

Evaluation of the Efficacy and Prognosis of MRI Combined with miR-134 in Neo-adjuvant Chemotherapy Combined with Breast-conserving Surgery

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To explore the application effect of MRI and miR-134 in neo-adjuvant chemotherapy combined with breast-conserving surgery. Sixty-one patients who received neo-adjuvant chemotherapy combined with breast-conserving surgery were collected as observation group (OG), and other 53 patients who received breast-conserving surgery at the same time were collected as control group (CG). The positive surgical margins rate, axillary lymph node metastasis rate, 5-year survival rate, recurrence rate and miR-134 expression before and after treatment were compared between the two groups. The diagnostic ability of MRI and miR-134 before treatment for axillary lymph node metastasis and the prognostic significance of miR-134 after treatment were explored. The positive surgical margins rate in OG was obviously lower than that in CG. There was no significant difference in axillary lymph node metastasis rate. There was no obvious difference in 5-year survival rate in both groups. The 5-year recurrence rate in OG was obviously lower than that in CG. Before therapy, the area under ROC curve (AUC) of miR-134 in diagnosing axillary lymph node metastasis was 0.788, and the specificity and sensitivity were 70.59% and 86.25%. The specificity and sensitivity of MRI diagnosis were 90.00% and 76.47%, and the combined diagnosis was 63.75% and 97.06%, so the sensitivity was improved. After treatment, the AUC of miR-134 in predicting 5-year survival was 0.810, and that of miR-134 in predicting 5-year recurrence was 0.767. To sum up, neo-adjuvant chemotherapy combined with breast-conserving surgery can decline the postoperative recurrence rate of patients. Preoperative miR-134 combined with MRI can diagnose axillary lymph node metastasis, and preoperative miR-134 can predict the prognosis.

Keywords: MRI, miR-134, neo-adjuvant chemotherapy, breast-conserving surgery

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INTRODUCTION

Breast cancer (BC), as one of the malignant tumors with the highest prevalence among women, is the sixth reason of cancer-related death among women in China, and the diagnostic rate and mortality rate were 12.2% and 9.6% in China^{1,2}. Surgery is a common clinical treatment for BC at present, and BC surgery has gradually developed from large-scale elimination to precise elimination. Compared with mastectomy, breast-conserving surgery can preserve the complete breast shape to a greater extent, so more women in the early phase of BC are more likely to choose breast-conserving surgery if their condition permits³. Breast-conserving surgery combined with some treatments such as radiotherapy and chemotherapy can obviously ameliorate the recurrence rate and survival rate of patients, and can effectively provide local control rate^{4,5}. Neo-adjuvant chemotherapy can achieve pathological response to many locally advanced BC patients, and neo-adjuvant chemotherapy can also reduce the tumor size of BC patients, so that some patients can meet the conditions for breast-conserving surgery^{6,7}. Therefore, neo-adjuvant chemotherapy combined with breast-conserving surgery has gradually become the focus of research.

MRI has been used to evaluate many tumors because of its multiplanar imaging and better soft tissue discrimination ability, so MRI has been used in the diagnosis and treatment of BC^{8,9}. In breast-conserving surgery, MRI can better determine the location and spread of tumor, so it is a common detection item before operation¹⁰. Non-coding RNAs (such as miRNA) have the value as indicators or therapeutic targets because they can participate in and regulate the development of cancer diseases^{11,12}. For example, studies by Han et al.¹³ have shown that detecting miR-1204 in patients' serum has the potential to be a marker for diagnosis and prognosis of BC. However, some miRNA combined with imaging techniques can better classify some tumor phenotypes and characteristics, and increase the ability of differential diagnosis and prognosis prediction¹⁴. miR-134 has been found to regulate

the biological functions of various cancer cells and inhibit BC cells, which may become a potential treatment^{15,16}.

In this study, MRI and miR-134 were explored to evaluate the prognosis of patients undergoing neo-adjuvant chemotherapy combined with breast-conserving surgery.

METHODS AND DATA

Patients' Data

A total of 114 patients with BC were collected from February 2014 to April 2016. All the patients were female. Among them, 61 patients who received neo-adjuvant chemotherapy combined with breast-conserving surgery were included in the OG with an average age of (41.3±5.7) years old, and other 53 patients who received breast-conserving therapy were included in the CG with a mean age of (43.3±6.2) years old. The research was conducted according to Helsinki Declaration. This research has been ratified by the Medical Ethics Committee of our hospital. All patients were informed and signed informed consent.

Inclusion and Exclusion Criteria

Inclusion criteria: All sufferers were diagnosed as early BC by pathological examination, and the lesion range was less than 4cm. They were predicted to meet the indications of breast-conserving surgery, and they were diagnosed as single tumor by imaging examination. The follow-up data and clinical data of patients were complete.

Exclusion criteria were as follows: patients who had failed breast-conserving surgery and turned to mastectomy, patients who had no intention of breast-conserving surgery, patients who were allergic to the drugs used, patients with heart, liver and kidney dysfunction, and other malignant tumors.

Treatment Methods

In both groups, patients underwent breast-conserving surgery. After general anesthesia, an incision was made at the patient's lesion. Then,

the tumor was resected about 1 ~2cm from the tumor edge, and the rapid freezing pathological examination was performed. If the test result was positive, the tumor enlarged by 1cm was removed. If the test result was positive again, the breast-conserving surgery was abandoned and replaced by radical surgery. Axillary lymph nodes were removed in all the patients, followed by dressing and suture. Besides, conventional radiotherapy was performed in both groups after the operation. On this basis, the patients in OG received neo-adjuvant chemotherapy before operation. The protocol was intravenous drip of docetaxel (75 mg/m²) + epirubicin (60 mg/m²) for a course of 21 days. The patients were treated with 6 cycles of chemotherapy. The surgery was performed after the end of chemotherapy for 1 week.

MRI Examination Method

In both groups, the patients were examined by MRI before treatment. Breast MRI was performed with GE 750 3.0T MR scanner, and 8-channel special phased array breast coil was used for imaging. The patient was prone on the bed, and then the prone position was suspended in the coil, and axial fat suppression T2WI and axial STIR were performed. Scanning parameters were as below: TR/TE =8200 ms/ 35 ms, TI: 170 ms; OAX STIR: TR/TE =6 000ms/48.2ms, TI: 150ms, slice thickness 5mm, Fov: 32cm, interlayer spacing 1 mm. Since the plain scan was finished, the dynamic contrast-enhanced scan was performed consecutively for 5 times with a time resolution of 60 s. GD-DTPA was used as the contrast media, the dose was 0.1 mmol/kg, and the injection velocity was 2.5 ml/s, followed by 15-20ml of normal saline. Parameters were as below: TI: 13.0 ms, TE 2.9 ms, TR 6.1 ms, flip angle: 10°, slice thickness: 3mm, no interval, matrix: 416×256. At the same time, the saturated fat technology was applied.

RT-qPCR Method

The 5mL of venous blood was taken from all patients in the morning after admission and

breast-conserving surgery, and the blood was placed in a coagulation-promoting tube and centrifuged to collect serum (3000 xg, 4°C for 10min). The total RNA was extracted from collected serum by mirVana™ PARIS™ kit (AM1556, ThermoFisher corporation, USA). The purity of total RNA was measured by ultraviolet spectrophotometer (UV-1800, Shimadzu, Japan). The PrimeScript™ RT Master Mix (Takara Bio company, RR036A) was used for reverse transcription. Reverse transcription system was as follows: 0.5μl of revistin, 0.5μl of reverse transcriptase, 2.0μl of buffer, 2μl of RNA. Finally, DEPC water was added to supplement to 15 μl. Reaction conditions were 37°C for 10 minutes and 95°C for 5 minutes. Then, TaqMan™ MicroRNA Assay Kit (ThermoFisher Company, USA, 4427975) was used for amplification, and the reaction conditions were as below: initial denaturation at 94°C for 30s, denaturation at 94°C for 5s, anneal and extension at 60°C for 30s, for a total of 45 cycles. U6 was used as internal reference gene to detect miR-134, and 2^{-ΔΔCq} was used for data processing.

Follow-up

All participants were followed up for 5 years, including telephone follow-up and outpatient re-examination, once every 3 months in the first 2 years, once every 6 months from the third year to the fourth year, and once every year in the last year. The end points were overall survival and recurrence.

Statistical methods

SPSS 20.0 (SPSS Co., Ltd., Chicago, USA) was applied for statistical analysis. The continuous variables were represented by the number of cases, average and standard deviation. Independent T-test was applied between the two groups. The paired T-test was used for testing at different time periods in the same group, and the results were expressed by t. For classified variables, the data were expressed as the number or percentage of classified cases, and the chi-square analysis was applied to test, and the results were expressed by X². ROC curve was applied to detect the diagnosis value of

miR-134 in patients with axillary lymph node metastasis before treatment and the predictive value of miR-134 in prognosis after treatment. The K-M curve of patients was drawn, and the 5-year survival and recurrence results were compared according to the difference status. Log-rank analysis was applied to compare the differences.

RESULTS
Baseline Data of Patients

By comparing the clinical data, we found that there was no obvious difference in age, post-menopausal, pathological stage, histological grade, tumor diameter, ER, PR, Her-2 and pathological type in both groups ($P<0.05$). (Table 1)

Table 1.
Baseline data

		CG (n=53)	OG (n=61)	X ² /t	P
Age		41.3±5.7	43.3±6.2	1.783	0.077
	Post-menopausal	8 (15.09)	11 (18.03)	0.176	0.675
Pathological staging	Ia	11 (20.76)	10 (16.39)	0.709	0.701
	Ib	18 (33.96)	25 (40.98)		
	Ila	24 (45.28)	26 (42.62)		
Histological grading	I	18 (33.96)	28 (45.90)	1.680	0.195
	II	35 (66.04)	33 (54.10)		
Tumor diameter	>2cm	20 (37.74)	21 (34.43)	0.135	0.713
	≤2cm	33 (62.26)	40 (65.57)		
ER	Negative	14 (26.42)	19 (31.15)	0.309	0.578
	Positive	39 (73.58)	42 (68.85)		
PR	Negative	25 (47.17)	32 (52.46)	0.317	0.573
	Positive	28 (52.83)	29 (47.54)		
Her-2	Negative	34 (64.15)	37 (60.66)	0.147	0.701
	Positive	19 (35.85)	24 (39.34)		
Pathological type	Carcinoma in situ	13 (24.53)	18 (29.51)	1.868	0.393
	Invasive carcinoma	37 (69.81)	36 (59.02)		
	Other	3 (5.66)	7 (11.47)		

Characteristics of Patients in Both Groups

According to statistics, there were 12 patients with positive surgical margins in both groups. By comparing the positive surgical margins in both groups, we found that the incidence of positive surgical margins in OG were obviously lower than

that in CG ($P>0.05$). Pathological examination showed that there were 34 patients with axillary lymph node metastasis in both groups, and there was no difference in both groups ($P<0.05$). (Table 2)

Table 2.
Patient's characteristics

	CG (n=53)	OG (n=61)	X ²	P
Positive surgical margins	9 (16.98)	3 (4.92)	4.392	0.036
Axillary lymph node metastasis	19 (35.85)	15 (24.59)	1.718	0.190

Diagnosis of Axillary Lymph Node Metastasis by MRI and miR-134

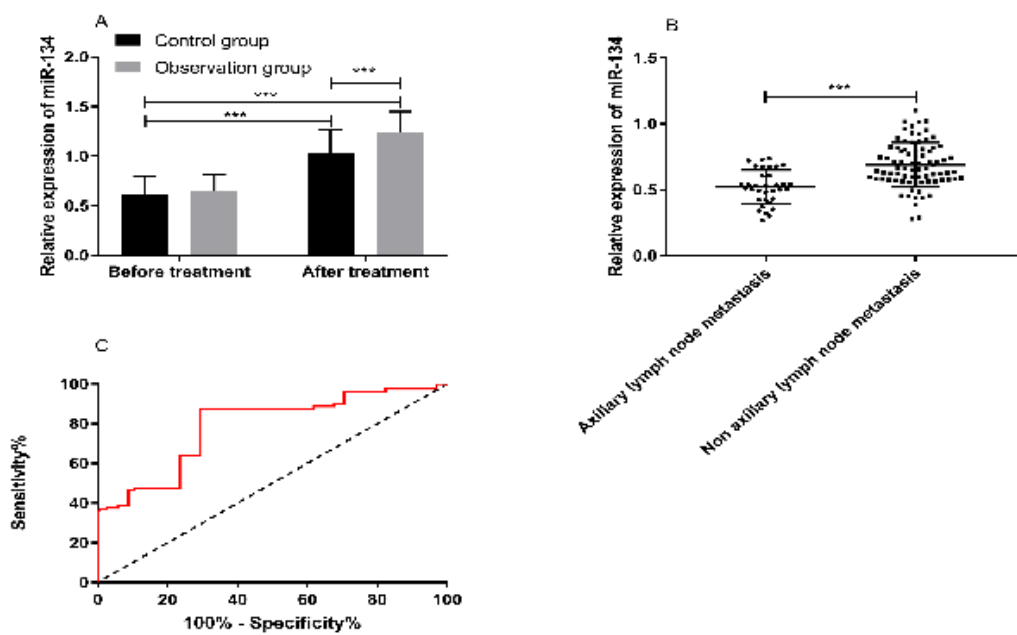
By observing the expression of miR-134 in the two groups before and after treatment, it was found

that miR-134 in both groups after therapy was obviously higher than that before therapy ($P>0.05$), and the OG after therapy was obviously higher than the CG ($P>0.05$). The MRI results showed

that the specificity and sensitivity of MRI were 90.00% and 75.00%. By comparing the expression of miR-134 between patients with axillary lymphatic metastasis and those without axillary lymphatic metastasis before treatment, it was found that the expression of miR-134 was higher in patients without axillary lymphatic metastasis

($P>0.05$). ROC curve was drawn to explore the diagnosis value of miR-134 in axillary lymph node metastasis before treatment, and it was found that AUC of miR-134 was 0.788. Through combined diagnosis, we found that the combined diagnosis could significantly improve the diagnostic sensitivity. (Figure 1 and Table 3)

Figure 1. Diagnosis value of miR-134 in axillary lymph node metastasis



A, after treatment, the level of miR-134 in the two groups was obviously higher than that before treatment, and that in the OG was significantly higher than that in the CG after treatment ($t=5.095$, $P<0.001$). B, the miR-134 in patients without axillary lymph node metastasis was obviously higher than that in patients with metastasis before treatment ($t=5.192$, $P<0.001$). *** means $P<0.001$. C, ROC curve of miR-134 in diagnosing axillary lymph node metastasis before treatment. The AUC and 95%CI of miR-134 were 0.788 and 0.699~0.877 respectively. When the cut-off was >0.554 , the specificity and sensitivity were 70.59% and 86.25%, and the youden index was 56.84%.

Table 3.
Diagnosis of axillary lymph node metastasis by MRI combined with miR-134

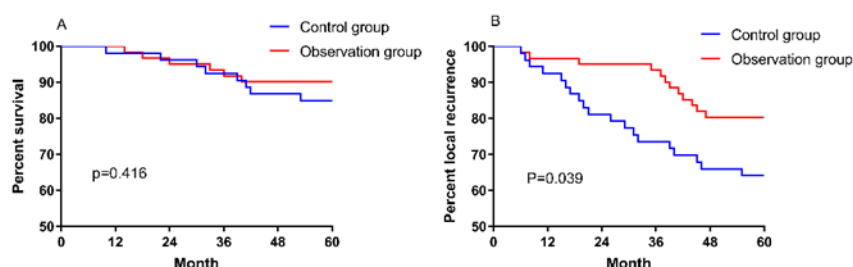
		Positive axillary lymph node metastasis (n=34)	Negative axillary lymph node metastasis (n=80)	Specificity	Sensitivity	Accuracy
MRI	Positive	26 (76.47)	8 (10.00)	90.00%	76.47%	85.96%
	Negative	8 (23.53)	72 (90.00)			
Combined diagnosis	Positive	33 (97.06)	30 (37.50)	63.75%	97.06%	73.68%
	Negative	1 (2.94)	51 (63.75)			

Prognosis of Patients in Both Groups

We counted the 5-year survival rate and 5-year recurrence of patients in the two groups, and concluded that the 5-year survival rate of patients was 87.72% in the two groups, with a total of 14 deaths and 100 survivals within 5 years. Among them, 8 cases died in the CG with a survival rate of 84.91%, while 6 cases died in the OG with a survival rate of 90.16%. By comparing with K-M

curve, it was found that there was no obvious difference in 5-year survival rate in both groups ($P < 0.05$). By comparing the local recurrence between the two groups, it was found that 12 cases recurred in the OG and 19 cases recurred in the CG, and the recurrence rate in OG was significantly lower than that in CG ($P > 0.05$). (Figure 2)

Figure 2.
Prognosis of patients in both groups.



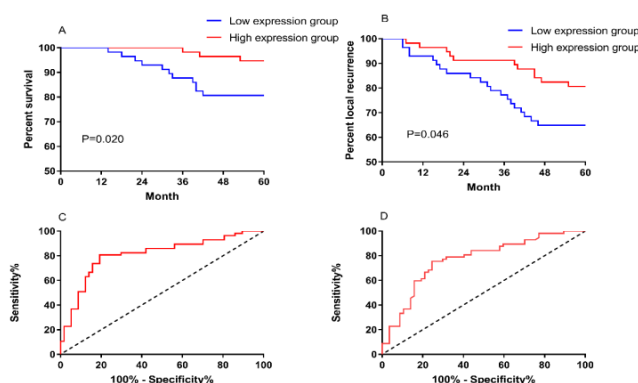
A, there was no obvious difference in 5-year survival rate in both groups ($P = 0.416$). B, the 5-year recurrence rate in OG was obviously lower than that in CG ($P = 0.039$).

Postoperative miR-134 could Predict the Prognosis of Patients

All sufferers were subdivided into high and low expression groups on the basis of the median expression of miR-134 after operation. The 5-year mortality and recurrence rate of the high expression

group were obviously lower than those of the low expression group by K-M curve. The area under ROC curve (AUC) of miR-134 for predicting death and recurrence was 0.810 and 0.767 respectively. (Figure 3)

Figure 3.
The area under ROC curve (AUC) of miR-134 for predicting death and recurrence



A, after operation, the 5-year survival rate of miR-134 high expression group was obviously higher than that of CG ($P = 0.020$). B, after operation, the recurrence rate of miR-134 high expression group was obviously

lower than that of CG ($P=0.046$). C, ROC curve of miR-134 in predicting 5-year survival after operation. The AUC and 95%CI were 0.810 and 0.728-0.892 respectively. When the cut-off was >1.138 , the specificity and sensitivity were 80.70% and 78.95%, and the youden index was 59.65%. D, ROC curve of miR-134 in predicting 5-year recurrence after operation. The AUC and 95%CI were 0.767 and 0.679-0.855 respectively. When the cut-off was >1.138 , the specificity and sensitivity were 75.44% and 73.68%, and the youden index was 49.12%.

DISCUSSION

Nowadays, the mortality rate of BC is in a downward trend, which is also contributed by the development of imaging technology, diagnostic methods and treatment programs^{17,18}. Breast-conserving surgery has gradually become the first choice for patients with early BC, but breast-conserving therapy requires complete resection of the lesion and negative margins¹⁹.

In this study, we compared patients with positive surgical margins in both groups, and found that the incidence of positive surgical margins in the OG was obviously lower than that in the CG, which might be because preoperative neo-adjuvant chemotherapy reduced the scope of the lesion. If the cutting edge of tumor is positive in BC surgery, it will greatly increase the recurrence rate of patients after surgery, and the tumor often need to be resected again, which will lead to anxiety and shaping effect of patients²⁰. However, studies by Smith et al.²¹ have revealed that some patients may have tumor resection margins due to the limitations of preoperative imaging and surgical techniques. However, many studies have also shown that some preoperative imaging methods, such as ultrasound and MRI, are very helpful to guide the operation process and reduce the positive surgical margins^{22,23}. In the studies of Hanna et al.²⁴, a multivariate analysis of 1,170,284 patients with BC who had received breast-conserving surgery showed that patients who had not received neo-adjuvant chemotherapy were more likely to have positive surgical margins, which also indicated that neo-adjuvant chemotherapy could decline the incidence of positive surgical margins. At the same time, we detected miR-134 of patients in the two groups, and concluded that the miR-134 in both groups was obviously higher than that before therapy, and

the miR-134 in OG was obviously higher than that in CG, indicating that the remission of patients' illness would improve miR-134. However, the researches of Zhang et al.²⁵ have mentioned that miR-134 can inhibit the proliferation of BC cells, indicating that miR-134 is a tumor suppressor gene.

In this study, the patients' lymph node metastasis was detected, and it was found that 34 patients had axillary lymphatic metastasis. Axillary lymph node metastasis is one of the most important factors to determine the prognosis of BC patients and optimize the treatment plan, so it is very important to determine whether axillary lymph node metastasis develops in BC patients²⁶. At present, the sentinel lymph node biopsy will be conducted to determine whether patients have axillary lymph node metastasis, but it cannot be used as the standard of whether the patient needs to be detected only by whether the patient has lymph node enlargement²⁷. Therefore, we conducted the following experiments to determine whether MRI and miR-134 could be used as a preliminary screening tool for axillary lymphatic metastasis in patients. Firstly, we compared the level of miR-134 between patients with axillary lymphatic metastasis and those without axillary lymphatic metastasis, and found that the level of miR-134 in patients with axillary lymphatic metastasis was lower. Through ROC curve, we found that the specificity and sensitivity of miR-134 in axillary lymph node metastasis were 70.59% and 86.25%. We diagnosed axillary lymph node metastasis by MRI, and found that the specificity, sensitivity and accuracy were 90.00%, 76.47% and 85.96%, while the specificity, sensitivity and accuracy of combined diagnosis were 63.75%, 97.06% and 73.68%. We

found that the combined diagnosis could significantly improve the sensitivity to patients, and then reduce the probability of missed diagnosis in patients with axillary lymphatic metastasis. In the researches by Golshan et al.²⁸, MRI can also better predict the therapeutic effect of patients with triple negative breast carcinoma.

At the same time, we also collected the 5-year survival rate and recurrence of patients. We concluded that the 5-year survival rate in OG was higher than that in CG, but there was no statistical difference in the survival rate in both groups, indicating that the two treatment methods did not significantly affect the 5-year survival of patients. However, the 5-year recurrence rate in OG was obviously lower than that in CG, indicating that neo-adjuvant chemotherapy combined with breast-conserving surgery could significantly decline the recurrence rate of patients compared with breast-conserving surgery alone. By comparing the 5-year survival rate and recurrence rate in the miR-134 high and low expression groups, we found that the survival rate of patients with low expression was obviously lower than that of patients with high expression group, and the recurrence rate was obviously higher than that of patients with high expression group. This also suggested that postoperative miR-134 might predict the prognosis of patients, so we finally tested the predictive value of postoperative miR-134 on the 5-year survival and recurrence of patients²⁹. By drawing ROC curve, we found that AUC for predicting 5-year survival was 0.810, while AUC for predicting recurrence of patients was 0.767, indicating that miR-134 has the ability to predict the prognosis of patients after surgery.

However, there are some shortcomings in this study. First of all, we excluded patients with triple negative breast carcinoma from the selected survey population. Therefore, it is not clear whether there is a difference in miR-134 between patients with triple negative breast carcinoma and non-triple negative breast carcinoma, and whether there is diagnostic and predictive value in triple negative breast carcinoma also needs to be discussed in the future. Secondly, all of our patients have received

MRI before treatment, so it has not been proved whether MRI before treatment will make a difference in the treatment results of patients. Finally, the cost of MRI is relatively high, so it is hoped that a more cost-effective, convenient and efficient detection method can be explored in future studies.

To sum up, neo-adjuvant chemotherapy combined with breast-conserving surgery can reduce the postoperative recurrence rate of patients. Preoperative miR-134 combined with MRI can diagnose axillary lymph node metastasis, and preoperative miR-134 can predict the prognosis.

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