

miR-210 is a Serological Biomarker for Predicting Recurrence and Prognosis of Colon Carcinoma Patients with Liver Metastases After Radiofrequency Ablation Treatment

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Purpose: Hepatic metastasis of colon carcinoma seriously affects the prognosis of patients, and miRNA has attracted much attention in predicting hepatic metastasis of colon carcinoma (CC). This research aimed to explore the predictive role of miR-210 in serum for recurrence and prognosis of CC patients with hepatic metastasis.

Methods: Altogether, 150 patients with liver metastases of CC (research group, RG) and 130 patients with non-metastatic of CC (control group, CG) admitted to People's Hospital of Deyang City from March 2012 to March 2015 were obtained and their serum was collected. miR-210 in the RG and the CG, and miR-210 in the RG after radiofrequency ablation treatment were detected, the relationship between miR-210 and pathological parameters of CC patients with hepatic metastasis was analyzed, and patients in the RG were followed up for 5 years to analyze the recurrence, overall survival (OS) and disease-free survival (DFS). The area under the curve (AUC) of receiver operating characteristic curve (ROC) was applied to test the predictive value of miR-210. Cox regression was applied to analyze the independent prognostic factors of patients.

Results: miR-210 in the RG was evidently higher than that in the CG, and AUC for distinguishing hepatic metastasis of CC was 0.907. miR-210 had a close correlation with lymph node metastasis, distant metastasis and pathological differentiation. After treatment, miR-210 in the RG was evidently reduced, and the serum was higher in patients with recurrence and with poor prognosis. AUC for predicting recurrence was 0.858, and AUC for predicting poor prognosis was 0.843. High miR-210 was closely related to lower 5-year OS and DFS and is also an independent prognostic factor affecting patients' 5-year OS.

Conclusion: miR-210 is enhanced in hepatic metastasis of CC, which is a serological biomarker for predicting recurrence and prognosis of patients with hepatic metastasis of CC after radiofrequency ablation, and has great clinical application value.

Keywords: hepatic metastasis of colon carcinoma, miR-210, radiofrequency ablation, recurrence, prognosis

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Introduction

Colon carcinoma, as a digestive tract tumor, is an important factor of carcinoma death in developed countries.^{1,2} Hepatic metastasis is the main reason for colon carcinoma death and has poor prognosis. The OS can be as low as 10% in 5 years.³ Radiofrequency ablation is a non-surgical minimally invasive treatment method for

colon carcinoma patients with hepatic metastasis, in which heat energy is deposited by high-frequency current pulses, thus destroying the tumor and hindering the disease process.^{4,5} Although the treatment mode is continuously optimized, the liver of colon carcinoma patients with hepatic metastasis is still in an immunosuppressive state, resulting in rapid disease progression and high recurrence rate (up to 86.1%).^{6,7} Therefore, it is still of great value to investigate the effect of radiofrequency ablation on the recurrence and prognosis of colon carcinoma patients with hepatic metastasis.

microRNA (miRNA) is an organism's physiological and pathological regulator composed of 20–25 nucleotides, which has regulatory effects on cell cycle, migration, invasion and other cell processes, and also has certain influence on the survival and pathological changes of various tumors.^{8,9} In addition, miRNA, as a serological indicator, has certain clinical value for tumor diagnosis, prognosis and recurrence prediction.^{10,11} For example, miR-4772-3p in serum is helpful to predict tumor recurrence in patients with stage II/III colon carcinoma. miR-629 is a potential biological indicator for diagnosis and prognosis of pancreatic carcinoma.^{11,12} In this study, we mainly focused on miR-210 in serum. Previous researches have shown that miR-210 is carcinogenic in colon carcinoma and can be applied for diagnosis and prognosis prediction.¹³ In addition, it is closely related to the chemoresistance and radiation sensitivity of 5-fluorouracil in colon carcinoma cells, and participates in the pathological regulation mechanism.^{14,15} It has been reported that miR-210 has potential value in differentiating the differential expression between colon carcinoma and hepatic metastasis, but there are still few related reports.¹⁶

The research intended to analyze the predictive role of miR-210 in serum for recurrence and poor prognosis after radiofrequency ablation in hepatic metastasis of colon carcinoma, hoping to provide reference for the treatment and prevention of such patients.

Materials and Methods

General Data

Altogether 150 patients with liver metastases of colon carcinoma from March 2012 to March 2015 were selected as the research group (RG), including 79 men and 71 women with an average age of (62.02 ± 15.37) years. Another 130 patients with non-metastatic colon carcinoma were selected as the control group (CG), including 75 men

and 55 women, with an average age of (61.56 ± 13.87) years. The study was approved by the Ethics Committee of Deyang people's Hospital and in accordance with the Helsinki Declaration. The participants and their guardians have signed the informed consent form.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) The follow-up data were complete; (2) All patients have received radiofrequency ablation; (3) Patients were diagnosed as colon cancer by pathology, and there was liver metastasis;¹⁷ (4) Patients with no cognitive and communication barriers.

Exclusion criteria: (1) Patients with other malignant tumors or other severe diseases; (2) Colon cancer patients with distant metastasis except liver; (3) The estimated survival time was no more than 3 months; (4) Pregnant or lactating women; (5) Patients with infectious diseases or autoimmune diseases.

All standards are applicable to the research group. The control group was non-metastatic colon cancer patients. In the inclusion criteria (3), patients were diagnosed as colon cancer by pathology. In the exclusion criteria (2), all patients with distant metastasis including live were excluded, and all other criteria were applicable.

Treatment Method

The RG was treated with radiofrequency ablation: patients were fasted for at least 8 hours before operation and applied the lying posture. The puncture point was marked according to CT and ultrasound influence results, the maximum diameter of the tumor was inserted through cool-tip bundle or single needle after local anesthesia, and then the ablation was performed for 12–15min. The first radio frequency was maintained for 15min, and then the single region was repeatedly ablated. The ablation time was determined by the degree of the disease, and the number of repeated ablation in a single region was not more than 3 times. Radiological observation showed that the ablation was ended after the ablation scope was complete.

Detection Method

One week before and after treatment, 5mL elbow venous blood of the participants in the RG was collected at about 8 o'clock in the morning, placed in a vacuum blood collection tube containing EDTA-K2, centrifuged at 1500Xg and at 4°C for 15min, and the supernatant was placed in a new EP tube at -75°C for later use. The participants in the CG only needed to collect once according to the above steps. The total RNA

was extracted according to the specification of PURELINK MIRNA ISOLATION KIT (HuiJia Biotechnology Co., Ltd., Xiamen, China, K157001). The concentration of RNA was determined by SpectroArt 200S ultraviolet-visible spectrophotometer (Anatech Co., Ltd., Beijing, China). Referring to the reverse transcription kit (Biolab Technology Co., Ltd., Beijing, China, ALH266-PTO), RNA was reverse transcribed into cDNA and PCR amplification experiments were carried out. U6 was used as the internal reference, and the primer sequences were all collected from Shanghai Qiantu Biotechnology Co., Ltd. miR-210 was quantitatively detected on a real-time fluorescence quantitative PCR system (Nanjing ZhongkeBio Medical Technology Co., Ltd, Nanjing, China, ZKBIO-003) with reference to miRNA qPCR research kit (Genetimes Technology Inc., Shanghai, China, 110001S). Among them, miR-210 upstream: TAATATAGCCCCCTGCCACC, downstream: TATGC TTGTTCTCGTCTCTGTGTC; U6 upstream: ATTGGA ACGATACAGAGAAGATT, downstream: GGAACGCT TCACGAATTTG. All samples were repeatedly tested for 3 times, and the results were tested by $2^{-\Delta CT}$.

Follow-Up

The patients were followed up once every 3 months for 5 years by telephone, interview and pathological inquiry to understand the final outcome after intervention. The total survival (OS) was from the beginning of treatment to the time of death or the deadline of the last follow-up, and the disease-free survival time (DFS) was from the beginning of treatment to the time of death or the deadline of the last follow-up due to disease recurrence or disease progression of the patients.

Statistical Analysis

Statistical analysis was conducted by SPSS20.0 (EasyBio, Beijing, China), and figures were visualized by Graphpad Prism6 (Graphpad Software, San Diego, USA). Counting data was represented by the number of cases/percentage [n (%)], and chi-square test was applied for comparison between groups. The measurement data were represented by mean \pm SD and compared by independent sample *t* test, and the comparison before and after treatment was conducted by paired *t* test. ROC was applied to test the value of miR-210 in diagnosis, recurrence and prognosis of patients. Kaplan-Meier was applied to test OS and DFS.

Table 1 Baseline Data of RG and CGs of Patients [n (%), mean \pm SD]

Factor	n	RG (n=150)	CG (n=130)	χ^2/t	P
Gender				0.711	0.399
Male	154	79 (52.67)	75 (57.69)		
Female	126	71 (47.33)	55 (42.31)		
Age (years)				0.054	0.816
<60	125	66 (44.00)	59 (45.38)		
≥ 60	155	84 (56.00)	71 (54.62)		
Average age (years)	280	62.02 ± 15.37	61.56 ± 13.87	0.261	0.794
Drinking history				0.117	2.451
No	154	76 (50.67)	78 (60.00)		
Yes	126	74 (49.33)	52 (40.00)		
Smoking history				1.961	0.161
No	173	87 (58.00)	86 (66.15)		
Yes	107	63 (42.00)	44 (33.85)		
TNM phase				0.591	0.442
I-II	121	68 (45.33)	53 (40.77)		
III-IV	159	82 (54.67)	77 (59.23)		
Invasion depth				1.141	0.285
T1-T2	124	62 (41.33)	62 (47.69)		
T3-T4	156	88 (58.67)	68 (52.31)		
Lymph node metastasis				1.022	0.312
No	159	81 (54.00)	78 (60.00)		
Yes	121	69 (46.00)	52 (40.00)		
Distant metastasis				0.188	0.665
M0	162	85 (56.67)	77 (59.23)		
M1	118	65 (43.33)	53 (40.77)		
Tumor size (cm)				0.511	0.475
<5	125	64 (42.67)	61 (46.92)		
≥ 5	155	86 (57.33)	69 (53.08)		
Degree of pathological differentiation				0.584	0.445
Medium and high differentiation	97	55 (36.67)	42 (32.31)		
Poor differentiation	183	95 (63.33)	88 (67.69)		

Abbreviations: RG, research group; CG, control group.

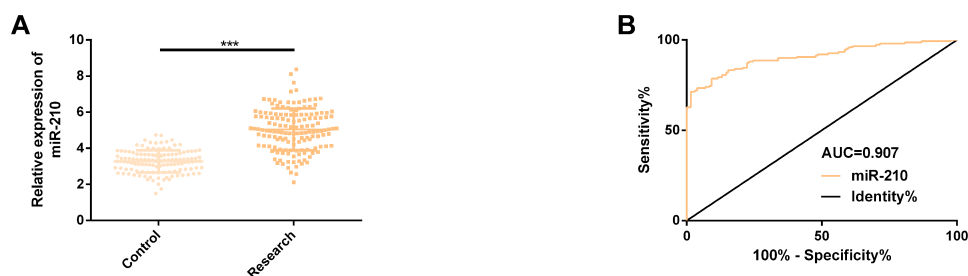


Figure 1 Expression of miR-210 in serum of colon carcinoma patients with hepatic metastasis. (A) miR-210 was up-regulated in serum of colon carcinoma patients with hepatic metastasis. (B) ROC curve of miR-210 in identifying hepatic metastasis of colon carcinoma.

Note: ***Means compared between the RG and the CGs, $P < 0.001$.

Abbreviations: miR, microRNA; ROC, receiver operating characteristic curve; AUC, area under the curve; RG, research group; CG, control group.

Log rank test was applied to test the difference in survival between groups. Univariate and multivariate Cox regression analysis were applied to analyze the prognostic factors of patients. $P < 0.05$ was considered to be statistically different.

Result

Baseline Data

There was no evident difference in gender, age, average age, drinking history, smoking history, TNM stage, invasion depth, lymph node metastasis, distant metastasis, tumor size and pathological differentiation degree between the RG and the CG ($P > 0.05$). See Table 1.

miR-210 Up-Regulated in Serum of Patients with Hepatic Metastasis of CC

In order to explore whether miR-210 has imbalance in hepatic metastasis of colon carcinoma, we detected its serum expression in two groups of patients. The results showed that the miR-210 in the RG was evidently higher than that in the CG ($P < 0.001$). We also visualized the ROC curve for distinguishing liver metastases from CC. The data showed that the AUC was as high as 0.907 (95% CI: 0.872–0.942), the sensitivity and specificity were 71.33%, 98.46%, respectively, and the optimal cut-off value was 4.47. See Figure 1.

miR-210 Was Associated with Pathological Parameters of CC Patients with Hepatic Metastasis

In order to explore whether serum miR-210 could evaluate the pathological parameters of patients with liver metastases of CC, we analyzed its expression in the pathological parameters of patients. The results showed that miR-210 had no evident correlation with sex, age, TNM stage, invasion depth,

and tumor size ($P > 0.05$), but had evident correlation with lymph node metastasis, distant metastasis and pathological differentiation degree ($P < 0.05$). See Table 2.

Table 2 Relationship Between miR-210 and Pathological Parameters of CC Patients with Hepatic Metastasis (mean \pm SD)

Parameter	n	miR-210	t	P
Gender			1.405	0.161
Male	154	5.11 \pm 0.85		
Female	126	4.98 \pm 0.66		
Age (years)			1.812	0.071
≤ 60	125	4.94 \pm 0.78		
> 60	155	5.13 \pm 0.94		
TNM stage			1.189	0.236
I–II	121	4.95 \pm 0.87		
III–IV	159	5.09 \pm 1.05		
Invasion depth			1.870	0.063
T1–T2	124	4.90 \pm 0.90		
T3–T4	156	5.13 \pm 1.11		
Lymph node metastasis			6.306	< 0.001
No	159	4.78 \pm 1.02		
Yes	121	5.50 \pm 0.84		
Distant metastasis			4.461	< 0.001
No	162	4.84 \pm 1.15		
Yes	118	5.41 \pm 0.91		
Tumor size (cm)			1.088	0.278
< 5	125	5.13 \pm 0.92		
≥ 5	155	5.00 \pm 1.05		
Degree of pathological differentiation			6.326	< 0.001
Medium and high differentiation	97	4.78 \pm 1.02		
Poor differentiation	183	5.50 \pm 0.84		

Abbreviations: miR, microRNA; CC, colon carcinoma; TNM, tumor node metastasis.

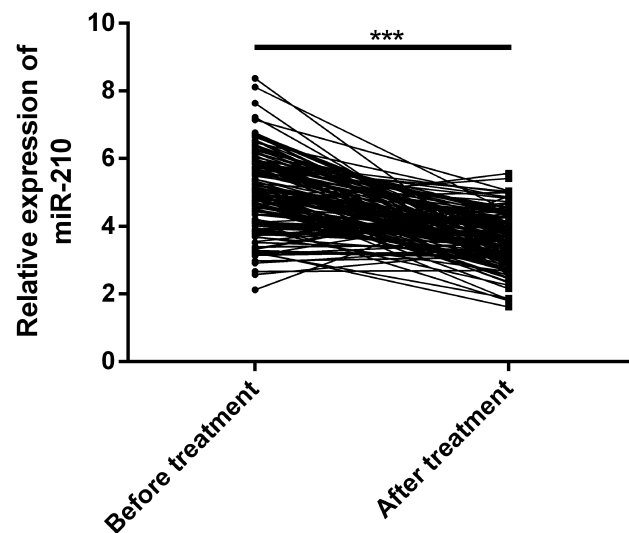


Figure 2 Expression of miR-210 in colon carcinoma patients with hepatic metastasis before and after treatment. miR-210 was evidently down-regulated after treatment for liver metastases of colon carcinoma.

Note: ***Means compared between the RG and the CGs, $P < 0.001$.

Abbreviations: miR, microRNA; RG, research group; CG, control group.

miR-210 Down-Regulated Evidently After Treatment for Hepatic Metastasis of CC

In order to explore whether miR-210 responded to the therapeutic effect of radiofrequency ablation, we analyzed its expression before and after treatment. The results revealed that miR-210 in the RG and the CG after intervention was

evidently lower than that before intervention ($P < 0.001$). See Figure 2.

miR-210 Up-Regulated Evidently in Patients with Hepatic Metastasis and Recurrence of CC and Even Patients with Poor Prognosis

Further exploring the recurrence and prognostic value of miR-210 in hepatic metastasis of colon carcinoma revealed that miR-210 had higher serum expression in recurrent patients and patients with poor prognosis ($P < 0.001$). By visualizing the ROC curve for predicting recurrence, we found that the AUC reached 0.858 (95% CI: 0.807–0.894), the sensitivity and specificity were 72.41% and 87.30%, respectively, and the best cut-off value was 4.96. However, AUC for predicting poor prognosis was 0.843 (95% CI: 0.780–0.907), the sensitivity and specificity were 77.33% and 78.67%, respectively, and the best cut-off value was 4.58. See Figure 3 and Table 3.

High-Level miR-210 Was Evidently Associated with Lower OS and DFS in 5 Years in Patients with Liver Metastases from CC

In order to understand the relationship between miR-210 and the survival of CC patients with hepatic metastasis, the

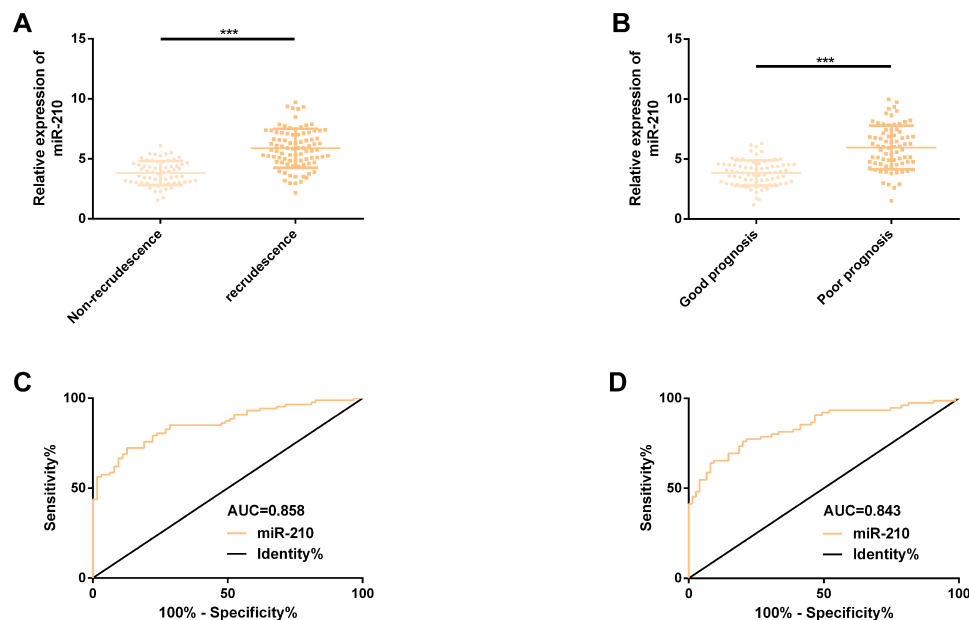


Figure 3 Expression and predictive value of miR-210 in hepatic metastasis, recurrence and poor prognosis of colon carcinoma. (A) miR-210 was evidently up-regulated in patients with hepatic metastasis and recurrence of colon carcinoma. (B) miR-210 was evidently up-regulated in patients with poor prognosis. (C) ROC curve of miR-210 predicting hepatic metastasis and recurrence of colon carcinoma. (D) ROC curve of miR-210 predicting poor prognosis of hepatic metastasis from colon carcinoma.

Note: ***Means compared between the RG and the CGs, $P < 0.001$.

Abbreviations: miR, microRNA; ROC, receiver operating characteristic curve; AUC, area under the curve; RG, research group; CG, control group.

Table 3 ROC Parameters of miR-210 for Predicting Recurrence or Poor Prognosis of CC Patients with Hepatic Metastasis

Objective	AUC	95% CI	Standard Error	Cut-off Value	Sensitivity (%)	Specificity (%)
Recurrence prediction	0.858	0.800–0.916	0.030	4.96	72.41	87.30
Prognostic prediction	0.843	0.780–0.907	0.032	4.58	77.33	78.67

Abbreviations: ROC, receiver operating characteristic curve; miR, microRNA; CC, colon carcinoma; AUC, area under the curve.

5-year OS and DFS curves were visualized. In this study, the 5-year follow-up was successfully completed, with OS and DFS of 50.00% (75/150) and 40.00% (60/150) in 5 years. In our survival curve, the median expression of miR-210 (4.57) was taken as the critical point. The results showed that high-level miR-210 was evidently correlated with lower OS and DFS in 5 years ($P<0.001$). We also analyzed the prognostic factors of hepatic metastasis of CC by Cox analysis. The results showed that TNM stage ($P=0.019$), lymph node metastasis ($P=0.023$), distant metastasis ($P=0.015$) and miR-210 ($P=0.009$) were independent prognostic factors of poor prognosis of hepatic metastasis of CC. High stage TNM, lymph node metastasis, distant metastasis and high miR-210 (>4.57) increased the risk of poor prognosis of hepatic metastasis of CC. See Figure 4 and Table 4.

Discussion

Hepatic metastasis of CC is a dangerous state of CC, which still has high recurrence rate and low survival rate even after surgical resection.^{18,19} Radiofrequency ablation, as an effective treatment for colon carcinoma patients with hepatic metastasis, can even replace hepatectomy in some cases to exert therapeutic effect.²⁰ miR-210, as a biological indicator of colon carcinoma, has shown better diagnostic value,²¹ but there is still little research on recurrence and prognosis prediction after radiofrequency ablation. In this study, we will carry out correlation analysis based on miR-210, which is of great significance for optimizing the treatment strategy for hepatic metastasis of colon carcinoma.

Previous studies have shown many evidences, which proved that miR-210 was highly correlated with colon carcinoma. For example, in the research of Ullmann et al,²² miR-210 could inhibit the self-renewal ability of tumor initiation cells around ISCU by targeting in hypoxic colon carcinoma cells. Another report of Bigagli et al²³ indicated that miR-210, as an exosome, can affect the adhesion of colon carcinoma metastatic cells and has an important regulatory role on the metastatic behavior of tumor cells. In our research, miR-210 was evidently high in patients with hepatic metastases of CC, indicating that miR-210 may be involved in the pathological process of hepatic metastases of CC. In the report of Wang et al,¹³ miR-210 was also up-regulated in the serum of colon carcinoma patients, which was similar to our research results. In addition, miR-210 also had abnormal up-regulation in other malignant tumors, such as breast carcinoma, glioma, and venous metastatic hepatocellular carcinoma.^{24–26} Further analyzing the diagnostic effect of miR-210 in hepatic metastasis of colon carcinoma, we found that the AUC for differentiating hepatic metastasis of colon carcinoma from non-metastatic colon carcinoma was 0.907, and the sensitivity and specificity were 71.33% and 98.46%, respectively, suggesting that miR-210, as a serum index, had higher diagnostic value and specificity for identifying hepatic metastasis of colon carcinoma. We also explored the correlation of miR-210 with pathological parameters of patients. The results showed that miR-210 had a close correlation with lymph node metastasis, distant metastasis and degree of pathological differentiation.

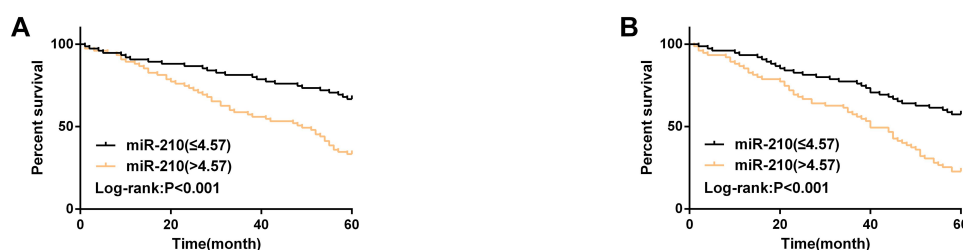


Figure 4 The correlation of the 5-year OS and DFS of colon carcinoma patients with hepatic metastasis with miR-210. (A) High-level miR-210 was associated with lower 5-year OS in patients with liver metastases of colon carcinoma. (B) High-level miR-210 was associated with lower 5-year DFS in patients with liver metastases of colon carcinoma.

Abbreviations: miR, microRNA; OS, overall survival; DFS, disease-free survival.

Table 4 Cox Analysis on Prognosis of Patients with Hepatic Metastasis from CC

Parameter	Single Factor		Multiple Factors	
	HR (95% CI)	P	HR (95% CI)	P
Gender	1.209 (0.789–2.164)	0.220		
Age	1.108 (0.902–1.544)	0.103		
TNM stage	3.343 (2.009–2.163)	0.017	1.963 (1.226–3.078)	0.019
Invasion depth	0.001 (2.321–4.125)	0.001	0.828 (0.374–1.000)	0.295
Lymph node metastasis	1.698 (1.218–2.649)	0.025	1.733 (1.192–3.622)	0.023
Distant metastasis	3.877 (1.491–3.462)	<0.001	2.371 (1.560–4.289)	0.015
Tumor size	1.735 (1.006–2.996)	0.048	1.064 (0.581–1.927)	0.831
Degree of pathological differentiation	2.220 (1.202–2.507)	0.009	1.475 (0.898–2.416)	0.124
miR-210	2.879 (1.340–2.714)	0.001	3.006 (2.457–6.008)	0.009

Abbreviations: CC, colon carcinoma; TNM, tumor node metastasis; miR, microRNA.

Higher level miR-210 had a correlation with lymph node metastasis, distant metastasis and degree of low differentiation, indicating that miR-210 was helpful to evaluate the above pathological parameters of patients.

miR-210 was also actively responsive to the treatment of radiofrequency ablation in patients with hepatic metastases of CC, and its expression was evidently down-regulated after treatment. In addition, the recurrence rate of our 150 patients was 58.0%, which was similar to 60.6% of Min et al.²⁷ In the follow-up results, the 5-year OS and DFS were 50.0% and 40.0%, respectively, which were similar to the results of Spelt et al.²⁸ (the 5-year OS: 52.0%, the 5-year DFS: 37.0%). We also evaluated its predictive value in predicting recurrence and poor prognosis of patients after radiofrequency ablation. The results showed that its AUC for predicting the recurrence was 0.858, while that for predicting the prognosis was 0.843, suggesting that miR-210 had multiple predictive efficacy, which not only can be used as a potential predictive

indicator for recurrence of CC patients with hepatic metastasis, but also has gratifying value for prognosis prediction. In the report by Chen et al,²⁹ up-regulation of miR-210 was helpful to identify pathological conditions of colon carcinoma, such as local recurrence, distant metastasis and poor prognosis, which were similar to our results. In the research of Zhang et al,³⁰ high miR-210-3p was also pointed out to increase the recurrence risk of renal cell carcinoma (RCC), which can be used as a recurrence prediction index of RCC. In addition, Tang et al³¹ reported that the high miR-210 in acute myeloid leukemia was significantly related to the lower recurrence-free survival rate of patients, suggesting that miR-210 also had certain recurrence prediction potential in this disease. All the above results confirmed that miR-210 had certain recurrence prediction value in different disease backgrounds. Subsequently, we also made an analysis of survival and prognosis factors, indicating that patients with high-level miR-210 (>4.57) had lower OS and DFS for 5 years, which was evidently related to poor prognosis. Cox analysis showed that TNM stage, lymph node metastasis, distant metastasis and miR-210 were independent prognostic factors for poor prognosis of CC patients with hepatic metastasis. Patients with high stage TNM, lymph node metastasis, distant metastasis and high miR-210 (>4.57) had an increased risk of poor prognosis.

Although our research confirmed that miR-210, as a serological indicator, had potential high value for predicting the recurrence and prognosis of hepatic metastasis of CC. However, there are still some shortcomings in our research. First, we can supplement the predictive value analysis of miR-210 for the curative effect of colon carcinoma hepatic metastasis. Secondly, we can also supplement the analysis of risk factors that affect the curative effect of hepatic metastasis or recurrence of colon carcinoma. In addition, we can also focus on the molecular mechanism of miR-210 in hepatic metastasis of colon carcinoma and conduct basic research to explore potential therapeutic methods. We will gradually improve the research based on the above improvement points in the future.

Conclusion

To sum up, we proposed for the first time that miR-210 is a serological biomarker for predicting recurrence and prognosis of colon carcinoma patients with liver metastases after radiofrequency ablation, providing new clues for recurrence and prognosis prediction of patients.

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Disclosure

The authors report no conflicts of interest in this work.

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