Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

Clinical Application of Liquid Biopsy In CNS Tumors With Reference To Exosomes And Mirna

Manish Tenguria[1], Vishal Rajput[1]*, Meenu Gupta[2], Neha Sharma[3], Sanjay Gupta[1]

[1]Himalayan School of Biosciences, Swami Rama Himalayan University, Uttarakhand, India
[2]Department of Radiation Oncology, Cancer Research Institute, SRHU, India
[3]Department of Life Sciences, J.S. University, Uttar Pradesh, India

***Corresponding Author: -** Vishal Rajput
*****Email: vishalrajput@srhu.edu.in

KEYWORDS
Exosomes, Circulating miRNAs, liquid biopsy, CNS Tumour, Diagnosis

ABSTRACT:
In most cases, it is difficult to make an earlier diagnosis of the Central nervous system (CNS) tumour, which continues to be the most lethal cancer. Patients with chemo-resistance who completed their primary therapy are shown to later develop recurrent illnesses. Brain biopsies present hazards and challenges when used when evaluating the effectiveness of treatment and tumour recurrence in CNS tumours. Brain biopsies, on the other hand, are viewed as a surgical procedure with poor specificity and sensitivity. Based on a blood and cerebrospinal fluid (CSF) examination, the liquid biopsy that is less intrusive and involves serial bodily fluids, is based on a test that is acceptable to patients since it uses just a small amount of blood and CSF. Liquid biopsy has the ability to observe the growth of tumours, present fresh perspectives in real-time, and administer accurate medical care. Circulating exosomes, cell-free microRNAs, circulating tumour DNA, and circulating cancer cells (CTCs) are the main analytical components of a liquid biopsy. Recent years have seen a significant increase in the number of CNS malignancies treated with liquid biopsy, and research into CTCs and ctDNA has received a lot of focus. The clinical application of liquid biopsy indicators for cancer related to the central nervous system will be discussed to determine diagnosis, prognosis, and therapeutic response.

Introduction

A wide range of malignancies with severe morbidity and high mortality rates belong to the category of central nervous system (CNS) tumours.Several different types of cells, including those from the CNS or from systemic tumours that metastasize to the CNS, are frequently the origins of these cancers. According to the outcomes of the surgical resection's pathological evaluation, the primary therapeutic plan at this time is radio-chemotherapy (Heitzer et al., 2019; Li et al., 2020). Temozolomide (TMZ) is mostly used as adjuvant postoperative chemotherapy. The first tissues determine the subsequent therapy because the tumour may undergo longitudinal change over time, leading to therapeutic resistance after initial therapy (Piccioni et al., 2019; Cantor et al., 2022). In the meantime, the therapeutic approach is also impacted by variations in individual genotypes, resection of the surgical edge and its blood-brain barrier presence, which reduces its efficacy. Currently, the diagnosis and prognosis of CNS tumours are frequently determined by imaging analysis and cytology (Osti et al., 2019). In particular, the therapeutic effect is difficult to prove due to the early stage of the medication intervention's impact on the tumour's imaging characteristics, and this occurrence is known as "false progression". Second, unless there are apparent changes in the imaging examinations of glioma patients, hysteresis in the imaging examination makes it impossible to represent the precise changes in the tumour accurately and makes it invariable in medication advice. However, conventional cytological investigation has certain flaws.

Initially, it may be challenging to collect the necessary materials for a cytological examination, which frequently relies solely on tissue removed during surgery for evaluation and is therefore unable to dynamically track tumour changes. The sampling site, the collecting method, and the amount of time required for processing the sample are several factors that can affect the positive cytology rate. Additionally, there are significant dangers due to the intrusive nature of the procedure, particularly for tumour patients in specific areas, which makes postoperative issues more likely to arise. The detection and treatment of CNS cancers have thus become challenging problems that require the development of more accurate and sensitive tumour markers that can dynamically express tumour genetic

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

information and treatment responses.
Liquid biopsy is used to track the circulating tumour extracellular vesicles (EVs), circulating tumour DNA, circulating cfmiRNAs, and in urine, CSF, and blood samples, CTCs from primary or metastatic cancers (Van Schaijik et al., 2019; Sun et al., 2021). Numerous studies have established that patients with malignant tumours in their blood can provide the genetic information needed to identify the tumour. Blood has now evolved into the most widely used liquid biopsy specimen for a range of malignancies due to its benefits of simplicity, non-invasive testing, and dynamic growth of tumours.The spinal cord's ventricles and cisterns can accommodate continuous CSF circulation for the CNS. For a CNS tumour fluid biopsy, CSF is the ideal sample since it can extensively contact the CNS, contain cancer metabolites, and exfoliate tumour cells. Herpes encephalitis patients' CSF samples contained viral DNA. In the CSF of glioma patients in 1994, Researcher discovered tumour-specific p53 gene mutations (Miller et al., 2019; Page et al., 2021). After that, CSF liquid biopsy gained popularity as a research topic. In contrast to conventional biopsies, liquid biopsies can be carried out continuously at all stages of the disease and will not damage brain tissue, making them easier to accept by patients and having fewer side effects. It can also dynamically monitor the illness. Additionally, advising to modify the treatment strategy in light of the liquid biopsy's results for detection The development of targeted therapies is facilitated by the identification of tumour-specific targets. Over the past 30 years,Multiple studies have demonstratedthe clinical significance of ctDNA and CTCs in the CNS (Liu et al., 2019; Pages et al., 2022).
Non-coding RNA (ncRNA) is a subclass that includes circulating miRNA. Almost all body fluids include single-stranded ncRNA fragments, which are composed of 18–22 nucleotides.Recent studies demonstrate a critical function for circulating miRNAs in the regulation of a wide range of gene targets using gene regulatory networks. Intercellular communication is facilitated by circulating miRNAs, Increasing or decreasing the expression of their target genes is their primary function (Mair et al., 2019). Based on these findings, cfmiRNA might have a role in cancer marker in addition to being an essential therapeutic target because their expression reflects a range of gene information. Exosomes of a specific form called circulating exosomes, which are found in the bloodstream or extracellular cavity, are also released by live cells at the same time. Exosomes may alter receptor cell molecular activity and develop intercellular communication by releasing biological chemicals. As a result, tumour-specific biomarkers are present in the exosomes generated by tumour cells, which can be used to identify the features of primary tumours. Currently, a significant amount of research has demonstrated that cancer genetic information is abundant in humoral circulating exosomes, which is capable of predicting the growth of tumours and the effectiveness of treatment.
This attempt provides an in-depth review of the studies on circulating cfmiRNA and exosomes and discusses the most recent advances in the investigation of ctDNA and CTCs in nervous system malignancies (Yan et al., 2020; Li et al., 2021). In this study, an effort was made to describe the clinical importance of the use of liquid biopsy to diagnose, analyse the prognosis, and monitor the effectiveness of treatment for CNS malignancies (Duan et al., 2020). The clinical potential of liquid biopsy in CNS malignancies is further observed.

Circulating tumor cells (CTCs)
Tumour cells known as CTCs are shed from primary or metastatic tumours and end up in the blood, CSF, or urine. Based on the findings of multiple studies, CTCs are a reliable biomarker for predicting the prognosis of several malignancies, includes melanoma, osteosarcoma, lung cancer, and pheochromocytoma (Bang-Christensen et al., 2019; Liu et al., 2021). It is important to note that CTCs can be employed to study tumour molecular biomarkers and to replace actual tumours. EpCAM, which is found on the surface of the majority of cancerous cells but not glioma cells is a type of epithelial cell adhesion molecule and is the most widely used method for finding CTCs. CTCs observed in the CSF of glioma patients are therefore being monitored using a variety of CTC enrichment and identification approaches (Zhang et al., 2019). According to several investigations, CTCs are crucial for the prognosis, monitoring of medication resistance, and early detection of CNS malignant tumours.

According to studies, CTCs from glioma patients' CSF had a high mesenchyme content and a low level of nerve signature. Chromosome numbers also change (chromosomes 3, 7, and 12 are gained, chromosomes 10, 13, and 22 are deleted), which is synchronous with the primary tumour, EGFR (epidermal growth factor receptor) production increases (Hamidi et al., 2019; Izquierdo et al., 2021). In the analysis of CTC mutations in the CSF in patients with CNS malignancies, applying more caution to targeted detection techniques or next-generation sequencing (NGS) technology may assist in identifying individuals at higher risk of recurrence and guide dynamic interventional treatment approaches. In order to more precisely identify the molecular subtypes, CTCs in CSF were analyzed (Shao et al., 2019). As a result, it can be used as a biomarker to assess the prognosis and gauge its effectiveness. Additionally, the glioblastocyte epithelial-mesenchymal transition pathway, which regulates the growth and metastasis of tumours and is also present in the CTCs of GBM patients. As a result, analyzing CTCs may also reveal crucial hints about the pathogenesis and pathophysiology of intracranial

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

tumour physiology (Lan et al., 2020; Louis et al., 2021). Nevertheless, certain research findings suggest that in individuals with advanced CNS tumours, dynamic monitoring of CTCs can distinguish between pseudo-progression and tumour recurrence (Yin et al., 2019). Additionally, The number of CTCs indicates how serious the condition is;it rises as the condition worsens and falls following chemoradiotherapy. To accurately observe changes in a patient's condition, CTCs analysis may be performed in addition to traditional MRI.

The importance of CTCs in CNS tumours has been thoroughly established in earlier investigations. CTCs offer reliable and minimally invasive tumour detection samples. The growth of the main tumour and the modification of particular genetic characteristics throughout the recurrence phase can both be reflected by identifying the genetic characteristics and particular genotypes of CTCs. This theory was established through the study of a CTC fraction from breast cancer patients with metastatic disease, which also demonstrated a profile of inflammatory (also known as CXCL8, CXCR4, and CD86, 3 chemokine receptors), immune-modulatory (TNF and the Notch pathways, IL-1, as well as nuclear factor kB (NF-kB)), and pathways that arePlatelet-derived growth factor (PDGF)-BB, also known as mitogenic (Yue et al., 2019; Azad et al., 2020). This helps to provide a thorough understanding of the molecular factors that influence the incidence and growth of tumours in the central nervous system and serves as an accurate tumour biomarker (Osti et al., 2019).

Circulating tumor DNA (ctDNA)

The breakdown of sick tissues releases the ctDNAs into the blood, CSF, and urine. The challenge with ctDNA analysis is that It is necessary to extract high levels of circulating free RNA and DNA are generated by healthy cells and extracted from the circulation using highly sensitive and specialised technology. It has been demonstrated that blood ctDNA concentrations are higher in individuals with advanced solid tumours, such as lung cancer patients (Xu et al., 2019). It is an early indicator of the systemic therapeutic response, according to a large body of research.

According to current study, patients with primary CNS tumours such as oligodendroglioma and astroglioma have ctDNAs found in their tumours. The blood of patients with oligodendrogliomas and 80.5% of those with astrogliomas included greater levels of ctDNAs, and these ctDNAs showed the MGMT gene is methylated (10q LOH/1p or 19q LOH) with tumour-specific biomarkers (Lecero et al., 2020). In various study, 33 patients with CNS tumours (7 with primary GBM, 8 with astrocytoma, 2 with glioma, 6 with meningiomas, and 10 with metastatic tumours) had their serum studied to determine the levels of methylation of genes correlated with primary CNS malignancies include MGMT, RASSF2B, and CDKN2A. The results showed that in the blood ctDNAs of 70% of patients with astrocytomas, at least one gene promoter methylation was present (Bounajem et al., 2020). In a similar vein, 3 meningioma patients and 7 patients with metastases both demonstrated at least one gene promoter methylation. Five GBM patients had serum samples with lower ctDNA concentrations and were also found to have biomarkers for the underlying tumour (Garcia et al., 2020). However, glioma patients' serum has a low concentration of ctDNA and a low positive ctDNA rate compared to other tumours. Researchers have demonstrated the value of using CSF as a sample to detect ctDNAs generated by primary brain tumours. Researchers sequenced the ctDNAs from 35 patients with CNS tumours. The results demonstrated that primary tumour DNA was present in 74% of samples and that the likelihood of identifying tumour DNA was determined by the tumor's grade and anatomical location rather than its size. As a result, certain clinical studies have demonstrated the collection of blood and CSF from patients during treatment is less difficult. These deficiencies are made up for by the ability to detect ctDNAs in bodily fluids (Fontanilles et al., 2020; Siegel et al., 2021).

Individualized tumour treatment has been encouraged by introduction of precision medicine and its application to the treatment of cancer. In a central nervous system tumour, a single tissue biopsy or the collection of tumour-specific mutant gene targets during intraoperative collection may be challenging. These deficiencies are made up for by the finding of ctDNA in bodily fluid. The growth of the underlying cancer is dynamically expressed by ctDNA, in addition to revealing information on a specific gene mutation and treatment resistance mechanism (Murlidharan et al.,2021). In patients with central nervous system cancers, ctDNA demonstrates the molecular make-up of the tumours, specific therapy, detection of specific mutations, and drug resistance mechanisms. While irreversible alterations frequently happen at this stage, Analysis of ctDNA can identify early-stage cancer development and drug-resistance mutations (Kritensen et al., 2019; Carta et al., 2020).The success of treatment may be enhanced by this information, which could deliver earlier and more accurate information.

Circulating cell-free miRNAs and exosomes

MicroRNAs (miRNAs), which are non-coding short RNAs with lengths of 18 to 22 bp, control post-transcriptional levels of gene expression by destroying or inhibiting target mRNA. Additionally, microRNA is crucial for cell-to-cell communication as well as the dynamic coexistence of benign and malignant diseases.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

MicroRNA is a significant biomarker that can be used for tumour diagnosis, detection, and prognosis. In recent years, it has been thought to be connected to carcinogenesis and tumour suppression. MiRNA has received increased attention in recent years, and it has been found that several miRNA subtypes are expressed in various CNS tumour types. For instance, miR-21 inhibits caspase in glioblastoma cells, which is how it functions. MiR-21 expression in glioblastoma tissues is still significantly greater than in normal brain cells, though this is not the case for all miRNAs (Manjunath et al., 2021). For glioblastoma, a specific tumour marker known as miR-21 has been found to be able to predict both overall survival and therapeutic response (Li et al., 2021). In spite of the fact that some authors reached the same conclusion, their conclusions are still in conflict. There is yet more evidence supporting the significance of a single miRNA in tumour samples.

Extracellular vesicles called exosomes typically measure 40–100 nm in diameter and are membrane-wrapped. Exosomes are actively secreted by many cells in both healthy and pathological states. They include a variety of biological components including lipids, proteins, and nucleic acids (mRNA, DNA, and ncRNA) (Hovestadt et al., 2020). Exosomes, which release biological substances, can mediate cell-to-cell contact and alter the molecular processes of receiving cells. To determine the characteristics of the main tumour, the exosomes that the tumour cells release contain tumour-specific biomarkers (Escudero et al., 2020; Miklja et al., 2019). According to research, extracellular vesicles connected to tumour cells were found in after transplanting human cancer stem cells into a mouse model, the mouse CSF (Bobillo et al., 2021). As mentioned in another study, both low-grade and high-grade glioma patients could isolate extracellular vesicles in their CSF, which are a sign of the degree of disease development. These findings demonstrate the clinical prognostic biomarker potential of exosomes. In extracellular vesicles made from CSF, for instance, IDH1-R132H mutations were discovered (Grommes et al., 2019).

Diagnosis

In last few years have seen a significant advancement in gene chip technology, which has been extremely beneficial for the detection of circulating miRNAs. By screening specific circulating miRNAs, which are important for early detection and effective treatment of tumours, many researchers seek to comprehend the molecular properties of tumours. Consequently, the focus of tumour research has shifted to circulating miRNA (Hiemcke-Jiwa et al., 2019). Currently, research has shown that some solid tumours exhibit aberrant miRNA expression that has guiding importance. In a meta-analysis study, it was discovered that miR-125b showed good specificity (66.40%–91%) and sensitivity (63%–89.4%) in the detection of thyroid cancer, breast cancer, bladder cancer, and non-small cell lung cancer. According to researcher, early ovarian cancer patients had overexpressed circulating miR-205, which could be found in their blood. The effectiveness of miR-205 in association with CA-125 was evaluated using the ROX curve (AUS = 0.831) for detecting ovarian cancer. Discovered that early endometrial cancer patients had considerably lower levels of miR-145 expression in their serum than healthy individuals. The ROX curve was used to assess the diagnostic usefulness of this finding, and the AUC value was 0.82. Additionally, scientists discovered that the miR-221/222 family is useful for diagnosing thyroid, breast, and oral cancers (Hickmann et al., 2019). The findings mentioned above advance research on ctRNAs in CNS tumours. Compared to the control group, patients with primary central nervous system diffused large B lymphoma showed higher plasma levels of miR-21 and miR-210.

The potential of miRNA as an indicator marker for central nervous system cancers is reviewed for the first time in this finding. Since then, many scientists have become interested in the significance of miRNA in tumours of the central nervous system (Rimelen et al., 2019). In 2012, in a small-sample study, researchers determined the plasma concentrations of S100B, miR-21 secretagogues (SCGN), and neuropeptide-Y (NPY) in 10 patients with glioblastoma and 10 healthy people.The outcomes showed that, whereas other proteins did not substantially change between the two groups (P = 0.06), miR-21 expression was four times higher in the groups receiving treatment compared to the control group, indicating that miR-21 overexpression may be related to glioblastoma. 20 glioblastoma patients and 20 healthy controls had their blood samples analysed by to determine the distribution of miRNAs. 52 miRNAs were selected using a gene chip containing 1158 miRNAs.MiR-128 expression was significantly down-regulated while miR-317 expression was considerably up-regulated in comparison to the control group, after multiple changes and corrections. According to the findings, higher specificity (71%–85%) and sensitivity (75%–83%) for the detection of GBMare associated with miR-128 downregulation and miR-317 overexpression. Using a Keegan microarray, researcher evaluated other aberrant expressions of circulating cfmiRNAs (Miller et al., 2019). In blood samples of glioblastoma patients, 115 miRNAs were increased and 24 decreased (multiple change 2.0). Progressive verification confirmed highly up-regulated expressions of the MiR-137, miR-203, miR-485, and miR-16-5p expression were all significantly downregulated by the miRNAs miR-124, miR-27a, miR-29, miR-210, miR-122, miR-182, and miR-223, but not by the miRNAs miR-27, miR-27b,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

miR-210, miR-122, or miR-223.It might aid in the diagnosis of glioma patients by medical professionals (Truong et al., 2019).

Patients with mixed glioblastoma(10 cases), meningiomas (10 cases), and pituitary adenomas (10 cases), and gliomas (WHO II-IV, 30 cases) were all investigated in a study of patients with glioblastoma two weeks following surgery. In the plasma of glioma patients, miR-21 expression increased while miR-128 and miR-342-3p levels were significantly down-regulated. The specificity of plasma miR-21, miR-128, and miR-342-3p in the diagnosis of glioma is demonstrated by the observation that these three expressions are normal in other brain tumours. MiR-185 expression was measured in the blood ofPatients with 66 gliomas, 11 pituitary adenomas, 32 meningiomas, and 14 acoustic neuromas were included. According to studies, patients with gliomas had higher levels of plasma miR-185 expression, whereas that of other benign patients was lower. In patients with glioblastoma, plasma miR-185 expression levels nearly returned to normal after surgery and chemotherapy, but there were no evident changes in the brain tumours. As a result, it is possible to assume that miR-185 expression is a potential biomarker for the diagnosis of gliomas. correlates with the growth of gliomas (Yeo et al., 2021). According to research, gliomas can be distinguished from other types of brain tumours or disorders using the combination of plasma miR-15b and miR-21, which includes secondary brain metastases (16 cases), various neurological disorders (30 cases), gliomas (30 cases), and PCNSLs (36 cases), which are classified as large B-cell lymphomas of the CNS.According to research, patients with gliomas had significantlyincreased serum miR-15b and miR-21 expression levels (P=0.02). Other tumours did not, however, exhibit the aberrant expression (P=0.09). A glioma diagnosis may have 90% and 100% sensitivity and specificity, respectively, at the same time. It is important to consider whether several circulating miRNAs have a higher diagnostic impact than a single miRNA in CNS malignancies (Gonzalez et al., 2020).

According to some academics, a single plasma miRNA lacks a biomarker with high specificity and sensitivity for detecting low-grade gliomas, but it does have some value in the diagnosis of high-grade gliomas.In a study of 83 patients with different stages of gliomas, the expression of the plasma miR-29 family was shown to be significantly lower than that of healthy controls. This study also demonstrated that the miR-29 family had an AUC = 0.91, which represents a high detection value for high-grade gliomas, although sensitivity and specificity for poor-quality gliomas are lower.As a result, high-grade glioma findings may be contributed to by a high level of miR-29 in the blood, according to the researchers (Hallal et al., 2020). Serum miR-29 expression and significance in 120 glioma patients and 120 healthy individuals were balanced in terms of age and gender. It was discovered that glioma patients' blood miR-29b levels were down regulated while VEGFA expression was upregulated. Additionally, with AUCs of 0.913 and 0.752, the ability of miR-29b and VEGFA in glioma patients to provide diagnostic data was evaluated by the researchers using ROX curves. In addition, a study of 112 glioma patients (including 69 WHO I and II, 43 WHO III and IV, and 54 healthy controls) discovered that there was no difference in the expression of serum miR-182 between healthy patients (P > 0.05) and low-grade gliomas. High-grade glioma patients had significantly higher serum levels of miR-182 expression than did low-grade glioma patients and healthy controls. The findings demonstrate a diagnostic role for serum miR-182 in high-grade gliomas (Olioso et al., 2021).

In another study that investigated serum samples, 30 healthy people participated as controls, while 44 GBM patients were also included by using RT-qPCR, the expression of miR-21, miR-222, and miR-124-3 in serum. A ROC curve was used to demonstrate the sensitivity and specificity of circulating miRNA diagnosis. According to the data, there were no discernible differences in expression levels of miR-21, miR-222, and miR-124-3p in low-grade glioma and healthy groups, but combined detection significantly improved diagnosis accuracy (Ali et al., 2021). Patients with high-grade gliomas had blood concentrations of miR-21, miR-222, and miR-124-3p which were significantly higher than in the general population. The detection of miR-21 (AUC=0.81, P 0.003) and miR-23 combined did not significantly differ from one another. According to previous research, it can be concluded that the concurrent diagnostic value of blood miRNA detection is significantly higher compared to the value of circulating miRNA alone in patients with low-grade glioma (Kitano et al., 2021). Serum miRNA may be used as a biomarker for the rapid detection patients with low-grade gliomas. In individuals with high-grade gliomas, there was no discernible difference between the diagnostic value of a particular blood miRNA and combination detection (Morokoff et al., 2020).

The majority of the serum or plasma samples used in the aforementioned study's liquid biopsy were from individuals with CNS tumours. CSF has been utilised in CNS malignancies more frequently and is suitable for liquid biopsies as a result of our improved understanding of CSF. Tumour-related miRNAs have been discovered in the CSF of patients with CNS malignancies, which has increased the significance of CSF miRNAs in the detection of CNS tumours. Three miRs: miR-21, miR-19, and miR-92a were analysed in the CSF of PCNSL patients, and they discovered that PCNSL can be distinguished with 96.7% specificity and 95.7% sensitivity against CNS malignancy.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

Previous studies have shown that the presence of the glioma may be identified by two genes, miR-15b and miR-21, in the CSF of patients with primary CNS lymphoma and a control group. Malignant gliomas may be differentiated from other illnesses by the miR-200 family, miR-10b, and miR-21, as well as by brain metastases, according to recent literature (Swellam et al., 2021). Scientists also developed a method with an accuracy of about 90% to separate them using an independent variable made up of 7 miRNAs (miR-10b, miR-21, miR-125br-141, miR-200a, miR-200b, and miR-200c).Malignant glioma, brain metastasis from a solid tumour, and regular, non-tumour control. During the comparison to serum miRNA, tumour cell-related miRNA may be fully contacted in CSF and is present with excellent specificity, reproducibility, and stability. Several studies have been conducted on the clinical efficacy of cfmiRNAs as CNS malignancy diagnostic markerswith the majority of the tests being done on blood plasma, serum, or CSF.These studies observed that the expression patterns of cfmiRNAs correlated with tumours in CSF and blood, and they were connected based on their cfmiRNA signatures to the development of CNS tumours, the course of the disease, and metastasis. The relevant publications on circulating miRNA to learn more about the diagnostic value of different circulating miRNA types in CNS malignancies.Although the examination may not be exhaustive, we offer significant clinical insights into the diagnosis of CNS tumours based on the author's research perspective (Garcia-Romero et al., 2019).

Prognosis

In patients with CNS tumours, circulating miRNA has a significant diagnostic value. In addition, it demonstrates some benefits in predicting prognosis and the progression of tumours. In the study's first stages, 50 controls and 136 patients with different grades of glioma were compared for their plasma miR-210 expression levels. Scientist discovered that MiR-210 expression has been demonstrated to be higher in glioma patients and it correlated with tumour grade and prognosis . MiR-20a expression levels in the blood of 70 glioma patients and 70 healthy controls were examined, and it was discovered that the glioma patients' expression levels were significantly higher than the expression levels in the healthy controls when compared to before surgery, expression of miR-20a in plasma was significantly down-regulated. As a result, it was found that the patients' lower life times were associated with the rise in blood miR-20a expression. Later investigations further supported the association between aberrant plasma miRNA expression and overall survival in glioma patients. Using RT-PCR to compare the serum miR-137 expression levels in the two groups simultaneously, it was shown that the miR-137 expression in the GBM group's serum was significantly decreased compared to that of the 64 healthy human beings and 64 GBM patients of various grades. High-grade GBM patients had significantly lower serum levels of miR-137 than patients with low-grade gliomas (P = 0.003), and low miR-137 expression in the blood was correlated with a poor clinical prognosis (Ding et al., 2021).

The detection of circulating miRNA combinations has been demonstrated to be an objective and important measure for examining prognosis in CNS patients malignancies. Additionally, researchers discovered that patients with astrocytomas had blood levels of nine different miRNAs that were significantly higher than those of the control group, including miR-15b, miR-21, miR-19a, miR-19b, miR-182, miR-520h, miR-20a, miR-106a, and miR-182. These nine miRNAs were also clearly higher in the blood of patients after surgery to remove the tumour (Bagley et al., 2020). In a subsequent categorization according to their data, increased levels of miR-20a, miR-106a, and miR-181b are linked to the advanced clinical stage of astrocytoma. The high expression of miR-19a, miR-106a, and miR-181b was found to be significantly correlated with patient survival according to Kaplan-Meier analysis. The findings and other recent research show more evidence that the decreased survival rate in glioma patients is correlated with high levels of miR-20a and miR-106a expression. The prognosis of glioblastoma has also been correlated with a combination of increased miR-222 and miR-17 expression in the blood and decreased miR-145 expression (Piccioni et al., 2019).

Numerous studies have demonstrated that specific circulating cfmiRNAs that are overexpressed or underexpressed have a strong correlation with patients with CNS cancers who may benefit from shorter overall survival (OS) and/or progression-free survival (PFS) for predicting prognosis.MiR-21, miR-15b, miR-221, miR-182, miR-20a, miR-106a, miR-222, miR-223, and miR-520h were found to be overexpressed in the circulation, whereas miR-137, miR-203, miR-485, miR-205, miR-122, and miR-16 were found to be under expressed and were both positively linked to shorter OS (Mazard et al., 2021).

Response of treatment

Clinicians have always been primarily concerned with evaluating the impact of treatment on patients with CNS tumours. As a result, research has turned its attention to identifying a biomarker that may correctly indicate efficacy (Fig 1). For instance, chemotherapy resistance may be a significant factor influencing a patient's prognosis when treating glioblastoma. The level of circulating miRNA expression can be utilised for predicting treatment response, as additional research has demonstrated. After diagnosis, the

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

optimum treatment plan can be directly updated to avoid the development of chemotherapy and radiation resistance. miRNA expression suppression or inhibition, which can prevent metastasis, invasion, and growth of tumours, is the basis for the rationale behind employing circulating cfmiRNA as a therapeutic target. A synthetic miRNA that successfully repressed a variety of target genes in phase I and phase II clinical trials using the herpes simplex virus (HSV) as a carrier may open the door to a new therapeutic approach for the treatment of gliomas. Phase I clinical trials have also looked into similar questions about the improvement of tumour selectivity in GBM by miRNA using the MV virus as a carrier (Lourenco et al., 2021).

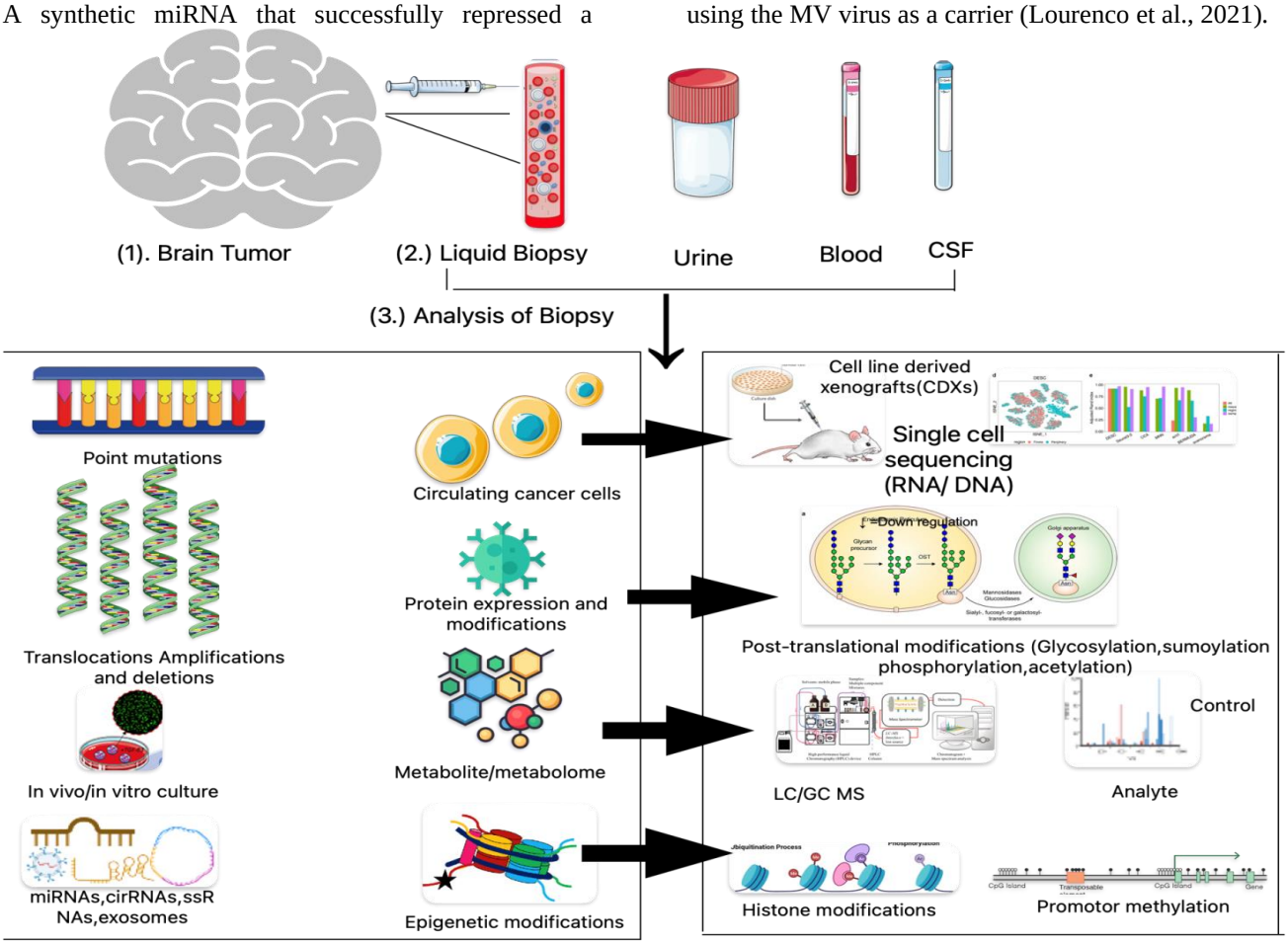

Fig 1. application of Liquid biopsy technique used for diagnosing brain tumours.

Glioma development, differentiation, apoptosis, invasion, metastasis, and resistance to therapyare all governed by signal pathways that are regulated by miR-21. There have been numerous studies done utilising a lot of statistics on the circulating cfmiRNA can be detected in one or more fluids while treating gliomas. Inhibiting miR-21 expression in glioma cells can reduce tumour invasiveness, cause apoptosis, increase glioma cell sensitivity to paclitaxel, and possibly slow the progression of GBM via inhibiting the EGFR/STAT-3 signal pathway. Additionally, 5-FU and miR-21 inhibitors may stimulate glioma cell death and decrease the spread of glioma cells.In U87-MG cells, the expression of circulating cfmiR-21 was decreased after temozolomide (TMZ) treatment (Garcia et al., 2020). In a follow-up study, it was discovered that while first-line medication caused the plasma miR-21 levels of 9 patients to drastically drop, they actually rose in the last patient. Following that, this patient had a tumour recurrence. According to the results, miR-21 could be employed as a diagnostic biomarker inglioblastoma patients and may be useful in determining the patient's prognosis (Jones et al., 2021). The identification of chromatin-modifying compounds like 5-aza-20-deoxycytidine and 4-phenyl-butyric acid in glioma cells provides additional evidence that miRNAs may be able to inhibit tumour growth. In studies, MiR-153 has been discovered to decrease the expression of Akt Ser473, Bcl-2, and Its-2, and its expression has been found to be lower in glioma patients compared to the healthy group of controls. Consequently, raising it could be detrimental. Glioma treatment is efficient. Experiments demonstrate the simultaneous control of 5-aza-20-deoxynucleoside

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

and 4-phenyl butyric acid can cause apoptosis, which peaks at 72 hours, in GBM cell lines. MiR-153 may function through hs-2 as part of the proposed mechanism of action for these drugs.In specific, Expression levels of miR-128, miR-125b, miR-16, miR-181d, miR-497, and miR-29b were decreased. increased expression of miR-21, miR-106a, miR-27a, miR-210, and miR-200a. Meanwhile, the expression of six miRNAs was down-regulated (Pan et al., 2019).

According to TMZ, surgical excision is currently the gold standard for the treatment of glioblastoma. Unfortunately, a few patients are resistant to TMZ therapy because these patients developed chemotherapy resistance because in patients with functional levels of the protein, Guanine methylation triggered by TMZ was corrected by the MGMT DNA repair protein. A biomarker known as the measurement of serum miR-181d may asses the efficacy of the treatment after taking TMZ as MGMT is one potential miR-181d target. The high sensitivity of glioma patients to TMZ is strongly correlated with the high blood levels of miR-181d and the decreased MGMT levels. Following primary therapy, the tumour microenvironment will change in a manner that promotes the progression of chemotherapy resistance in people with particular genetic predispositions. Patients with CNS cancers can be diagnosed using circulating miRNA, it appears that a solution has been discovered since circulating miRNA actively reflects the response of tumour cells to therapy and demonstrates the genetic information present in primary tumours (Sareen et al., 2020). There is still a lack of circulating miRNA that are more accurate and dependable, necessitating additional research.

Circulating exosomal miRNAs

Exosomes include miRNA, which is secreted into physiological fluids to regulate the biological behavior of tumours, and previous research has shown that malignant tumour cells will enhance their production of exosomes (Table 1). According to studies, the exosomes secreted by nervous system tumour cells share many components with tumour tissues. As with chemotherapeutic drug resistance, the contents produced may have an impact on the host's immune system, boosting tumour invasion and proliferation. As a result, potential biomarker is the miRNA expression profile of exosomes with the ability to provide information regarding cancer grading and prognosis, enabling the development of more effective cancer-specific therapeutics.

Exosomes that had been collected from the plasma of patients suffering glioblastoma were shown to have exosomes with overexpressed levels of one short nuclear RNA (rnu6-1) and two miRNAs (miR-320 and miR-5743-3p).Upon further investigation, As a biological marker for the diagnosis of glioblastoma, rnu6 has been identified by researchers as a combination of miR-320, miR-574-3p, and rnu6-1.The research presented here shows that exosomal miRNA can be used as a biomarker for glioma identification (Simonelli et al., 2020). In patients with glioma, in the vesicles outside of the CSF, the gene IDH1 RNA mutation (G595A) was only detected in EVs derived from blood, according to the use of emulsion, amplification, magnetic beads, digital PCR, and BEAMing PCR (emulsion, amplification, magnetics, and beads). Using a TaqMan open-array human miRNA gene chip, three miRNAs were simultaneously found in exosomes. According to the research, mir-218, mir-193b, and miR-21 had a positive correlation with tumour size and significantly greater expression levels than in the group of healthy controls (Tang et al., 2020).

Recent research attempts have recorded the elevation in the concentrations of human glioblastoma cell-derived GBM-EVs of miR-21 and miR-451.Glioma cell growth and migration are significantly influenced by the miR-451 gene. Glioma cell proliferation and migration are significantly influenced by miR-451. If a miRNA is tumour-specific or not, it can be determined by its selective output. Typically, non-tumour exosomes do not include miR-451, which originates from tumour cells. It has been demonstrated that miR-451 suppresses the action of the adenosine monophosphate-activated protein kinase (AMPK) signalling pathway, and frequently requires to be treated to carry out metabolic requirements. As a result, GBM-produced exosomes contain miR-451may indicate the growth of the tumourin a dynamic manner and may be used as a biomarker for the detection and prognosis of tumour progression. Numerous studies have shown that in the body fluids of patients with glioma, miR-21 is overexpressed, whereas circulating exosomal in comparison with healthy controls, miR-21 expression is 10 times higher and it is additionally higher in brain tissue than it is in blood or CSF.miR-21 cannot be expressed in exosomes as a particular marker for gliomas because it is sensitive to most malignancies as well. MiR-10b has been detected cancers of the normal brain tissue does not contain the central nervous system. Circulating exosomal miR-10b was discovered to be positively connected with tumour malignancy when various circulating miRNAs were examined in the CSF of glioma patients. As a result, miR-10b is a crucial cancer marker for estimating prognosis (Strauss et al., 2019).

One of the most effective chemotherapy drugs for gliomas is temozolomide. Treatment failure is mostly caused by resistance to chemotherapy. Exosomes have developed into a method for regulating resistance to chemotherapy in glioma cells as a result of recent

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

studies showing that they can influence signalling pathways through the mediation of miRNAs and other substances. In vitro cell models were developed by researchers. Following a 48-hour TMZ treatment, the apoptotic rate of various cell model groups was measured by flow cytometry (Soleman et al., 2020). Exosomes in glioma cells may be a factor in the mechanism that makes TMZ more resistant to chemotherapeutic effects, as shown by the finding that the group utilizing models of cells co-incubated with exosomes had the lowest apoptotic capacity. Similar findings were made, which showed that miR-1238 was more abundant in tumour patients' circulating exosomes than in healthy adults' plasma and tissue samples from people with glioblastoma. According to the research outcomes, the exosome created by receptor cells, miR-1238, might trigger TMZ-sensitive cells to generate more of the miRNA, which can then trigger cavein (cav1) to express at a significantly decreased levels of receptor cells. The egfr-pi3k-akt-mTOR pathway was activated cavein (cav1), which ultimately resulted in the development of drug resistance in TMZ-sensitive cells.Similar investigations have been conducted with radiation. The expression of TCEAL7 in recipient cells was discovered to be selectively decreased by the exosome miR-301a generated by glioblastoma in hypoxic tumour microenvironments. TCEAL7 can also prevent -catenin from being transported from the cytoplasm to the nucleus, which has a negative impact on the Wnt/-catenin signalling pathway andhelps glioblastoma cells develop radiation resistance (Kozyrev et al., 2021).

In overall, current research has suggested that the molecular mechanism behind glioma resistance to chemotherapy and radiation therapy may involve exosome-derived miRNAs. In the future, Researchers may discover important exosome miRNAs or their associated pathways that control the process of chemoradiotherapy in glioma cells, mainly due to the quick development of gene chips and high-throughput DNA sequencing technology. This could be done by ratiometrically using appropriate inhibitors or blocking a crucial molecular pathway. Radiation sensitivity of glioma cells then increased as a result of chemotherapy and radiotherapy (Soleman 2021). For the purpose of offering fresh perspectives on the diagnosis, prognosis, and treatment effectiveness of CNS tumours, Exosomal miRNA and CNS malignancies have been correlated in the research that we compiled and synthesized.

Table 1. Application of circulating miRNA in CNS tumors

miRNA	**Site of collection**	**Expression (↑ =up-regulation) (↓ =Down regulation)**	**Prognosis**	**Diagnosis**
miR-21	CSF/Plasma	↑ =up-regulation	✓	✓
miR-15a/b	CSF/Plasma	↑ =up-regulation	✓	✓
miR-221	Plasma	↑ =up-regulation	✓	✓
miR-182	Plasma	↑ =up-regulation	✓	✕
miR-128	CSF/Plasma	↓ =Down regulation	✕	✓
miR-20a	Plasma	↑ =up-regulation	✓	✓
miR-125b	CSF/Plasma	↓ =Down regulation	✕	✓
miR-106a	CSF/Plasma	↑ =up-regulation	✓	✕
miR-19	CSF	↑ =up-regulation	✕	✓
miR-27a/b	CSF	↑ =up-regulation	✕	✕
miR-92a	CSF	↑ =up-regulation	✕	✓
miR-137	Plasma	↓ =Down regulation	✓	✕
miR-203	Plasma	↓ =Down regulation	✓	✕
miR-485	Plasma	↓ =Down regulation	✓	✓
miR-205	Plasma	↓ =Down regulation	✓	✓
miR-210	Serum	↑ =up-regulation	✓	✕
miR-100	Serum	↓ =Down regulation	✓	✕
miR-222	Plasma	↑ =up-regulation	✓	✓
miR-26a	Plasma	↓ =Down regulation	✓	✕
miR-122	Plasma	↓ =Down regulation	✓	✓
miR-376a/b/c	Plasma	↓ =Down regulation	✓	✓
miR-200a/b/c	CSF	↓ =Down regulation	✕	✓
miR-124	Plasma	↓ =Down regulation	✓	✕

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

miR-29b	Plasma	↓ =Down regulation	✕	✓
miR-223	CSF/Plasma	↑ =up-regulation	✓	✓
miR-185	Serum	↑ =up-regulation	✓	✕
miR-29	Serum	↑ =up-regulation	✓	✓
miR-497	Plasma	↓ =Down regulation	✕	✓
miR-181d	Plasma	↓ =Down regulation	✕	✕
miR-16	CSF/Plasma	↓ =Down regulation	✓	✕
miR-520h	Plasma	↑ =up-regulation	✓	✓
miR-21	CSF/Plasma	↑ =up-regulation	✓	✓

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

Future perspectives

Multiple studies have demonstrated that plasma and CSF liquid biopsies from Brain malignancies may replace tissue biopsies for the purposes of cancer diagnosis and prognostic biomarker analysis. The identification of biomarkers associated with tumour development is crucial to the trend towards individualized treatment of CNS tumours, given the relative difficulty and high danger of conventional biopsy. Liquid biopsy offers a more effective and secure way of collecting genomic information about tumours, enabling low-invasive and dynamic disease detection, modifying treatment plans, and developing drugs that are specifically targeted. Although these studies were small in scope, there is currently no sufficient statistical evidence to support a relationship between tumour biomarker detection and disease-related variables. The requirement to use cutting-edge technology, such as digital PCR, next-generation sequencing, and others, comes with significant technical costs and high requirements for testing personnel, which further restricts the practical applicability of liquid biopsy (Li et al., 2021). Efficiency and dependability must therefore be confirmed by a large number of studies, and we must constantly develop simpler and more precise approaches for biomarker monitoring and efficacy evaluation.

The traditional concept of carcinogenesis and development will be altered and supplemented by circulating miRNA and exosomes, and these will greatly advance our understanding of the molecular processes involved in tumour growth. MiRNA, which is widely distributed and controls how genes are expressed and how proteins are translated, is essential for the emergence and growth of CNS tumours. Exosomes are an innovative form of miRNA-rich intercellular communication. According to multiple studies, exosomal miRNA is specifically sealed, released, and packaged and influences CNS cancer progression, invasion, angiogenesis, immune evasion, and therapeutic resistance (Saenz-Antonanzas et al., 2019). In the cancer microenvironment, exosomal miRNA also takes part in intercellular communication. The ability of circulating miRNA and exosomes to penetrate biological barriers (like the blood-brain barrier) and to exist in numerous body fluids from various sources. In the diagnosis and treatment of CNS malignancies, there is significant potential.

Exosomes and circulating miRNA have both been demonstrated to be potential indicators in CNS tumours by an increasing number of studies, However, there is ongoing debate regarding its use in clinical practise. The majority of the cfmiRNA in blood is really produced bya few high-flow tissues (liver, kidney, or lung), endothelial cells, red blood cells, and white blood cells. Consequently, the separate and accurate identification of miRNA and exosomes from tumour-derived cells require advanced technology and strict staffing requirements, Their broad clinical application has come under investigation and limitations (Gajjar et al., 2021).

Investigating exosomes and circulating miRNA in the bodily fluids of individuals with CNS malignancies is an essential component of research for biomarkers of cancer.With a focus on analysing and discussing the values of various circulating miRNAs and exosomal miRNAs in patients with CNS tumours, we primarily summarised the relevant publications in this area (Wang et al., 2022). We believe that the primary elements of liquid biopsy analysis—circulating miRNAs and exosomes—may help in the creation and implementation of personalised treatment plans for people with CNS tumours. Our understanding of the process of creation, biological operation, and connection has improved between circulating miRNA and exosomes, thanks to the standardisation of the detecting techniques for these molecules. Exosomes and Circulating miRNA are predicted to be widely utilised in future studies on the prognosis, diagnosis, and therapeutic response of patients with CNS malignancies.

Conclusion

The results of clinical trials on the various liquid biopsy techniques that will offer patients with primary brain tumours the best value are anticipated to be presented during the ensuing years. Personalised genetic profiling of a tumour from an initial tissue biopsy is expected to reveal a number of potential markers that can be used in a liquid biopsy to later assess the treatment's effectiveness. Such genetic markers exhibit close to 100% specificity already. Integrating liquid biopsy into clinical practise will be difficult since it will be difficult to evaluate trustworthy standards and raise the sensitivity, which is now low and varied and frequently only ranges from 10 to 60%. To improve the reduced sensitivity, sample numbers, technological advancements, and artificial intelligence applications must be optimised. Blood samples seem to be superior to CSF samples most of the time, although with advancements in technology, both methods may be useful. Although primary brain tumours are uncommon and there are few effective treatments, urine samples may offer a potential for diagnostic screening of brain tumours with panels of miRNA. However, diagnostic screenings may not be available within the next 10 years due to these factors. The authors are hopeful that liquid biopsy will enhance the tracking of disease and therapy response in people with brain tumours.

Funding information: No funding has been received in this project.

Contribution

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

Original writing: Manish Tegnuria, Dr. Vishal Rajput
Supervision and conceptualization: Dr. Vishal Rajput, Dr. Meenu Gupta, Dr. Sanjay Gupta
Editing: Neha Shrama, Manish Tenguria

Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: The conducted research is not related to either human or animal use.

Data availability statement: The datasets generated during the current study are available from the corresponding author on reasonable request.

References

1. Ahle G, Rimelen V, Pencreach E, Zinniger N, Debliquis A, Zalmaï L, *et al.* Tumor cell-free DNA detection in CSF for primary CNS lymphoma diagnosis. Acta Neuropathol Commun 2019;7:43.
2. Ali, H.; Harting, R.; de Vries, R.; Ali, M.; Wurdinger, T.; Best, M.G. Blood-Based Biomarkers for Glioma in the Context of Gliomagenesis: A Systematic Review. *Front. Oncol.* **2021**, *11*, 2134.
3. Azad, T.D.; Jin, M.C.; Bernhardt, L.J.; Bettegowda, C. Liquid Biopsy for Pediatric Diffuse Midline Glioma: A Review of Circulating Tumor DNA and Cerebrospinal Fluid Tumor DNA. *Neurosurg. Focus* **2020**, *48*, E9.
4. Bagley, S.J.; Nabavizadeh, S.A.; Mays, J.J.; Till, J.E.; Ware, J.B.; Levy, S.; Sarchiapone, W.; Hussain, J.; Prior, T.; Guiry, S.; et al. Clinical Utility of Plasma Cell-Free DNA in Adult Patients with Newly Diagnosed Glioblastoma: A Pilot Prospective Study. *Clin. Cancer Res.* **2020**, *26*, 397–407.
5. Bang-Christensen SR, Pedersen RS, Pereira MA, Clausen TM, Løppke C, Sand NT, Ahrens TD, Jørgensen AM, Lim YC, Goksøyr L, Chou- dhary S, Gustavsson T, Dagil R, Daugaard M, Sander AF, Torp MH, Søgaard M, Theander TG, Østrup O, Lassen U and Agerbæk M. Capture and detection of circulating glioma cells using the recombinant VAR2CSA malaria protein. Cells 2019; 8: 998.
6. Bobillo S, Crespo M, Escudero L, Mayor R, Raheja P, Carpio C, *et al.* Cell free circulating tumor DNA in cerebrospinal fluid detects and monitors central nervous system involvement of B-cell lymphomas. Haematologica 2021;106:513-21.
7. Bounajem, M.T.; Karsy, M.; Jensen, R.L. Liquid Biopsies for the Diagnosis and Surveillance of Primary Pediatric Central Nervous System Tumors: A Review for Practicing Neurosurgeons. *Neurosurg. Focus* **2020**, *48*, E8.
8. Cantor, E.; Wierzbicki, K.; Tarapore, R.S.; Ravi, K.; Thomas, C.; Cartaxo, R.; Nand Yadav, V.; Ravindran, R.; Bruzek, A.K.; Wadden, J.; et al. Serial H3K27M Cell-Free Tumor DNA (Cf-TDNA) Tracking Predicts ONC201 Treatment Response and Progression in Diffuse Midline Glioma. *Neuro-Oncol.* **2022**, noac030.
9. Carta, R.; Del Baldo, G.; Miele, E.; Po, A.; Besharat, Z.M.; Nazio, F.; Colafati, G.S.; Piccirilli, E.; Agolini, E.; Rinelli, M.; et al. Cancer Predisposition Syndromes and Medulloblastoma in the Molecular Era. *Front. Oncol.* **2020**, *10*, 566822.
10. Ding, Y.; Lu, C.; Zhang, W.; Wang, Y.; Li, Y.; Zhu, Y.; Lv, S.; Zhang, J. The Emerging Role of Circular RNAs in Cardiovascular Diseases. *J. Physiol. Biochem.* **2021**, *77*, 343–353.
11. Duan H, Hu JL, Chen ZH, Li JH, He ZQ, Wang ZN, Zhang GH, Guo XY, Liang L and Mou YG. Assessment of circulating tumor DNA in cere-brospinal fluid by whole exome sequencing to detect genomic alterations of glioblastoma. Chin Med J (Engl) 2020; 133: 1415-1421.
12. Escudero L, Llort A, Arias A, Diaz-Navarro A, Martínez-Ricarte F, Rubio-Perez C, *et al.* Circulating tumour DNA from the cerebrospinal fluid allows the characterisation and monitoring of medulloblastoma. Nat Commun 2020;11:5376
13. Fontanilles M, Marguet F, Beaussire L, Magne N, Pépin LF, Alexandru C, *et al.* Cell-free DNA and circulating TERT promoter mutation for disease monitoring in newly-diagnosed glioblastoma. Acta Neuropathol Commun 2020;8:179
14. Gajjar, A.; Robinson, G.W.; Smith, K.S.; Lin, T.; Merchant, T.E.; Chintagumpala, M.; Mahajan, A.; Su, J.; Bouffet, E.; Bartels, U.; et al. Outcomes by Clinical and Molecular Features in Children with Medulloblastoma Treated with Risk-Adapted Therapy: Results of an International Phase III Trial (SJMB03). *JCO* **2021**, *39*, 822–835.
15. Garcia CM and Toms SA. The role of circulating microRNA in glioblastoma liquid biopsy. World Neurosurg 2020; 138: 425-435.
16. Garcia, C.M.; Toms, S.A. The Role of Circulating MicroRNA in Glioblastoma Liquid Biopsy. *World Neurosurg.* **2020**, *138*, 425–435.
17. García-Romero, N.; Carrión-Navarro, J.; Areal-Hidalgo, P.; Ortiz de Mendivil, A.; Asensi-Puig, A.; Madurga, R.; Núñez-Torres, R.; González-Neira, A.; Belda-Iniesta, C.; González-Rumayor, V.; et al. BRAF V600E Detection in Liquid Biopsies from Pediatric Central Nervous System Tumors. *Cancers* **2019**, *12*, 66.
18. Gonzalez-Beltran, A.N.; Masuzzo, P.; Ampe, C.; Bakker, G.-J.; Besson, S.; Eibl, R.H.; Friedl, P.; Gunzer, M.; Kittisopikul, M.; Dévédec, S.E.L.; et al. Community Standards for Open Cell Migration Data. *GigaScience* **2020**, *9*, giaa041.
19. Grommes C, Tang SS, Wolfe J, Kaley TJ, Daras M, Pentsova EI, *et al.* Phase 1b trial of an

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

ibrutinib-based combination therapy in recurrent/ refractory CNS lymphoma. Blood 2019;133:436-45.

20. Hallal, S.; Ebrahim Khani, S.; Wei, H.; Lee, M.Y.T.; Sim, H.-W.; Sy, J.; Shivalingam, B.; Buckland, M.E.; Alexander-Kaufman, K.L. Deep Sequencing of Small RNAs from Neurosurgical Extracellular Vesicles Substantiates MiR-486-3p as a Circulating Biomarker That Distinguishes Glioblastoma from Lower-Grade Astrocytoma Patients. *Int. J. Mol. Sci.* **2020**, *21*, 4954.
21. Heitzer, E.; Haque, I.S.; Roberts, C.E.S.; Speicher, M.R. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat. Rev. Genet.* **2019**, *20*, 71–88.
22. Hickmann AK, Frick M, Hadaschik D, Battke F, Bittl M, Ganslandt O, *et al.* Molecular tumor analysis and liquid biopsy: A feasibility investigation analyzing circulating tumor DNA in patients with central nervous system lymphomas. BMC Cancer 2019;19:192.
23. Hiemcke-Jiwa LS, Leguit RJ, Snijders TJ, Bromberg JEC, Nierkens S, Jiwa NM, *et al.* MYD88 p.(L265P) detection on cell-free DNA in liquid biopsies of patients with primary central nervous system lymphoma. Br J Haematol 2019;185:974-7.
24. Hovestadt V, Ayrault O, Swartling FJ, Robinson GW, Pfister SM, Northcott PA. Medulloblastomics revisited: Biological and clinical insights from thousands of patients. Nat Rev Cancer 2020;20:42-56.
25. Izquierdo, E.; Proszek, P.; Pericoli, G.; Temelso, S.; Clarke, M.; Carvalho, D.M.; Mackay, A.; Marshall, L.V.; Carceller, F.; Hargrave, D.; et al. Droplet Digital PCR-Based Detection of Circulating Tumor DNA from Pediatric High Grade and Diffuse Midline Glioma Patients. *Neuro-Oncol. Adv.* **2021**, *3*, vdab013.
26. Jones, J.; Nguyen, H.; Drummond, K.; Morokoff, A. Circulating Biomarkers for Glioma: A Review. *Neurosurgery* **2021**, *88*, E221–E230.
27. Kitano, Y.; Aoki, K.; Ohka, F.; Yamazaki, S.; Motomura, K.; Tanahashi, K.; Hirano, M.; Naganawa, T.; Iida, M.; Shiraki, Y.; et al. Urinary MicroRNA-Based Diagnostic Model for Central Nervous System Tumors Using Nanowire Scaffolds. *ACS Appl. Mater. Interfaces* **2021**, *13*, 17316–17329.
28. Kozyrev, D.A.; Soleman, J.; Tsering, D.; Keating, R.F.; Hersh, D.S.; Boop, F.A.; Spennato, P.; Cinalli, G.; Tamburrini, G.; Thomale, U.-W.; et al. Pediatric Thalamic Incidentalomas: An International Retrospective Multicenter Study. *J. Neurosurg. Pediatrics* **2021**, *29*, 1–9.
29. Kristensen BW, Priesterbach-Ackley LP, Petersen JK, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol 2019;30:1265-78.
30. Lan F, Yue X and Xia T. Exosomal microRNA-210 is a potentially non-invasive biomarker for the diagnosis and prognosis of glioma. Oncol Lett 2020; 19: 1967-1974.
31. Li D, Bonner ER, Wierzbicki K, Panditharatna E, Huang T, Lulla R, *et al.* Standardization of the liquid biopsy for pediatric diffuse midline glioma using ddPCR. Sci Rep 2021;11:5098.
32. Li, D.; Bonner, E.R.; Wierzbicki, K.; Panditharatna, E.; Huang, T.; Lulla, R.; Mueller, S.; Koschmann, C.; Nazarian, J.; Saratsis, A.M. Standardization of the Liquid Biopsy for Pediatric Diffuse Midline Glioma Using DdPCR. *Sci. Rep.* **2021**, *11*, 5098.
33. Li, D.; Romanski, K.; Kilgallon, M.; Speck, S.; Bowman, R.; DiPatri, A.; Alden, T.; Tomita, T.; Lam, S.; Saratsis, A.M. Safety of Ventricular Reservoir Sampling in Pediatric Posthemorrhagic Hydrocephalus Patients: Institutional Experience and Review of the Literature. *J. Neurosci. Nurs.* **2021**, *53*, 11–17.
34. Li, J.; Zhao, S.; Lee, M.; Yin, Y.; Li, J.; Zhou, Y.; Ballester, L.Y.; Esquenazi, Y.; Dashwood, R.H.; Davies, P.J.A.; et al. Reliable Tumor Detection by Whole-Genome Methylation Sequencing of Cell-Free DNA in Cerebrospinal Fluid of Pediatric Medulloblastoma. *Sci. Adv.* **2020**, *6*, eabb5427.
35. Liu, A.P.Y.; Smith, K.S.; Kumar, R.; Paul, L.; Bihannic, L.; Lin, T.; Maass, K.K.; Pajtler, K.W.; Chintagumpala, M.; Su, J.M.; et al. Serial Assessment of Measurable Residual Disease in Medulloblastoma Liquid Biopsies. *Cancer Cell* **2021**, *39*, 1519–1530.e4.
36. Liu, B.L.; Cheng, J.X.; Zhang, W.; Zhang, X.; Wang, R.; Lin, H.; Huo, J.L.; Cheng, H. Quantitative detection of multiple gene promoter hypermethylation in tumor tissue, serum, and cerebrospinal fluid predicts prognosis of malignant gliomas. *Neuro Oncol.* **2010**, *12*, 540–548. *Cancers* **2019**, *11*, 950 19 of 20
37. Louis, D.N.; Perry, A.; Wesseling, P.; Brat, D.J.; Cree, I.A.; Figarella-Branger, D.; Hawkins, C.; Ng, H.K.; Pfister, S.M.; Reifenberger, G.; et al. The 2021 WHO Classification of Tumors of the Central Nervous System: A Summary. *Neuro-Oncol.* **2021**, *23*, 1231–1251.
38. Lourenço, C.; Constâncio, V.; Henrique, R.; Carvalho, Â.; Jerónimo, C. Urinary Extracellular Vesicles as Potential Biomarkers for Urologic Cancers: An Overview of Current Methods and Advances. *Cancers* **2021**, *13*, 1529.
39. Lucero R, Zappulli V, Sammarco A, Murillo OD, Cheah PS, Srinivasan S, Tai E, Ting DT, Wei Z, Roth ME, Laurent LC, Krichevsky AM, Breakefield XO and Milosavljevic A. Glioma-derived miRNA-containing extracellular vesicles induce

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

angiogenesis by reprogramming brain endo- thelial cells. Cell Rep 2020; 30: 2065-2074, e4.

40. Mair, R.; Mouliere, F.; Smith, C.G.; Chandrananda, D.; Gale, D.; Marass, F.; Tsui, D.W.Y.; Massie, C.E.; Wright, A.J.; Watts, C.; et al. Measurement of Plasma Cell-Free Mitochondrial Tumor DNA Improves Detection of Glioblastoma in Patient-Derived Orthotopic Xenograft Models. *Cancer Res.* **2019**, *79*, 220–230.
41. Manjunath N, Jha P, Singh J, Raheja A, Kaur K, Suri A, *et al*. Clinico-pathological and molecular characterization of diffuse midline gliomas: Is there a prognostic significance? Neurol Sci 2021;42:925-34.
42. Mazard, T.; Cayrefourcq, L.; Perriard, F.; Senellart, H.; Linot, B.; de la Fouchardière, C.; Terrebonne, E.; François, E.; Obled, S.; Guimbaud, R.; et al. Clinical Relevance of Viable Circulating Tumor Cells in Patients with Metastatic Colorectal Cancer: The COLOSPOT Prospective Study. *Cancers* **2021**, *13*, 2966.
43. Miklja, Z.; Pasternak, A.; Stallard, S.; Nicolaides, T.; Kline-Nunnally, C.; Cole, B.; Beroukhim, R.; Bandopadhayay, P.; Chi, S.; Ramkissoon, S.H.; et al. Molecular Profiling and Targeted Therapy in Pediatric Gliomas: Review and Consensus Recommendations. *Neuro-Oncol.* **2019**, *21*, 968–980.
44. Miller AM, Shah RH, Pentsova EI, Pourmaleki M, Briggs S, Distefano N, *et al.* Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid. Nature 2019;565:654, 65.
45. Miller, A.M.; Shah, R.H.; Pentsova, E.I.; Pourmaleki, M.; Briggs, S.; Distefano, N.; Zheng, Y.; Skakodub, A.; Mehta, S.A.; Campos, C.; et al. Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid. *Nature* **2019**, *565*, 654–658.
46. Morokoff, A.; Jones, J.; Nguyen, H.; Ma, C.; Lasocki, A.; Gaillard, F.; Bennett, I.; Luwor, R.; Stylli, S.; Paradiso, L.; et al. Serum MicroRNA Is a Biomarker for Post-Operative Monitoring in Glioma. *J. Neurooncol.* **2020**, *149*, 391–400.
47. Muralidharan K, Yekula A, Small JL, Rosh ZS, Kang KM, Wang L, *et al*. TERT promoter mutation analysis for blood based diagnosis and monitoring of gliomas. Clin Cancer Res 2021;27:169,78.
48. Olioso, D.; Caccese, M.; Santangelo, A.; Lippi, G.; Zagonel, V.; Cabrini, G.; Lombardi, G.; Dechecchi, M.C. Serum Exosomal MicroRNA-21, 222 and 124-3p as Noninvasive Predictive Biomarkers in Newly Diagnosed High-Grade Gliomas: A Prospective Study. *Cancers* **2021**, *13*, 3006.
49. Osti D, Del Bene M, Rappa G, Santos M, Matafora V, Richichi C, Faletti S, Beznoussenko GV, Mironov A, Bachi A, Fornasari L, Bongetta D, Gaetani P, DiMeco F, Lorico A and Pelicci G. Clinical significance of extracellular vesicles in plasma from glioblastoma patients. Clin Cancer Res 2019; 25: 266-276.
50. Osti, D.; Del Bene, M.; Rappa, G.; Santos, M.; Matafora, V.; Richichi, C.; Faletti, S.; Beznoussenko, G.V.; Mironov, A.; Bachi, A.; et al. Clinical Significance of Extracellular Vesicles in Plasma from Glioblastoma Patients. *Clin. Cancer Res.* **2019**, *25*, 266–276.
51. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, n71.
52. Pagès, M.; Rotem, D.; Gydush, G.; Reed, S.; Rhoades, J.; Ha, G.; Lo, C.; Fleharty, M.; Duran, M.; Jones, R.; et al. Liquid Biopsy Detection of Genomic Alterations in Pediatric Brain Tumors from Cell-Free DNA in Peripheral Blood, CSF, and Urine. *Neuro-Oncol.* **2022**, noab299.
53. Pan, Y.; Long, W.; Liu, Q. Current Advances and Future Perspectives of Cerebrospinal Fluid Biopsy in Midline Brain Malignancies. *Curr. Treat. Options Oncol.* **2019**, *20*, 88.
54. ParvizHamidi M, Haddad G, Ostadrahimi S, Ostadrahimi N, Sadeghi S, Fayaz S and Fard-Esfahani P. Circulating miR-26a and miR-21 as biomarkers for glioblastoma multiform. Biotechnol Appl Biochem 2019; 66: 261-265.
55. Piccioni, D.E.; Achrol, A.S.; Kiedrowski, L.A.; Banks, K.C.; Boucher, N.; Barkhoudarian, G.; Kelly, D.F.; Juarez, T.; Lanman, R.B.; Raymond, V.M.; et al. Analysis of cell-free circulating tumor DNA in 419 patients with glioblastoma and other primary brain tumors. *CNS Oncol.* **2019**.
56. Piccioni, D.E.; Achrol, A.S.; Kiedrowski, L.A.; Banks, K.C.; Boucher, N.; Barkhoudarian, G.; Kelly, D.F.; Juarez, T.; Lanman, R.B.; Raymond, V.M.; et al. Analysis of Cell-Free Circulating Tumor DNA in 419 Patients with Glioblastoma and Other Primary Brain Tumors. *CNS Oncol.* **2019**, *8*, CNS34.
57. Saenz-Antoñanzas, A.; Auzmendi-Iriarte, J.; Carrasco-Garcia, E.; Moreno-Cugnon, L.; Ruiz, I.; Villanua, J.; Egaña, L.; Otaegui, D.; Samprón, N.; Matheu, A. Liquid Biopsy in Glioblastoma: Opportunities, Applications and Challenges. *Cancers* **2019**, *11*, 950.
58. Sareen, H.; Garrett, C.; Lynch, D.; Powter, B.; Brungs, D.; Cooper, A.; Po, J.; Koh, E.-S.; Vessey, J.Y.; McKechnie, S.; et al. The Role of Liquid Biopsies in Detecting Molecular Tumor Biomarkers in Brain Cancer Patients. *Cancers* **2020**, *12*, 1831.
59. ShaoN,XueL,WangR,LuoK,ZhiFandLanQ. miR-454-3p is an exosomal biomarker and functions as a

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 2574-2588 | ISSN:2251-6727

tumor suppressor in glioma. Mol Cancer Ther 2019; 18: 459-469.

60. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA A Cancer J. Clin.* **2021**, *71*, 7–33.
61. Simonelli, M.; Dipasquale, A.; Orzan, F.; Lorenzi, E.; Persico, P.; Navarria, P.; Pessina, F.; Nibali, M.C.; Bello, L.; Santoro, A.; et al. Cerebrospinal Fluid Tumor DNA for Liquid Biopsy in Glioma Patients 'Management: Close to the Clinic? *Crit. Rev. Oncol. Hematol.* **2020**, *146*, 102879.
62. Soleman, J. MRI-Based Diagnosis and Treatment of Pediatric Brain Tumors: Is Tissue Sample Always Needed? *Childs Nerv. Syst.* **2021**, *37*, 1449–1459.
63. Soleman, J.; Kozyrev, D.A.; Ben-Sira, L.; Constantini, S.; Roth, J. Management of Incidental Brain Tumors in Children: A Systematic Review. *Childs Nerv. Syst.* **2020**, *36*, 1607–1619.
64. Strauss, S.B.; Meng, A.; Ebani, E.J.; Chiang, G.C. Imaging Glioblastoma Posttreatment: Progression, Pseudoprogression, Pseudore- sponse, Radiation Necrosis. *Radiol. Clin. N. A.* **2019**, *57*, 1199–1216.
65. Sun, Y.; Li, M.; Ren, S.; Liu, Y.; Zhang, J.; Li, S.; Gao, W.; Gong, X.; Liu, J.; Wang, Y.; et al. Exploring Genetic Alterations in Circulating Tumor DNA from Cerebrospinal Fluid of Pediatric Medulloblastoma. *Sci. Rep.* **2021**, *11*, 5638.
66. Swellam, M.; Bakr, N.M.; El Magdoub, H.M.; Hamza, M.S.; Ezz El Arab, L.R. Emerging Role of MiRNAs as Liquid Biopsy Markers for Prediction of Glioblastoma Multiforme Prognosis. *J. Mol. Neurosci.* **2021**, *71*, 836–844.
67. Tang, K.; Gardner, S.; Snuderl, M. The Role of Liquid Biopsies in Pediatric Brain Tumors. *J. Neuropathol. Exp. Neurol.* **2020**, *79*, 934–940.
68. Truong, H.Q.; Lieber, S.; Najera, E.; Alves-Belo, J.T.; Gardner, P.A.; Fernandez-Miranda, J.C. The Medial Wall of the Cavernous Sinus. Part 1: Surgical Anatomy, Ligaments, and Surgical Technique for Its Mobilization and/or Resection. *J. Neurosurg.* **2019**, *131*, 122–130.
69. Van Schaijik, B.; Wickremesekera, A.C.; Mantamadiotis, T.; Kaye, A.H.; Tan, S.T.; Stylli, S.S.; Itinteang, T. Circulating tumor stem cells and glioblastoma: A review. *J. Clin. Neurosci.* **2019**, *61*, 5–9.
70. Wang, C.; Liu, Y.; Chen, R.; Wang, X.; Wang, Y.; Wei, J.; Zhang, K.; Zhang, C. Electrochemical Biosensing of Circulating MicroRNA- 21 in Cerebrospinal Fluid of Medulloblastoma Patients through Target-Induced Redox Signal Amplification. *Microchim. Acta* **2022**, *189*, 105.
71. Xu J, Liao X, Lu N, Liu W and Wong CW. Chromatin-modifying drugs induce miRNA-153 expression to suppress Irs-2 in glioblastoma cell lines. Int J Cancer 2011; 129: 2527-2531. Basu B and Ghosh MK. Extracellular vesicles in glioma: from diagnosis to therapy. Bioessays 2019; 41: e1800245.
72. Yan W, Xu T, Zhu H and Yu J. Clinical applications of cerebrospinal fluid circulating tumor DNA as a liquid biopsy for central nervous sys-tem tumors. Onco Targets Ther 2020; 13: 719- 731.
73. Yeo, E.C.F.; Brown, M.P.; Gargett, T.; Ebert, L.M. The Role of Cytokines and Chemokines in Shaping the Immune Microenvironment of Glioblastoma: Implications for Immunotherapy. *Cells* **2021**, *10*, 607.
74. Yin J, Zeng A, Zhang Z, Shi Z, Yan W and You Y. Exosomal transfer of miR-1238 contributes to temozolomide-resistance in glioblastoma. EBioMedicine 2019; 42: 238-251.
75. Yue X, Lan F and Xia T. Hypoxic glioma cell-secreted exosomal miR-301a activates Wnt/β- catenin signaling and promotes radiation re- sistance by targeting TCEAL7. Mol Ther 2019; 27: 1939-1949.
76. Zhang H, Wang J, Wang Z, Ruan C, Wang L and Guo H. Serum miR-100 is a potential biomark- er for detection and outcome prediction of glioblastoma patients. Cancer Biomark 2019; 24: 43-49.