

Original Article

The correlation between tumor tissue miR-373 and miR-124 expressions and prognosis in patients with endometrial cancer

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Abstract: Objective: To explore the correlation between tumor tissue miR-373 and miR-124 expressions and prognosis in patients with endometrial cancer (EC). Methods: Cancer tissues from 106 EC patients (the observation group) and normal endometrial tissue from 70 patients (the control group) who underwent panhysterectomy due to uterine fibroids were collected, and their miRNA-373 and miRNA-124 expression levels were determined. Results: The observation group had a higher relative expression of miR-373 and a lower relative expression of miR-124 than the control group (both $P < 0.001$). The area under the ROC curve (AUC) of miR-373 for predicting EC was 0.874, with a (sensitivity of 0.840, and a specificity of 0.971. The AUC of miR-124 for predicting EC was 0.867, with a sensitivity of 0.849, and a specificity of 0.886. The miR-373 expression is negatively related to the degree of EC cancer differentiation and positively related to the depth of myometrial infiltration and the International Federation of Gynecology and Obstetrics (FIGO) stage (all $P < 0.05$). The miR-124 expression is just the opposite. Patients with high expression levels of miRNA-373 and low expression levels of miR-124 have lower overall survival ($P < 0.05$). Conclusion: In EC patients, the degree of malignancy is associated with high miRNA-373 levels and low miR-124 levels, which indicates a poor prognosis.

Keywords: miR-373, miR-124, endometrial cancer, diagnosis, pathological features, prognosis

Introduction

Endometrial cancer (EC) is a kind of female genital tract malignant tumor which accounts for 20-30% of all genital tract tumors. The disease mainly tends to strike women over 50 years of age, and the incidence has an increasing tendency in China [1, 2]. In China, about 61,900 new cases arise every year, and the onset age of this disease tends to be younger [3, 4]. The incidence of EC in some areas even exceeds that of cervical cancer [5]. At present, the pathogenesis of EC has not yet been clarified [6].

Surgical treatment has been widely used to control EC, but studies have reported that cancer recurrence and metastasis can easily occur within 3 years after surgery [7, 8]. As regards prognosis, the 5-year survival rate of EC patients at the early stage can reach 80-95%.

However, most EC patients are diagnosed at the middle and late stages, so their 5-year survival rate is significantly lower [9]. According to a 2018 study, patients with EC recurrence and metastasis have a median survival of less than 16 weeks, and the survival period of patients who relapse with metastasized EC is less than 16 weeks [10]. Therefore, the early diagnosis and treatment of EC has a positive and important significance for patient prognosis. The expression of miRNA in tumor tissues is closely related to the occurrence and progression of tumors and provides new dimension for the diagnosis and treatment of tumors [11, 12].

Studies have found that inhibiting certain miRNA expressions can regulate cell differentiation, proliferation, and apoptosis. miRNA plays an extremely important role in the occurrence and development of cancer. More than 50% of human malignant tumor occurrences are asso-

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ciated with miRNA abnormalities [13, 14]. Among them, miR-373 is highly expressed in human embryos [15]. One study found that miR-373 can promote stem cell regeneration and the occurrence of various cell tumors by regulating wnt/ β -catenin and other signaling pathways [16]. The increased expression of miR-373 promotes tumor cell proliferation in a variety of tumors, such as rectal cancer, kidney cancer, and esophageal cancer [17-19]. As a tumor suppressor gene, miR-124 is down-regulated in cervical, breast, and gastric cancers [20, 21]. However, studies of miR-373 and miR-124 expressions in EC are rarely reported. Therefore, our study explored the expressions of miR-373 and miR-124 in EC tissues and their correlation with disease prognosis.

Materials and methods

General information

A total of 106 EC patients treated in our oncology department were enrolled in the observation group, and their cancer tissues were collected (ages: 25-71 years old, average age: 57.1 ± 10.0). A total of 70 patients with uterine fibroids who underwent panhysterectomy were enrolled in the control group, and their normal endometrial tissues were collected (average age: 51.82 ± 7.9 years).

All the patients enrolled in this prospective study were treated in the Affiliated Tumor Hospital of Xinjiang Medical University from March 2013 to July 2017. All the above patients signed an informed consent. This study was approved by our hospital's ethics committee.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who met an EC or uterine fibroid diagnosis [22]; (2) Patients aged 18-75 years; (3) Patients who underwent endometrial cancer surgery or panhysterectomy in the Affiliated Tumor Hospital of Xinjiang Medical University, and whose endometrial cancer or normal endometrial tissues were collected and stored at -80°C .

Exclusion criteria: (1) Patients with incomplete clinical data; (2) Patients with severe heart, liver, kidney, or other diseases; (3) Patients with mental illness or cerebrovascular disease; (4)

Patients with other cancers or non-primary endometrial cancer.

Clinical and pathological stages

The patients clinical and pathological stages were evaluated with reference to the UICC/AJCC 7th edition diagnostic criteria [23].

Grouping

The grouping was performed according to the average values of the relative expression levels of miRNA-373 and miRNA-124 in the 106 EC patients [16, 20].

qRT-PCR

The tissue specimens ($2-3 \text{ mm}^2$) which had been confirmed by pathology as endometrial cancer and the normal endometrial tissues were removed from the -80°C freezer. The miR-373 and miR-124 expressions were determined using fluorescent real-time quantitative polymerase chain reaction (qRT-PCR). The instrument used in this study was an ABI 7500 real-time fluorescent quantitative PCR instrument (ABI Applied Biosystems, USA), and the upstream and downstream primers were designed and provided by Guangzhou Ruibo Biotechnology Co., Ltd. [24]. The miRNA-373 upstream and downstream primer sequences were as follows: 5'-TGCGCGAAGTGCTTCGATTTGG-3') and 5'-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACACACCCCA-3', the miRNA-124 upstream primer and downstream sequences were as follows: 5'-GGCTCTCCAGACATCAT-3' and 5'-CACCTGGTGCTCAGTGTA-3'.

Total RNA was exacted using a Trizol kit (Molecular Research Center, USA). Then, a reverse transcription kit (Fermentas, Canada) was used to reverse transcribe the miRNA into cDNA. The cDNA was used as a template to amplify the DNA. The PCR reaction system is $25 \mu\text{l}$ in total, including $12.5 \mu\text{l}$ of SYBR premix ($2\times$), $0.5 \mu\text{l}$ of target gene upstream and downstream primers for each, $2.0 \mu\text{l}$ of cDNA template and $9.5 \mu\text{l}$ of ddH_2O . Reaction conditions: Pre-denaturation at 95°C for 5 min, denaturation at 98°C for 10 s, annealing at 60°C for 10 s, elongation at 68°C for 30 s, 40 cycles in total, 72°C for 10 min. U6 was used as the internal reference, and the relative expressions of miRNA-373 and miRNA-124 were calculated

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Table 1. General information of the 106 patients with EC

Event	Number of cases (n (%))
Age	
≥50 years old	60 (56.6)
<50 years old	46 (43.4)
Histological grade	
Highly differentiated	17 (16.0)
Moderately differentiated	57 (53.8)
Poorly differentiated	32 (30.2)
No infiltration	15 (14.2)
Myometrial infiltration	
Infiltration depth <50%	68 (64.2)
Infiltration depth ≥50%	43 (40.6)
FIGO stage	
I	50 (47.2)
II	25 (23.6)
III	18 (17.0)
IV	13 (12.2)
Lymphatic metastasis	
No	73 (68.9)
Yes	33 (31.1)

Note: EC: endometrial cancer, FIGO: Federation of Gynecology and Obstetrics.

using the $2^{-\Delta\Delta Ct}$ method. The experiment was repeated three times.

Outcome measures

Overall survival (OS): The time from the end of the operation to the death of the patient or the end of the observation period of this study.

Grouping: According to each patient's age (≥50 years old), histological grade, myometrial infiltration degree, International Federation of Gynecology and Obstetrics (FIGO) classification, and lymphatic metastasis, the 106 included cases were grouped to compare their relative expressions of miR-373 and miR-124 in their EC tissues.

Statistical analysis

SPSS 17.0 statistical software was used for the statistical analysis. The measurement data was expressed as the mean ± standard deviation (mean ± sd) and analyzed using t tests if the data met a normal distribution and homogeneity of variance. If the data did not meet the

normal distribution and homogeneity of variance, rank-sum tests were used, and the statistical value was expressed as Z. The count data were expressed as case numbers and percentages and tested using Pearson chi-square tests. Receiver operating characteristic (ROC) diagnostic curves were used to evaluate the diagnostic performance of miR-373 and miR-124 for EC. MedCalc software was used to draw the ROC pictures. An AUC greater than 0.7 was of diagnostic value. The survival analysis was performed using the Kaplan-Meier method, and the univariate analysis was tested using log-rank tests. $P < 0.05$ was considered statistically significant.

Results

General information

The general information of the 106 EC patients included in this study is shown in **Table 1**.

The relative expressions of miR-373 and miR-124 in the cancer tissues

The relative expression of miR-373 in the observation group was higher than it was in the control group, and the relative expression of miR-124 was lower than it was in the control group ($P < 0.001$) (**Table 2**).

The diagnostic value of miR-373 and miR-124 in the EC patients

The area under the ROC curve (AUC) of miR-373 for the EC diagnosis was 0.874, with a sensitivity of 0.840 and a specificity of 0.971. The AUC of miR-124 for the EC diagnosis was 0.867, with a sensitivity of 0.849 and a specificity of 0.886. See **Figure 1**.

Comparison of the relative expressions of miR-373 and miR-124 in the EC patients at different ages

There was no difference in the relative expressions of miR-373 between the EC patients who were 50 years old or older ($n=60$, 3.04 ± 1.82) and the EC patients who were under 50 years old ($n=46$, 3.35 ± 1.38) ($P > 0.05$). There was no difference in the relative expressions of miR-124 in the EC patients who were 50 years old or older (1.30 ± 1.70) and the EC patients who were under 50 years old (1.33 ± 0.73) ($P > 0.05$).

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Table 2. Comparison of the miR-373 and miR-124 expression level in the two groups of patients

Group	Number of cases	Relative expression of miR-373	Relative expression of miR-124
Control group	70	1.13±0.41	2.49±0.78
Observation group	106	3.18±1.64	1.32±0.71
t		12.289	10.156
P		<0.001	<0.001

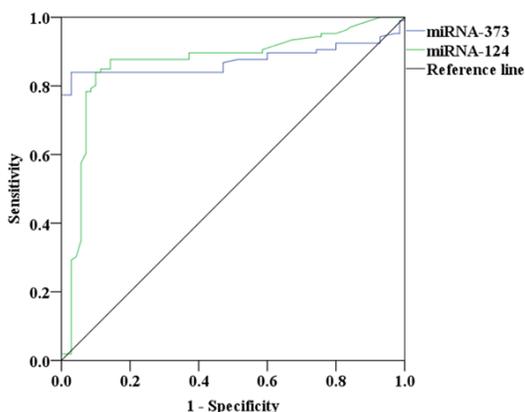


Figure 1. ROC diagnostic curves of miRNA-373 and miRNA-124 for EC patients. EC: endometrial cancer, ROC: receiver operating characteristic.

Comparison of the miR-373 and miR-124 relative expression levels in the tissues with different histological grades

The relative expression levels of miR-373 in the highly differentiated group were significantly lower than those in the moderately differentiated and poorly differentiated groups (both $P < 0.001$); the relative expression of miR-373 in the highly differentiated group was significantly lower than it was in the poorly differentiated group ($P < 0.001$). The relative expression of miR-124 in each group trended the opposite of the other group (all $P < 0.05$). See **Table 3**.

Comparison of the relative expressions of miR-373 and miR-124 in patients with different infiltration degrees in their muscular layers

The relative expression levels of miR-373 in the non-infiltration group were significantly lower than they were in the infiltration depth $< 50\%$ group and the infiltration depth $\geq 50\%$ group (both $P < 0.001$). The relative expressions of miR-373 in the infiltration depth $< 50\%$ group were significantly lower than they were in the infiltration depth $\geq 50\%$ group ($P < 0.001$). The relative expressions of miR-124 in each group

trended the opposite of the other group. See **Table 4**.

Comparison of the relative expressions of miR-373 and miR-124 in the patients at different FIGO stages

The FIGO stage was positively related to the relative expression of miR-373 and negatively related to the relative expression of miR-124 ($P < 0.05$). See **Table 5**.

Comparison of the relative expressions of miR-373 and miR-124 in the patients with or without lymph node metastases

The relative expression levels of miR-373 in the patients with lymph node metastases were higher than they were in the patients without lymph node metastases, but the relative expression of miR-124 was lower than it was in patients without lymph node metastases ($P < 0.001$). See **Table 6**.

The correlation between the relative expressions of miR-373 and miR-124 and prognosis

Six of the 106 follow-up patients were lost to follow-up, so 100 of the EC patients were ultimately included in the analysis (**Figures 2 and 3**).

According to the average value of the relative expression of miR-373 (3.18), there were 44 patients with high expressions and 56 cases with low expressions. The average survival time of the miR-373 high expression group was 36.0 months, which was lower than of the average survival time in the low expression group (44.7 months, $\chi^2 = 7.462$, $P = 0.006$).

According to the average value of the relative expression of miR-124 (1.32), there were 49 cases with high expressions and 51 cases with low expressions. The average survival time of the miR-124 low-expression group was 33.1 months, which was lower than the average survival time in the high-expression group (44.9 months, $\chi^2 = 16.127$, $P < 0.001$).

Discussion

The early diagnosis of malignant tumors is receiving more and more clinical attention. Finding reliable and accurate markers in

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Table 3. Comparison of the miR-373 and miR-124 relative expression levels in tissues with different histological grades

Group	Number of cases	Relative expression of miR-373	Relative expression of miR-124
Highly differentiated group	17	1.58±0.95	2.73±0.81
Moderately differentiated group	57	2.88±1.35 ^{***}	1.10±0.13 ^{***,#}
Poorly differentiated group	32	4.57±1.35 ^{***,###}	0.94±0.11 ^{***}
F		32.753	180.162
P		<0.001	<0.001

Note: Compared with the highly differentiated group, ^{***}P<0.001; compared with the moderately differentiated group, [#]P<0.05, ^{###}P<0.001.

Table 4. Comparison of the relative expression levels of miR-373 and miR-124 in tissues with different muscular infiltration levels

Group	Number of cases	Relative expression of miR-373	Relative expression of miR-124
Non-infiltration	15	1.54±1.00	2.72±0.86
Infiltration depth <50%	68	3.12±1.51 ^{***}	1.15±0.32 ^{***}
Infiltration depth ≥50%	43	4.43±1.37 ^{***,###}	0.90±0.79 ^{***,#}
F		32.753	180.162
P		<0.001	<0.001

Note: Compared with the non-infiltration group, ^{***}P<0.001; compared with the infiltration depth <50% group, [#]P<0.05, ^{###}P<0.001.

Table 5. Comparison of the relative expressions of miR-373 and miR-124 in the FIGO stages

Group	Number of cases	Relative expression of miR-373	Relative expression of miRNA-124
I	50	1.93±1.09	1.98±0.65
II	25	3.47±0.56 ^{***}	1.54±0.72 ^{**}
III	18	4.26±0.54 ^{***,###}	1.20±0.62 ^{***,##}
IV	13	5.94±1.02 ^{***,###,@@@}	0.87±0.34 ^{***,###,@@}
F		81.771	35.823
P		<0.001	<0.001

Note: FIGO: Federation of Gynecology and Obstetrics. Compared with the I group, ^{**}P<0.01, ^{***}P<0.001; compared with the II group, ^{##}P<0.01, ^{###}P<0.001; compared with the III group, ^{@@}P<0.01, ^{@@@}P<0.001.

patients' serum is beneficial to early diagnosis and has a positive effect on the patient's prognosis. Clinically, for EC patients, diagnosis only by clinical signs, symptoms and commonly used clinical tumor indexes often leads to a lack of specificity, which makes some patients miss the optimal treatment period and then deteriorate [25].

With the development of gene detection technology, researchers have found that certain miRNAs can inhibit or promote the process of

tumor occurrence, development, invasion, and metastasis [26-28]. miRNAs are also abnormally expressed in EC patients and have similar effects on tumor cells. For example, miR-107 and miR-93 expressions are up-regulated in EC tissues, and this up-regulation can promote the cell development, invasion and metastasis, so they could be used as markers to evaluate the prognosis [29, 30]. In contrast, the down-regulation of miR-381 expression can promote the invasion and metastasis of EC and is related to malignancy in EC patients [31]. The current diagnostic methods of EC are mainly ultrasound, magnetic resonance imaging (MRI), and serum markers. Histopathological examination remains the gold standard. In our study, we found that miR-373 is up-regulated and miR-124 is down-regulated in EC tissues. Both miR-373 and miR-124 have good diagnostic value for the EC diagnosis and may be potential markers for the diagnosis of EC.

It is reported that miR-373 can promote the regeneration of stem cells and the development of various cell tumors by regulating the

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Table 6. Comparison of the relative expressions of miR-373 and miR-124 in patients with different lymph node metastases

Group	Number of cases	Relative expression of miR-373	Relative expression of miR-124
Lymph node metastases			
No	73	2.56±1.38	1.48±0.80
Yes	33	4.55±1.34	0.96±0.17
t		6.912	5.213
P		<0.001	<0.001

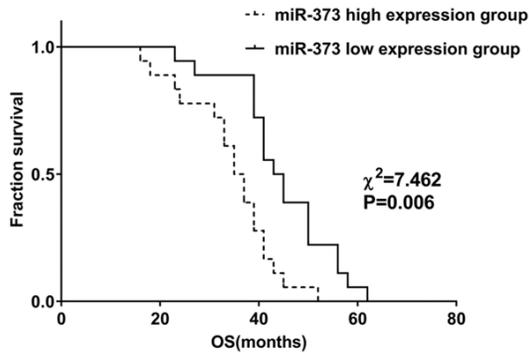


Figure 2. Comparison of the mean overall survival time of the different miR-373 relative expression groups. OS: overall survival.

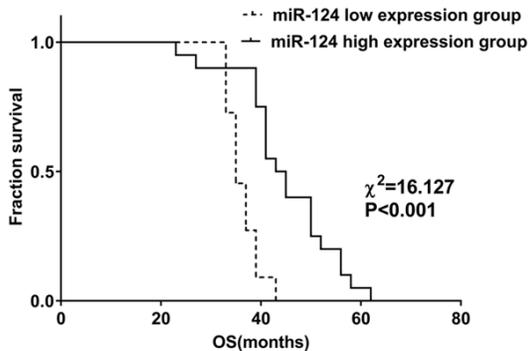


Figure 3. Comparison of the mean overall survival time of the different miR-124 relative expression groups. OS: overall survival.

wnt/ β -catenin and other signaling pathways [16]. An increased expression of miR-373 promotes tumor cell proliferation in various tumors, such as rectal cancer, renal cancer, and esophageal cancer [17-19, 32]. However, some studies have found that the increased expression of miR-373 in ovarian cancer tissues can inhibit the invasion and spread of cancer cells and can also inhibit bladder cancer by regulating the expression of cadherin in patients [33, 34].

Studies on miR-124 showed that the down-regulated expression of miR-124 in cervical cancer tissues plays a role in inhibiting the proliferation of cervical cancer cells, as well as suppressing lung cancer and gastric cancer [35-37]. In the current studies on miR-

124, its main effect is to suppress cancer, but no cancer-promoting effect has been found. In our study, the expression of miR-373 and miR-124 in EC patients was found to be independent of age. But the high expression of miR-373 and the low expression of miR-124 in cancer tissue were associated with the low differentiation of EC cancer, deep myometrial infiltration, and high FIGO stage. This indicates that a higher expression of miR-373 and a lower expression of miR-124 in EC cancer tissues can make the tumor cells have a stronger invasiveness, which is related to promoting the role of miR-373 and inhibiting the role of miR-124 in cancer progression.

In prognostic studies, different pathological types have been found to be significantly associated with prognosis, and some studies have shown that EC patients with lymph node metastasis have a worse prognosis than those without metastasis [38, 39]. In our study, the high expression of miR-373 and the low expression of miR-124 are related to a poor prognosis and correlated with pathological types, which is consistent with the abovementioned studies.

However, this study had a small sample size and was single-centered, and we did not examine the related mechanisms. Therefore, the mechanism of action can be further explored, and the sample size can be expanded by conducting a multi-center randomized control study.

In conclusion, a high expression of miRNA-373 and a low expression of miR-124 in EC patients are associated with the degree of malignancy and indicate a poor prognosis.

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Disclosure of conflict of interest

None.

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