

The role of exosomes in brain tumors: Mechanisms, diagnosis, and therapeutic prospects

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ABSTRACT

Cancer remains a leading cause of mortality worldwide, with metastases significantly impacting patient prognosis. Brain metastases (BM) and primary malignant gliomas, such as glioblastoma (GBM), are among the most aggressive forms, with survival rates often below 12 months. GBM alone accounts for 2.5% of cancer-related deaths globally and is a leading cause of mortality in young adults aged 15–34. One of the major challenges in treating brain tumors is the blood-brain barrier (BBB), which limits the delivery of therapeutic agents to the central nervous system (CNS). Exosomes, a subset of extracellular vesicles (EVs), have emerged as promising candidates for overcoming these challenges due to their natural ability to transport bioactive molecules across biological barriers. These nanosized vesicles (30–150 nm) are actively involved in tumor progression, angiogenesis, immune modulation, and drug resistance. Recent studies have highlighted their potential as biomarkers for early cancer detection and as drug delivery vehicles capable of crossing the BBB. Despite their promise, challenges such as large-scale production, efficient cargo loading, and targeted delivery remain critical hurdles to clinical translation. This review explores the role of exosomes in brain malignancies, focusing on their involvement in tumor progression, potential utility as diagnostic biomarkers, and prospective therapeutic applications.

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Introduction

Cancer is a leading cause of mortality worldwide, with metastases being a primary contributor. Brain metastases (BM) significantly impact neurological function, quality of life, and prognosis, with most cases originating from melanoma, breast cancer, and lung cancer (1). Treatment options include surgical excision, radiation therapy, chemotherapy, immunotherapy, and targeted therapies. However, survival rates for BM remain low, often below 12 months. Among primary brain tumors, GBM is the most prevalent and aggressive, comprising about 70% of all gliomas and resulting in a median survival of only approximately 15 months (2, 3).

A major challenge in treating brain tumors is the BBB, which restricts the entry of therapeutic agents into the CNS. This limitation has necessitated the development of novel drug delivery strategies. Exosomes, a subset of extracellular EVs, have emerged as promising candidates due to their natural ability to transport bioactive molecules across biological barriers (4). These nanosized vesicles (30–150 nm) are secreted by various cell types and are involved in intercellular communication, immune modulation, and

tumor progression (5). Exosomes contain proteins, lipids, and nucleic acids that reflect their cell of origin, making them valuable for both diagnostic and therapeutic applications (6).

Recent studies have shown that exosomes play a crucial role in the tumor microenvironment by facilitating tumor progression, angiogenesis, immune escape, and drug resistance (7, 8). Additionally, their ability to traverse the BBB makes them attractive candidates for targeted drug delivery in brain tumors.

Exosomes have also been investigated for their potential as biomarkers for early cancer detection and treatment monitoring, offering a non-invasive approach to brain tumor diagnosis via liquid biopsy (9). Given their ability to carry therapeutic agents, exosomes are being explored as drug-delivery vehicles to enhance the efficacy of chemotherapy and immunotherapy in brain tumors. Their biocompatibility and ability to evade immune clearance further enhance their potential as therapeutic tools. Despite their therapeutic promise, challenges such as large-scale production, cargo loading efficiency, and targeted delivery specificity remain critical hurdles to clinical translation (10). This review examines the role of exosomes in brain malignancies, focusing

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on their involvement in tumor progression, their potential as diagnostic biomarkers, and their therapeutic applications.

Literature search strategy

A systematic literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar to identify relevant studies on the role of exosomes in brain tumors. The search was published articles covering the period from their inception to May 2025, with particular emphasis on the past decade.

Search strings

• PubMed
 ("Exosome"[Title/Abstract] OR "Extracellular Vesicles"[Title/Abstract]) AND ("Glioblastoma"[Title/Abstract] OR "Brain Tumors"[Title/Abstract] OR "Neuroblastoma"[Title/Abstract] OR "Brain Metastases"[Title/Abstract]) AND ("Blood-Brain Barrier"[Title/Abstract] OR "Drug Delivery"[Title/Abstract] OR "Tumor Microenvironment"[Title/Abstract] OR "Exosomal miRNA"[Title/Abstract])

• Scopus

TITLE-ABS-KEY (exosome OR "extracellular vesicle*") AND TITLE-ABS-KEY ("glioblastoma" OR "brain tumor*" OR "neuroblastoma" OR "brain metastas*") AND TITLE-ABS-KEY ("blood-brain barrier" OR "drug delivery" OR "tumor microenvironment" OR "exosomal miRNA")

• Web of Science

TS=(exosome OR "extracellular vesicle*") AND TS=("glioblastoma" OR "brain tumor*" OR "neuroblastoma" OR "brain metastas*") AND TS=("blood-brain barrier" OR "drug delivery" OR "tumor microenvironment" OR "exosomal miRNA")

• Google Scholar

A custom search combining the above keywords was manually screened for relevance.

Search results and screening

• Total records found in all database searching: n = 523

• Total after duplicates removed: n = 503

• Not meet the inclusion: n= 434

• All Articles were included: 77

Titles and abstracts were screened, and full texts were retrieved for potentially relevant studies.

Inclusion criteria

- Peer-reviewed original research, systematic reviews, and meta-analyses
- Studies addressing the biological role, diagnostic significance, or therapeutic potential of exosomes in primary or metastatic brain tumors
- Articles exploring exosome-mediated drug delivery across the BBB, signaling pathways, or tumor progression mechanisms

Exclusion criteria

- Non-english publications
- Conference abstracts, editorials, and commentaries without original experimental data
- Studies unrelated to exosomes or not focused on brain malignancies
- A PRISMA flow diagram is provided in Figure 1.

Exosome biology and blood-brain barrier interaction

Exosomes are nanosized extracellular vesicles (30–150 nm) secreted by diverse cell types (11), such as blood (12), cerebrospinal fluid (13), saliva (14), urine (15, 16), and breast milk (17). These vesicles faithfully represent the molecular profile of their parent cells, both in physiological and pathological conditions (18). Specific proteins, including TSG101, HSP70, CD81, and CD63, serve as exosomal markers and are actively involved in exosome biogenesis (Figure 2) (19, 20). RNA sequencing analyses of exosomal cargo show diverse RNA types—including mRNA, miRNA, rRNA, snRNA, tRNA, and lncRNA—that are key to cellular regulation and communication (21). Exosome formation begins within the endosomal pathway, where early sorting endosomes mature into multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs). ILVs may be degraded in lysosomes, recycled to the trans-Golgi network, or released as exosomes via fusion with the plasma membrane

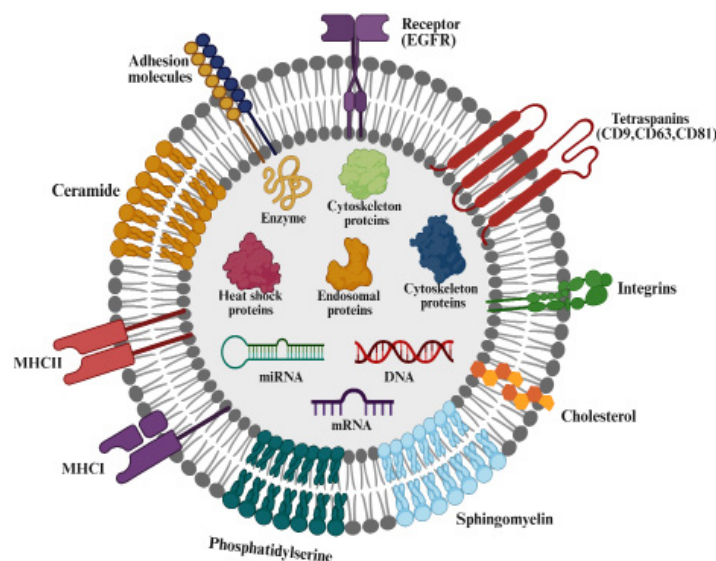


Figure 1. This schematic diagram shows the search strategy of the present study

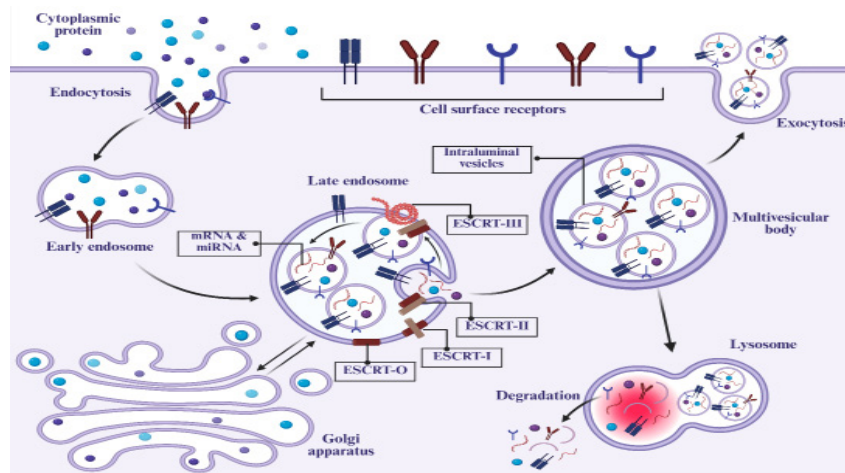


Figure 2. Composition and structure of exosomes

Exosomes are small extracellular vesicles enclosed by a lipid bilayer. They contain lipids, proteins, and nucleic acids. Membrane-associated proteins include major histocompatibility complexes I and II, tetraspanins, endosomal origin proteins, heat shock proteins, receptors, adhesion proteins, and integrins. The vesicle also carries cytoskeletal and cytosolic proteins, as well as RNA, miRNA, and DNA.

(22). The Rab GTPase family controls exosome secretion by aiding membrane fusion, while flotillin and other cell-specific proteins are incorporated during biogenesis. Exosome formation is chiefly regulated by the ESCRT machinery—comprising ESCRT-0, I, II, III, and associated proteins (VPS4, TSG101, ALIX)—with ESCRT-0 recognizing and sequestering ubiquitinated proteins in endosomal domains (23). Subsequently, ESCRT-I and ESCRT-II drive membrane budding, leading to ILV formation, which is completed when ESCRT-III facilitates the final step of membrane scission and detachment (24). The coordinated action of these complexes results in MVB maturation (Figure 3).

A pivotal feature of exosomes is their ability to traverse the blood–brain barrier (BBB). They do so primarily via receptor-mediated endocytosis and transcytosis, utilizing receptors such as transferrin, ICAM-1, GLUTs, and CD46. Once internalized by endothelial cells, exosomes are trafficked via endosomes and released into the brain parenchyma through exocytosis (Figure 4). Studies also show that the efficiency of BBB penetration varies by exosome origin and cargo composition, influenced by both physiological and pathological states (25, 26).

Methodological considerations: EV isolation, characterization standards, and implications for biomarker variability

Methodological heterogeneity in extracellular vesicle (EV) isolation and characterization remains a major obstacle to biomarker discovery and validation in brain tumor research (Table 1). To address this, the International Society for Extracellular Vesicles (MISEV) recommends using the generic term “extracellular vesicles” unless biogenesis is explicitly demonstrated. MISEV further emphasizes transparent reporting of protocols—including sample source and volume, pre-processing steps, separation and concentration methods, characterization markers, and evaluation of non-EV contaminants—to enhance reproducibility. Adherence to the MISEV minimal reporting checklist, which requires evidence of EV-enriched proteins, appropriate negative controls for common contaminants, and application of orthogonal characterization techniques, helps reduce misinterpretation and prevents overstatement of exosome-specific functions (27).

Common isolation approaches (differential

ultracentrifugation, density gradients, size-exclusion chromatography, precipitation, ultrafiltration, immunoaffinity capture, and emerging microfluidic platforms) differ in yield, purity, processing time, scalability, and the type of co-isolated material (protein aggregates, lipoproteins, and nucleoprotein complexes). These differences systematically affect the molecular readout, particularly protein and RNA cargo profiles, and therefore a given biomarker's measured abundance and reproducibility across studies. For example, precipitation-based methods often yield high particle counts but co-precipitate protein/lipoprotein contaminants that can distort proteomic and small-RNA measurements. At the same time, SEC generally increases purity at the expense of lower yield and greater sample requirements—features that make SEC preferable for sensitive downstream omics but potentially less suitable for low-volume clinical samples (28).

In brain-tumor studies (including those summarized in this review), methodological variability likely accounts for some of the inconsistent biomarker signatures reported across cohorts. To mitigate this, we recommend: (a) explicit declaration of the chosen separation strategy and rationale tied to downstream assays; (b) reporting of sample handling (freeze–thaw cycles, anticoagulant used, centrifugation steps) and all instrument/column parameters; (c) orthogonal characterization (size distribution by NTA or TRPS, electron microscopy, and at least three EV-associated protein markers, plus negative markers for contaminants) per MISEV; and (d) when possible, orthogonal validation of candidate biomarkers across at least two isolation methods to confirm robustness. Implementing these practices will reduce biomarker variability and accelerate the translation of EV-based liquid biopsies for brain tumors (27).

Utilizing exosomes for cancer diagnosis and therapy

Recent research highlights the potential of exosomes as innovative tools for both diagnosing and treating brain tumors (29). Exosome-based liquid biopsy has emerged as a promising non-invasive method for detecting GBM and BM. Studies have identified tumor-derived exomes (TDEs), such as EGFRvIII-mutated exomes, that carry specific biomarkers, are prevalent in the plasma of GBM patients, and serve as a reliable diagnostic marker (30). Additionally,

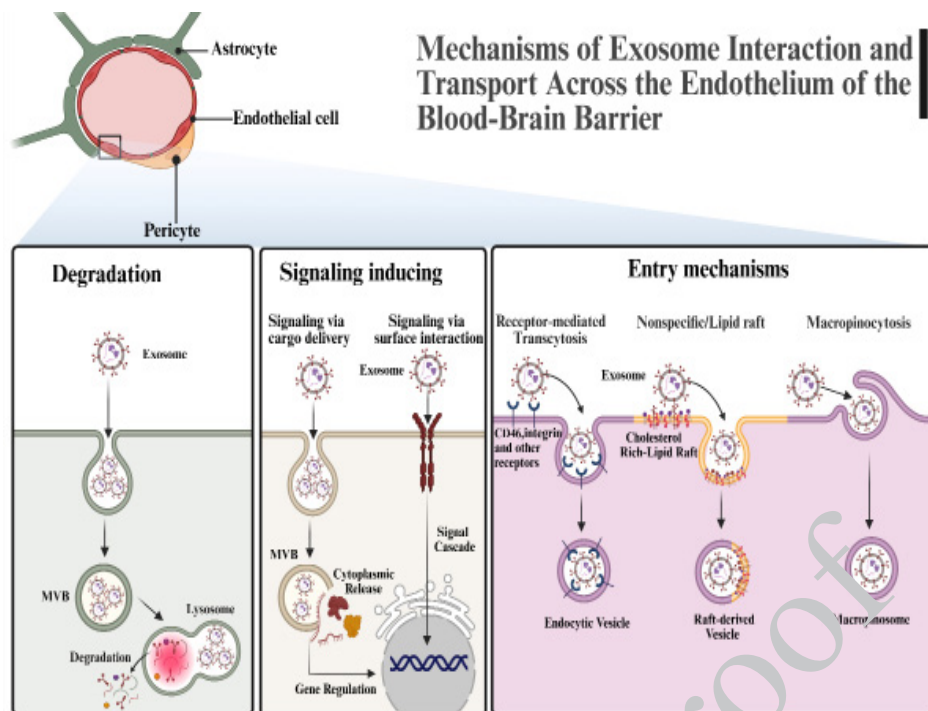


Figure 3. Exosomes are formed through the inward budding of the multivesicular body (MVB) membrane within early endosomes. Invagination of late endosomal membranes inside large MVBs generates intraluminal vesicles (ILVs). Evidence suggests that the ESCRT (endosomal sorting complex required for transport) machinery plays a crucial role in this process.

exosomal miR-21 and miR-222 have been found to correlate with glioma progression and prognosis (31). Exosomes also play a critical role in therapeutic applications as natural drug-delivery vehicles. Their ability to cross the BBB makes them ideal candidates for targeted drug delivery in brain tumors. Research has demonstrated that engineered exosomes loaded with siRNA or chemotherapeutic agents can effectively inhibit glioblastoma (GBM) cell proliferation and enhance sensitivity to temozolomide (TMZ), the standard chemotherapy for GBM (32). Furthermore, exosome-mediated delivery of miR-124 has been shown to suppress GBM stem-like cells, reducing tumor growth and increasing therapeutic response (33). Despite their therapeutic promise, challenges such as scalability, cargo loading efficiency, and targeted delivery specificity remain major hurdles for clinical applications. Future research should focus on optimizing exosome engineering and production to harness their full potential in brain tumor management (34).

The method of exosome-mediated BBB penetration

The BBB is a biological barrier composed of brain capillary endothelial cells that serve to block the entry of potentially dangerous chemicals into the brain. Cells that lack fenestrations, have tight junctions, and allow the passage of small-sized molecules distinguish the BBB. Most chemotherapeutic or biotech drugs cannot cross the blood-brain barrier because of a specialized transport mechanism that only allows specific large molecules through. This means that they aren't as effective at treating brain disorders. Although many illness-relieving agents are available, only a small fraction (2%) of medications can cross the BBB (35). This limitation significantly reduces their efficacy in treating brain ailments. Exosomes can cross the BBB through receptor-mediated transcytosis. The BBB expresses a greater number of cell receptors, such as transferrin, low-density

lipoprotein receptor family members, intracellular adhesion molecules (ICAM 1), insulin, and glucose receptors (GLUTs). An *in vitro* study showed that targeting these receptors via exosome-based nanomedicine could improve drug delivery to the brain. The BBB allows hormones, small molecules, ions, and nutrients to enter the brain, making it a viable route for therapeutics (36).

An *in vitro* study on the BBB penetration capacity of exosomes found that CD46 is a key receptor for facilitating tumor metastasis by internalizing cancer cells' exosomes into the brain (37). The *in vitro* work conducted by Chen et al. demonstrates that exosomes can cross the BBB via multiple mechanisms (38). The researchers found that exosomes primarily enter endothelial cells via endocytosis. Once inside, they accumulate in endosomes and subsequently traverse cells via MVBs and exocytosis to reach the brain parenchyma. This effective transportation guarantees targeted cell distribution in situations similar to stroke. Furthermore, a significant number of exosomes can penetrate the brain by exploiting the spaces between endothelial cells. The BBB crossing capacity of ten distinct exosome types from various animals and cell types was investigated by Banks et al. (39). They determined that all of these exosomes could cross the BBB, although the traversing pace differed by up to ten times. Wheatgerm agglutinin (WGA) and lipopolysaccharide (LPS) improved the ability of most exosome types to penetrate the BBB, while WGA altered the transport of most exosomes. These results were true regardless of the origin or markers of endothelial cells. It was discovered that mouse macrophage cells may employ the mannose-6-phosphate receptor as a transport receptor. However, exosomes' capacity to cross the BBB may be compromised by cargo molecules bigger than 1100 Da (40). The *in vitro* findings indicate that the origin of the cells and the disease state influence the capacity of exosomes to cross the BBB (41).

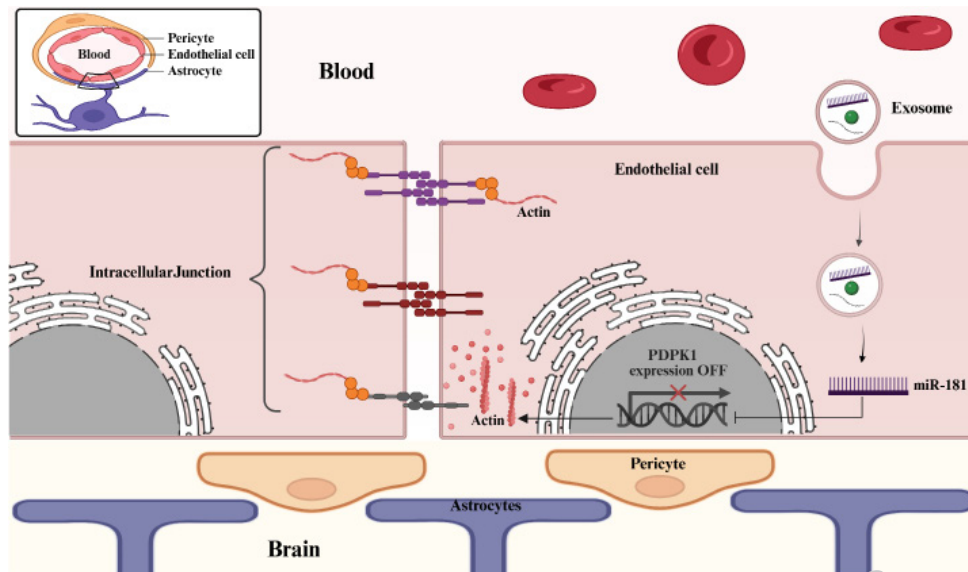


Figure 4. Transport and fate of exosomes across the blood-brain barrier (BBB)

Exosomes can cross the BBB through multiple pathways, including: (A) macropinocytosis, lipid raft-mediated uptake, or nonspecific exosome-endothelium interaction; (B) receptor-mediated transcytosis. After entering target cells, exosomes can traffic from multivesicular bodies (MVBs) to the plasma membrane as de novo intraluminal vesicles. Their fate may include: (1) degradation by lysosomes; (2) release of contents into the cytoplasm via backfusion in MVBs; (3) activation of α_1 signaling through interaction with G protein-coupled receptors; or (4) fusion with the plasma membrane to release their cargo and initiate molecular events in endothelial cells.

Tumors of the brain and exosomes

Glioblastoma

Recent studies have demonstrated that exosomes have significant therapeutic potential in the treatment of brain tumors. Tumor cells in the brain release exosomes that transport cancer cell constituents to neighboring cells (42). Treating brain cancer is particularly challenging due to the presence of the BBB and the complex environment of the CNS (43). However, exosomes have shown therapeutic efficacy in treating various brain malignancies, including GBM, neuroblastoma, medulloblastoma, astrocytoma, gliosarcoma, and oligodendroglioma. These vesicles are particularly valuable for drug delivery and in enhancing therapeutic responses (44).

Exosomes, especially in the context of GBM treatment, have therapeutic applications. For example, exosomes can deliver specific drugs, such as temozolomide (TMZ), to tumor cells, thereby enhancing treatment efficacy and reducing side effects (45). Moreover, exosomes can transport therapeutic molecules, such as miRNAs and other RNAs, into the brain's microenvironment, facilitating targeted treatment strategies for brain tumors (46).

Therapeutic role of exosomes in GBM

- Exosomes can deliver therapeutic molecules, including chemotherapy drugs or inhibitory proteins, to tumor cells, thereby improving therapeutic efficacy and minimizing side effects (47).
- Exosomes derived from therapeutic cells can transfer genetic material (such as miRNA or non-coding RNA) to cancer cells, reducing drug resistance. For instance, exosomal miR-151a may enhance GBM cells' sensitivity to TMZ (48).

Exosome-mediated drug resistance therapy

- Exosomes can serve as a tool for overcoming drug resistance. For example, exosomes can transfer miR-34a from mesenchymal stem cells (MSCs) to GBM cells, thereby increasing their sensitivity to TMZ (49).

- In cases of TMZ resistance caused by elevated levels of proteins such as MGMT and APNG, exosomes can effectively target these proteins, thereby enhancing treatment response (50).

Clinical potential of exosomes in glioblastoma

Recent advances highlight the substantial clinical potential of exosomes in the diagnosis, prognosis, and treatment of GBM. These nanoscale vesicles carry bioactive molecules—particularly non-coding RNAs and microRNAs—that reflect the molecular profile of their parental GBM cells, enabling real-time, non-invasive tumor monitoring (51-53). Several exosomal miRNAs, including miR-21, miR-221, and miR-124, exhibit dysregulated expression in GBM and correlate with tumor grade, therapeutic resistance, and patient survival (52). Their remarkable stability in biofluids and accessibility through liquid biopsy position them as promising biomarkers for early detection and disease stratification (51, 53). Beyond their diagnostic value, engineered exosomes provide an innovative therapeutic platform for the targeted delivery of drugs, siRNAs, or antisense oligonucleotides to tumor sites, effectively bypassing the blood-brain barrier and minimizing systemic toxicity (53). Preclinical studies have demonstrated that exosome-mediated transfer of tumor-suppressive miRNAs or chemotherapeutic agents can suppress GBM proliferation, angiogenesis, and invasion (51, 53). Furthermore, exosomal molecular signatures may help predict therapeutic responses, facilitating personalized therapeutic strategies (52). Although challenges remain in standardizing isolation, characterization, and large-scale production, the integration of exosome-based diagnostics and therapeutics into clinical practice holds considerable promise for transforming GBM management in the era of precision oncology (51, 53).

Neuroblastoma

Neuroblastoma (NB), particularly common in infants and young children, is one of the most prevalent malignancies

of the nervous system (54). In NB, exosomes not only facilitate the transfer of signaling molecules but also serve as therapeutic vehicles to enhance immune responses and treatment outcomes. Exosomes extracted from specific cells can deliver therapeutic agents directly to tumor cells, thereby improving treatment efficacy (55).

Therapeutic applications of exosomes in neuroblastoma

- Exosomes can transfer specific miRNAs such as miR-21 and miR-155 from immune cells to tumor cells. This process may reduce chemotherapy resistance and improve prognosis (56).
- In NB, exosomes can transfer hsa-miR199a-3p to tumor cells, which decreases NEDD4 activity, enhancing therapeutic effects. Moreover, this miRNA can serve as a biomarker for early detection and prognosis of NB (57).

Exosomes and brain metastasis: A therapeutic role

Recent research highlights the need for therapies targeting metastatic brain tumors, which are often more aggressive and cause significant damage to brain tissue compared to primary tumors (58). Exosomes have shown significant therapeutic potential in combating brain metastasis, especially those originating from lung and breast cancers. These vesicles can transport proteins and miRNAs to brain tumor cells, helping to reduce metastatic spread and improve treatment outcomes (59).

Therapeutic role of exosomes in brain metastasis

- Exosomes can transfer miRNAs like miR-105 from breast cancer cells to brain endothelial cells, disrupting the BBB and facilitating metastasis. In this context, inhibiting miR-105 could serve as a promising therapeutic strategy to prevent brain metastasis (60).
- In non-small cell lung cancer, exosomal miR-451a and miR-4257 are associated with metastasis and poor prognosis. Targeting these miRNAs may offer a potential strategy to prevent tumor spread to the brain and improve prognosis in patients (61).

Clinical potential of exosomes in neuroblastoma

Exosomes hold significant clinical promise in NB by serving as minimally invasive biomarkers, prognostic indicators, and potential therapeutic targets. Tumor-derived exosomes (TDEs) from NB carry DNA, RNA, and proteins reflecting the molecular status of their parent cells, enabling real-time disease monitoring without surgical biopsy (62, 63). Proteomic and genomic profiling of NB exosomes has revealed tumor-specific mutations (e.g., ALK, CHD5, PHOX2B) and distinct protein signatures—such as NCAM, NCL, and VASP—that can discriminate NB patients into high- versus low-risk groups (62, 64). Exosomal miRNAs, including miR-199a-3p, miR-29c, and let-7b, correlate with tumor aggressiveness, therapy response, and drug resistance, providing opportunities for early intervention (62, 63). Functionally, NB exosomes modulate the tumor microenvironment, promoting angiogenesis, immune evasion, and pre-metastatic niche formation in bone marrow and liver (63). They can also transfer oncogenic proteins (e.g., PKM2, B7-H3) that enhance glycolysis, metastasis, and chemoresistance (63, 64). Given their stability and accessibility in biofluids, NB exosomes are being investigated for integration into liquid biopsy platforms, with the dual aim of improving early detection and enabling personalized,

adaptive therapeutic strategies (62-64).

Clinical potential of exosomes in brain metastases

Exosomes hold significant clinical potential in the management of BM, particularly as non-invasive diagnostic and prognostic biomarkers. Studies have demonstrated that tumor-derived exosomes carry specific molecular cargo, such as miR-206-3p and vinculin (VCL), which are upregulated during BM progression in lung cancer, providing opportunities for early detection before conventional imaging methods can identify lesions (65). These exosomal biomarkers reflect dynamic intercellular communication between metastatic cells and the brain microenvironment, including blood-brain barrier (BBB) modulation and immune evasion. Additionally, exosomes' natural ability to cross the BBB positions them as promising drug delivery vehicles for targeted therapies, potentially overcoming the limitations of current treatments (2, 65). Their role in forming pre-metastatic niches further highlights their utility in understanding metastatic mechanisms and developing therapeutic interventions. Moreover, exosomal profiles can stratify patients at risk of BM, enabling personalized treatment strategies. Despite challenges in isolation and standardization, exosomes represent a transformative tool for improving BM diagnosis, monitoring, and therapy, ultimately enhancing patient outcomes (2, 65).

As summarized in Table 2, the clinical translation of exosome-based approaches in brain tumors remains at an early stage. Only a limited number of registered clinical trials directly involve exosomes in gliomas or other central nervous system malignancies. Most efforts focus on liquid biopsy applications, where circulating exosomes are analyzed for genomic or molecular abnormalities (e.g., NCT06116903). Other trials explore exosome dynamics in combination with blood-brain barrier modulation strategies, such as focused ultrasound (NCT04202770), or assess their therapeutic potential in neurological conditions not involving tumors (NCT04202783). A pilot glioma immunotherapy study (NCT02507583) has examined tumor-derived exosomes as antigen sources. In contrast, additional early-phase oncology studies outside the CNS provide proof of concept for drug-loaded exosome therapeutics. Collectively, these trials highlight the translational promise of exosomes. Still, they also underscore the current scarcity of CNS tumor-specific therapeutic applications and the need for further well-designed clinical studies.

Conclusion

Brain tumors present both physical and cognitive difficulties, and their treatment is intricate. The surgical procedure remains the most pivotal stage; however, it presents challenges due to the extended recuperation time and the potential for complications. Chemotherapy and radiation are recommended for malignant tumors; nevertheless, despite their increased efficacy, they are not yet capable of entirely eliminating some malignant and metastatic brain tumors. Chemotherapy is associated with serious problems. Overall, the management of brain tumors poses several challenges in the medical domain.

Exosomes and EVs play a vital role in facilitating tumor growth and metastasis, offering significant diagnostic and prognostic value. Additionally, they provide novel therapeutic opportunities for the treatment of metastatic cancer, including BM. Recent research indicates that

EVs play a crucial role in intercellular communication by carrying biomolecules, including proteins, lipids, mRNA, and miRNA. This mechanism helps regulate both normal and aberrant brain functions. Recent studies have shown that exosomes have a pivotal role in the progression, invasion, resistance to treatment, and dissemination of gliomas. Investigating exosomes will further our comprehension of carcinogenesis and the molecular mechanisms associated with tumors, facilitating the identification of effective diagnostics and targeted therapeutics for tumors. Nevertheless, further research using sophisticated technologies such as machine learning, scRNA-seq, and high-throughput screening is necessary to enhance understanding of exosomal drugs as carriers and to validate their efficacy as potential therapeutic agents and biomarker tools for gliomas and other cancers.

While exosomes show considerable promise for brain tumor diagnosis and therapy, their clinical translation is hindered by several unresolved challenges. First, there is a lack of standardized protocols for exosome isolation, purification, and characterization, leading to variability in yield, purity, and reproducibility across studies. This technical heterogeneity complicates biomarker validation and regulatory approval. Second, large-scale production of clinical-grade exosomes remains a bottleneck, as current methods are labor-intensive and may alter vesicle integrity or bioactivity (73). Third, efficient and selective cargo loading—particularly for therapeutic nucleic acids or drugs—remains suboptimal, and off-target delivery poses a risk of unintended effects on healthy brain tissue. Targeting specificity is further complicated by the diverse cell origins of circulating exosomes and the complex tumor microenvironment. Fourth, while exosomes can cross the BBB, the mechanisms governing their tropism, uptake, and biodistribution in vivo are incompletely understood, raising concerns about variable therapeutic delivery. Additionally, most preclinical evidence derives from in vitro systems or small animal models, which may not fully recapitulate human CNS pathophysiology. Finally, there are safety considerations—such as the potential for tumor-derived exosomes to promote angiogenesis, immune evasion, or drug resistance—that require careful mitigation before clinical application. Addressing these limitations through standardized methodologies, scalable manufacturing, advanced targeting strategies, and rigorous clinical testing will be critical for realizing the full therapeutic and diagnostic potential of exosomes in brain tumors.

Future directions and research gaps

Despite rapid progress in elucidating the diagnostic and therapeutic potential of exosomes in brain tumors, several research avenues remain underexplored. Future work should prioritize the development of standardized, reproducible isolation and characterization protocols to enable cross-study comparability and accelerate regulatory approval. Advances in scalable biomanufacturing technologies are needed to produce clinical-grade exosomes with consistent quality, while preserving vesicle integrity and bioactivity. Research on precision cargo engineering—including selective loading of therapeutic agents and enhancing targeting specificity—should be coupled with deeper mechanistic studies on blood–brain barrier (BBB) crossing, biodistribution, and clearance kinetics in human-relevant models. The integration of multi-omics profiling, single-cell analysis, and machine

learning may yield robust biomarker panels and improve patient stratification for personalized therapy. Furthermore, long-term safety studies are essential to assess risks such as off-target effects, immune modulation, and the inadvertent delivery of pro-tumorigenic signals. Addressing these gaps through interdisciplinary collaborations will be critical for translating exosome-based strategies from experimental promise to clinical reality.

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Authors' Contributions

A A and H F contributed to the study's conception and design. W K and W M performed data collection. A A and H F wrote the first draft of the manuscript. W K and W M designed the photos. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Declaration

During the preparation of this work, the author(s) used AI-assisted technologies (QuillBot, Grammarly, and iThenticate) to rephrase, reduce plagiarism, and improve grammar.

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References

- Proescholdt MA, Schödel P, Doenitz C, Pukrop T, Höhne J, Schmidt NO, *et al.* The management of brain metastases: Systematic review of neurosurgical aspects. *Cancers* 2021; 13: 1616-1632.
- Oliveira FD, Castanho MA, Neves V. Exosomes and brain metastases: A review on their role and potential applications. *Int J Mol Sci* 2021; 22: 10899.
- Tâmaş F, Bălaşa R, Manu D, Gyorki G, Chinezu R, Tâmaş C, *et al.* The importance of small extracellular vesicles in the cerebral metastatic process. *Int J Mol Sci* 2022; 23: 1449-1459.
- Tambaro S, Mitra S, Gera R, Linderth B, Wahlberg LU, Darreh-Shori T, *et al.* Feasibility and therapeutic potential of local intracerebral encapsulated cell biodelivery of BDNF to App NL-G-F knock-in Alzheimer mice. *Alzheimers Res Ther* 2023; 15: 137-155.
- Fang X, Gong R, Yang D, Li C, Zhang Y, Wang Y, *et al.* NIR-II light-driven genetically engineered exosome nanocatalysts for efficient phototherapy against glioblastoma. *J Am Chem Soc* 2024; 146: 15251-15263.
- Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science* 2020; 367: eaau6977.
- Mehryab F, Rabbani S, Shahhosseini S, Shekari F, Fatahi Y, Baharvand H, *et al.* Exosomes as a next-generation drug delivery system: an update on drug loading approaches, characterization, and clinical application challenges. *Acta Biomater* 2020; 113: 42-62.
- Zhang Y, Lv P, Zhang Q, Xiang W, Jiang X, Guo Z, *et al.* Exosomal miR-21-5p from glioma-associated mesenchymal stem cells promotes the progression and glycolysis of glioblastoma via PDHA1. *Sci Rep* 2025; 15: 2320-2334.
- Wang Y, Huo Y, Zhao C, Liu H, Shao Y, Zhu C, *et al.* Engineered exosomes with enhanced stability and delivery efficiency for

- glioblastoma therapy. *J Control Release* 2024; 368: 170-183.
10. Lee H, Bae K, Baek AR, Kwon EB, Kim YH, Nam SW, *et al.* Glioblastoma-derived exosomes as nanopharmaceutics for improved glioma treatment. *Pharmaceutics* 2022; 14: 1002-1021.
11. Yang J, Li Y, Jiang S, Tian Y, Zhang M, Guo S, *et al.* Engineered brain-targeting exosome for reprogramming immunosuppressive microenvironment of glioblastoma. *Exploration* 2024; 5:20240039.
12. Pecankova K, Pecherkova P, Gasova Z, Sovova Z, Riedel T, Jäger E, *et al.* Proteome changes of plasma-derived extracellular vesicles in patients with myelodysplastic syndrome. *PLoS One* 2022; 17: e0262484.
13. Chiasserini D, Bijnsdorp I, Bellomo G, Orvietani PL, Piersma SR, Pham TV, *et al.* Proteomic analysis of extracellular vesicles in cerebrospinal fluid of patients with Alzheimer's disease. *MedRxiv* 2020;2020.02.22.20026609.
14. Liew FF, Chew BC, Ooi DJ. Wound healing properties of exosomes: a review and modelling of combinatorial analysis strategies. *Curr Mol Med* 2022; 22: 165-191.
15. El Fekih R, Hurley J, Tadigotla V, Alghamdi A, Srivastava A, Coticchia C, *et al.* Discovery and validation of a urinary exosome mRNA signature for the diagnosis of human kidney transplant rejection. *J Am Soc Nephrol* 2021; 32: 994-1004.
16. Momen LT, Abdolmaleki A, Asadi A, Akram M. Regeneration and diagnosis of kidney disease using exosomes. *Jentashapir J Cell Mol Biol* 2021; 12: e120113.
17. Słyk-Gulewska P, Kondracka A, Kwaśniewska A. MicroRNA as a new bioactive component in breast milk. *Noncoding RNA Res* 2023; 8: 1-10.
18. Wortzel I, Dror S, Kenific CM, Lyden D. Exosome-mediated metastasis: Communication from a distance. *Dev Cell* 2019; 49: 347-360.
19. Remec Pavlin M, Hurley JH. The ESCRTs: Converging on mechanism. *J Cell Sci* 2020; 133: jcs240333.
20. Portilla Y, Mulens-Arias V, Paradela A, Ramos-Fernández A, Pérez-Yagüe S, Morales MP, *et al.* The surface coating of iron oxide nanoparticles drives their intracellular trafficking and degradation in endolysosomes differently depending on the cell type. *Biomaterials* 2022; 281: 121365.
21. Zhao S, Wang Q, Ni K, Zhang P, Liu Y, Xie J, *et al.* Combining single-cell sequencing and spatial transcriptome sequencing to identify exosome-related features of glioblastoma and constructing a prognostic model to identify BARD1 as a potential therapeutic target for GBM patients. *Front Immunol* 2022; 14: 1263329.
22. Yue B, Yang H, Wang J, Ru W, Wu J, Huang Y, *et al.* Exosome biogenesis, secretion and function of exosomal miRNAs in skeletal muscle myogenesis. *Cell Prolif* 2020; 53: e12857.
23. Gioseffi A, Edelmann MJ, Klena PE. Intravacuolar pathogens hijack host extracellular vesicle biogenesis to secrete virulence factors. *Front Immunol* 2021; 12: 662944.
24. Huang Z, Keramat S, Izadirad M, Chen ZS, Soukhtanloo M. The potential role of exosomes in the treatment of brain tumors: recent updates and advances. *Front Oncol* 2022; 12: 869929.
25. Sun C, Wang P, Dong W, Liu H, Sun J, Zhao L. LncRNA PVT1 promotes exosome secretion through YKT6, RAB7, and VAMP3 in pancreatic cancer. *Aging (Albany NY)* 2020; 12: 10427-10440.
26. Feix AS, Tabaie EZ, Singh AN, Wittenberg NJ, Wilson EH, Joachim A. An in-depth exploration of the multifaceted roles of extracellular vesicles in pathogenic single-cell microorganisms. *Microbiol Mol Biol Rev* 2024; 88: e00037-24.
27. Bielska E, Harrison PJ. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): A position statement of the International Society for extracellular vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles* 2018;7:1535750.
28. Sidhom K, Obi PO, Saleem AJ. A review of exosomal isolation methods: is size exclusion chromatography the best option? *Int J Mol Sci* 2020;21:6466-6484.
29. Best MG, Sol N, Zijl S, Reijneveld JC, Wesseling P, Wurdinger T. Liquid biopsies in patients with diffuse glioma. *Acta Neuropathol* 2015; 129: 849-865.
30. Yadav R, Singh AV, Kushwaha S, Chauhan DS. Emerging role of exosomes as a liquid biopsy tool for diagnosis, prognosis, and monitoring treatment response of communicable and non-communicable diseases. *Indian J Med Res* 2024; 159: 163-180.
31. Santangelo A, Rossato M, Lombardi G, Benfatto S, Lavezzari D, De Salvo GL, *et al.* A molecular signature associated with prolonged survival in glioblastoma patients treated with regorafenib. *Neuro Oncol* 2021; 23: 264-276.
32. Bouzari B, Mohammadi S, Bokov DO, Krasnyuk II, Hosseini-Fard SR, Hajibaba M, *et al.* Angioregulatory role of miRNAs and exosomal miRNAs in glioblastoma pathogenesis. *Biomed Pharmacother* 2022; 148: 112760.
33. Hong S, You JY, Paek K, Park J, Kang SJ, Han EH, *et al.* Inhibition of tumor progression and M2 microglial polarization by extracellular vesicle-mediated microRNA-124 in a 3D microfluidic glioblastoma microenvironment. *Theranostics* 2021; 11: 9687-9706.
34. Nie M, Huang D, Chen G, Zhao Y, Sun L. Bioadhesive microcarriers encapsulated with IL-27 high expressive MSC extracellular vesicles for inflammatory bowel disease treatment. *Adv Sci* 2023; 10: 2303349.
35. Finbloom JA, Sousa F, Stevens MM, Desai TA. Engineering the drug carrier biointerface to overcome biological barriers to drug delivery. *Adv Drug Deliv Rev* 2019; 167: 89-108.
36. Ramalho MJ, Loureiro JA, Coelho MA, Pereira MC. Transferrin receptor-targeted nanocarriers: overcoming barriers to treat glioblastoma. *Pharmaceutics* 2022; 14: 279-309.
37. Saint-Pol J, Cosset E, Duban-Deweer S, Pottiez G, Karamanos V. Targeting and crossing the blood-brain barrier with extracellular vesicles. *Cells* 2020; 9: 851-863.
38. Chen C, Liu L, Ma F, Wong CW, Guo XE, Chacko JV, *et al.* Elucidation of exosome migration across the blood-brain barrier model *in vitro*. *Cell Mol Bioeng* 2016; 9: 509-529.
39. Barakat WA, Sharma P, Bullock KM, Hansen KM, Ludwig N, Whithers JL. Transport of extracellular vesicles across the blood-brain barrier: brain pharmacokinetics and effects of inflammation. *Int J Mol Sci* 2020; 21: 4407-4427.
40. Tang B, Zeng W, Song LL, Wang HM, Qu LQ, Lo HH, *et al.* Extracellular vesicle delivery of neferine for the attenuation of neurodegenerative disease proteins and motor deficit in an Alzheimer's disease mouse model. *Pharmaceutics* 2022; 15: 83-105.
41. Rehman FU, Liu Y, Zheng M, Shi B. Exosomes-based strategies for brain drug delivery. *Biomaterials* 2023; 293: 121949.
42. Allegra A, Petrarca C, Di Gioacchino M, Casciaro M, Musolino C, Gangemi S. Exosome-mediated therapeutic strategies for management of solid and hematological malignancies. *Cells* 2022; 11: 1128-1160.
43. Steeg PS. The blood-tumour barrier in cancer biology and therapy. *Nat Rev Clin Oncol* 2021; 18: 696-714.
44. Fanelli GN, Grassini D, Ortenzi V, Pasqualetti F, Montemurro N, Perrini P, *et al.* Decipher the glioblastoma microenvironment: The first milestone for new groundbreaking therapeutic strategies. *Genes* 2021; 12: 445-468.
45. Wang R, Liang Q, Zhang X, Di Z, Wang X, Di L. Tumor-derived exosomes reversing TMZ resistance by synergistic drug delivery for glioma-targeting treatment. *Colloids Surf B Biointerfaces* 2022; 215: 112505.
46. Mardi N, Salahpour-Anarjan F, Nemati M, Baher NS, Rahbarghazi R, Zarebkohan A. Exosomes: multifaceted nanopatform for targeting brain cancers. *Cancer Lett* 2023; 557: 216077.
47. Zhang M, Hu S, Liu L, Dang P, Liu Y, Sun Z, *et al.* Engineered exosomes from different sources for cancer-targeted therapy. *Signal Transduct Target Ther* 2023; 8: 124-143.
48. Movahedpour A, Khatami SH, Khorsand M, Salehi M, Savardashtaki A, Mirmajidi SH, *et al.* Exosomal noncoding RNAs: Key players in glioblastoma drug resistance. *Mol Cell Biochem* 2021; 476: 4081-4092.
49. Liu X, Guo Q, Gao G, Cao Z, Guan Z, Jia B, *et al.* Exosome-transmitted circCABIN1 promotes temozolomide resistance in glioblastoma via sustaining ErbB downstream signaling. *J*

Nanobiotechnology 2023; 21: 45-69.

50. Li X, Wang N, Leng H, Yuan H, Xu L. Hsa_circ_0043949 reinforces temozolomide resistance via upregulating oncogene ITGA1 axis in glioblastoma. *Metab Brain Dis* 2022; 37: 2979-2993.
51. Jin P, Bai X. Exploring the roles and clinical potential of exosome-derived noncoding RNAs in glioma. *IBRO Neurosci Rep* 2025; 18: 323-337.
52. Yang L, Niu Z, Ma Z, Wu X, Vong CT, Li G, *et al.* Exploring the clinical implications and applications of exosomal miRNAs in gliomas: A comprehensive study. *Cancer Cell Int* 2024; 24:323-340.
53. Ramezani A, Rahnama M, Mahmoudian F, Shirazi F, Ganji M, Bakhshi S, *et al.* Current understanding of the exosomes and their associated biomolecules in glioblastoma biology, clinical treatment, and diagnosis. *J Neuroimmune Pharmacol* 2025; 20: 1-30.
54. Tan WQ, Yuan L, Wu XY, He CG, Zhu SC, Ye M. Exosome-delivered circular RNA DLGAP4 induces chemoresistance via miR-143-HK2 axis in neuroblastoma. *Cancer Biomark* 2022; 34: 375-384.
55. Degli Esposti C, Iadarola B, Maestri S, Beltrami C, Lavezzari D, Morini M, *et al.* Exosomes from plasma of neuroblastoma patients contain double-stranded DNA reflecting the mutational status of parental tumor cells. *Int J Mol Sci* 2021; 22: 3667-3686.
56. Morini M, Raggi F, Bartolucci M, Petretto A, Ardito M, Rossi C, *et al.* Plasma-derived exosome proteins as novel diagnostic and prognostic biomarkers in neuroblastoma patients. *Cells* 2023; 12: 2516-2543.
57. Panachan J, Rojsirikulchai N, Pongsakul N, Khawawisetsut L, Pongphitcha P, Siriboonpiputtana T, *et al.* Extracellular vesicle-based method for detecting MYCN amplification status of pediatric neuroblastoma. *Cancers* 2022; 14: 2627-2640.
58. Nag S, Bhattacharya B, Dutta S, Mandal D, Mukherjee S, Anand K, *et al.* Clinical theranostics trademark of exosomes in glioblastoma metastasis. *ACS Biomater Sci Eng* 2023; 9: 5205-5221.
59. Catelan S, Oliosio D, Santangelo A, Scapoli C, Tamanini A, Pinna G, *et al.* miRNAs in serum exosomes for differential diagnosis of brain metastases. *Cancers* 2022; 14: 3493-3504.
60. Yang C, Wu Y, Wang L, Li S, Zhou J, Tan Y, *et al.* Glioma-derived exosomes hijack the blood-brain barrier to facilitate nanocapsule delivery via LCN2. *J Control Release* 2022; 345: 537-548.
61. Huang G, Xu G, Cao Q, Li S, Li H, Zhang X, *et al.* Role of GPX3+ astrocytes in breast cancer brain metastasis activated by circulating tumor cell exosomes. *NPJ Precis Oncol* 2025; 9: 64-82.
62. Ghufuran SM, Brown ML, Beierle EA. Role of exosomes in diagnosis, prognostication, and treatment of pediatric solid tumors. *Med Treat Oncol* 2025; 33: 1-10.
63. Dhamdhare MR, Spiegelman VS. Extracellular vesicles in neuroblastoma: Role in progression, resistance to therapy, and diagnostics. *Front Immunol* 2024; 15: 1385875.
64. Bhavsar SP, Morini MJ. The emerging role of exosomal proteins in neuroblastoma. *Front Oncol* 2024; 14: 1414063.
65. Lim J, Kang M, Ahn YH, Cho MS, Lee JH, Kang JL, *et al.* Comprehensive profiling of serum exosomes by a multi-omics approach reveals potential diagnostic markers for brain metastasis in lung cancer. *Cancers* 2025; 17: 1929-1948.

Corrected Proof