). This suggests that the expression of miR-93-5p is up-regulated in patients with esophageal cancer. The previous study (29), in exploring the expression and role of miR-93-5p in gastric cancer, indicated that miR-93-5p was highly expressed in patients with gastric cancer and could promote metastasis of gastric cancer by activating the STAT3 signaling pathway, which is consistent with our conclusion. Then we investigated the relationship between the miR-93-5p expression in serum and clinical-pathological features in patients with esophageal cancer. The results showed that there was no significant correlation among the miR-93-5p expression, sex, age, pathological type and tumor location in patients with esophageal cancer, but there was a significant correlation between the miR-93-5p expression and pathological stages (P< 0.05). This suggests that the later the clinical-pathological stage of the patients, the higher

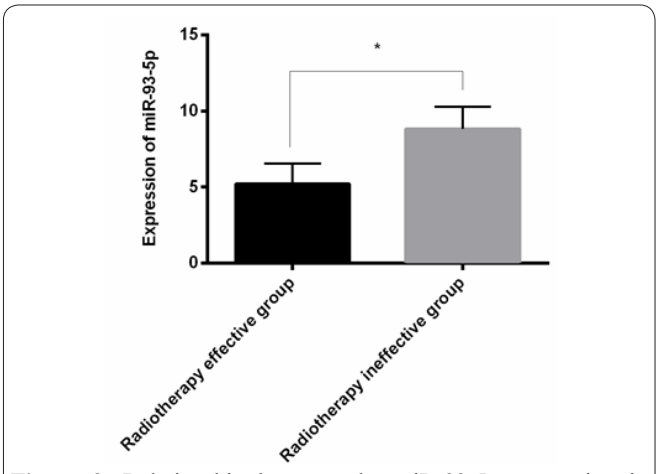

Figure 2. Relationship between the miR-93-5p expression in serum of esophageal cancer patients and the therapeutic effect of radiotherapy. RT-PCR results showed that miR-93-5p expression in patients with effective radiotherapy was significantly decreased than that in patients with ineffective radiotherapy (P< 0.05). Note: * indicates that P < 0.05.

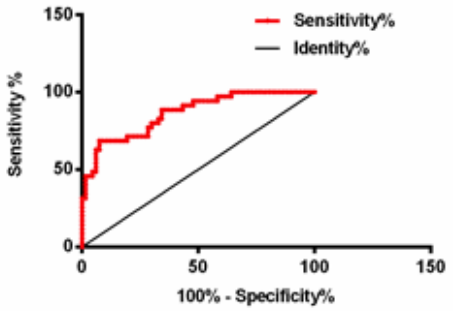

Figure 3. ROC curve for predicting radiotherapy response of esophageal cancer patients with miR-93-5p. The sensitivity and specificity of miR-93-5p in predicting radiotherapy effect of esophageal cancer were 88.57% and 64.69% respectively, AUC was 0.864 (95%CI: 0.791~0.936), P< 0.001.

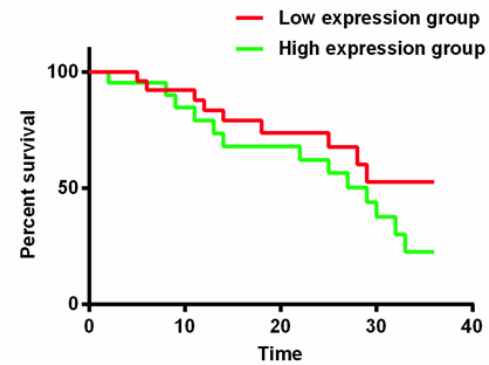

Figure 4. Survival analysis of miR-93-5p in high and low expression groups. The 3-year survival rate of the low expression group was significantly higher than that of the high expression group (P< 0.05.

the miR-93-5p expression, and indirectly suggests that miR-93-5p may play an important role in promoting the proliferation and metastasis of esophageal cancer cells. A previous study (30) investigated the miR-93-5p expression in 138 cases of colorectal cancer, indicating that the miR-93-5p expression was significantly correlated with the tumor stage and lymph node metastasis of the patients, which is consistent with our conclusion. Previous studies (31) have clearly shown that miR-93-

5p can promote the proliferation of hepatocellular carcinoma cells, which is consistent with our conjecture. Finally, we further explored the relationship between miR-93-5p and radiotherapy effect and prognosis in patients with advanced esophageal cancer. The results showed that the miR-93-5p expression in patients with effective radiotherapy was significantly lower than that in patients with ineffective radiotherapy ($P< 0.05$). miR-93-5p also had a certain value in predicting the curative effect of radiotherapy in patients with esophageal cancer. And about the 3-year survival rate, the results showed that the 3-year survival rate of miR-93-5p low expression group was significantly higher than that of the high expression group ($P< 0.05$). These results suggest that miR-93-5p may be used as a predictor of radiotherapy effect in patients with esophageal cancer. The higher the expression, the worse the curative effect of radiotherapy and the worse the prognosis of patients with esophageal cancer. A previous study (32) on the expression and significance of miR-93-5p in non-small cell lung cancer indicated that the up-regulation of miR-93-5p is a predictor of poor prognosis in patients with non-small cell lung cancer. Further study (33) also showed that the up-regulation of miR-93-5p expression is closely related to the poor prognosis of head and neck squamous cell carcinoma. All of these confirmed some of our conclusions. However, there are few studies on the relationship between miR-93-5p and radiotherapy efficacy, and a large number of experiments are still needed to verify our conclusions and further explore the mechanism.

In conclusion, miR-93-5p is highly expressed in patients with esophageal cancer, and the higher the expression, the worse the curative effect of radiotherapy and the worse the prognosis, which may be a new predictor of radiotherapy effect and prognosis of patients with esophageal cancer.

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Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions
LC and XF conceived and designed the study, and drafted this paper. LC, XF, XWang and XWu collected, analyzed and interpreted the experiment data, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Yiwu Central Hospital. Signed written informed consent was obtained from the patients and/or guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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