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Signature of MicroRNAs Associated with Pluripotency in Multiple Meningiomas: Potential Biomarkers in Tumor Regulation

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Abstract

Meningiomas are common primary tumors of the central nervous system, affecting the intracranial and spinal dural surfaces. Multiple meningiomas account for approximately 1% to 10% of diagnosed cases and may occur synchronously or metachronously, being associated with alterations in the NF2 gene or arising sporadically. To date, little is known about the pathophysiology of these tumors. The capacity for pluripotency and self-renewal are well-known characteristics of embryonic stem cells, regulated by the transcription factors SOX2, OCT4, and NANOG, which govern the stem phenotype. One hypothesis of tumor development is that tumor stem cells exhibit a phenotype similar to embryonic stem cells; therefore, understanding the role of these transcription factors is crucial for elucidating mechanisms involved in tumor development. MicroRNAs also participate in regulating factors associated with pluripotency, presenting themselves as potential markers involved in this regulatory axis. Our objective was to evaluate the expression of the microRNAs miR-145, miR-143, and miR-200b in synchronous and metachronous multiple meningiomas. Real-time PCR was used for expression analysis. In our study, we observed a statistical difference only for miR-145 between the metachronous and synchronous groups, indicating hypoexpression of miR-145 in the metachronous group ($p = 0.03$). In the ROC curve analysis, miR-145 demonstrated better performance in distinguishing metachronous cases from controls, with an AUC of 81%, sensitivity of 93%, and specificity of 60%. Our results suggest that miR-145 has potential as a tumor marker associated with the pluripotency axis in multiple meningiomas, and further studies are needed to clarify the roles of miR-143 and miR-200b in multiple meningiomas.

Keywords

Multiple Meningiomas, Biomarkers, MicroRNA, Cellular Pluripotency

1. Introduction

Meningiomas are common intracranial tumors of the central nervous system. They originate from arachnoid cells and, therefore, may occur in any region of the cranial and/or spinal dural surface, as well as within the cerebral ventricles [1].

Multiple meningiomas represent fewer than 10% of diagnosed cases and are histologically defined as the presence of ≥2 distinct lesions occurring at diagnosis (synchronous multiple meningiomas) or as spatially separated tumors that develop during follow-up (metachronous multiple meningiomas), typically arising in different anatomical locations. These tumors are strongly associated with alterations in the NF2 gene; however, they may also occur sporadically [2]-[5].

The prevalence of these tumors increases with age and they are most commonly diagnosed in individuals over 60 years old. Females show the highest incidence rates, reaching 2 - 7 cases per 100,000 women, compared with approximately 1.5 per 100,000 men [1] [6]. Ionizing radiation, hereditary disorders such as neurofibromatosis type 2 (NF2 gene), female sex hormones, and other factors have been associated as risk factors for their development [7].

The World Health Organization (WHO) classifies meningiomas into three grades based on histopathological criteria: grade 1 (benign), grade 2 (atypical), and grade 3 (anaplastic or malignant). This classification is essential for determining diagnosis and prognosis [8]. Despite existing knowledge, the pathogenesis of multiple meningiomas remains poorly understood, and two main hypotheses have been proposed [9] [10].

One hypothesis suggests that tumors arise independently due to histological and cytogenetic differences observed between lesions within the same patient, each lesion resulting from distinct genetic mutations and aberrant pathway alterations. The second hypothesis proposes the transformation of a single clone that subsequently disseminates through the cerebrospinal fluid and leptomeninges [4].

Given the limited number of studies and the clinical relevance of these tumors, deeper investigation and the identification of molecular markers that could elucidate mechanisms involved in their development, progression, and outcomes are essential. For neoplastic transformation to occur, cells must acquire certain essential biological capabilities. These properties allow tumor cells not only to survive inside or outside their tumor niche but also to proliferate and self-renew. One leading concept in tumor development is that tumors originate from embryonic stem cells (ESCs) present in human tissues [11].

Clonal heterogeneity resulting from genomic instability is a major contributor

to tumor heterogeneity and promotes the existence of various cellular subtypes within the tumor mass. Among these, the most important are cancer stem cells (CSCs) [12]. CSCs possess key characteristics that contribute to malignancy, particularly their ability to self-renew and maintain pluripotency, similar to ESCs [13]. Pluripotency and self-renewal in ESCs are controlled by a restricted self-regulatory network comprising specific transcription factors that act in coordination to maintain this state [14] [15].

NANOG, OCT4, and SOX2 are the principal transcription factors governing the pluripotency and self-renewal network. They act as repressors of cellular differentiation, ensuring that cells remain undifferentiated and capable of self-renewal and pluripotency. Their overexpression in tumors may correlate with CSC presence and increased malignancy [14].

Understanding the regulatory mechanisms controlling pluripotency transcription factors, as well as their relationships with CSC phenotypes and tumor characteristics, could significantly contribute to clinical practice by enabling the identification of reliable biological markers for tumor behavior [16].

MicroRNAs are endogenously transcribed non-coding RNAs, 20 - 24 nucleotides in length, involved in post-transcriptional gene regulation. They act by cleaving or repressing translation of target messenger RNAs (mRNAs), typically by binding to the 3' untranslated region, thereby reducing protein expression [17] [18]. Pluripotency transcription factors SOX2, OCT4, and NANOG are post-transcriptionally regulated by microRNAs that induce cell differentiation. Specifically, miR-145 and SOX2 are known to participate in the regulation of neural stem cell maintenance and differentiation [19] [20].

Another microRNA involved in pluripotency regulation is miR-143, considered a tumor suppressor. In hepatocellular carcinoma, SOX2 expression is elevated when miR-143 is downregulated, correlating with poor prognosis [21]. Additionally, miR-200b, another frequently downregulated tumor suppressor microRNA, has been linked to pluripotency regulation [22].

Thus, understanding the involvement of miR-145, miR-143, and miR-200b in the regulatory axis of SOX2, NANOG, and OCT4, which governs pluripotency and cellular self-renewal, may be essential for elucidating mechanisms related to CSC biology and tumorigenesis, contributing to improved understanding of the pathophysiology of multiple meningiomas.

2. Patients and Methods

Thirty samples were selected from patients diagnosed with multiple meningiomas confirmed according to WHO classification criteria, where they were divided into two groups: synchronous group and metachronous group, where each group remained with 15 patients each.

The material was collected during surgery performed by the medical team of the Neurosurgery Division of Hospital das Clínicas, Ribeirão Preto Medical School, University of São Paulo (HCFMRP/SP). Meningiomas are tumors originating from

arachnoid cells, which give rise to the leptomeninges (arachnoid, and pia mater). Therefore, to compose the control group, 5 tissue samples from arachnoid tissue areas were used. These samples were collected by the Center for Legal Medicine (CEMEL) of the Ribeirão Preto Faculty of Medicine of the University of São Paulo (FMRP/SP) and obtained from patients who died suddenly and who had no prior history of chronic or neurological diseases.

The selection of microRNAs miR-145, miR-143 and miR-200b was carried out using available bioinformatics platforms (Gene Cards, TatgetScan and Mirdb databases), where microRNAs targeting the regulation of SOX2, NANOG and OCT4 were identified.

RNA Isolation and Real-Time Polymerase Chain Reaction

Total RNA was extracted using Trizol reagent (Applied Biosystems, Foster City, United States) in accordance with the manufacturer's instructions. In preparation of the real-time polymerase chain reaction (PCR), reverse transcription of RNA samples was performed using the High-Capacity cDNA kit (Applied Biosystems).

The cDNA was amplified with quantitative real-time polymerase chain reaction (q-PCR) using TaqMan Master Mix (Applied Biosystems) for the reaction of microRNAs. The U6 gene was used as an endogenous control (housekeeping) for the reaction of the microRNA. The PCR conditions included pre-heating at 50˚C for two minutes, denaturation at 95˚C for ten minutes, and 50 cycles of amplification and quantification (15 seconds at 95˚C, and one minute at 60˚C). All reactions were performed in duplicate and analyzed with the 7500 Sequence Detection System apparatus (Applied Biosystems). The data were analyzed using ABI-7500 SDS software. Dissociation curves were performed (melting curves) after amplification by RQ-PCR. The samples that showed dissociation curves with different temperatures or more than one point of dissociation in the same sample were discarded and repeated.

For the statistical analysis of comparing the expression of microRNAs in the different groups, simple linear regression models were performed, considering the group variable as an isolated predictor of expression. Due to the asymmetric distribution of expressions, models were adjusted after logarithmic transformation of outcome variables. Multiple comparisons were conducted using Tukey's post-test with 95% confidence intervals (95% CI). Model assumptions were evaluated by graphical inspection of residuals and formal normality tests, including the Shapiro-Wilk test. Receiver operating characteristic (ROC) curves were constructed to evaluate the discriminatory capacity of the miRNAs of interest (miR-145, miR-200b and miR-143). The area under the curve (AUC) was used as a measure of global accuracy, accompanied by the respective 95% confidence intervals (95% CI). Cutoff points (thresholds) that maximized the sum between sensitivity and specificity were also identified, according to the Youden index (J = sensitivity + specificity − 1). The significance level adopted was 5%

for all analyses. All analyses were performed using RStudio software (version 2024.12.1).

3. Result

3.1. Descriptive Analysis of Clinicopathological Aspects

When analyzing Table 1, we observed the distribution of cases of multiple meningiomas divided between synchronous and metachronous groups, in which 86.67% and 66.67% of patients were female and only 13.33% and 33.33% were male, respectively. The average age at diagnosis in the synchronous group was 54 years and in the metachronous group was 40 years.

Table 1. Description of the clinicopathological characteristics of the study.

Descriptions by Group		
Characteristics	**Synchronous (n = 15)**	**Metachronic (n = 15)**
Sex		
F	13 (86.67%)	10 (66.67%)
M	2 (13.33%)	5 (33.33%)
Age		
Average (Standard Deviation)	54.13 (13.11)	40.80 (19.17)
Median (Min; Max)	58.00 (18.00; 72.00)	39.00 (13.00; 73.00)
Histological Subtype		
Anaplasic	0 (0.00%)	1 (6.67%)
Atypical	1 (6.67%)	7 (46.67%)
Fibrous	1 (6.67%)	1 (6.67%)
Meningothelial	6 (40.00%)	0 (0.00%)
Microcystic and Transitional	0 (0.00%)	1 (6.67%)
Mixed	0 (0.00%)	1 (6.67%)
Psamomatous	1 (6.67%)	1 (6.67%)
Ssecretory	0 (0.00%)	1 (6.67%)
Transitional	6 (40.00%)	2 (13.33%)
Degree		
Grade 1	14 (93.33%)	7 (46.67%)
Grade 2	1 (6.67%)	7 (46.67%)
Grade 3	0 (0.00%)	1 (6.67%)

Continued

Location		
Skull Base/Fossa	3 (20.00%)	3 (20.00%)
Convexity	3 (20.00%)	5 (33.33%)
Brain Lobe	2 (13.33%)	2 (13.33%)
Meninges and Derivatives	0 (0.00%)	2 (13.33%)
Other Structures	0 (0.00%)	1 (6.67%)
Parasellar Region	4 (26.67%)	1 (6.67%)
Unspecified Location	3 (20.00%)	1 (6.67%)
Death		
Yes	1 (6.67%)	2 (13.33%)
No	14 (93.33%)	13 (86.67%)

Cerebral lobe: temporal fossa, frontotemporal, temporal, perietal; Meninges and derivatives: sicklecerebral, tentorial; Other structures: ventricles. Source: Own preparation (RStudio software version 2024.12.1).

In the synchronous group, approximately 93.33% of patients were classified as WHO grade 1, followed by 67% as grade 2. No patient in this group had a grade 3 classification. On the other hand, in the metachronous group, the distribution between WHO grade 1 and grade 2 classification was equally distributed among patients in 46.67% of cases, followed by grade 3 classification in 6.67%. The meningothelial and transitional histological subtypes were more prevalent in the synchronous group, equally distributed in 40% of cases. In the metachronous group, the most prevalent histological subtype was the atypical one in 46.67% of cases.

Regarding location in the synchronous group, tumors in the parasellar region predominated in 26.67%, followed by regions such as the skull base and convexity in 20% of cases, and the cerebral lobe in 13.33% of cases. In the metachronous group, the predominant location was tumors affecting the cerebral convexities in 33.33%, followed by skull base tumors in around 20% of cases. Of the patients included in the study only, 6.67% of the synchronous group and 13.33% of the metachronous group died, according to data obtained from medical records.

3.2. Expression of MicroRNAs

The results presented in the following graphs descriptively demonstrate the distributions of microRNA expressions for each group. When analyzing the graphs, we observed that the boxes represent the variation of the data in each group, through differences in the height or position of the boxes. The inner lines indicate the median, the edges of the boxes correspond to the interquartile range (IQR), where 50% of the responses are concentrated (between the 1st and 3rd quartile). This measure indicates the degree of variation in scores within the group. Therefore,

differences in the height or position of the boxes suggest possible changes in expression levels (Figures 1-3). These possible expression differences were explored in subsequent statistical analyses.

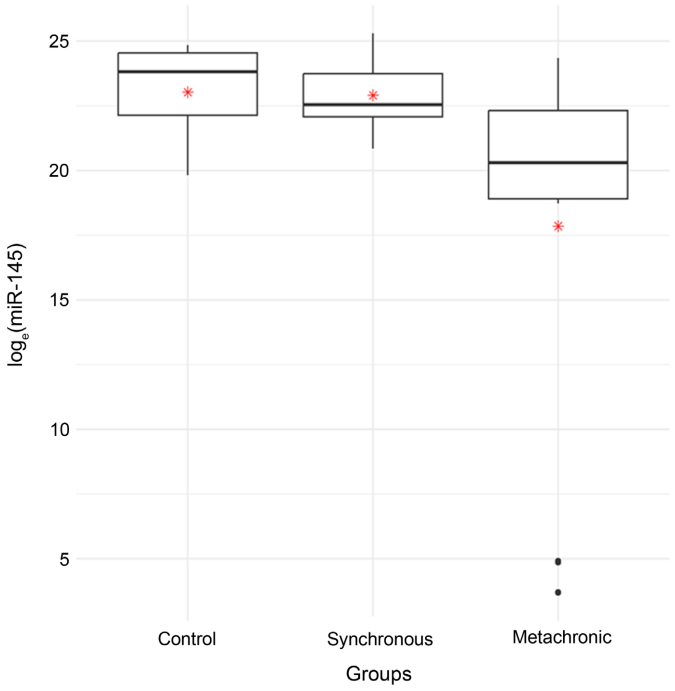

Figure 1. Graphical representation of microRNA-145 expression between study groups. Source: Own preparation (RStudio software version 2024.12.1).

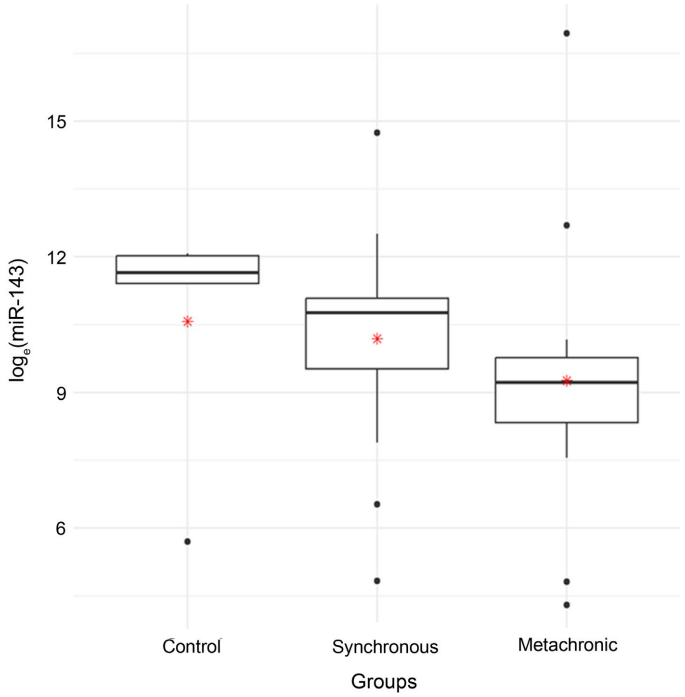

Figure 2. Graphical representation of microRNA-143 expression between study groups. Source: Own preparation (RStudio software version 2024.12.1).

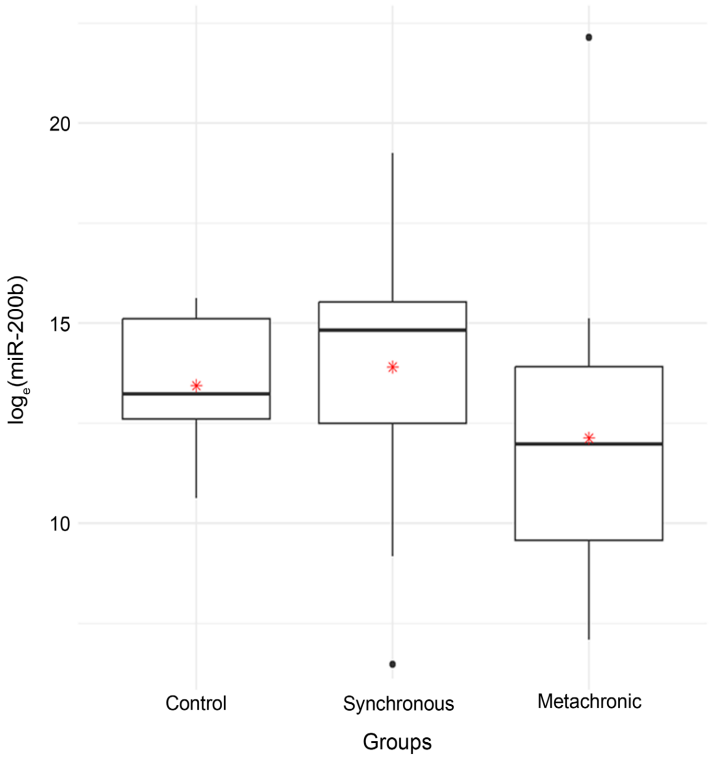

Figure 3. Graphical representation of microRNA-200b expression between study groups. Source: Own preparation (RStudio software version 2024.12.1).

The graphs represent a descriptive analysis so that we can analyze how the expression of microRNAs behaves in the samples in each group. When analyzing the graphs visually at first, we observed that the microRNAs miR-145 and miR-200b demonstrated lower values in the metachronous group compared to the synchronous and control groups, which may be indicative of reduced expression in these patients. When observing the graphical representation of miR-143, we observed that the control group maintains the highest expression levels, while both the synchronous and metachronous groups demonstrate a reduction in the expression of this microRNA (observing the decline of the boxes in relation to the control group). This analysis is still exploratory, and apparent differences were tested in the following tables.

To really analyze and confirm whether or not there is a statistical difference between the expressions of microRNAs in relation to the groups, in the following tables (**Table 2** and **Table 3**), we performed an analysis of gross and adjusted estimated difference (by histological grade and tumor location), using the linear regression model. In this model, the average difference in expression between groups was calculated. This estimated difference represents how much higher or lower the average microRNA expression is in the compared group in relation to the reference groups. When this difference is positive (>0), the expression will be greater than the reference group, and when the expression is negative (<0), it means that the expression is smaller than the reference group.

Table 2. Gross estimated difference between microRNAs in different groups.

Comparison	Gross[1]			
	Estimated Difference	95% Confidence Interval		p-value
miR-145				
Control vs Metachronics	8.50E+09	−9.35E+08	4.55E+10	0.11
Control vs Synchronous	1.15E+09	−1.41E+10	4.14E+10	0.99
Metachronic vs Synchronous	−7.35E+09	−1.59E+10	−5.61E+08	0.03
miR-200b				
Control vs Metachronics	5.03E+05	−6.01E+05	1.55E+07	0.74
Control vs Synchronous	−4.10E+05	−3.71E+06	1.52E+07	0.96
Metachronic vs Synchronous	−9.13E+05	−3.88E+06	8.13E+05	0.34
miR-143				
Control vs Metachronics	2.84E+04	−2.43E+04	4.50E+05	0.62
Control vs Synchronous	1.23E+04	−6.65E+04	4.44E+05	0.96
Metachronic vs Synchronous	−1.60E+04	−6.98E+04	3.38E+04	0.62

1: Raw linear regression model. Source: Own preparation (RStudio software version 2024.12.1).

Among the three microRNAs evaluated by this model, when looking at Table 2, we found a significant difference estimated only in the expression of miR-145 in relation to the metachronous vs synchronous group (p = 0.03), indicating, on average, a hypoexpression of miR-145 in the metachronous group in relation to the synchronous group.

Table 3. Adjusted estimated difference between microRNAs in different groups.

Comparison	Adjusted[2]			
	Estimated Difference	95% Confidence Interval		p-value
miR-145				
Control vs Metachronics				
Control vs Synchronous				
Metachronic vs Synchronous	−2.29E+10	−3.96E+10	−1.12E+10	<0.01
miR-200b				
Control vs Metachronics				
Control vs Synchronous				
Metachronic vs Synchronous	−1.24E+06	−5.04E+06	9.14E+05	0.20

Continued

miR-143				
Control vs Metachronics				
Control vs Synchronous				
Metachronic vs Synchronous	−1.42E+04	−5.14E+04	2.41E+04	0.38

2: Linear regression model adjusted for the degree and location of the injury. Source: Own work (RStudio software version 2024.12.1).

Table 3 represents the linear regression model adjusted by degree and location in order to control possible confounding variables. Even after adjustment, we observed that the statistical difference between the expression of miR-145 in the metachronous vs synchronous group remained ($p < 0.01$), where the difference between metachronous and synchronous increased to 22.9 billion units less in the metachronous group (95% CI: 39.2 billion to 11.2 billion).

3.3. ROC Curves

ROC (receiver operating characteristic) curves were constructed (Figures 4-9) to evaluate the discriminatory capacity of microRNAs in distinguishing sick patients from the control group. Curves closer to the upper left corner indicate better performance, while curves closer to the 45˚C line represent discrimination close to chance.

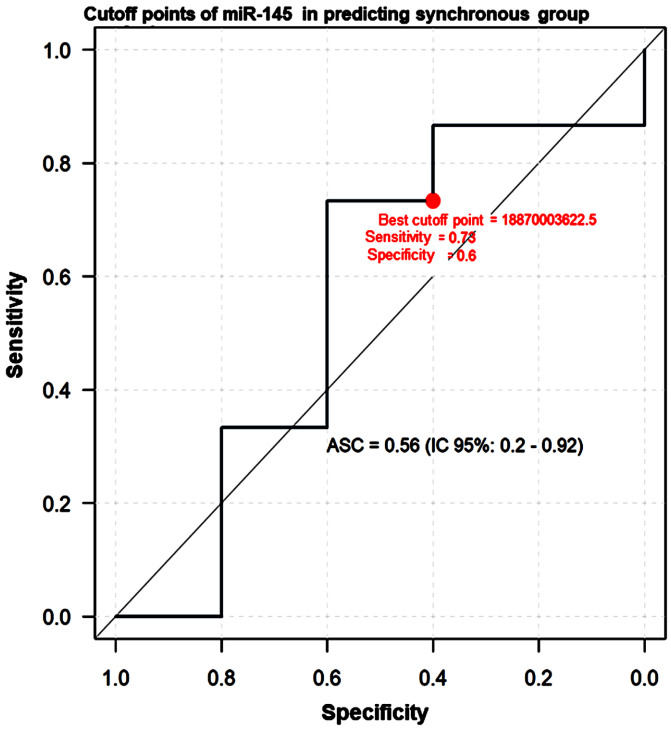

Figure 4. ROC curve for FOLD values of miR-145 in the synchronous and controls. Source: Own preparation (RStudio software version 2024.12.1).

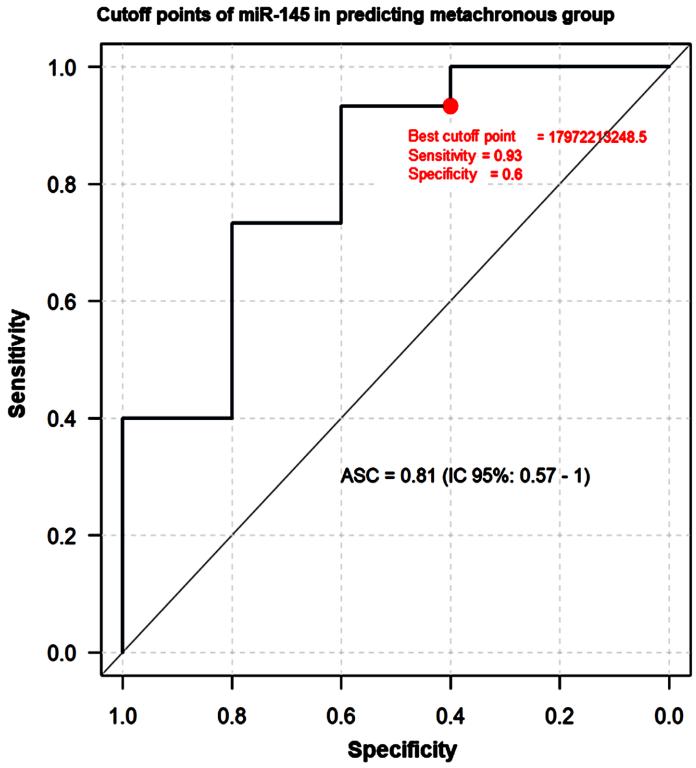

Figure 5. ROC curve for FOLD values of miR-145 in the metachronous group and controls. Source: Own preparation (RStudio software version 2024.12.1).

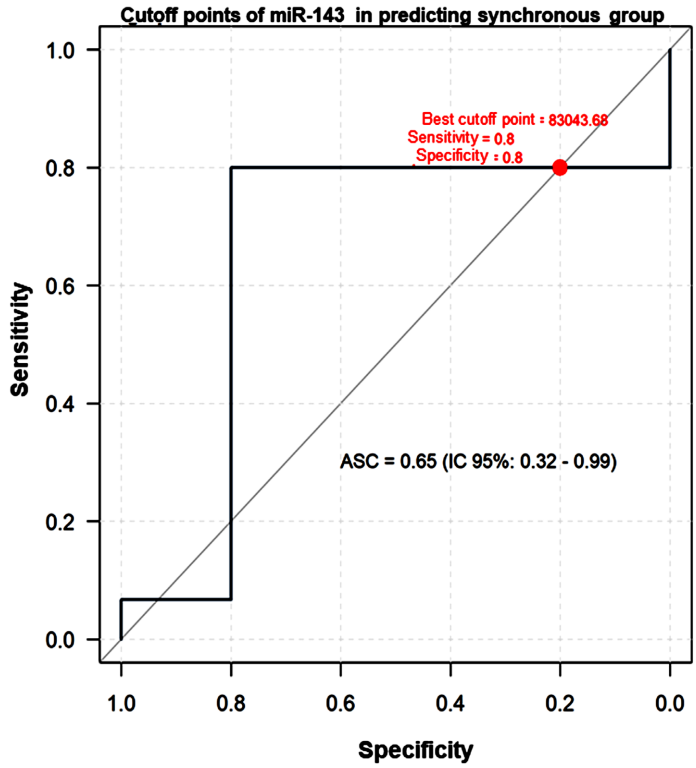

Figure 6. ROC curve for FOLD values of miR-143 in the synchronous group and controls. Source: Own preparation (RStudio software version 2024.12.1).

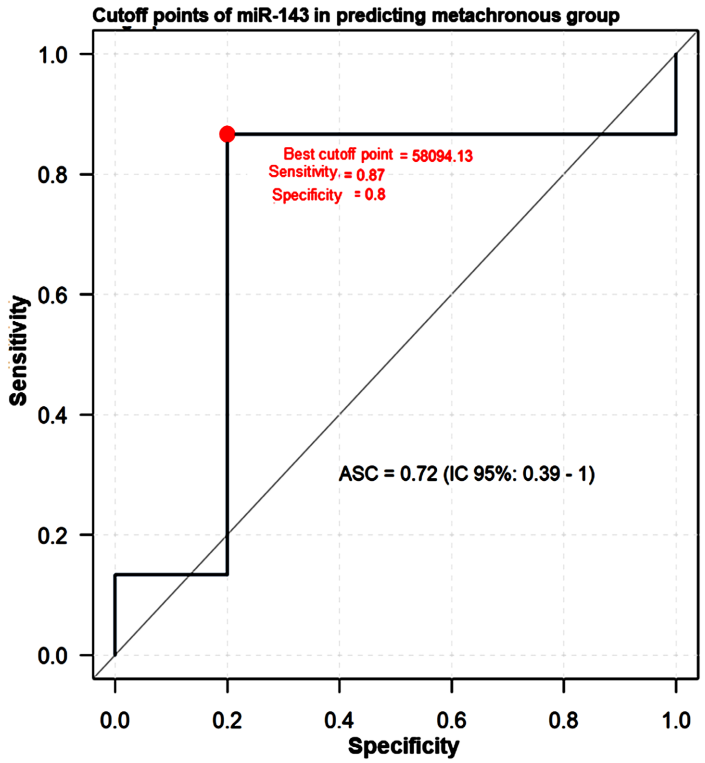

Figure 7. ROC curve for FOLD values of miR-143 in the metachronous group and controls. Source: Own preparation (RStudio software version 2024.12.1).

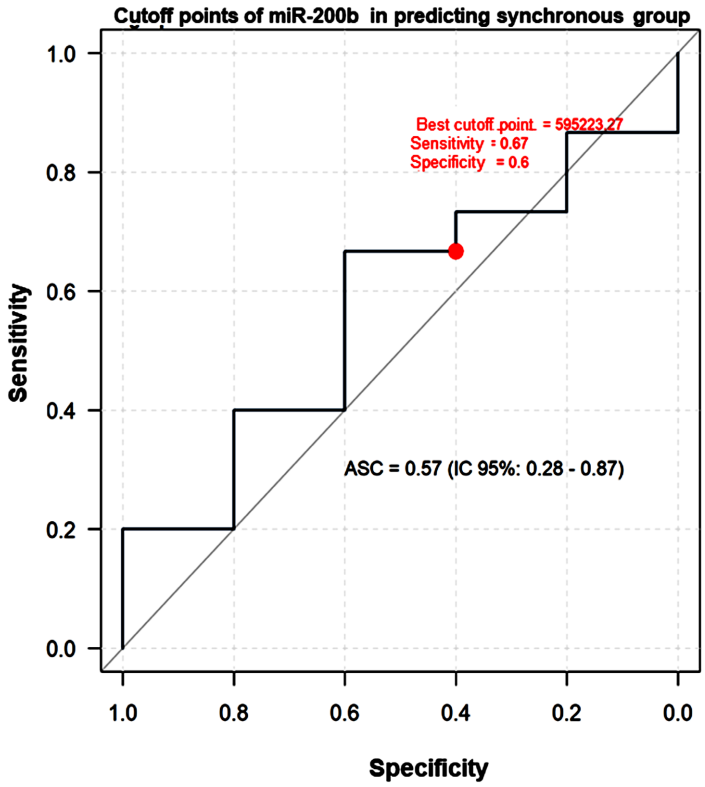

Figure 8. ROC curve for FOLD values of miR-200b in the metachronous group and controls. Source: Own preparation (RStudio software version 2024.12.1).

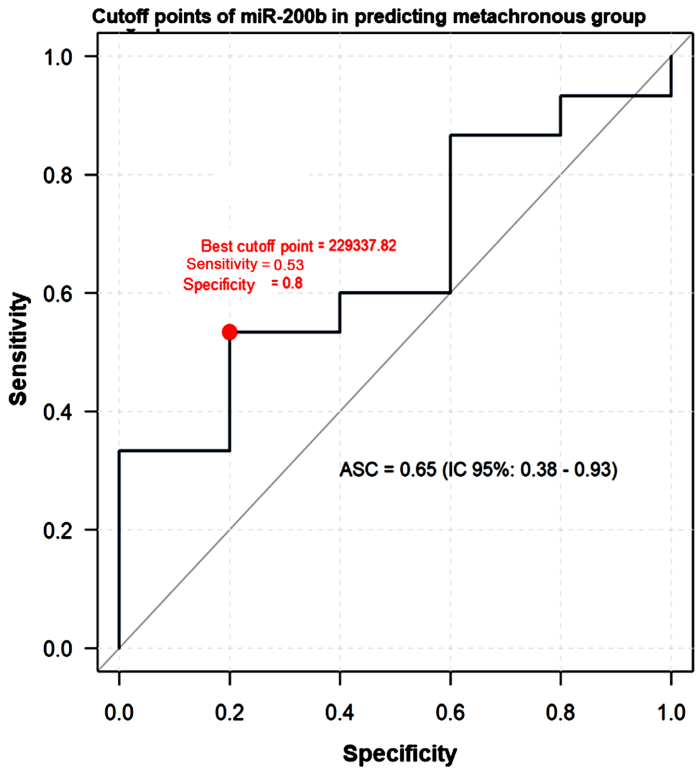

Figure 9. ROC curve for FOLD values of miR-200b in the metachronous group and controls. Source: Own preparation (RStudio software version 2024.12.1).

Among the markers evaluated, miR-145 performed best in distinguishing metachronous cases from the control group with an AUC of 81% (95% CI: 0.57 - 1), presenting high Se (sensitivity) in 93%, but not as specific (Es—specificity—in 60%), demonstrating its potential as a discriminatory marker in this context. In the synchronous group, this marker was poorly demonstrated with an AUC of 56% and low Se and Es respectively at 73% and 60%. miR-143 demonstrated reasonable performance in both groups, especially in the metachronous group with AUC of 72% (95% CI: 0.39 - 1) with Se of 87% and Es of 80%. On the other hand, miR-200b demonstrated low discriminatory capacity for both synchronous and metachronous group tumors, respectively, at AUC 57% and 65%.

4. Discussion

When comparing our data in relation to the clinical pathological findings of the study, we observed that our findings corroborate the findings described in the literature. In our study, the incidence in females was higher in both the synchronous and metachronous groups at 86.67% and 66.67% respectively. These data corroborate the data presented in the study by Ishi and colleagues (2022) on multiple meningiomas, where 79.4% of cases were female [23]. In another work presented by Fahlstrom and collaborators (2023), where the proportion of cases in females compared to males was also higher (ratio of 3.2:1 females and 2.9:1 males) [2].

The average age of patients in our study was 54 and 40 years for the synchro-

nous and metachronous groups, respectively. In the work of Erson-Omay and collaborators (2022), the average age of patients was 48 years old, similar to our findings [24].

In another study, Kopf and colleagues (2023) found that the average age of patients with multiple meningiomas was 72 years. In this study, around 11% and 19% of patients presented high-grade injuries (WHO grade 3) in synchronous and metachronous groups, respectively [25].

In our sample, in the synchronous group, approximately 93.33% of patients were classified as grade 1, 67% as grade 2 and no patient in this group had a grade 3 classification. In the metachronous group, the distribution between WHO grade 1 and grade 2 classification was equally distributed in 46.67% of cases, followed by grade 3 classification in 6.67%. In the work of Juratli and collaborators (2021), 82.3% of multiple meningiomas were classified as WHO grade 1. These data reinforce that, like single meningiomas, MM also have a greater predominance of tumors classified as grade 1 [26]. Interestingly, although grade 1 tumors are considered benign tumors, these tumors may present a distinct behavior profile in clinical practice, and behave in a similar way to high-grade tumors, such as high recurrence capacity, where their histological classification may not reflect their potential for biological aggressiveness.

The meningothelial and transitional histological subtypes show greater predominance in the synchronous group (40% of cases in the synchronous group) and in the metachronous group, the atypical subtype prevailed in atypical in 46.67% of cases, followed by the transitional subtype in 13.33%. These data are coherent when we analyze the predominance of WHO grade classification in these groups. Regarding the distribution of the location of the tumors in our study, the distribution demonstrated somewhat heterogeneity in both groups, as reported in the work of Zuniga and collaborators (2025), but in general, parasellar regions, convexity of the skull base were those most affected [27].

As mentioned, when writing the present study, the mechanisms that control the state of cellular pluripotency during embryological development are seen through ESCs, which derive from the embryo's epiblast at the blastocyte stage, maintaining the ability to originate any cell type [28]. Due to its distinct capacity for self-renewal and differentiation, understanding the mechanisms of its regulatory circuit is fundamental to understanding human development, and also the pathophysiology of various diseases, such as cancer [28].

The transcription factors SOX2, OCT4 and NANOG are highly expressed in ESCs, and studies demonstrate that the overexpression of these markers in somatic cells induces the pluripotency phenotype, highlighting the importance of these factors in regulating the signaling networks that govern this state. The overexpression of these factors has been observed in several malignancies, such as pancreatic tumors, high-grade gliomas, prostate and others, linked to the worse clinical outcome of patients, such as reduced survival time [29].

The transcription factor SOX2 governs numerous characteristics of CSCs, such

as tumor initiation, proliferation, epithelial-mesenchymal transition, migration, and the processes of invasion and metastasis. In meningiomas, a study described SOX2 as a marker of tumor aggressiveness, which interestingly was observed in tumors classified as WHO grade 1 [10].

This factor is considered one of the main transcription factors associated with pluripotency, where it is actively involved in the self-renewal and maintenance of the capacity of ESCs and NSCs, and also in the reprogramming of somatic cells into iPSCs. Furthermore, its oncogenic role in tumor development has been increasingly described in the literature. CSCs that overexpress SOX2 are capable of driving malignancy, as they serve as populations of "founder cells" with the potential to restart and propagate tumor growth, giving rise to a diversity of differentiated progenitor cells, which will compose the tumor microenvironment [30].

In CNS tumors such as high-grade gliomas and medulloblastomas, tumor growth was driven by CSCs overexpressing SOX2, which is essential for the maintenance of these tumors, restarting and driving tumorigenesis. In bladder tumors, the potential of SOX2 as a marker of CSCs was demonstrated, where cell lines that expressed this factor were able to repopulate the tumor microenvironment, and in contrast, ablation of the lineage that expressed SOX2 improved tumor regression [30] [31].

The increasing studies on the role played by SOX2 in different types of tumors, in addition to those mentioned above, but others such as lung, head and neck squamous cell carcinoma, pancreas and others, reinforce the participation of this transcription factor linked to the initiation and maintenance of CSCs. An aberrant activation of the SOX2 promoter, influenced by genetic and epigenetic changes in the tumor microenvironment, may be capable of inducing differentiated tumor cells, causing them to return to the CSCs phenotype, a mechanism known as cellular plasticity, which facilitates the formation of these cell subpopulations. Therefore, the ablation of a CSCs lineage that overexpresses SOX2 or depletion of expression would possibly delay the tumorigenic process, by deregulating the pluripotency network that favors the generation and maintenance of CSCs [30].

Transcription factors are capable of forming complexes with each other in order to co-regulate the transcription of their target genes, and to self-regulate themselves and each other through feedback mechanisms. Although its functions are independent, SOX2 is also capable of interacting synergistically with the OCT4 factor to bind to DNA efficiently and recruit other factors essential for gene activation, jointly activating many target genes, such as NANOG, forming a regulatory circuit of the cellular pluripotency axis [31].

Therefore, differential expression of OCT4 and NANOG is also observed in highly malignant tumors, as well as SOX2, and is associated with the presence of CTTs and critical events in tumor development, such as reduced survival time [29].

Part of the pluripotency potential of transcription factors, destined for CSCs, also depends on the participation of microRNAs. These factors are regulated post-transcriptionally by the action of microRNAs, controlling the capacity for pluripotency

otency through the regulation of the SOX2, OCT4 and NANOG genes.

MicroRNAs play important roles in the regulatory circuit of SOX2, OCT4 and NANOG. However, even today, little is known about the interaction of microRNAs with the regulatory axis of transcription factors, controlling the regulation of self-renewal and pluripotency in tumors [28].

Given all of the above, in this study, we sought to elucidate the participation of the microRNAs miR-145, miR-143 and miR-200b in the context of the axis of regulation of transcription factors that govern the state of cellular pluripotency in multiple meningiomas. To date, no article has been found published in a database such as PubMed that has the same research objective of interest, which gives the originality of this work.

miR-145 acts as a tumor suppressor by suppressing oncogenes and their participation in several signaling pathways, inhibiting cell proliferation, invasion and metastasis and chemosensitivity. However, its expression is reduced in several tumors that are highly malignant [32].

In the work of Gao and colleagues (2017), overexpression of miR-145 in a cell line with acquired resistance to gemcitabine (Bxpc-3-Gem) promoted the negative regulation of pluripotency factors OCT4, NANOG, SOX2, and also the protein ZEB1, which plays an important role in inducing EMT, a process characteristic of the CSCs phenotype [33].

A characteristic of CSCs is cell migration and in their study, Lin and collaborators (2016) evaluated the effects of miR-145 on cell migration by inducing its forced expression in Bxpc-3 and Panc-1 cells, where they demonstrated that the overexpression of miR-145 decreased by 65% and 50% respectively. Also in this study, it was demonstrated that the overexpression of miR-145 significantly increased the chemosensitivity of cells to treatment with gemcitabinen [32].

Drawing a parallel between the aforementioned studies, miR-145, when overexpressed, acts as a tumor suppressor in several signaling pathways. As mentioned, SOX2, NANOG and OCT4 are direct targets of miR-145, so overexpression of this microRNA reduces the expression of their targets, resulting in the induction of cell differentiation. We know that CSCs belong to a subpopulation of cells within the tumor mass responsible for the initiation and maintenance of the tumor, as well as for the characteristics of malignancy presented, such as therapeutic resistance.

In this context, possibly, when overexpression of miR-145 occurs, the central triad of pluripotency, SOX2, OCT4 and NANOG, is negatively regulated, causing CSCs to reduce their ability to maintain pluripotency and self-renewal in the state, inducing cells to cell differentiation, which increases the eliminative potential of these cells, for example, by increasing chemosensitivity.

In the present study, when analyzing the expression behavior of the microRNA miR-145 in relation to the synchronous and metachronous groups, we observed a significant difference in expression ($p = 0.03$), where this microRNA presented a hypoexpression in relation to the metachronous group when compared to the syn-

chronous group. Furthermore, when we adjusted the analyses excluding possible confounding effects such as degree and location, this statistical difference remained ($p < 0.01$).

When we observed the results obtained in the construction of ROC curves, to identify the discriminatory capacity of microRNAs in differentiating patients in the metachronous and synchronous groups in relation to the control group, miR-145 showed high performance in distinguishing patients in the metachronous group from the control group, presenting an AUC of 81% (95% CI: 0.57 - 1), with high sensitivity in 93%, however, not as specific (Es in 60%). In parallel, the behavior of miR-145 in the synchronous group was poor, with an AUC of 56% and low sensitivity and specificity (73% and 60% respectively).

The involvement of miR-145 with the mechanisms of pluripotency has already been observed in other tumors, for example, in endometrial carcinoma, where increased expression of miR-145 in cells with CSCs phenotype negatively regulated the expression of OCT4 and induced cell differentiation.

In another study, increased expression of miR-145 in pancreatic cancer correlated with negative expression of NANOG, where the author demonstrated that NANOG is a direct target of miR-145 [33]. In breast tumors, miR-145 was downregulated and correlated with the development of metastases. On the other hand, upregulation of miR-145 has been shown to inhibit cell growth by targeting SOX2 [34].

In another study, increased expression of miR-145 in pancreatic cancer correlated with negative expression of NANOG, where the author demonstrated that NANOG is a direct target of miR-145 (Gao *et al.*, 2017) [33]. In breast tumors, miR-145 was downregulated and correlated with the development of metastases. On the other hand, upregulation of miR-145 has been shown to inhibit cell growth by targeting SOX2. One possible explanation for the differences between synchronous and metachronous tumors is that they may arise from distinct evolutionary trajectories within the primary lesion. Synchronous lesions could originate from subclones that disseminate very early, whereas metachronous disease may reflect the outgrowth of cellular populations that acquire metastatic competence later in tumor evolution, either through increased plasticity or reactivation from a quiescent state. In this context, examining spatially distinct regions of these tumors and comparing their microRNA profiles, particularly the expression of miR-145, may offer insights into the biological mechanisms underlying these divergent patterns of dissemination. Another aspect to consider is the time interval before the appearance of metachronous lesions. During this period, tumor cells remain exposed to additional rounds of mutational events, epigenetic remodeling, and selective pressures imposed by the microenvironment. These cumulative influences can reshape the phenotype of residual clones, potentially enhancing their adaptability and malignant potential [34].

Among the regulators of cells with the stem phenotype, SOX2 plays an active role not only in ESCs, but also in NSCs, whose role is essential for brain development and

in the maintenance of neurogenesis in specific areas such as the subventricular zone. This factor provides conditions for maintaining pools of NSCs in a state of cellular quiescence, and also for maintenance and differentiation when neurogenesis is required [30].

SOX2-expressing tumor cells drive malignancy with their ability to underlie tumor initiation, giving rise to a great diversity of differentiated cells. When overexpressed, they act in the maintenance of cellular pluripotency, possibly through the mechanism of cellular plasticity, contributing to reprogramming differentiated somatic cells of the tumor microenvironment, to the stem state (dedifferentiation), replenishing the subpopulation of CSCs [30].

That said, the active role of the transcription factors that make up the pluripotency triad, especially SOX2, in maintaining the state of pluripotency in the tumor microenvironment, whether through mechanisms of cellular plasticity or reversion of the state of quiescence of CSCs, could possibly be a hypothesis for the hypoexpression of miR-145 in the metachronous group in our study, since this tumor suppressor microRNA is a direct regulator of transcription factors, where several studies cited herein work, demonstrated their participation in the regulatory axis of these factors associated with the characteristics of CSCs present in tumorigenesis. In this context, we can assume that miR-145 may be considered a potential marker, contributing to clinical practice by predicting patients with a higher potential to develop metachronous tumors when its expression is reduced in patients diagnosed with meningioma, thus contributing to better monitoring of the disease.

Another microRNA with a tumor suppressor function is miR-143, which was also analyzed in the present study. When observing the descriptive Boxplot graph used in the microRNA expression analysis in our study, at first, we thought it was possible to find a difference between the expressions of miR-143, with a decrease in expression in the synchronous and metachronous groups when compared to the control. However, when we actually performed the comparison analyses using a statistical linear regression model, we observed that there was no statistical difference in the expression of miR-143 between the different study groups.

This variation initially observed in the Boxplot graphs was possibly influenced by the sample number, including the number of patients belonging to the control group. In the construction of ROC curve, miR-143 showed a reasonable performance in both groups, especially in the metachronous group with AUC at 72% (95% CI: 0.39 - 1) with sensitivity and specificity of 87% and 80% respectively.

Like miR-145, the microRNA miR-143 also behaves as a tumor suppressor, and its participation in the pluripotency axis in tumors has already been reported in other studies. In the work of Ngalame and colleagues (2016), increased expression of miR-143 correlated with decreased expression of OCT4 in prostate tumor CSCs [35].

In another study, overexpressed miR-143 prevented the proliferation of PDAC cells, reduced cell migration capacity, and resulted in reduced invasion and me-

tastasis capacity, indicating that overexpressed miR-143 can inhibit the proliferative, migratory, and invasive capacity of cells [36]. Therefore, the overexpression of miR-143 would possibly be negatively regulating the expression of the transcription factors OCT4, SOX2 and NANOG, direct targets of miR-143, forcing CSCs to enter the state of cellular differentiation, losing the characteristics that favor their high malignancy.

Analyzing the formation of spheres to evaluate the self-renewal capacity of CSCs, in a prostate tumor, the overexpression of miR-145 and miR-143 suppressed the capacity for formation of spheres, therefore, reducing the properties of the stem phenotype of these cells. Furthermore, determining the participation in the regulation of these microRNAs and their relationship with pluripotency factors, when analyzing their expressions, it was observed that the overexpression of both miR-145 and miR-143 negatively regulated the expression of the central pluripotency transcription factors OCT4, SOX2, NANOG, and also other factors involved, such as Myc and Klf4 [37].

These data reinforce the participation of these microRNAs in the context of pluripotency, which is a critical state of the most important regulation of CSCs, essential to maintain their malignant characteristics.

In our study, we also analyzed the expression of the microRNA miR-200b, which demonstrated low performance in the analysis of the estimated difference in its expression when comparing groups, not showing statistical significance, and in the construction of the ROC curve, which also demonstrated low discriminatory capacity for both the synchronous and metachronous groups at AUC of 65% and 57% respectively, as well as low sensitivity and specificity in both groups.

The miR-200b microRNA belongs to the miR-200 microRNA family (which also includes the miR-200a, miR-200c, miR-141 and miR-429 microRNAs). This microRNA also has an important role as a tumor suppressor, acting on pathways related to the regulation of EMT, where its targets are ZEB1 and 2 and also E-cadherin, and when hyperexpressed, it reduces the expression of mesenchymal markers and increases the expression of epithelial markers, maintaining cell adhesion and reducing tumor migration and invasion. This microRNA is also related to the maintenance and repression of cellular pluripotency, influencing the regulatory circuit of the transcription factors OCT4, SOX2 and NANOG [38].

In the work of Zhang and collaborators (2015), by inhibiting the expression of the microRNAs miR-200b and miR-200c, in an experimental study carried out with mouse embryonic stem cells, they observed a reduction in the expression of genes such as OCT4 and NANOG, resulting in the differentiation of cells from cells with a stem phenotype [39].

In another study carried out in the city of Zhengzhou, China, the expression of SOX2 and miR-200b was evaluated in patients diagnosed with primary gliomas. In this study, analyzes carried out by real-time PCR demonstrated an increase in the expression of miR-200b in the control group and a decrease in expression in gliomas. The hypoexpression of this microRNA correlated with an increase in the

histopathological grade of gliomas, where lower expression of miR-200b was observed in high-grade gliomas (grade 4 glioblastoma) [22].

In breast cancer, the expression of miR-200b by real-time PCR technique was negatively expressed, compared to the control group. Furthermore, the authors correlated the expression of these microRNAs with clinical pathological findings, where they showed that hypoexpression of miR-200b was associated with the incidence of late TNM stage levels, negative estrogen receptor (ER) and positive human epidermal growth factor (HER-2) status. Using Kaplan-Meier survival analyses, the authors also demonstrated that low expression of miR-200b presented a worse prognosis, compared to patients with high expression, demonstrating the association of miR-200b expression levels with the overall survival of patients [40]. These data corroborate the hypothesis of participation of CSCs in tumor progression, since they are associated with highly malignant events in these tumors, characteristics attributed to the participation of CSCs.

Given the data presented, microRNAs are potentially useful as tumor markers, by directly regulating the transcription factors SOX2, OCT4 and NANOG, essential for CSCs to maintain their capacity for self-renewal and pluripotency, as well as maintenance.

Although the low sample number in our study was possibly a limiting factor for the expression performance of some targets, such as miR-143 and miR-200b, it is still possible to observe the potential of these microRNAs as markers of cellular pluripotency and multiple meningiomas. Part of this limitation of the sample number is due to the low incidence of MM, and for this reason, multicenter studies should be considered in future research, so that the sample number is increased, improving and expanding research and analysis on these tumors.

During the writing of this work, we did not find any study in the literature that evaluated the participation of the aforementioned microRNAs in MM that correlates with the expression of these transcription factors. To date, little is known about the participation of microRNAs in the regulation of processes involved in the tumorigenesis of multiple meningiomas, as well as their involvement in the state of cellular pluripotency, and therefore, the lack of studies on the subject makes it difficult to understand how these microRNAs act directly in MM, and how we could use them in clinical practice.

Study Limitations

The small sample size of our study, especially the control group (n = 05), became a limiting factor for the performance of the expression and comparison of the targets. The small sample size of this group is due to the difficulty in finding individuals who died from sudden death and who met the inclusion criteria of this study in this group, such as the absence of a previous history of neurological diseases.

5. Conclusion

We concluded that the microRNA miR-145 had potential as a tumor marker as-

sociated with the cellular pluripotency axis, where its underexpression correlated with metachronous multiple meningiomas. Furthermore, a promising role of the microRNA miR-143 as a potential marker for these tumors was also demonstrated. On the other hand, miR-200b demonstrated poor performance in the present study, which highlights the need for further studies to elucidate its participation in the axis of cellular pluripotency and multiple meningiomas.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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