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Expression and clinical significance of miR-193a-3p in invasive pituitary adenomas

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Abstract. – OBJECTIVE: Our study aimed to investigate miR-193a-3p expression and its clinical significance in pituitary adenomas (PAs). Moreover, the correlation between miR-193a-3p expression and the invasiveness of PAs was explored.

PATIENTS AND METHODS: In this study, the relative expression levels of miR-193a-3p were detected via quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The correlations between miR-193a-3p and tumor size, clinical features, and prolactinomas postoperative prolactin (PRL) levels early remission were further analyzed.

RESULTS: Compared with non-invasive PAs, there was a lower miR-193a-3p expression in invasive PAs. MiR-193a-3p expression had reverse relevance to tumor size. A higher risk of postoperative residual and recurrence was found in patients with downregulated miR-193a-3p. Prolactinomas patients with postoperative PRL levels early remission were at lower risk to relapse and patients with high-expression miR-193a-3p had a higher early remission rate, suggesting that miR-193a-3p was a significant prognostic factor for prolactinomas.

CONCLUSIONS: MiR-193a-3p could have potential therapeutic value for invasive pituitary adenomas.

Key Words:
MicroRNA, Pituitary adenomas, MiR-193a-3p, Invasiveness, Prognosis.

Introduction

Pituitary adenomas (PAs) are a common type of benign intracranial tumors, accounting for approximately 10%-15% of all brain tumors[1]. Based on their biological behavior, PAs could be divided into non-invasive pituitary adenomas (non-IPAs) and invasive pituitary adenomas (IPAs). Like malignant tumors, IPAs usually grow in an aggressive way. They can invade surrounding structures like parasellar cavernous sinus (CS), wrap the internal carotid arteries (ICAs), even erode the sellar floor and protrude into sphenoid sinus[2]. It is extremely difficult to radically remove all tumor tissues through surgery, leading to dismal prognosis in IPAs. Therefore, it is significant to further investigate the biological mechanism of tumorigenesis and invasiveness in IPAs.

MicroRNAs (miRNAs), consisting of 19-25 nucleotides, are a class of short non-coding RNA. By binding to the 3'untranslated region (3'UTR) of target genes, miRNAs can inhibit translation or initiate transcriptional degradation and thus regulate the expression of post-transcriptional genes[3]. In recent years, it is widely reported that miRNAs play a significant role in tumorigenesis, cell proliferation, and apoptosis. Some are able to promote the origin and proliferation of tumors, acting as oncogenes. Some may act as tumor suppressor genes and inhibit tumor progression[4]. It has been reported that the abnormal expression of miRNAs has close connection with tumor proliferation and invasiveness in bladder cancer, gastric cancer, lung cancer, and glioma[5-8]. Besides, some studies[9,10] have supported that the abnormal expression of miRNAs could promote the proliferation and invasiveness of PAs. Of note, our previous research[11] demonstrated that miR-193a-3p was downregulated in growth hormone (GH)-secreting PAs. Besides, downregulated miR-193a-3p can inhibit the growth, invasiveness and distant metastasis of tumor cells and promote apoptosis in other types of tumors[12,13]. However, there is little evidence on the role of miR-193a-3p in PAs. Therefore, the association between miR-193a-3p and the invasiveness of PAs warrants further investigation. Our study was a pilot study to investigate the role of miR-193a-3p in the invasiveness of PAs. The expression levels of miR-193a-3p in IPAs and non-IPAs were determined by quantitative Real Time-Polymerase Chain Reaction (qRT-

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PCR). We compared the miR-193a-3p expression of IPAs and non-IPAs. Besides, we explored the relationships between miR-193a-3p expression and tumor size, clinical characteristics, and prolactinomas postoperative PRL levels early remission. Our results indicated a potential biomarker for IPAs treatment.

Patients and Methods

Patient Samples

Altogether 82 patients diagnosed with PAs by imaging and postoperative immunohistochemistry from November 2011 to October 2019 were enrolled into this study. Experimental samples were obtained from patients who received endoscopic trans-sphenoidal adenomectomy in the East Division of the First Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). Other pituitary tumors, such as Rathke's cyst, pituitary carcinoma, and PAs with other tumors were excluded. For prolactinomas patients, we enrolled patients with dopamine agonists (DA) non-response or intolerance and those who had not taken DA due to microprolactinomas, progressive visual impairment and pituitary apoplexy. No drug, chemotherapy, operation or other related treatment were applied preoperatively.

82 patients (44 males and 38 females) aged 21-70 years (mean 45.83 ± 13.23 years). Of them, there were 42 (51.22%) non-functional adenomas, 33 (40.24%) PRL adenomas, 5 (6.1%) GH adenomas, and 2 (2.44%) follicle-stimulating hormone (FSH) adenomas. There were 52 cases of macro-adenomas [1<largest tumor diameter (d<3 cm) and 30 huge adenomas (d≥3 cm)]. The diagnosis and functional status of PAs were based on the hormonal levels, clinical characteristics, and histopathology. IPAs patients accounted for 33 (40.24%) cases and 49 (59.76%) cases were non-IPAs. We used following criteria to define IPAs: (1) Knosp grades were 3 or 4; (2) the tumor was proved to invade CS or penetrate into sellar diaphragm and sellar floor by surgical document or pathological analysis. All patients signed informed consent. The study was approved by the Ethics Committee for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China). Postoperative follow-up ended on January 2020, ranging 2.9-63.57 months (average, 22.20 ± 14.76 months).

Tissue Collection and RNA Isolation

Experimental tumor samples were collected from PAs patients who underwent endoscopic transsphenoidal surgery. All fresh tumor samples were initially preserved in liquid nitrogen and kept at -80°C for the subsequent experiment. TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was employed to isolate total RNA from PAs in accordance with manufacturer's protocols.

QRT-PCR for gene expression

MiR-193a-3p expression levels were measured by qRT-PCR. cDNA for miR-193a-3p was synthesized with miR-193a-3p-specific stem-loop primer and random primer. SYBR-Green qPCR SuperMix (Invitrogen, Carlsbad, CA, USA) was used to conduct qRT-PCR. There were three steps in PCR (1 cycle at 95°C for 5 min, and then 40 cycles at each of 95°C for 15 s and 60°C for 32 s). PCR primers were as follows: miR-193a-3p, F: 5'-ACACTCCAGCTGGGAACTGGCCTACAAAGTCCCA-3', R: 5'-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGACTGGGAC-3'; U6, F: 5'-CTCGCTTCGGCAGCACA-3', R: 5'-AACGCTTCACGAATTTGCGT-3'. The cycle threshold (Ct) method () was applied in calculating relative expression levels. Each sample was performed in triplicate separately.

Statistical Analysis

Data collection and analysis were performed through Statistical Product and Service Solutions (SPSS) 25.0 (IBM Corp., Armonk, NY, USA). The results in the text were presented in the form of mean ± standard deviation (SD). x^2 test was employed to assess difference among categorical data. Student's *t*-test was applied to determine the difference between the two groups. Regression analysis was applied to generate correlation coefficients. Patient relapse-free interval curve was constructed by Kaplan-Meier method. The correlation between miR-193a-3p expression and tumor recurrence was analyzed by univariate logistic regression. Statistical significance was based on value of $p<0.05$.

Results

MiR-193a-3p Expression in IPAs was Significantly Lower Than That in Non-IPAs

The study investigated miR-193a-3p expression levels in non-IPAs and IPAs using qRT-PCR. Taking the mean value of miR-193a-3p expression as boundary line, patients could be separated into

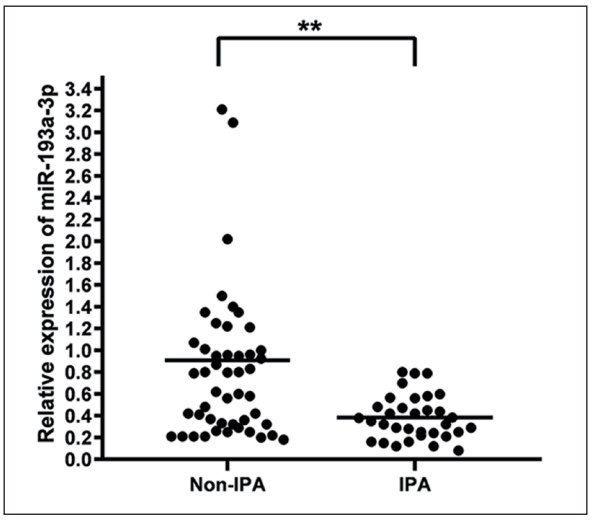

Figure 1. Expression of miR-193-3p in non-IPAs (n=49) and IPAs (n=33) tissues were determined by qRT-PCR. Data represented mean ± SD of three replicates (Student's *t*-test: ***p*=0.003).

miR-193a-3p high expression and low expression groups. MiR-193a-3p expression in IPAs was obviously lower than that in non-IPAs (p=0.003) (Figure 1). This result demonstrated that miR-193a-3p could inhibit the invasiveness of PAs.

MiR-193a-3p Expression was Reversely Associated with Tumor Size

Based on the largest tumor diameter (d), PAs were classified as macro-adenomas (1<d<3 cm) and huge adenomas (d≥3 cm). The mean maximum diameter in non-IPAs group and IPAs group were 2.02 ± 0.59 cm and 3.29 ± 0.69 cm, respectively (p<0.001) (Figure 2A). The average largest diameter in miR-193a-3p high expression group and low expression group were 2.27 ± 0.98 cm and 2.71 ± 0.81 cm, respectively (p=0.03). Through regression analysis, the study found a reverse correlation between miR-193a-3p expression and tumor size (r coefficient=-0.235; p=0.03) (Figure 2B). Thus, tumor size was closely related to the invasiveness of PAs and miR-193a-3p was reversely associated with tumor size, suggesting that miR-193a-3p could suppress the growth and invasiveness of PAs.

Association between Expression of MiR-193a-3p and Clinical Features of Patients

The clinical features of 82 patients were summarized in Table I. Compared with macroadenomas, huge adenomas had much lower miR-193a-3p expression (p=0.002). Besides, expression of miR-193a-3p in those patients with compression symptoms was lower (p=0.035). Compression symptoms included headache, dizziness, vision loss, visual impairment, and even blindness, in which visual disturbance was essential. With respect to the surgical resection degree, 16 (30.19%) patients had residual in the miR-193a-3p low-expression group while only 1 case (3.45%) had residual in the high-expression group. The rate of residual after operation was significantly higher in miR-193a-3p low-expression patients than that in miR-193a-3p high-expression patients (p=0.004).

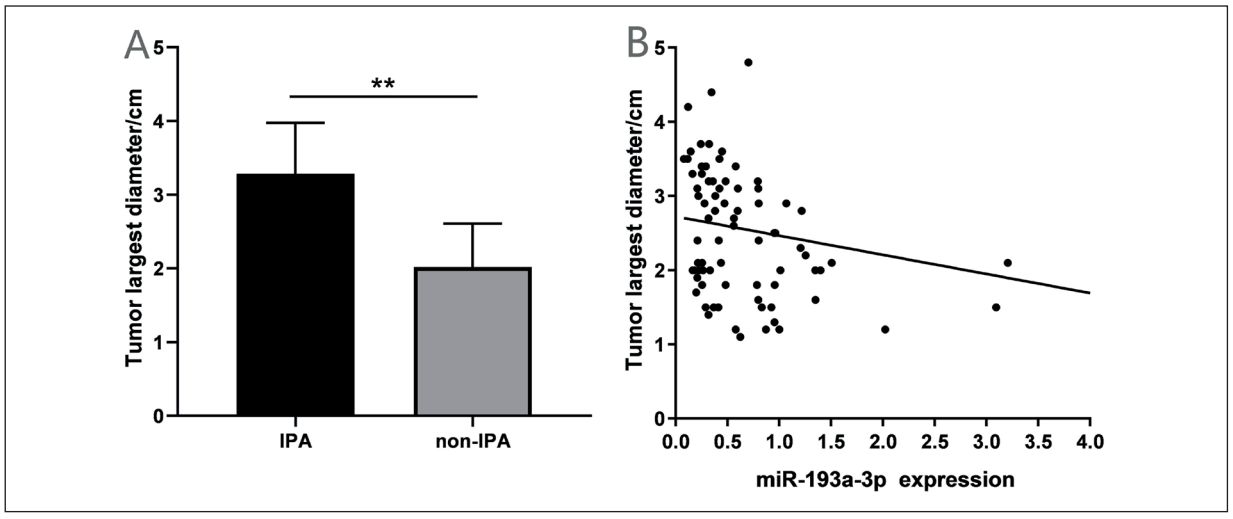

Figure 2. Relationships between PAs invasiveness, miR-193a-3p and tumor size. **A**, Tumor size in IPA and non-IPA (Student's t-test: ***p*<0.001). **B**, Relationship between miR-193a-3p expression and tumor size of PAs. The regression equation was y=-0.258X + 2.724 (r=-0.235; p=0.03).

Table I. Relationship between miR-193a-3p and clinical features of patients.

Clinical features	N	MiR-193a-3p expression		*p*	χ^2
		High	Low		
Sex					
Male	44	16	28	0.041	0.839
Female	38	13	25		
Age (year)					
<50	52	17	35	0.444	0.505
≥50	30	12	18		
Tumor largest diameter					
<3 cm	52	25	27	10.046	0.002
≥3 cm	30	4	26		
Invasiveness					
Non-IPA	49	25	24	13.054	<0.001
IPA	33	4	29		
Adenoma type					
Non-function	42	15	27	2.484	0.478
GH	5	3	2		
PRL	33	11	22		
FSH	2	0	2		
Compression symptoms					
Yes	44	11	33	4.463	0.035
No	38	18	20		
Endocrine symptoms					
Yes	34	12	22	0.000	0.991
No	48	17	31		
Pituitary apoplexy					
Yes	17	8	9	1.283	0.257
No	65	21	44		
Tumor texture					
Cystic	3	3	0	5.769	0.056
Solid	53	18	35		
Cystic & solid	26	8	18		
Resection degree					
Total	65	28	37	8.156	0.004
Residual	17	1	16		
Recurrence*					
Yes	21	2	19	8.247	0.004
No	61	27	34		

*Tumor recurrence was defined as: 1. the presence of a 0.1 cm^3 tumor volume after total resection; 2. residual tumor increase 25% after subtotal resection; 3. aggravation of clinical symptoms or reappearance after disappearance with a rise of hormone levels.

In total, 21 (25.61%) patients had tumor relapse and the average time to recurrence was 24.45 ± 10.78 months. 14 of 33 (42.42%) IPA patients recurred with 22.71 ± 11.70 months. Univariate logistic regression was used to further investigate the association between miR-193a-3p expression and recurrence. It turned out that patients with downregulated miR-193a-3p had a higher risk of recurrence (OR: 0.133, CI: 0.028-0.62, p=0.01) (Figure 3). None evident correlation was found among expression levels of miR-193a-3p and other clinical features of PAs, including gender, age, adenoma type, endocrine symptoms, pituitary apoplexy and tumor texture. These findings further supported that PAs patients with low expression of miR-193a-3p had worse outcomes than those with high expression of miR-193a-3p.

MiR-193a-3p Affected Postoperative PRL Levels Early Remission of Prolactinomas

There were 33 PRL adenomas (40.24%) among total patients. Preoperative PRL levels, PRL levels of the first day, one week and three months after operation of prolactinomas patients were collected. Changes of PRL levels of these four groups and association between miR-193a-3p

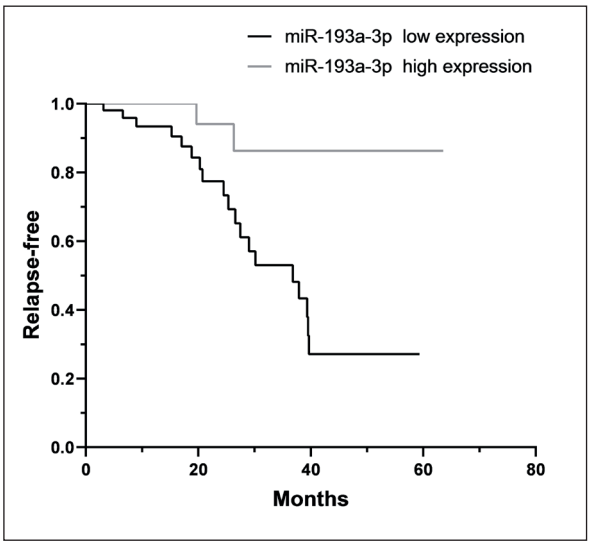

Figure 3. Kaplan-Meier curves for relapse-free interval for miR-193a-3p high expression (gray line) and low expression (black line).

and prolactinomas postoperative PRL levels early remission were analyzed (Figure 4). The study did not analyze other hormone-secreting PAs due to the small sample size of them. The mean preoperative PRL levels was 153.14 ± 60.99 ng/ml while PRL levels of the first day, one week and three months after operation were 62.73 ± 71.48 ng/ml, 63.68 ± 72.57 ng/ml and 64.38 ± 72.56 ng/ml, respectively. Though PRL levels of one week and three months after operation were both higher than that of the first day after operation, the differences among these three groups were not significant (p of three groups>0.05) (Figure 4A). Compared with preoperative PRL levels, PRL levels of the first day after surgery significantly decreased (p<0.001) (Figure 4A). Postoperative PRL levels early remission was defined when PRL levels returned to normal within one week after surgery. On the contrary, persistent hyperprolactinemia was defined when PRL lev-

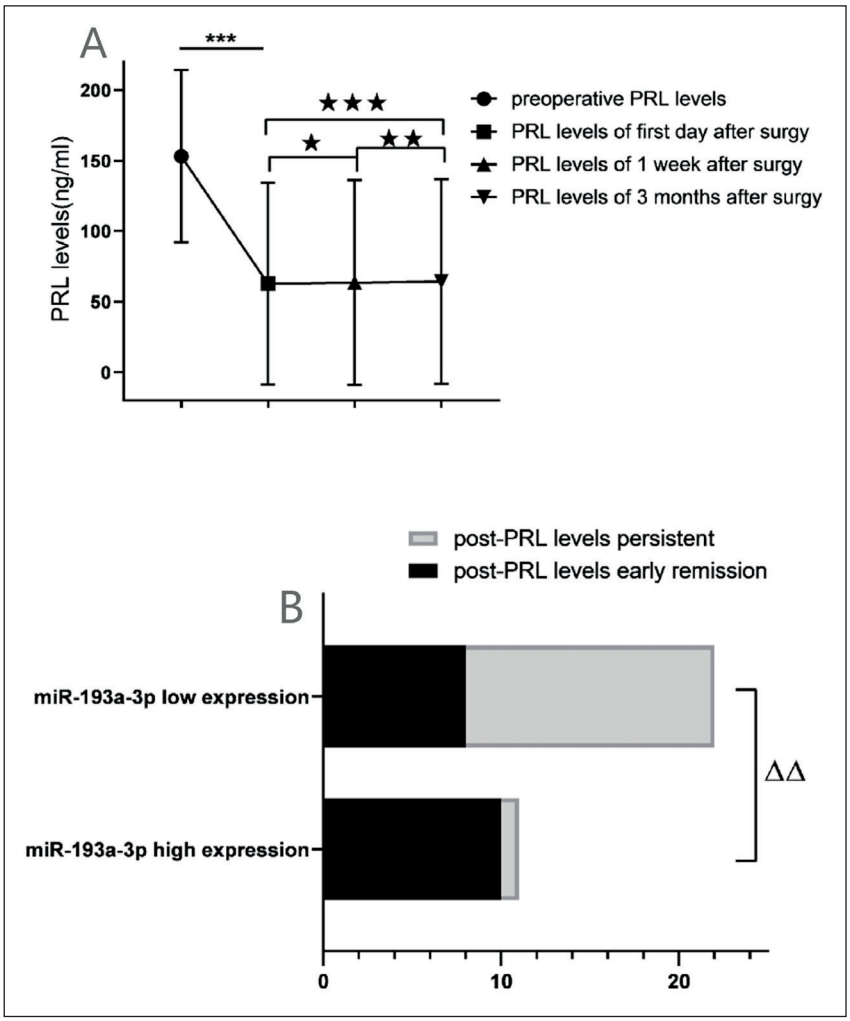

Figure 4. A, Changes of prolactinomas PRL levels of preoperation, first day, one week and three months after operation (Student's t-test: ***p<0.001, ★p=0.224, ★★p=0.341, ★★★p=0.052). **B**, Relationship between miR-193a-3p and post-operative PRL levels early remission of prolactinomas (Chi-square test: $^{\Delta\Delta}p$=0.004).

els remained higher than normalization for more than three months after operation. In the study, early remission was achieved in 54.55% (18/33) of all PRL adenomas patients while the ratio of patients with persistent hyperprolactinemia was 45.45% (15/33). The ratios of early remission and persistent hyperprolactinemia in miR-193a-3p high expression group were 30.30% and 3.03%, respectively. While in the group of miR-193a-3p low expression, early remission ratio was 24.24% and persistent hyperprolactinemia ratio was 42.42%. Prolactinomas patients with high miR-193a-3p expression had a higher early remission ratio while a higher persistent hyperprolactinemia ratio was found in patients with downregulated miR-193a-3p (p=0.004) (Figure 4B). Thus, miR-193a-3p was an influencing factor of postoperative PRL levels early remission of prolactinomas.

Postoperative PRL Levels Early Remission Affected the Prognosis of Patients in Prolactinomas

Of 33 PRL adenomas patients, 11 patients (33.33%) had recurrence after surgery. We performed further analysis on the relationship between PRL levels and recurrence (Figure 5). There was no significant correlation between preoperative PRL hormone levels and recurrence (p>0.05) (Figure 5A). Among patients with postoperative PRL levels early remission, 3 patients underwent recurrence. By contrast, 8 patients with persistent hyperprolactinemia met with recurrence. The correlation between postoperative PRL levels early remission and recurrence was significant (p=0.03) (Figure 5B). Consequently, normalized early postoperative PRL level could be a prognostic indicator for PRL adenomas.

Discussion

PAs, a common type of benign intracranial tumors, can be classified into non-functional pituitary adenomas (NFPAs) and functional pituitary adenomas (FPAs). Based on the specific immunohistochemical features and hormone content, FPAs include GH-secreting PAs, PRL-secreting PAs, thyroid stimulating hormone (TSH)-secreting PAs, adrenocorticotropic hormone (ACTH)-secreting PAs, FSH/luteinizing hormone (LH)-

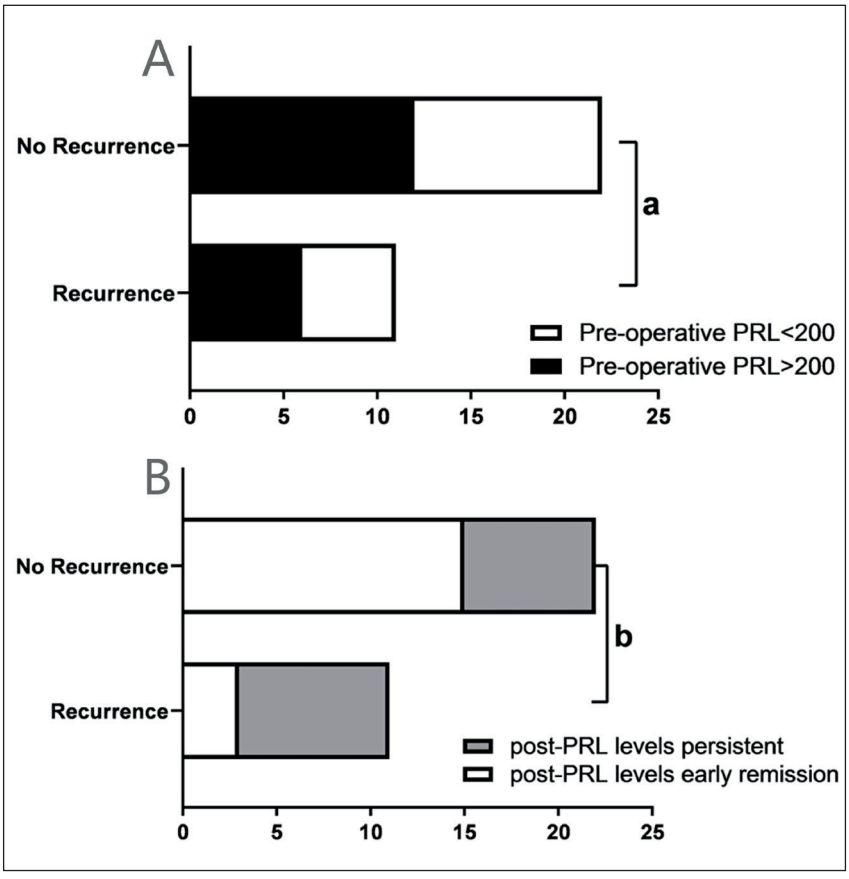

Figure 5. Relationships between pre-operative, post-operative PRL levels early remission and recurrence in 33 prolactinomas patients. **A**, Relationships between preoperative PRL and recurrence (χ^2-test: a p=0.98). **B**, Postoperative PRL levels early remission and recurrence (χ^2-test: b p=0.03); PRL levels unit: ng/ml.

secreting PAs and plurihormonal and double PAs[14]. Surgical resection serves as the main therapy for PAs and most patients can be cured with appropriated surgery. However, some PAs grow aggressively. It is more difficult to perform radical surgery and more tumor recurrence occur in these PAs. This kind of PAs is termed as IPAs. In recent years, a lot of studies have shown that miRNAs serve as oncogenes or tumor suppressor genes during the course of origin and progression of PAs. Some miRNAs are closely related to the aggressive growth of PAs, for instance, He et al[15] discovered that by suppressing the expression of target activated leukocyte cell adhesion molecule (ALCAM), the overexpressed miR-148b-3p and miR-152 played a role in inhibiting the development and invasiveness in PAs cells. With regard to miR-193a-3p, it was considered as a tumor suppressor. For example, miR-193a-3p had the ability to repress the occurrence and progression of colorectal cancer by inhibiting plasminogen activator urokinase (PLAU) expression[16]. Nevertheless, miR-193a-3p could also faciliate tumor growth. For instance, upregulated miR-193a-3p contributed to the tumorigenesis and development *via* targeting the serine and arginine rich splicing factor 2 (SRSF2) in hepatocellular carcinoma[17].

In our study, miR-193a-3p expression in PAs was determined using qRT-PCR. Our study was a pilot one to discover that the expression levels of miR-193a-3p in IPAs were significantly lower than that in non-IPAs, which was consistent with our previous experimental results[11]. Buchfelder[18] showed that invasion of PAs was closely related to tumor size. Invasiveness of PAs could be found in nearly 80% of giant adenomas, but only in 22% of macroadenomas and 2% of microadenomas. Similarly, a follow-up analysis of 444 patients who experienced trans-sphenoidal adenomectomy found that larger tumor size was a strong predictor of poor surgical outcome and patients with tumor diameter larger than 2 cm were more likely to develop hypopituitarism[19]. Herein, we found that the average tumor size in IPAs was larger than that in non-IPAs and miR-193a-3p expression was reversely related with tumor size. The expression of miR-193a-3p was lower in huge adenomas than that in macroadenomas. Compression to the optic nerves and chiasm due to the growing tumor can cause visual field deficit. Uy et al[20] reported that owning to the invasive growth of IPAs, visual disturbance was more common in IPAs than in non-IPAs. In our research, patients with downregulated miR-193-3p were at higher risk of compression symptoms. Therefore, miR-193a-3p could have an effect on repressing the growth and invasiveness of PAs, functioning as a tumor suppressor. Moreover, patients with residual after surgery had lower expression levels of miR-193a-3p. It is well known to us that surgical resection degree is closely correlated with recrudescence. This study also detected that patients with low miR-193a-3p expression were at higher risk to recur than those with high miR-193a-3p expression. Therefore, miR-193a-3p was a potential influencing factor of prognosis in PAs patients. It was reported that high preoperative PRL levels were closely related to poor prognosis in PRL adenomas[21]. Postoperative PRL hormone levels were considered as an independent prognostic factor in PRL adenomas. DA was the first-line treatment for prolactinomas due to the high efficacy and tolerability. Large numbers of studies manifested that DA could effectively lower PRL hormone levels and reduce tumor volume. However, parts of invasive PRL adenomas patients are DA-resistant and hyperprolactinemia still exists after successful surgery in these patients. In the study, we analyzed the relationship between PRL levels and recurrence in prolactinomas, as well as the correlation between miR-193a-3p and postoperative hyperprolactinemia, excluding the influences of DA through inclusion criteria. However, our experiment did not investigate the relationship between DA resistance and postoperative hyperprolactinemia and whether miR-193a-3p was related to DA resistance. During the research, we found that there was a significant correlation between postoperative PRL levels early remission and the recurrence of PRL adenomas. However, preoperative PRL levels were not significantly related to recurrence. Moreover, PRL adenomas patients with postoperative PRL levels early remission had better outcomes than those with persistent hyperprolactinemia. For prolactinomas, the PRL early remission rate in patients with high miR-193a-3p expression was higher than that in patients with low miR-193a-3p expression. Therefore, miR-193a-3p was a potential influencing factor of prognosis in prolactinomas patients.

Conclusions

Compared with non-IPAs patients, IPAs patients had lower miR-193a-3p expression. Besides, miR-193a-3p expression was reversely associated with tumor size and patients with low miR-193a-

3p expression had higher residual rate after operation, suggesting that miR-193a-3p was capable of repressing the growth and invasiveness of PAs and acted as a tumor suppressor. Furthermore, a higher recurrence risk was found in patients with low miR-193a-3p expression. For PRL adenomas, postoperative PRL levels early remission was a potential prognostic indicator and miR-193a-3p was a factor influencing early remission. To sum up, miR-193a-3p was a potential prognostic factor and therapeutic target of IPAs.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

1) Gittleman H, Ostrom QT, Farah PD, Ondracek A, Chen Y, Wolinsky Y, Kruchko C, Singer J, Kshettry VR, Laws ER, Sloan AE, Selman WR, Barnholtz-Sloan JS. Descriptive epidemiology of pituitary tumors in the United States, 2004-2009. J Neurosurg 2014; 121: 527-535.
2) Micko AS, Wohrer A, Wolfsberger S, Knosp E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. J Neurosurg 2015; 122: 803-811.
3) Wang Z, Du Q, Chen ZY, Wang X, Jian MY, Zhu DM, Hu CH, Wang HJ, Zhu YH. MicroRNA-524-5p functions as a tumor suppressor in a human pituitary tumor-derived cell line. Horm Metab Res 2017; 49: 550-557.
4) Girish C, Shukla, Jagjit S, Sailen B. MicroRNAs: processing, maturation, target recognition and regulatory functions. Mol Cell Pharmacol 2011; 3.
5) Jin LJ, Li HY, Wang JY, Lin D, Yin K, Lin LG, Lin Z, Lin GJ, Wang H, Ying XW, Wang LS, Zhang YQ, Teng LF. MicroRNA-193a-5p exerts a tumor suppressor role in glioblastoma via modulating NOVA1. J Cell Biochem 2019; 120: 6188-6197.
6) Li JC, Zou XM. MiR-652 serves as a prognostic biomarker in gastric cancer and promotes tumor proliferation, migration, and invasion via targeting RORA. Cancer Biomark 2019; 26: 323-331.
7) Liu WT, Qi L, Lv H, Zu XB, Chen MF, Wang J, Liu LF, Zeng F, Li Y. MiRNA-141 and miRNA-200b are closely related to invasive ability and considered as decision-making biomarkers for the extent of PLND during cystectomy. BMC Cancer 2010; 15: 92.
8) Wang ZL, Wu XF, Hou XW, Zhao WQ, Yang C, Wan W, Chen LX. MiR-548b-3p functions as a tumor suppressor in lung cancer. Lasers Med Sci 2020; 35: 833-839.
9) Wang RJ, Liang HQ. MiR-132, miR-15a and miR-16 synergistically inhibit pituitary tumor cell proliferation, invasion and migration by targeting Sox5. Cancer Lett 2015; 356: 568-578.
10) Wierinckx A, Roche M, Legras-Lachuer C, Trouillas J, Raverot G, Lachuer J. MicroRNAs in pituitary tumors. Mol Cell Endocrinol 2017; 456: 51-61.
11) Mao ZG, He DS, Zhou J, Yao B, Xiao WW, Chen CH, Zhu YH, Wang HJ. Differential expression of microRNAs in GH-secreting pituitary adenomas. Diagn Pathol 2010; 5: 79.
12) Chou NH, Lo YH, Wang KC, Kang CH, Tsai CY, Tsai KW. MiR-193a-5p and -3p play a distinct role in gastric cancer: miR-193a-3p suppresses gastric cancer cell growth by targeting ETS1 and CCND1. Anticancer Res 2018; 38: 3309-3318.
13) Liu YF, Xu X, Xu XL, Li SQ, Liang Z, Hu ZH, Wu J, Zhu Y, Jin XD, Wang X. MicroRNA-193a-3p inhibits cell proliferation in prostate cancer by targeting cyclin D1. Oncol Lett 2017; 14: 5121-5128.
14) Mete O, Lopes MB. Overview of the 2017 WHO classification of pituitary tumors. Endocr Pathol 2017; 28: 228-243.
15) He W, Huang L, Li M, Yang Y, Chen Z, Shen XL. MiR-148b, MiR-152/ALCAM axis regulates the proliferation and invasion of pituitary adenomas cells. Cell Physiol Biochem 2017; 44: 792-803.
16) Lin MS, Zhang Z, Gao MJ, Yu H, Sheng HH, Huang JX. MicroRNA-193a-3p suppresses the colorectal cancer cell proliferation and progression through downregulating the PLAU expression. Cancer Manag Res 2019; 11: 5353-5363.
17) Khordadmehr M, Shahbazi R, Sadreddini S, Baradaran B. MiR-193: a new weapon against cancer. J Cell Physiol 2019; 234: 16861-16872.
18) Buchfelder M. Management of aggressive pituitary adenomas: current treatment strategies. Pituitary 2009; 12: 256-260.
19) Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, Wang C, Swerdloff RS, Kelly DF. Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. Neurosurgery 2008; 63: 709-718.
20) Uy B, Wilson B, Kim WJ, Prashant G, Bergsneider M. Visual outcomes after pituitary surgery. Neurosurg Clin N Am 2019; 30: 483-489.
21) Esposito V, Santoro A, Minniti G, Salvati M, Innocenzi G, Lanzetta G, Cantore G. Transsphenoidal adenomectomy for GH-, PRL- and ACTH-secreting pituitary tumours: outcome analysis in a series of 125 patients. Neurol Sci 2004; 25: 251-256.