Glioblastoma Multiforme Metastasis to the Parotid Gland: A Systematic Review of Case Series and Case Studies.

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Structured Abstract

Introduction

Glioblastoma multiforme (GBM) is a highly aggressive, IDH-wildtype grade IV brain tumor with rapid growth, invasiveness, and poor prognosis despite treatment. Extra-neural glioblastoma (GBM) metastasis to the parotid gland is exceedingly rare and inadequately documented.

Methods

A systematic review following PRISMA2020 guidelines for case-reports or case-series documenting histologically confirmed GBM metastasis to the parotid gland was conducted for studies published until 01/05/2024 (CRD42024517593).

Results

13 studies were included, with general good reporting quality. Average age on GBM diagnosis was 42.73 years (range: 25 – 58 years), with metastasis occurring after 9.77 months (range: 2.5 – 24 months). 8 patients had intracranial GBM metastasis and 9 had additional extra-neural metastasis, 7 being lymph-nodes. Frontal lobe and temporal lobe GBM involvement was noted in five tumours respectively, with two involving the parotid and one the occipital lobe. All parotid metastases were ipsilateral to the site of the original GBM tumour. All patients underwent resection and postoperative radiotherapy for their primary tumours.

Discussion

GBM metastasis to the parotid gland is exceedingly rare and occurred in younger individuals, with all documented cases showing ipsilateral spread which may suggest a pattern of lymphatic spread, though the limited data makes this challenging to confirm definitively. Additional research and case documentation are necessary to better understand the mechanisms and pathways of extra-neural metastasis, particularly to the parotid gland.

Keywords: GBM, Glioblastoma, Parotid Metastasis, Parotid, Case Studies.

Introduction

Glioblastoma multiforme (GBM) is the most aggressive and prevalent primary brain tumour in adults, classified as grade IV IDH-wildtype by the World Health Organisation (1, 2). Characterised by its rapid growth and invasiveness, GBM poses a significant clinical challenge, often leading to poor prognosis despite available treatments, with a median survival of 12-15 months (3, 4). With an incidence of approximately 3.2 cases per 100,000 people worldwide, GBM predominantly affects older adults, with the average age of occurrence being 64 years old (5). It shows an increased incidence and mortality in males, with females having a better prognosis (6). GBM has a complex pathophysiology, exhibiting immune escape, tumour heterogeneity and genetic mutations contributing to its poor prognosis (7). Their highly infiltrative nature due to a number of proposed theories for metastasis, also makes complete surgical resection difficult (3). Despite advances in multimodal therapies, including surgery, radiotherapy and temozolomide-based chemotherapy, there is still a critical need for ongoing research to better understand its biology and develop more therapeutic strategies (8). Extracranial metastasis is notably rare, occurring in less than 2% of patients (9). No specific value of central nervous system metastasis rate of glioblastoma has been found at the time of writing of this paper. However, metastasis to the parotid gland, while even rarer and less documented, presents a unique challenge in both diagnosis and management. Due to the scarcity of cases, the mechanisms of GBM metastasis to the parotid and its clinical implications remain poorly understood. The need for a systematic review becomes apparent as it would establish and analyse the limited available data, enabling healthcare professionals to better recognize and manage this rare phenomenon. Such a review could provide valuable insights into the diagnostic patterns, treatment strategies, and prognostic factors for patients with parotid metastasis from glioblastoma, ultimately contributing to improving patient care and outcomes in these rare cases.

Materials and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist 2020, and the Cochrane Handbook for Systematic Review of Interventions (10, 11)

Study Identification and Selection

PubMed, MEDLINE, Google Scholar, Science Direct, Scopus and Semantic Scholar databases were searched for relevant articles published up until 01/05/2024 without any language restrictions. Combinations of the following keywords were used to generate the search strategy: Glioblastoma, Parotid, Metastasis.

The inclusion criteria were as follows:

1. The articles were case reports or case series
2. The articles clearly described the development of histologically confirmed GBM and parotid metastasis, according to the latest CNS tumour classification guidelines at the time of the respective publication
3. Articles included cases of GBM metastasis to the parotid gland
4. Articles reported patient characteristics, prognostication and clinical outcomes

Snowballing manual review of the reference lists of retrieved articles was conducted to expand the sample. Gray literature was not searched in this review. Individual cases reported within case series that did not meet the above inclusion criteria were not included in our analysis.

Data Extraction and Analysis

Data from selected articles were extracted using a standardised data collection table. Descriptive statistical analysis coupled with qualitative assessment of results was conducted.

JBI

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports was used to assess the quality and risk of bias in 13 case reports by evaluating key aspects like patient demographics, clinical history, diagnosis, and outcomes. Each report was assessed against eight criteria, with responses marked as "Yes," "No," "Unclear," or "Not Applicable." Reports meeting at least five criteria were included, while those with more than two "Unclear"

Results

Study Characteristics

From the 13 included case reports, the earliest case was published in 1965, and the most recent case report was published in 2022; only 1 study was published after the new World Health Organization 2021 CNS tumour classification (1). Each article was evaluated using the JBI critical appraisal tool to assess for usability in this review. Of the 13 articles, 2 did not discuss the patient's prognosis after parotid metastasis was confirmed, however all the included texts exhibited an overall low risk of bias and high quality of reporting.

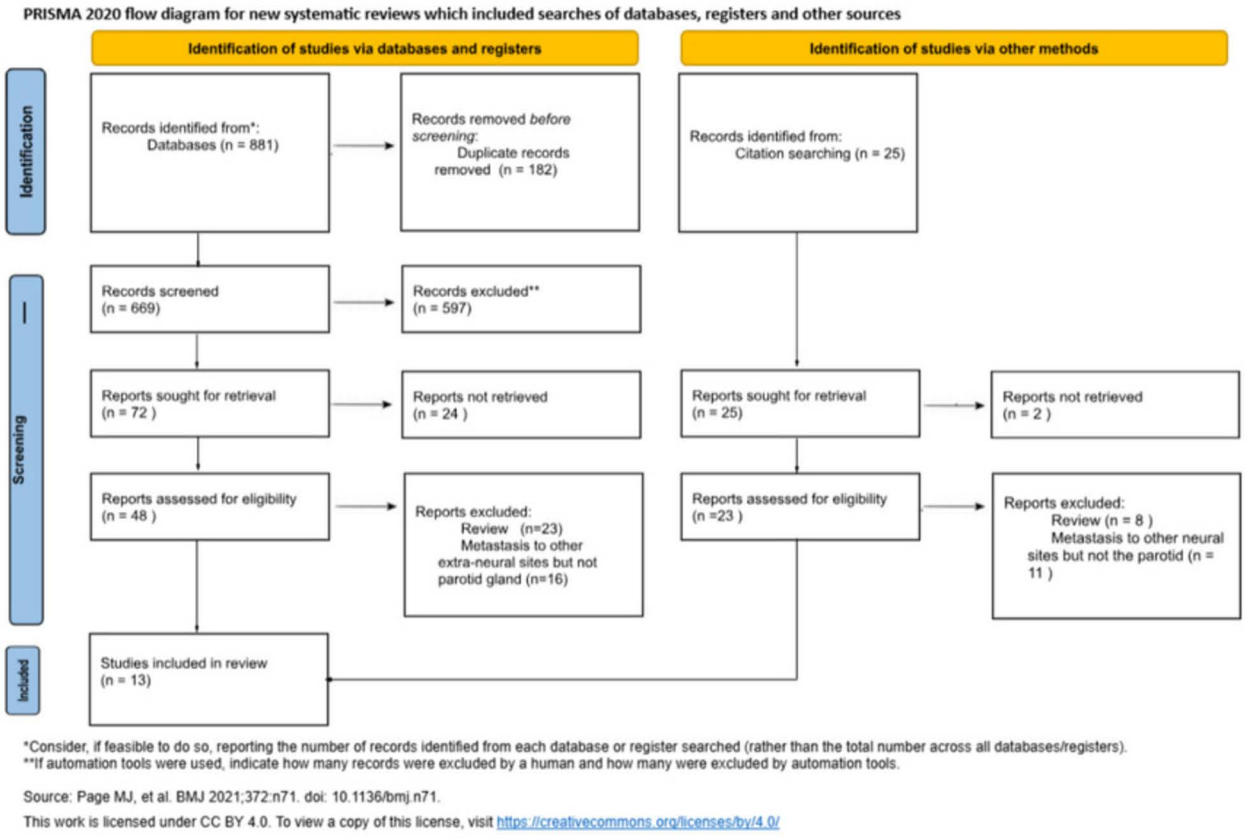

Figure 1: PISMA 2020 Flow Diagram: GBM, Parotid, Metastasis

Figure 2: JBI Appraisal Table

Glioblastoma Patient Characteristics and Management

The ages of the patients range from 24 to 64 at the age of presentation with GBM, with the majority being above the age of 40. Of the patients, 10 (76.92%) were male, and mean age of GBM detection was 46.2 years. 15.4% (n = 2) of patients had recorded concurrent diseases. Both cases had hypertension. 7 patients (53.8%) had GBM on the left hemisphere of the brain, and 8 (61.5%) patients had GBM tumour involvement in the temporal lobe.

All patients with specified data received radiotherapy and surgical resection for their primary GBM and 6 patients were recorded to receive chemotherapy (46.2%) , 5 of which received temozolomide (83.3%). 7 were recorded to have headache as a symptom of their primary tumour (53.8%).

Author, year	Gender	GBM Detection Age	Parotid Detection Age	Concurrent Diseases	GBM Mass Brain Hemisphere	Side of Parotid Mass	GBM Mass Size	Tumour Site	Duration between Primary Tumour and Metastsis	Radiotherapy received for Primary Tumour	Surgical Treatment received for Primary Tumour	Chemotherapy received for Primary Tumour	Radiotherapy received for Metastasis	Surgical Treatment received for Metastasis	Chemotherapy received for Metastsis	Symptoms of primary tumour	Symptoms of metastasis	Concominant metastasis	Prognosis as after dx of metastasis
Jie W, Bai J, Li B. 2018.	M	45	47	none	Right	Right	Not specified	mets: inferior right parotid, right parotid ear area, right deep parotid lobe	2 years	Y	Y: Brain GBM resection	N	N	Y: right total parotidectomy with selective neck dissection	N	Not specified	right parotid lump increasing in size, painful on touch	right deep cervical area and right temporal bone	Not specified
Alhoulaiby S, Abdulrahman A, Alouni G, Mahfoud M, Shihabi Z. 2020	M	53	53	10 year history of medically treated HTN and herpetic encephalitis 4 months earlier	Left	Left	On resection, 5cm in greatest dimension of multiple tissue fragments	original: left temporoparietal mass mets: recurrence in left temporal lobe expanding to left maxilla, mandible, parotid gland, infiltrating surrounding structures, hypoechoic lesions in parotid gland, enlarged left jugular lymph nodes	6 months post-surgery	Y: 60 Gray over 5 sessions/week for 2 months	Y: Craniotomy and resection of brain lesion	Y: Temozolomide 250mg tablets for 6 months, 5 consecutive days per month	N	N	N	Severe headaches, paraplegia (lower extremity)	Swelling in left cheek	cervical lymph nodes	Pt passed away 4 months after mets diagnosis, 9 months after initial surgical intervention
Taha M, Ahmad A, Wharton S, Jellinek D. 2005	M	33	33	none	Left frontal lobe	Left	/	Left frontal lobe primary tumour	7 months	Y: 60 Gy post craniotomy	Y:: 2 craniotomies for debulking	N: Planned but not started	Y	Y: Open biopsy of parotid	Y: PCV Chemo (Procarbazine, CCNU, Vincristine)	Generalised headache, behavioural changes	Painful, tender left-sided facial swelling initially misdiagnosed as infective parotitis	cervical lymph node mets	Pt passed away 3 months after detection of parotid mets
Ozan Baskurt , Yunus Kurtulus , Ahmed Yasin Yavuz and Idris Avci (2022)	M	42	43	none noted	Occurence 1: right temporal lobe Occurence 2: right temporal lobe	right	Occurence 1: 5*4cm Occurence 2: 6*5cm	original: right temporal lobe mets: right preauricular region, superficial lobe of parotid gland to upper part of previous craniotomy border, multiple pathological lymnadenopathies were detected in right submandibular area	between occurence 1 and 2: 7 months between occurence 2 and mets:(6 follow up + 15 months) = 21 months between occurence 1 and mets: 27 months	Y: 60 Gy/30 fractions RT	Y1: subtotal resection of the tumour via temporal craniotomy Y2: total removal of tumour within temporal lobectomy	Y1: Temozolomide at 75mg/m^2 one month after surgery Y2: bevacizumab irinotecan	Y	N	Y	Occ1: headache, syncope, tinnitus Occ2: left hemiparesis with muscle strength 2/5	Swelling in right neck region	right preauricular region. right submandibular area, subcutaneous to scalp of prior craniotomy scar, cortico-subcortical cystic encephalomalacia in right temporal lobe, multiple new distinct lesions and recurrent intracranial tumour growth	Pt declined further treatment and continues his life 39 months after the primary diagnosis of intracranial glioblastoma
Alfredo E. Romero-Rojas • Julio A. Diaz-Perez • Deirdre Amaro • Alfonso Lozano-Castillo • Sandra I. Chinchilla-Olaya (2013)	M	26	26	none noted	Left frontal lobe	Left	Not specified	left frontal lobe primary tumour	6 months	Y	Y	Y: temozolomide (140mg/day for 42 days)	Y	N	Y: temozolomide 300mg/day	severe hedaches and dysaesthesias	progressive growth of a nodule in left cheek and generalised bone pain	cervical lymph nodes (IIB, III and IV)	Total survival from dx of 2 years was documented
Jeroen Swinnen MD, Geert Gelin MD, Sabine Fransis MD, Jan Vandevenne MD PhD, Sofie Van Cauter MD PhD (2019)	F	56	56 (+6 months)	Arterial HTN, morbid obesity	Right temporal lobe	Right	Not specified	Right temporal lobe	6 months	Y: 30 doses of 2 gray on weekdays (Stupp protocol)	Y: resection of the mass and satellite lesions	Oral levetiracetam 500mg 2x daily as seizure prophylaxis as well as oral temozolomide at a ratio of 75mg/m^3 daily. After completion, adjuvant temozolomide regimen changed to 200mg/m^3 intake 5 days/week for 4 weeks repeated in 6 cycles	Not specified	Resection of cervical lymphadenopathy	oral VEGFR 1-3 inhibitor (axitinib) and anti-PD-L1 IgG1 antibody (avelumab) treatment	Headaches, nausea, vomiting, slightly unstable gait	Pain and swelling at right parotid gland	Lung nodules (right lung apex, bilateral millimetric nodules), cervical lymph nodules	Patient passed away 14.5 months after presentation

Author, year	Gender	GBM Detection Age	Parotid Detection Age	Concurrent Diseases	GBM Mass Brain Hemisphere	Side of Parotid Mass	GBM Mass Size	Tumour Site	Duration between Primary Tumour and Metastsis	Radiotherapy received for Primary Tumour	Surgical Treatment received for Primary Tumour	Chemotherapy received for Primary Tumour	Radiotherapy received for Metastasis	Surgical Treatment received for Metastasis	Chemotherapy received for Metastsis	Symptoms of primary tumour	Symptoms of metastasis	Concominant metastasis	Prognosis as after dx of metastasis
Kraft Marcel, Lang Florian, Braunschweig Richard, Janzer Robert Charles. (2008)	M	57 (15 mo before 58)	58	none noted	Right temporal lobe	Right	Not specified	Right temporal lobe	15 months	Y	Y: craniotomy and partial lobectomy	Y: temozolomide	Not specified	N	Y, palliative	Not specified	Pressure sensitive parotid tumour or the right with ipsilateral facial paralysis, House-Brackman n grade IV in a week	Right orbit, thyroid, lung, kidney, breast and colorectal cancer.	Approximately 1.5 months
Ogungbo, Biodun, Perry, Robert Henry, Bozzino, J. M., Mahadeva, Dhirendra. (2005)	F	49	49 (+5 months)	none noted	Left	left	4.5 cm x 3.5 cm	Left occipital lobe	6-8 months	Y: 30 Grey over 6 sessions in 3 weeks	Y: craniotomy and excision of left occipital tumours	Y: CCNU, Procarbazine and metopclopramide.	Palliative oncological treatment not otherwise specified	Palliative oncological treatment not otherwise specified	Palliative oncological treatment not otherwise specified	funny turns', headaches, visual disturbances in the form of recurrent flashing light episodes of 2 weeks duration lasting a few minutes at a time.	unusual swelling on left parotid gland	Lungs	died 16 months after onset of symptoms
U. Kühn1 - H. H. Köhler2 - P. Jecker1 (2003) *Only the 2nd case will be considered as the rest do not have parotid metastasis*	M	58 (minus 6 months)	58	none noted	right	right	Not specified	Right temporal lobe	9 months	Y	Y	not specified	not specified	y: total parotidectomy	not specified	Not specified	increased swelling of right parotid gland for a week	Renewed tumour in right tempora l lobe + liver mets	not specified
CATHERINE C. PARK, MD, CHRISTIAN HARTMANN, MD, REBECCA FOLKERTH, MD, JAY S. LOEFFLER, MD, PATRICK Y. WEN, MD, HOWARD A. FINE, MD, PETER MCL. BLACK, MD, PHD, TIMOTHY SHAFMAN, MD, AND DAVID N. LOUIS, MD (2000) *Only the 4th case will be considered as it is the only one with parotid metastasis*	F	25	25	none noted	right	Not specified	Not provided	Fronto-parietal region, had mets to the scalp	9 months	Y. External beam radiation therapy to 59.4 Gy. Radioactive iodnine seed placement in resection bed	Y. Subtotal resection	Y. Not specified	Not specified	Y. craniotomy for scalp metastases	Not specified	Headaches, nausea, left facial and arm weakness	Progressive symptoms of elevated intractanial pressure from neck mets	Scalp mets, large neck mass	She died 21 monts after diagnosis
Edwin Bolke and Christiane Matuschek (2014) *Only the 2nd case will be considered as it is the only one with parotid metastasis*	M	24	24	none noted	left	left	Not specified	Left temporal lobe, involving greater wing of sphenoid bone, invasion of MCF	Difficult to determine as no data on how long ago the first resection was. However it was ~4 months after presnetation of patient with anxiety and headaches post-resection.	Not specified	Yes: resection	not specified	yes	Y: Parotid and left hemi-neck nodal dissection	Y: temozolomide, paclitaxel, carboplatin, cisplatin, irinotecan and cetuximab	Not specified	anxiety and headaches	dural thickening and extraconal orbital changes, residul GMB outside the CNS with involvement of the sphenoid bone, soft tissues of the masticator space and extraconal orbit with proptosis, tumour in lower neck lymph nodes	Died after 22 months
R. Meqele' , P. Gruß ', K. Bührmonni (1989)	M	66	66	Not specified	left	left	Not specified	left temporal lobe	9 months	started 2.5 weeks post-op, 60 Gy. at 40 Gy to the entire cerebro and 20 Gy to the tumor bed	1. macroscopic removal of entire tumour. 2.macroscopic removal of recurrence, osteoplastic trepanation	not specified	not specified	1. Partial parotidectomy 2. Radical parotidectomy and radical neck dissection	not specified	word-finding and memory problems, speech problems and other typical temporal lobe lesion symptoms	left sided periauricular swelling.	Neck mets resembling lymph nodes, spreading to the tonsillar tract	Survived procedures well, died after 3months due to rapid cerebral decompensation
Ali Moghtader (1965)	M	64	64	not specified	left	left	3x4x5 cm	surface of left temporal lobe	3 months between craniotomy and noticing the masses, diagnosis 6 months after craniotomy and diagnosis of mets	total tumour dose of 5070 r with Cobalt 60	satisfactorally excised	not specified	total of 5000 r with a 250 KV machine over 5 weeks	total parotidectomy, with facial nerve sacrifice and radical neck dissection	not specified	not specified	patient noted rapidly growing masses on left side of neck	cervical nodes	died 2 months after paotid mets diagnosis

Figure 3: Data Extraction Table

Parotid Metastasis Patient Characteristics and Management

From all the 13 cases evaluated, 8 (61.5%) patients underwent surgical treatment for the metastasis, 5 (38.5%) patients received radiotherapy, and 6 (46.2%) patients received chemotherapy. Data that was not specified in the cases or left ambiguous e.g. "palliative oncological treatment" that was not otherwise specified, was not included as affirmative for either treatment due to lack of certainty. All 13 cases had concomitant metastases, with 7 cases of metastases to the cervical and/or other lymph nodes not otherwise specified. The duration between the primary tumour and the parotid metastasis ranged from 3 months after their craniotomy to 2 years.
From the cases, 12 out of 13 had ipsilaterally recorded metastasis, and one had the side of metastasis undocumented.

Discussion

Metastasis of GBM to the parotid gland, although rare, highlights the need to understand anatomical and physiological links between the brain's drainage systems and extracranial metastasis. Unlike common extracranial metastases of GBM, such as to the lungs or the pleura (3), parotid metastases are notably ipsilateral, suggesting an undefined route of spreading. While parotid tumours typically present as slow-growing and painless masses, rapid growth, pain, skin tethering/ulceration, cervical lymphadenopathy, or facial nerve palsy raise concern for malignancy, with tail-of-parotid lesions often mimicking cervical lymphadenopathy (13). While hematogenous dissemination often results in diffuse metastases, often bilateral, the parotid's proximity to the brain and shared drainage pathways, may explain this distinct pattern of metastasis.

Lymphatic drainage of the brain, meninges and scalp

Traditionally, the brain was thought to lack lymphatic drainage (14). However, recent studies have shown the presence of dural lymphatic vessels, particularly along the dural sinuses and major blood vessels, which play a role in draining interstitial fluid and cerebrospinal fluid into the cervical lymph nodes (15). When removing the brain from the skull, lymphatic vessels were notably absent in the brain parenchyma and pia mater. Surprisingly, however, a substantial network of lymphatic vessels was visible within the meninges located beneath the skull (15). This has been referred to as the "glymphatic system" (16), defined as a brain-wide clearance pathway that removes interstitial waste and solutes from the CNS by circulating CSF along perivascular spaces. This glymphatic system connects with the sinus-associated lymphatic network to clear solutes along perivascular pathways, suggesting a comprehensive clearance system for waste and immune cell trafficking in the brain (16). In a recent study by Safiye Çavdar et al (2023), the presence of meningeal lymphatic vessels was confirmed along both dorsal and basal dural sinuses in humans, with immunohistochemistry and Western blotting validating their existence (17). Though basal meningeal lymphatic vessels are less common than dorsal ones, their location near cranial exit points could enhance CSF drainage, which may suggest an alternative pathway for CSF transport outside the cranium (17). The scalp's lymphatic vessels follow the venous drainage, with the anterior scalp drains via the parotid nodes, which continue through the deep cervical and submandibular lymph nodes. The posterior scalp (behind the auricle), drains to the occipital and posterior auricular lymph nodes, also known as the mastoid lymph nodes, and then follow to drain into the occipital lymph nodes – which go on to drain the remaining posterior scalp area (18).

The presence of such lymphatic drainage systems can play a more active role in the progression of metastatic cancer than previously understood, even though this theory still needs further research to improve treatment strategies (19). This can be explained through changes in their microenvironment preparing for tumour cell arrival through immunosuppressive signalling and structural remodelling (19). These lymphatic vessels and endothelial cells facilitate the spread of tumour cells, with metastatic nodes often having the primary tumour's genetic composition/diversity (19). In a recent study by Nur et al (2022), a novel route of lymphatic communication between the brain and the parotid lymph nodes (as well as the mandibular lymph node) was revealed, using in vivo hyperspectral fluorescence imaging with Qdot nanoparticles (20). In this study, tracers injected into the left parietal lobe of rats travelled to the right lymph nodes before reaching the left, suggesting an unknown lymphatic pathway potentially involved in brain drainage (20). This further highlights the need for challenging our knowledge of the drainage systems of the brain for the possibility to discover new pathways and systems which could be a passageway for metastatic development.

Venous drainage systems

The brain has a complex venous drainage system, primarily using sinuses. A sinus is a channel / cavity that allows blood or lymph to pass through (21). These sinuses are small venous structures located inside the pia mater (22). These then connect to form cerebral veins, which pass through the subarachnoid space and enter dural sinuses (22). The inferior areas of the frontal and parietal lobes are drained by the cavernous sinus and the superior and inferior petrosal sinuses (23). The temporal lobe is drained by two routes: one using the superficial middle cerebral vein, which passes blood through to the inferior anastomotic vein, which goes on the join the transverse sinus. The other mainly involves the inferior part of the temporal lobe draining into the choroidal vein, which pairs with the thalamostriate vein behind the interventricular foramen to become the internal cerebral vein. This then joins the basal veins to become the great cerebral vein (24). A confluence of sinuses is formed via the superior sagittal sinus and the occipital sinus, which meet over the cerebellum, after which blood follows through to the transverse sinuses (25). The scalp, on the other hand, drains into venous systems, with superficial veins following the arteries, and deep venous veins (18). Small veins originating from the scalp communicate with the dural sinuses using emissary veins, that penetrate the skull (22). The deep scalp is drained by a venous complex in the infratemporal fossa bordered by the medial and lateral pterygoid and temporalis muscle, called the pterygoid plexus (18):. It also encloses the maxillary artery (26), and is drained by the maxillary vein (18). The retromandibular vein, which is the confluence of the maxillary vein and the superficial temporal vein, provides the venous drainage of the parotid gland (27).

Research on venous systems being considered for metastatic potential in the context of neurology currently doesn't give a high yield of literature. In an old study published in 2006 by Edward Tobinick and Charles P. Vega, the cerebrospinal venous system has been described as being a direct vascular route for tumour metastasis (28). Intraglandular lymph nodes which are located in the parotid space are found along the course of the retromandibular vein and in the parotid tail (29). These drain the parotid gland (28). It is also important to note that the parotid tail has been described as a preferential site of parotid metastasis, which might hint towards cancer metastasising via the retromandibular vein (29).

All observed parotid metastases were ipsilateral to the primary tumour, suggesting a direct anatomical

link. For instance, the temporal lobe drains via venous routes (24) and connects to the parotid gland through the pterygoid plexus and retromandibular vein (18, 26, 27). This anatomical continuity raises the possibility that tumour cells exploit such pathways for metastatic spread.

Hypothesised Mechanisms of Metastasis

The primary routes are proposed to explain parotid metastasis: hematogenous spread, venous spread and lymphatic seeding.

Hematogenous and Venous spread

The venous drainage using emissary veins and dural sinuses, along with the brain's proximity to these veins, could serve as a passageway for glioblastoma cells to enter the systemic circulation (30). Metastasis to the parotid gland could therefore potentially occur through direct hematogenous seeding.

Hematogenous spread is a documented phenomenon in brain cancers, with metastatic tumours using this route becoming implanted in the subarachnoid space and then being able to spread to other meningeal surfaces (31). With venous spread, tumour cells disseminate via the bloodstream and are typically entrapped at the grey-white matter junction, where blood vessel narrowing promotes cancel cell arrest (32). This arrest often occurs in the cerebral hemispheres, with the blood brain barrier presenting a major challenge for metastasis and drug delivery due to endothelial cells expressing high levels of efflux transporters like ATP-binding cassette (ABC) proteins that pump drugs and toxins out of the brain (33). Cancer cells that manage to cross the barrier will tend to adopt a perivascular position where they are able to proliferate and form metastases (32). Additionally, CSF drainage occurs via arachnoid granulations that reabsorb fluid into the venous sinuses, providing another potential method for tumour cell dissemination into the CNS through venous routes (32).

Lymphatic seeding

With the lymphatic connections between dura mater and cervical lymphatics and the dural lymphatics that drain into the deep cervical lymph nodes contributing to immune surveillance, these newfound structures have become a suspect in cancer metastasis. In a study by Hu. X et al., (2020), they indicate that meningeal lymphatic vessels (MLVs) play a vital role in brain tumour drainage and lymphatic seeding (32). Dorsal MLVs undergo extensive remodelling when tumours such as gliomas are present, aiding in the transport of immune cells from the brain to the deep cervical lymph nodes (33). This transport is essential for immune response, and disruption of the dorsal MLVs reduces tumour cell drainage to dorsal cervical lymph nodes and weakens the effectiveness of checkpoint therapy (32). This underscores MLVs' potential as a therapeutic target for enhancing immune responses in brain tumours (such as glioblastoma) (33). Historically believed to be an 'immune-privileged' organ, the revealed MLVs and glymphatic pathway challenge this notion by revealing an lymphatic network, including capillary and collecting lymphatics situated along the sigmoid sinus and petrosquamous sinus at the skull base, as well as along the trnsverse sinus and the superior sagittal sinus in the meninges (33). Further research focusing on mapping these routes could provide valuable insights into many aspects of neurology, from cancer treatments as well as treating CNS-associated neuroinflammatory conditions.

Complications and Unresolved Questions

Following the detailed anatomical description and theories of tumour spread, it is important to examine the details that point to a possible undiscovered pathway, possibly lymphatic in nature, in the spread of glioblastoma to the parotid gland. Notably, all cases in the aforementioned case studies reported additional metastases, predominantly to close lymph nodes and lungs.

The parotid metastases varied in treatment approaches. Importantly, regardless of patient survival outcomes, the primary tumour and concurrent metastases were dominant in influencing prognosis.

All observed metastases were ipsilateral to the primary tumour, suggesting a correlation with lymphatic or venous drainage routes – particularly from the temporal lobe, which has drainage patterns through both venous and the aforementioned newly discovered lymphatic systems. This raises the question of whether nearby venous structures, such as the pterygoid plexus, could facilitate metastasis to the parotid given that the maxillary vein transports blood from the pterygoid plexus and then enters the parotid gland (to join the superficial temporal vein and then go on to form the retromandibular vein) (32). Moreover, no direct anatomical structure currently confirms a consistent connection between specific brain regions and the parotid gland, but the consistent ipsilateral occurrence across cases is notable and may imply underlying anatomical pathways yet to be identified or noted as important or relevant.

In the paper by Hu X et al (2020), in which animal models showed that injected brain tracers reach cervical and parotid lymph nodes (which connect to the parotid gland), within minutes – suggesting that localised drainage pathways from the brain might facilitate ipsilateral metastasis. This aligns with the observed patterns of GBM metastasis, where tumour spread occurs on the same side as the primary tumour, supporting a region-specific drainage route that could theoretically transport tumour cells to local lymphatic areas (31). However, there are significant challenges. Differences in brain structures between humans and animals, especially rats (such as the lack of an arachnoid villus in the superior sagittal sinus – with it being in the skull base), limit the direct applicability of these findings to human cases (31). Additionally, the perivascular system's counterflow mechanisms may impede larger particles, like glioblastoma cells, from navigating these routes unless the system is notably compromised (31).

Conclusion

Information on GBM and its methods of metastasis has come a long way in recent years. The brain's newly discovered lymphatic pathways, such as the glymphatic system and meningeal lymphatic vessels (MLVs), have already challenged the traditional idea of the brain being "immune privileged". Ipsilateral parotid metastases in GMB correlate with anatomical drainage routes, such as the pterygoid plexus and retromandibular vein, as well as lymphatic connections to the cervical lymph nodes. These pathways suggest tumour cells could have a tendency to exploit proximity to shared brain-parotid drainage systems, offering a potential mechanism for parotid metastasis.

Despite the aforementioned hypotheses, significant gaps remain. The difference in brain anatomy between animal models and humans limit the applicability of available experimental findings. Additionally, the topic of the glymphatic system in tumour cell clearance and the perivascular system's counterflow mechanisms that may impede metastasis unless disrupted, raises several unanswered questions that require further research to solve and map these pathways conclusively. There are still difficulties in tracking tumour cells in real-time, and a focus on developing methods of tracking tumour cell trafficking could help us understand more about the routes of metastatic dissemination.

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None.

Declarations

Conflict of Interest: N/A

Ethics: N/A

Authors Contribution

Ruby Sciriha Camilleri wrote the manuscript with guidance from Andrea Cuscieri. Ruby Sciriha Camilleri and Nathaniel Gauci carried out the full-text screening and data extraction, Daniele Formosa and Axel Tonna carried out title and abstract screening, Andrea Cuschieri conceptualised the topic, set up the systematic review, draft editing and data analysis. Dr. Christian Zammit gave feedback and guidance.

List of Abbreviations

ABC	ATP-binding cassette
CNS	Central Nervous System
CSF	Cerebro-Spinal Fluid
GBM	Glioblastoma Multiforme
JBI	Joanna-Briggs Institute
MLVs	Meningeal Lymphatic Vessels
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses

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