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Prognostic value of miR-130, miR-148, miR-194 and miR-605 serum expression in glioblastoma patients

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ABSTRACT

Introduction. In modern neurooncology, molecular and clinical-morphological markers are used to assess prognosis and select treatment strategies for glioblastoma. Currently, researchers are focusing on microRNAs in biological fluids that can predict outcomes of disease.

Objective. To analyze serum expression of miR-130, miR-148, miR-194, and miR-605 in patients with glioblastoma depending on clinical and molecular genetic parameters of tumor.

Material and methods. The study included 39 patients with newly diagnosed glioblastoma (IDH-wildtype, WHO Grade 4) between 2021 and 2023 (median age 55 years; 95% CI 47—61). Expression of miR-130, miR-148, miR-194, and miR-605 was assessed in serum samples collected before chemoradiotherapy. Patients underwent combined therapy: maximal tumor resection, chemoradiotherapy (60 Gy) with temozolomide and adjuvant chemotherapy. MicroRNA levels were determined by real-time PCR. MGMT methylation, TP53 and Ki-67 expression, recurrence-free survival and tumor metabolic activity (SPECT) were analyzed.

Results. There was a significant association between miR-148 expression and MGMT promoter methylation (increase by 1.6 times). MiR-194 expression decreased by 1.2 times. MiR-130 increased by 1.5 times with MGMT methylation and Ki-67 >25%. In patients with TP53 expression >10%, MiR-130 increased by 3 times. No association was found between expression of microRNAs and SPECT data.

Conclusion. miR-148 is associated with MGMT methylation and can have prognostic significance. Reduced miR-194 with MGMT methylation and increased miR-130 with high Ki-67 and TP53 indicate involvement of these microRNAs in formation of aggressive glioblastoma phenotype and their potential as prognostic biomarkers.

Keywords: *microRNA, glioblastomas, TP53, MGMT, Ki-67, metabolic activity, SPECT.*

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Introduction

Glioblastomas accounting for up to 80% of all primary malignant CNS tumors are one of the most difficult medical problems due to aggressive course, insufficient effectiveness of treatments and poor survival [3]. Despite significant advances in neurooncology, including targeted and radiotherapy, prognosis for patients with IDH-wild type glioblastomas as the most malignant glioblastomas remains extremely poor (median survival <10 months) [4]. In this context, searching for new biomarkers capable of improving early diagnosis, prognosis of disease and response to therapy is a key area of modern research [1].

In neurooncology, molecular genetic (MGMT promoter methylation, IDH1/2 mutations, TP53 status) and clinical-morphological markers (Ki-67 index, tumor volume after surgery) are used for prognosis and treatment of glioblastomas. MGMT methylation reduces expression of DNA repair enzymes increasing the effectiveness of alkylating agents. TP53 mutations impair p53 function, contributing to therapeutic resistance. Large residual tumor after surgery is associated with high proliferative activity, hypoxia, and poorer prognosis [5].

The role of microRNAs in pathogenesis of glioblastomas has been actively studied in recent years. MicroRNAs are small non-coding RNA molecules approximately 18—25 nucleotides in length. They regulate gene expression at the post-transcriptional level by binding to 3'-untranslated regions (3'-UTR) of messenger RNA targets [6]. Dysregulation of microRNAs is associated with various

stages of carcinogenesis, including proliferation, apoptosis, angiogenesis, and tumor cell invasion [7]. Importantly, microRNAs have high stability in biological fluids, including blood serum, that makes them perspective noninvasive biomarkers [8]. Among various microRNAs implicated in pathogenesis of glioblastomas, miR-130, miR-148, miR-194, and miR-605 are of particular interest. According to recent studies, these molecules are essential in regulating signaling pathways associated with development and progression of brain tumors.

Despite evidence on the role of these microRNAs in pathogenesis of glioblastomas, their clinical significance as prognostic markers require further study. Therefore, the purpose of this study was to determine serum expression of miR-130, miR-148, miR-194, and miR-605 in patients with glioblastomas depending on clinical and molecular-genetic parameters of tumor.

Material and methods

The study included 39 patients with newly diagnosed glioblastoma. Age of patients ranged from 19 to 70 years (median 55, 95% CI 47; 61).

All patients underwent tumor resection, chemo- and radiotherapy (60 Gy) with temozolomide, as well as adjuvant chemotherapy with temozolomide. The diagnosis of IDH-wildtype glioblastoma WHO Grade IV was established after morphological, immunohistochemical and molecular analysis of specimens in accordance with the 2021 WHO classification of CNS tumors [3]. The MGMT gene promoter methylation status was assessed in 22 patients. We used quantitative methylation-specific real time polymerase chain reaction (PCR) from paraffin-embedded material. MGMT gene promoter methylation was diagnosed in 17 patients. Five patients had no methylation.

TP53 and Ki-67 protein expression was analyzed by immunohistochemistry (IHC) on paraffin-embedded tumor samples obtained after resection of glioblastoma. Monoclonal antibodies to nuclear antigen were used to evaluate TP53, and nuclear staining was interpreted as positive expression (mutation or protein stabilization). Tumor proliferation was assessed using antibodies to Ki-67. The Ki-67 index was calculated as a percentage of positively stained nuclear cells out of total tumor cells in multiple fields of view. Immunohistochemical staining was performed using an automated platform, and results were assessed by two morphologists.

We analyzed the outcomes in 28 patients. Of these, 3 ones were lost for follow-up due to change in place of residence. Twenty-five patients experienced recurrence or continued tumor growth within 2—31 months. Mean disease-free survival was 11.2 months (95% CI [9.8; 17]). Two patients had no recurrences throughout 47—53 months; 21 patients died. The median of overall survival was 22.3 months (95% CI [10.4; 18.0]). Most recurrences occurred within the first 8 months, deaths — within 20 months. We used these time frames as criteria for favorable and unfavorable prognosis.

Patients were divided into two groups depending on tumor volume before chemo- and radiotherapy. Mean tumor volume was 16.55 cm^3. The first group included patients with tumor $\leqslant$16.55 cm^3, the second group — >16.55 cm^3.

Single-photon emission computed tomography (SPECT) with 99mTc-1-thio-D-glucose was used to assess metabolic activity of glioblastomas [2]. Enhanced 99mTc-1-thio-D-glucose uptake indicated high metabolic activity of tumor (typical for high-grade glioblastomas). All data were interpreted by two specialists.

Moreover, patients were divided into two groups depending on disease-free survival. The first group included patients with recurrence within the first 11.2 months after surgery, the second group — with recurrence after 11.2 postoperative months. The diagnosis of recurrence was based on follow-up MRI and findings of multidisciplinary panel using the RANO-HGG (Response Assessment in Neuro-Oncology for High-Grade Gliomas) criteria [9]. No recurrence was defined as a stable clinical status without signs of disease progression according to clinical and diagnostic data.

All studies were conducted in accordance with the ethics committee of the Siberian State Medical University (Protocol No. 8785 dated September 13, 2021) and the Declaration of Helsinki. All subjects signed an informed consent.

MicroRNA harvesting

MicroRNA was harvested using a Lira reagent kit (Biolabmix, Russia) combining phenol-chloroform extraction and nucleic acid adsorption on a silicon membrane. Sample quality and integrity were assessed by capillary electrophoresis (TapeStation, Agilent Technologies, USA); RIN (RNA Integrity Number) values ranged from 2.2 to 3.3. Reverse transcription of microRNA was performed using the M-MuLV-RH reverse transcription (RT) kit (Biolabmix, Russia) synthesizing the first strand of complementary DNA using either mRNA or total RNA.

MicroRNA expression was estimated using real-time quantitative reverse transcriptase PCR (RT-qPCR) using an iCycler thermocycler (DTprime, DNA-Technology, Russia). To synthesize complementary DNA on RNA matrix, we performed RT reaction using m-MuLV-RH RT kit (BioLabmix, Russia) and random hexanucleotide primers according to the manufacturer's instructions. PCR reactions were performed in triplicate in a 25 µl volume containing BioMaster HS-qPCR SYBR Blue 12.5 µl (BioLabmix, Russia), forward, reverse and RT primers 300 nM, as well as complementary DNA 50 ng.

PCR primers:

Hsa-mir-130a: F: 5'- GCCGCCAGTGCAATGTTAAA-3'; R: 5'- GTGCAGGGTCGGAGGT -3';

Table 1. **Serum expression of miR-130, miR-148, miR-194 and miR-605 in patients with glioblastoma depending on tumor volume and metabolic activity.**

	Volume <16.55 cm³ (n=20)	Volume >16.55 cm³ (n=11)	p	Metabolic activity (n=22)	No metabolic activity (n=5)	p
	Me (Q_{25}; Q_{75})	Me (Q_{25}; Q_{75})		Me (Q_{25}; Q_{75})	Me (Q_{25}; Q_{75})	
miR-148	0.46 (0.0; 0.63)	0.45 (0.27; 1.09)	0.30	0.44 (0.0; 0.58)	0.44 (0.31; 0.67)	0.69
miR-194	1.75 (0.97; 1.94)	1.70 (1.28; 1.81)	0.65	1.81 (1.11; 1.94)	1.69 (1.58; 1.94)	0.37
miR-130	0.46 (0.0; 0.57)	0.46 (0.15; 0.80)	0.54	0.43 (0.0; 0.53)	0.40 (0.26; 0.46)	0.76
miR-605	1.24 (0.41; 1.76)	1.16 (0.25; 1.33)	0.17	1.24 (0.28; 1.52)	1.33 (0.94; 1.63)	0.66

RT primer: 5'-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACATGCCCT-3';

miR-148a-3p: F: 5'-TGCGCTCAGTGCACTACAGAAC-3'; R: 5'-CCAGTGCAGGGTCCGAGGTATT-3';

Hsa-mir-194 F: 5'-CACGCATGTAACAGCAAC-3'; R: 5'-CCAGTGCAGGGTCCGAGGTA-3'; RT-primer: 5`-GTCGTATCGAGAGCAGGGTCCGAGGTATT CGCACTCGATACGACTC CACAT-3`;

Hsa-mir-605: F: 5'-TGCGGTAAAATCCCATGGTGCCTTC-3'; R: 5'-CCAGTGCAGGGTCCGAGGT-3'; RT: 5'-GTCGTATCCAGTGCAGGGTCCGAGGTGCACTGGATACGACAGGAGAAG-3';

U6: F 5'-CTCGCTT CGGCAGCACATATACT-3', R 5'-ACGCTTCACGAATTTGCGTGTC-3', RT primer 5'-AAAATATGGAACGCTTC ACGAATTTGG-3'.

Amplification program included a two-step cycle: preliminary denaturation at 94°C for 10 min followed by 40 cycles (94°C for 10 s; 60°C for 20 s). The 2^-ΔΔCt method was used to quantify expression. U6 small nuclear RNA was used as an endogenous control.

Statistical analysis

Microsoft Excel 2019 spreadsheets (Microsoft Corp., USA) and STATISTICA 12 software (StatSoft Inc., USA) were used to evaluate data regarding between-group differences. The Shapiro–Wilk test was used to analyze distribution normality. However, all variables were characterized by non-parametric distribution, and we used the nonparametric Mann–Whitney test. Differences were significant at $p<0.05$. Results are presented as Me (Q_{25}; Q_{75}).

Results

Expression of miR-130, miR-148, miR-194 and miR-605 was similar in high- and low-tumor volume groups, as well as in groups with and without metabolic activity verified by SPECT. P-values for all comparisons ranged from 0.17 to 0.76 **(Table 1)** that significantly exceeded statistical significance.

Mean expression of miR-148 was 0.54 (0.31; 0.82) in patients with methylated MGMT promoter and 0.33 (0.27; 0.41) in patients without methylation (p=0.02). MiR-148 expression was 0.47 (0.0; 0.72) in case of TP53 expression >10% and 0.37 (0.31; 0.44) in TP53 expression <10% (p=0.5). In subgroups with different Ki-67 index, miR-148 expression was 0.42 (0.31; 0.58) for Ki-67 <25% and 0.47 (0.30; 0.77) for Ki-67 >25% (p=0.9).

MiR-194 expression was 1.47 (1.04; 1.81) in case of methylated MGMT and 1.81 (1.81; 2.23) without methylation (p=0.002). Regarding TP53 expression, these values were 1.69 (1.08; 2.01) in case of expression >10% and 1.56 (1.18; 1.94) in expression <10% (p=0.58). In subgroups with Ki-67 <25% and Ki-67 >25%, the values were 1.81 (1.24; 1.94) and 1.94 (1.81; 2.14), respectively (p=0.5).

Mean miR-130 expression was 0.46 (0.40; 0.75) in patients with methylated MGMT and 0.30 (0.30; 0.45) without methylation (p=0.003). TP53>10% was associated with miR-130 0.46 (0.40; 0.76), TP53 <10% — 0.32 (0.30; 0.45) (p=0.2). In groups with different Ki-67 index, miR-130 expression was 0.46 (0.40; 0.69) in case of Ki-67 <25% and 0.70 (0.46; 0.75) in Ki-67 >25% (p=0.003).

MiR-605 expression for methylated and unmethylated MGMT were 1.08 (0.28—1.42) and 1.24 (1.08—1.33), respectively (p=0.92). These values were 1.12 (0.94—1.27) for TP53 >10% and 1.21 (0.94—2.01) for TP53 <10% (p=0.4). Regarding Ki-67, miR-605 expression was 1.21 (0.33—1.52) for Ki-67 <25% and 1.24 (0.28—1.52) for Ki-67 >25% (p=0.79).

We found no significant associations between expression of miR-130, miR-148, miR-194 and miR-605 with recurrences and outcomes of disease. Statistical analysis revealed similar expression of all microRNAs in patients with recurrence within 11.2 months and after this period. Similarly, no significant differences were found in expression of miR-130, miR-148, miR-194 and miR-605 when comparing groups with favorable and unfavorable outcomes of disease. P-values for all comparisons ranged from 0.17 to 0.92 **(Table 3)** that indicated no significant between-group differences.

We found no significant association between miR-148 expression and glioma recurrence. Furthermore, there was association between miR-148 and MGMT gene promoter methylation (a 1.6-fold increase). MiR-148 is highly expressed in tissues, cells and circulating exosomes from blood samples of patients with glioblastoma [12]. MiR-148 is involved in formation of tumor microenviron-

Table 2. **Serum expression of miR-130, miR-148, miR-194 and miR-605 in patients with glioblastoma depending on expression of TP53, MGMT gene methylation status and Ki-67 index.**

	MGMT+ (n=14)	MGMT– (n=8)	p	p53 >10% (n=19)	p53 <10% (n=2)	p	Ki-67 <25% (n=18)	Ki-67 ⩾25% (n=11)	p
	Me (Q_{25}; Q_{75})	Me (Q_{25}; Q_{75})		Me (Q_{25}; Q_{75})	Me (Q_{25}; Q_{75})		Me (Q_{25}; Q_{75})	Me (Q_{25}; Q_{75})	
miR-148	0.54 (0.31; 0.82)	0.33 (0.27; 0.41)	0.02	0.47 (0.0; 0.72)	0.37 (0.31; 0.44)	0.42	0.44 (0.31; 0.58)	0.54 (0.0; 0.77)	0.97
miR-194	1.47 (1.04; 1.81)	1.81 (1.81; 2.23)	0.002	1.69 (1.08; 2.01)	1.76 (1.58; 1.94)	0.58	1.81 (1.28; 1.94)	1.81 (0.97; 1.94)	0.5
miR-130	0.46 (0.4; 0.75)	0.30 (0.0; 0.35)	0.003	0.46 (0.27; 0.7)	0.13 (0.0; 0.26)	0.02	0.30 (0.0; 0.49)	0.46 (0.46; 0.75)	0.003
miR-605	1.08 (0.28; 1.42)	1.24 (1.08; 1.33)	0.92	1.12 (0.22; 1.37)	1.47 (0.94; 2.01)	0.14	1.24 (0.33; 1.52)	1.08 (0.28; 1.52)	0.79

Table 3. **Serum expression of miR-130, miR-148, miR-194 and miR-605 in patients with glioblastoma depending om recurrence-free period and outcomes (favorable outcome — survival >19 months, unfavorable outcome — survival <19 months).**

	Recurrence within 11.2 months (n=20)	Recurrence after 11.2 months (n=5)	p	Favorable outcome (n=14)	Unfavorable outcome (n=14)	p
	Me (Q_{25}; Q_{75})	Me (Q_{25}; Q_{75})		Me (Q_{25}; Q_{75})	Me (Q_{25}; Q_{75})	
miR-148	0.58 (0.27; 1.54)	0.47 (0.41; 0.67)	0.17	0.46 (0.15; 0.62)	0.51 (0.44; 0.77)	0.87
miR-194	1.75 (1.37; 1.81)	1.69 (1.04; 2.08)	0.84	1.63 (1.08; 2.01)	1.63 (1.04; 1.81)	0.48
miR-130	0.53 (0.40; 0.80)	0.46 (0.35; 0.75)	0.92	0.43 (0.27; 0.70)	0.46 (0.35; 0.65)	0.29
miR-605	1.24 (1.08; 1.63)	1.33 (0.50; 1.52)	0.56	1.28 (0.41; 1.58)	1.24 (0.50; 1.52)	0.58

ment. These data suggest that in systemic circulation this microRNA has a functional role associated with tumor microenvironment remodeling and tumor reactivation [10]. MiR-148, like other microRNAs, is capable of suppressing tumor suppressor genes that can explain involvement of these molecules in resistance to therapy and tumor reactivation [11].

Conversely, miR-194 expression decreased by 1.2 times in case of MGMT methylation. Decrease expression can contribute to activation of signaling pathways associated with cell migration. MiR-130 expression increased by 1.5 times in patients with MGMT methylation and Ki-67 >25% that confirmed its association with aggressive tumor phenotype. There was association between miR-130 expression and p-53. MiR-130 expression increased by 3 times in patients with p-53 >10%. Increased miR-130 on the background of high p53 can indicate its involvement in p53-dependent regulatory pathways.

Surprisingly, microRNAs were not associated with tumor metabolic activity according to SPECT data. This contradicts some studies associating microRNAs, such as miR-21, with hypoxia [12]. However, this may be due to specificity of certain microRNAs or metabolic profile of glioblastomas. There was no association between microRNA expression and tumor volume after surgery. These results may be due to tumor nature involving functionally significant areas that limited extent of resection.

These data expand our understanding of the role of microRNAs in pathogenesis of glioblastomas. MiR-148, as a potential participant in MGMT-mediated epigenetic regulation, may be a target for therapy aimed at overcoming resistance to temozolomide. However, this hypothesis requires confirmation in large cohorts and research of molecular mechanisms. Expression of miR-194, miR-148 and miR-130 in MGMT methylation indicate their involvement in opposite processes. While miR-194 likely limits invasion, miR-130 and miR-148 enhance proliferation.

MiR-605 expression revealed no significant associations with any molecular genetic or clinical-morphological prognostic factors, such as MGMT methylation, p-53, Ki-67 or metabolic activity.

Conclusion

Our study revealed associations between miR-130 expression and Ki-67 index, as well as TP53 expression. Furthermore, we found correlation between expression of miR-148, miR-194 and miR-130 with MGMT gene methylation status. Our study demonstrates potential of microRNAs as important prognostic criteria in the future. However, other roles of microRNAs in patients with glioma require further study.

Author contribution:
Concept and design of the study — Spirina L.V., Ryabova A.I.
Collection and analysis of data — Mysik D.V., Ryabova A.I., Erokhina A.
Statistical analysis — Mysik D.V.
Writing the text — Mysik D.V.
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The authors declare no conflicts of interests.

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COMMENT

Brain tumors are one of the most serious problems in modern medicine, and high-grade glioma is a particularly important problem. Survival rates have not significantly improved despite advanced technologies and molecular genetic classifications. Therefore, early diagnosis and qualified prognosis of disease are particularly important. In 2024, the Nobel Prize was awarded to Victor Ambros and Gary Ruvkun for discovery of microRNAs in 1993. Researches demonstrated the role of microRNAs for epigenetic regulation of genome function. Conversely, some microRNAs have been found to play a significant role in tumors, for example, as suppressors or oncogenes. However, microRNAs are so-called «fine-regulating» molecules meaning their therapeutic effect is unlikely. However, they are quite suitable for diagnosis and prognosis. For example, the authors of this article examined expression of several key microRNAs and showed that microRNA-148 expression is increased with MGMT gene promoter methylation. At the same time, microRNA-194 expression decreases with MGMT methylation. Thus, analysis of these microRNA can underlie prognosis of disease. Unfortunately, small sample size in this study (39 patients with glioblastoma (IDH-wildtype, WHO Grade IV; median age 55 years, 95% CI [47; 61]) is insufficient for broad conclusions. Nevertheless, we can talk about a pilot study. Appropriate data will likely stimulate further study of microRNAs in tumors, as well as development of diagnostic test systems for predicting brain tumors.

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