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CLINICAL AND PATHOLOGICAL CHARACTERIZATION AND PROGNOSTIC IMPLICATIONS OF BRAIN METASTASES IN DOGS.

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Abstract

Cancer represents a major health concern in companion animal healthcare, serving as the primary cause of mortality in dogs exceeding 10 years of age.

Canine cancer pathology exhibits striking parallels with human malignancies regarding tissue structure, biological characteristics, genetic modifications, and therapeutic responses, establishing dogs as valuable subjects for comparative cancer research. Brain metastases (BMs) represent an unmet medical need in human medicine, and they are poorly documented in dogs.

This thesis aims to provide an integrated overview of the understanding and management of brain metastases in human and veterinary neuro-oncology, with the goal of inspiring future progress in diagnostic and therapeutic approaches for dogs.

Two parts composed this thesis. Part I (*General Background*) provides an in-depth examination of the fundamental aspects of brain tumors in both human and canine species. It begins with a comprehensive classification framework, distinguishing between primary and metastatic neoplasms of the central nervous system. Subsequently, it delineates the current understanding of the pathogenetic mechanisms, clinical features, state-of-the-art diagnostic imaging modalities, therapeutic strategies, and prognostic factors associated with metastatic brain tumors in both human and veterinary medicine.

Part II (*Experimental study*) described a retrospective study with the primary aim to report the clinical characteristics, primary solid cancer histology, advanced imaging findings, treatment modalities, and potential prognostic factors in dogs with presumed BMs that occurred either at the time of initial diagnosis or during follow-up. specimens obtained during necropsy. Regarding the second part, a total of 58 client-owned dogs with histologically proven solid cancer and BM were included. Haemangiosarcoma (53.4%) and carcinoma (27.6%) were the most common primary tumour histotypes. The prosencephalon was most commonly affected, with 79% of dogs showing neurologic deficits. The median survival post-BM was 3 days (range, 1-255) and the 3- and 6-month survival rates were 8.6% and 1.7%, respectively. Dogs with haemangiosarcoma and those with distant metastases at presentation had an increased likelihood of developing synchronous BM. The prognosis was poor, regardless of the primary cancer type.

PART I – GENERAL BACKGROUND

1. INTRODUCTION

1.1 Overview and relevance of primary and metastatic neoplastic disease in veterinary and human medicine

Cancer is the leading cause of death in dogs over 10 years old, affecting about 25% of dogs during their lives, and nearly half beyond that age (Fleming et al., 2011; Robson, 2013). Their high cancer incidence and shorter lifespan make dogs valuable spontaneous models for cancer research (Nasir et al., 2001). Canine tumors often resemble human cancers in structure, biology, and genetics, allowing comparative studies that reflect real-life carcinogenesis more accurately than rodent models (Paoloni et al., 2008).

Although less frequent than in humans, brain metastases in dogs significantly affect survival and quality of life (Song et al., 2013). True brain metastasis incidence in dogs is uncertain due to euthanasia practices, limited magnetic resonance imaging (MRI) access, and low necropsy rates. Estimates suggest 2–5% of cancer cases, mainly in middle-aged to older dogs (Song et al., 2013; Snyder et al., 2006).

The canine brain shares core features with the human brain, including a protective blood-brain barrier that restricts drug access and yet shelters metastatic cells (Vogelbaum et al., 2021; Niebla-Bedolla et al., 2021; Deeken et al., 2007). The comparative aspects of canine and human brain metastases offer unique translational research opportunities that can accelerate new diagnostic and therapeutic approach development (Jose-Lopez, 2023).

An understanding of the molecular mechanisms of brain metastasis, advanced imaging findings, treatment, and prognostic factors is essential and continues to advance in human research (Achrol et al., 2019; Suh et al., 2020). Unfortunately, information on brain metastases in veterinary medicine remains very limited.

The disparity between human and veterinary medicine in brain metastases diagnosis reflects fundamental differences in research infrastructure, patient populations, and healthcare economics (Hu et al., 2015). Human medicine benefits from large-scale clinical trials,

sophisticated molecular diagnostics, and access to novel therapeutic agents (Daphu et al. 2013), while veterinary medicine relies primarily on small case series and extrapolation from human studies (Hu et al., 2015). The molecular characterization of brain metastases, routinely performed in human medicine (Soffietti et al., 2020), is not yet reported in veterinary practice due to cost constraints and limited availability of appropriate testing. This prevents the identification of potentially targetable molecular alterations and limits the application of precision medicine approaches that have revolutionized human brain metastases treatment (Soffietti et al., 2020).

The most significant clinical implication of the current state of brain metastases treatment in veterinary medicine is the stark recognition that we lack fundamental knowledge about optimal therapeutic approaches. Unlike human medicine, where evidence-based guidelines provide clear treatment recommendations for various clinical scenarios, veterinary practitioners must make treatment decisions based on limited and often conflicting information.

Also, the lack of established prognostic factors specific to veterinary brain metastases prevents accurate counseling of pet owners regarding expected outcomes and treatment benefits (Daphu et al., 2013; Hu et al., 2015). This uncertainty complicates treatment decision-making and may lead to either overly aggressive interventions with minimal benefit or premature cessation of potentially helpful treatments.

1.2 Aims and structure of the thesis

The primary objective of this thesis is to provide an overview of understanding and managing the brain metastases in both human and veterinary neuro-oncology with the idea of providing insights and inspiration for potential future developments in the treatment of dogs.

Due to the limited availability of information on veterinary medicine, the thesis will mostly draw on human medicine literature.

This thesis comprises two parts. The first part (Part I: General Background) examines specific canine and human brain tumor aspects. Initially, an overall classification is presented, differentiating between primary and metastatic brain tumors. Then, information on the mechanisms, clinical presentation, advanced diagnostic imaging, therapeutic approaches, and

prognostic factors of metastatic brain tumors in human and veterinary medicine will be provided.

The second part (Part II: experimental study) describes a clinical study specifically focusing on clinical characteristics, advanced diagnostic imaging findings, treatment, and potential prognostic factors in 58 dogs with presumed brain metastases occurring either at initial diagnosis or during follow-up.

2. CLASSIFICATION OF BRAIN TUMORS

2.1 Introduction

Tumors of the nervous system can be broadly categorized into primary and secondary (Song et al., 2012; Snyder et al., 2006; Troxel et al., 2003; Snyder et al., 2008). Primary brain tumors arise from the constitutive tissues of the brain, such as neurons, glial cells, and the meninges. Metastatic (also called secondary) brain tumors represent those cancers that metastasize to the brain from a distant site or affect nervous tissue by direct extension from an adjacent tissue, such as pituitary gland, nasal, or calvarial tumors (Snyder et al., 2008).
This chapter provides an overview of primary tumors. Metastatic brain tumors will be discussed in subsequent chapters.

2.2. Overview on primary brain tumors

2.2.1 Introduction and Clinical Significance

Primary brain tumors represent one of the most challenging diagnostic and therapeutic entities in veterinary medicine. Primary central nervous system neoplasia occurs at a rate of 14.5 cases per 100,000 in dogs, whereas it is less common in cats, occurring at a rate of approximately 3.5 cases per 100,000 (Rossmeisl et al., 2024). The complexity of these neoplasms extends beyond their relatively low prevalence, as they pose significant diagnostic challenges and carry major implications for patient quality of life and survival (Rossmeisl et al., 2024). The spectrum of primary brain tumors in dogs closely mirrors that observed in human medicine, with meningiomas accounting for approximately 50% of cases in dogs and an impressive 85% in cats, followed by gliomas at 35% in dogs (12% in cats), and choroid plexus tumors comprising about 7% of all primary intracranial neoplasms (Koehler et al., 2018; Rossmeisl et al., 2024). Less commonly reported PBTs in dogs include ependymomas, primary central nervous system lymphoma, primitive neuroectodermal tumors, gliomatosis cerebri, and primary histiocytic sarcoma (Table 1).

This distribution pattern provides valuable insights into the comparative pathophysiology of brain tumorigenesis across species and has established the dog as an increasingly important translational model for human brain tumor research (Jose-Lopez, 2023).

Tissue of Origin	Tumor Types/Grades	Frequency of Tumor Diagnosis[a]	
		Canine	*Feline*
Meninges	Meningioma • Grade I • Grade II (atypical) • Grade III (malignant)	42%–52%	40%–59%
Neuroepithelium	Astrocytic tumors • Grade I (pilocytic) • Grade II (diffuse) • Grade III (anaplastic) • Grade IV (glioblastoma)	13%–60%	<1%–3%
	Oligodendroglial tumors • Grade II (oligodendroglioma) • Grade III (anaplastic)	1%–23%	<1%–3%
	Oligoastrocytic tumors • Grade II (oligoastrocytoma) • Grade III (anaplastic)	<5%	NA
	Choroid plexus tumors • Grade I (papilloma) • Grade II (atypical papilloma) • Grade III (carcinoma)	5%–8%	<1%
	Embryonal tumors • Primitive neuroectodermal tumor (Grade IV)	<0.5%	<1%
	Ependymoma • Grade II (ependymoma) • Grade III (anaplastic)	0.2%–6%	3%

Table 1 World Health Organization Classification and Frequency of Primary Brain Tumors in Dogs and Cats. From Small Animal Clinical Oncology—Withrow and Macwen, 6th Edition, Elsevier, 2020.

2.2.2 Epidemiological Patterns and Breed Predispositions

The epidemiological landscape of canine brain tumors reveals fascinating patterns that reflect both genetic predisposition and environmental factors. Most primary brain tumors manifest in middle-aged to older dogs, typically presenting after five years of age, with distinct median ages for different tumor types: gliomas at 8 years, meningiomas at 10.5 years, and choroid plexus tumors at 5.5 years (Koehler et al., 2018). Recent studies confirm that dogs with infratentorial tumors have significantly shorter median survival times (28 days) compared to those with supratentorial tumors (178 days) (Rossmeisl et al., 2024). Perhaps most striking is the pronounced breed predisposition observed in canine brain tumors, particularly for gliomas. Brachycephalic breeds demonstrate a remarkable susceptibility to glioma development, with Boxers representing 25-56% of affected dogs in various studies, followed

by Boston Terriers (11-31%), French Bulldogs, and Bullmastiffs (Young et al., 2011; Kani et al. 2019; Amphimaque et al., 2022; Carrera-Justiz, 2024). This breed clustering has led to significant advances in understanding the genetic basis of brain tumor susceptibility, culminating in the identification of a locus on canine chromosome 26 strongly linked to glioma risk.

Meningiomas display different patterns between species. In cats, meningiomas tend to be larger than in dogs and often present with clinical behavioral changes, though up to 20% can be clinically silent (Rossmeisl et al., 2024). The observation of male predilection for gliomas mirrors patterns observed in human medicine, indicating shared hormonal or genetic factors that influence tumor susceptibility across species. A recent study has also identified a locus on canine chromosome (CFA) 26 that is strongly associated with glioma across multiple dog breeds, with subsequent mapping of the region revealing single nucleotide variants in three neighboring genes, DENR, CAMKK2, and P2RX7, that are highly associated with glioma susceptibility. The CAMKK2 and P2RX7 genes have been previously recognized as relevant to the development or progression of human cancers (Truvè et al., 2016).

2.2.3 Clinical Presentation and Neurological Manifestations

The clinical presentation of primary brain tumors varies significantly between dogs and cats and is largely determined by tumor location, size, and associated secondary effects. Seizures represent the most common clinical manifestation in dogs, affecting approximately 50% of dogs with prosencephalic tumors, while in cats, behavioral changes are more commonly observed (Rossmeisl et al., 2024). The significance of new-onset seizure activity after five years of age, particularly in predisposed breeds, can be an important clinical indicator of potential structural brain disease.

Recent insights emphasize that gliomas commonly present with acute seizures or status epilepticus in dogs, while cats with meningiomas may remain clinically silent in up to 20% of cases (Rossmeisl et al., 2024). The pathophysiology underlying clinical signs involves multiple mechanisms beyond direct tissue invasion, including peritumoral edema, neuroinflammation, obstructive hydrocephalus, and intracranial hemorrhage (Miller et al., 2019).

Location-specific clinical signs provide valuable diagnostic information. Forebrain tumors typically present with seizures, circling, altered mentation, and behavioral changes, while brainstem tumors more commonly manifest as central vestibular dysfunction, ataxia, and cranial nerve deficits. The clinical picture can be complicated by obstructive hydrocephalus, particularly with tumors affecting the ventricular system or caudal fossa, that can cause an increase of intracranial pressure and secondary altered mental status, which may require urgent intervention with ventriculoperitoneal shunting (Rossmeisl et al., 2024).

2.2.4 Minimum database

Laboratory evaluation (complete blood count, serum biochemistry, urinalysis) is important, as anesthesia is recommended for diagnosis of structural brain disease. The risk population of middle-aged to older animals with brain tumors may also have significant concurrent disease that affects management.

Thoracic radiographs and an abdominal ultrasound should be considered in an attempt to identify concurrent unrelated neoplasia or other significant comorbidities. Studies have reported contemporaneous and unrelated neoplasms in 3% to 23% of dogs with primary brain tumors, the majority of which involved the thoracic or abdominal cavities (Snyder et al., 2006; Bigio et al., 2013). Recent studies have shown that although abnormalities are frequently identified on thoracic radiographs and abdominal ultrasound in dogs with primary brain tumors, the results of these procedures uncommonly (1.3%) negatively affected the decision to pursue advanced diagnostics imaging indicated for the neurologic condition of the patient, and significantly altered therapeutic recommendations for the brain tumor in 8.0% of cases (Marcello et al., 2015).

2.2.5 Advances in Diagnostic Imaging and Protocols

The evolution of diagnostic imaging has revolutionized the management of canine brain tumors, with magnetic resonance imaging (MRI) emerging as the gold standard for intracranial disease assessment. Recent advances have focused on standardization and optimization of MRI protocols to enhance repeatability and consistency across different

institutions and MRI systems (Loeber, 2025). Recent developments have expanded the diagnostic capabilities through advanced sequences such as diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC), fluid-attenuated inversion recovery (FLAIR) sequences, and T2* gradient echo sequences.

A systematic approach using standardized interpretation criteria has been developed to improve diagnostic consistency (Loeber, 2025). This involves evaluating:

- Tumor origin (intra-axial, extra-axial, intraventricular)
- Shape and margination characteristics
- Signal intensity and uniformity on various sequences
- Contrast enhancement patterns and degree
- Mass effect and peritumoral edema assessment
- Differentiation between intra-axial and extra-axial lesions using specific signs.

Meningiomas are the most common extraaxial origin tumors in dogs and cats (Forterre et al., 2007; Mc Donnell et al., 2007). Meningiomas typically have a broad-based skull attachment, have distinct tumor margins, and demonstrate marked and often uniform contrast enhancement. Some meningiomas will also display intratumoral fluid, large cystic regions, intratumoral mineralization, calvarial hyperostosis, or a dural tail sign. The “dural tail sign” the linear meningeal thickening and enhancement adjacent to peripherally located masses, has high predictive value for neoplasia and is common in meningiomas, though not specific to them (Loeber et al., 2025). Calvarial hyperostosis can result from tumor-induced reactive osseous changes or tumor invasion into bone (Rossmeisl et al., 2015). The dural tail sign is a contrast-enhancing, linear thickening of the dura mater extending from an adjacent extraaxial mass and is not specific for meningioma or for neoplastic diseases in general (Cherubini et al., 2005). Peritumoral edema is observed in more than 90% of canine meningiomas (Rodenas et al., 2011; Wisner et al., 2011). In canine studies, reported sensitivities of MRI to correctly identify intracranial meningiomas range between 60% and 100%, but specific grades and subtypes cannot be distinguished (Sturges et al., 2008).

As gliomas originate within and may infiltrate and displace the neuropil, they often appear poorly marginated and may or may not demonstrate contrast enhancement (Rodenas et al., 2011). Among contrast-enhancing gliomas, the patterns and degree of enhancement seen

can be highly variable. A “ring enhancing” pattern, in which a circular ring of contrast enhancement surrounds nonenhancing abnormal tissue, is often associated with gliomas. However, ring enhancement is a nonspecific finding that has been associated with neoplastic, vascular, and inflammatory brain diseases (Vite et al., 2011). Currently, using conventional CT or MRI sequences, it is not possible to reliably differentiate types of gliomas (astrocytomas from oligodendrogliomas) or accurately predict the grade of gliomas (Rodenas et al., 2011).

Choroid plexus tumors and ependymomas are the most common tumors found in an intraventricular location, and both of these tumor types often uniformly contrast enhance (Westworth et al., 2008).

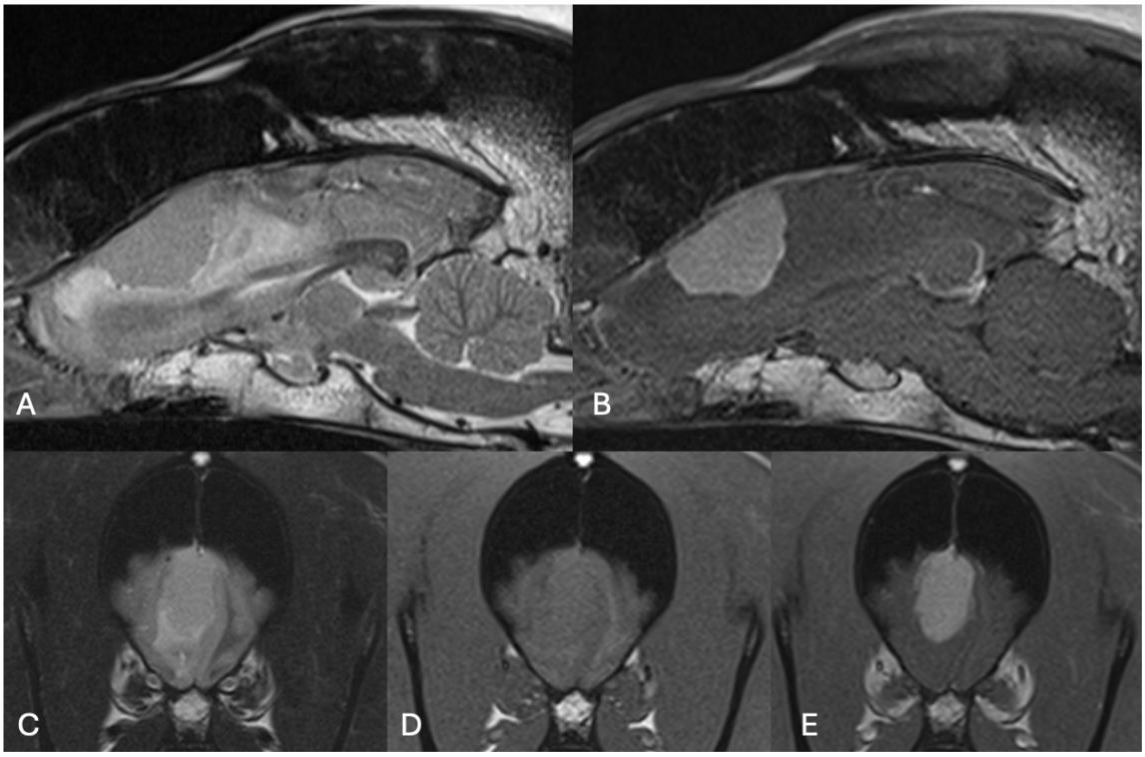

Figure 1: meningioma in a 9-year-old mixed-breed dog. Mid-sagittal T2-weighted image (A); mid-sagittal T1-weighted post-contrast image (B); transverse T2-weighted image (C); transverse T1-weighted pre-contrast image (D); transverse T1-weighted post-contrast image. Extra-axial, wide-broad-based contact with the frontal bone, oval-shaped, T2-weighted hyperintense, T1-weighted isointense, contrast-enhancing space-occupying lesion located in the right olfactory and frontal regions. Severe perilesional edema of the white matter is also evident.

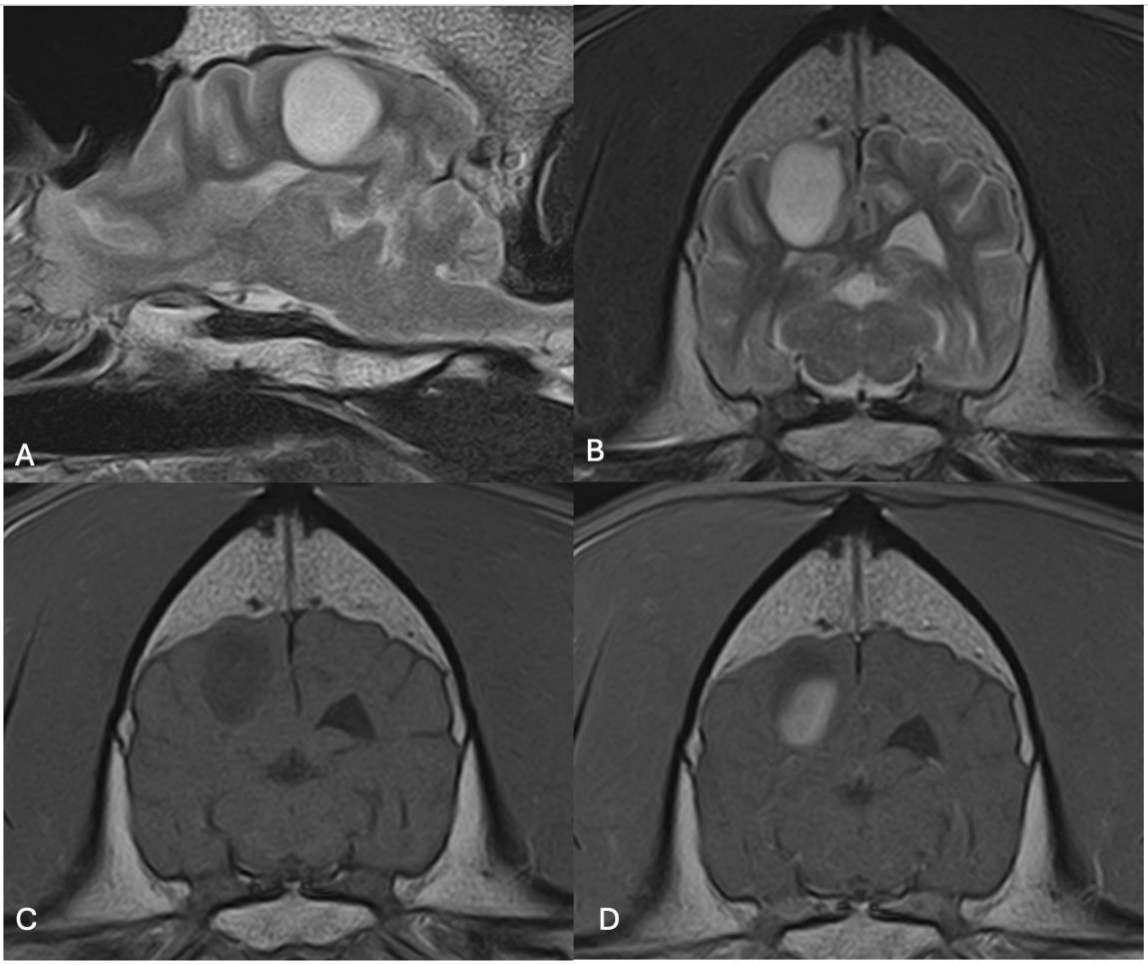

Figure 2: oligodendroglioma in a 6-year-old french bulldog. Para-sagittal T2-weighted image (A); transverse T2-weighted image (B); transverse T1-weighted pre-contrast image (C); transverse T1-weighted post-contrast image (D). Intra-axial, oval-shaped, T2-weighted hyperintense, T1-weighted isointense, and contrast-enhancing space-occupying lesion at the level of the right fronto-parietal region causing severe mass effect.

2.2.6 Cerebrospinal fluid analysis

Cerebrospinal fluid (CSF) analysis is a well-established method of detecting disease in the central nervous system, and most suspected autoimmune inflammatory lesions in humans and animals are presumptively diagnosed on imaging and CSF analysis without further attempts at biopsy (although there are some inflammatory lesions that do not appear to be associated with increased CSF cell count) (Jeffery, 2025). CSF analysis can reveal

nonspecific signs of inflammation and potentially also detect infectious organisms, such as bacteria and fungi (most commonly cryptococcus). Unfortunately, few tumors appear to exfoliate sufficient numbers of cells for CSF to be diagnostic, although choroid plexus tumors may be an exception (Butterfield et al., 2023).

In contrast, for the most common brain tumors in dogs (meningioma and glioma), CSF reveals, at best, nonspecific alterations such as a mild increase in cell counts in some individuals (Jeffery, 2025), but neoplastic cells are not detected on routine cytologic examination.

2.2.7 Enhanced Diagnostic Capabilities by Biopsy Techniques

Recent advances in brain biopsy techniques have significantly improved diagnostic accuracy while maintaining acceptable complication rates. Brain biopsy is increasingly recognized as essential for definitive diagnosis, as imaging alone often lacks sufficient specificity and sensitivity for reliable clinical decisions (Loeber et al., 2025).

Excisional biopsy performed during curative-intent surgery remains the most frequently employed biopsy technique for PBTs, but these procedures have been historically limited to patients with superficially located, extra-axial forebrain or cerebellar tumors. In cases in which surgical resection may not be possible or optimal, minimally invasive brain biopsy techniques are a viable alternative.

Several techniques have been used in dogs and cats with brain tumors, including endoscopic-assisted, free-hand image-guided biopsy, stereotactice frame-based biopsy, stereotactice biopsy by neuronavigation and three-dimensional-printed biopsy guides (Geiger et al., 2025; Jeffery, 2025). When minimally invasive brain biopsy is performed in animals with brain tumors by operators experienced with contemporary CT and MRI stereotactic systems, diagnostic yields approach 95%, and serious adverse events occur in approximately 5% of cases (Jeffery, 2025).

2.2.8 Treatment Modalities

Studies regarding the treatment of canine brain tumors are frequently limited by the inclusion of presumptively diagnosed cases, variable survival definitions and end-points, lack of inclusion of control groups, no reporting of objective imaging-based criteria of therapeutic response or other quantitative follow-up metrics, retrospective study designs, and small case numbers (Dickinson et al., 2014, Hu et al., 2015).

Palliative Care and Watchful Monitoring

The main goal of palliative care is to improve quality of life by controlling symptoms such as seizures, peritumoral edema, and pain. Antiseizure drugs (phenobarbital, levetiracetam, zonisamide) are widely used, often in combination. Corticosteroids reduce intracranial pressure and tumor-associated edema, even in cases without clear radiological evidence, and analgesics including opioids complement the treatment (Dickinson, 2014). Corticosteroids may also provide benefit to animals with tumors causing secondary obstructive hydrocephalus, although surgical CSF diversion via placement of an intraventricular shunt is a more effective method of alleviating clinical signs of intracranial hypertension from obstructive hydrocephalus (De Stefani et al., 2011).

In selected cases, small and asymptomatic tumors can be managed with watchful monitoring until progression requires intervention.

Chemotherapy

Data evaluating the efficacy of systemically administered chemotherapies for the management of brain tumors in dogs is significantly limited by the lack of definitive tumor diagnoses in the vast majority of reported cases, variable dosing regimens, and a preponderance of small case series examining specific drugs.

The most used drugs are alkylating agents (lomustine, carmustine, temozolomide) and hydroxyurea, all able to cross the blood–brain barrier. Survival benefits are inconsistent and often not superior to palliative care alone, although lomustine has shown modest improvement in some gliomas (Moirano et al., 2018). Toxicities are frequent but rarely life-threatening or require discontinuation of therapy in dogs with brain tumors.

Others therapies include COX-2 inhibitors, anti-angiogenic agents, and receptor tyrosine kinase inhibitors (Rossmeisl et al., 2009; Dickinson et al., 2006).

Translational research suggests that targeted drugs and metronomic chemotherapy might yield more consistent benefits in multimodal settings.

Surgery

Surgical resection rapidly reduces tumor mass, alleviates intracranial pressure, and provides histopathological confirmation. However, complete resections are rarely feasible due to tumor infiltration and localization. Superficial meningiomas are the most frequently operated, with median survival times (MST) around 10 months, extendable to several years with advanced surgical techniques or when combined with radiotherapy. Gliomas and intraventricular tumors are technically more challenging, with poorer outcomes. Perioperative mortality and morbidity remain significant, though they vary greatly depending on expertise and tumor type (Miller et al., 2019).

Radiation Therapy (RT)

Radiation therapy is among the most effective modalities, either alone or combined with surgery. Advances such as IMRT, VMAT, stereotactic RT (SRT), and radiosurgery (SRS) allow more precise targeting with reduced toxicity. Reported survival ranges from 7 to 24 months, with meningiomas generally showing better prognosis than gliomas. Surgery combined with RT provides the longest survival outcomes (16–30 months). However, approximately 10% of cases experience severe complications such as radiation necrosis, neurological deficits, or systemic side effects (Miller et al., 2019).

A recent multicenter retrospective cohort study compared survival outcomes in 285 dogs with suspected intracranial meningiomas treated by either surgery or radiotherapy revealed that radiotherapy was consistently associated with significantly longer survival than surgery (median survival 696 vs. 297 days) independent of lesion size or location, suggesting radiotherapy confers a substantial survival advantage in this population (Geiger et al., 2025).

Innovative Therapies

Ongoing research is testing novel strategies to overcome the limits of current treatments, especially the blood-brain barrier. Promising approaches include laser ablation, electroporation, convection-enhanced intratumoral drug delivery, and the use of nanoparticles. Immunotherapy, including tumor vaccines, checkpoint inhibitors, and targeted

cytokine-based strategies, has shown encouraging preliminary results in animal models and early trials (Miller et al., 2019). Comparative oncology in dogs with naturally occurring tumors offers a translational platform for human medicine, accelerating the development of new targeted drugs.

3. PATHOPHYSIOLOGY OF BRAIN METASTASES

3.1 Introduction

Brain metastases represent one of the most complex and challenging aspects of cancer biology, involving intricate interactions between circulating tumor cells and the unique neurovascular environment of the central nervous system (Fidler, 2003). The formation of brain metastases requires cancer cells to overcome multiple biological barriers, most notably the blood-brain barrier (BBB), and successfully colonize the brain's specialized microenvironment. Understanding the pathophysiology of brain metastases is crucial for developing effective therapeutic strategies, as these secondary brain tumors account for the majority of intracranial neoplasms and represent a significant cause of morbidity and mortality in cancer patients (Ballabh et al., 2004).

The process of brain metastasis formation involves a complex cascade of events, beginning with the dissemination of cancer cells from primary tumors and culminating in the establishment of secondary lesions within the brain parenchyma (Stamatovic et al., 2008). This multistep process is governed by specific molecular mechanisms, cellular interactions, and anatomical factors that collectively determine the success or failure of metastatic colonization. The blood-brain barrier serves as both a protective mechanism against cancer cell invasion and, paradoxically, a sanctuary that can protect established metastatic cells from systemic therapies (Fidler, 2003).

3.2 Central Nervous System Barriers

All organisms with a well-developed CNS have a blood-brain barrier (BBB) (Abbott, 2005). In the brain and spinal cord of mammals the BBB is created by the endothelial cells that form the walls of the capillaries with pericyte and astrocytic end-feet (Arvanitis et al., 2020). The combined surface area of these microvessels constitutes by far the largest interface for blood-brain exchange (Deeken et al., 2007).

Permeability of many molecules is regulated by the presence of tight junctions. Blood-brain barrier permeability may be regulated by the release of vasoactive peptides and other agents from cells associated with the endothelium. The movement of solutes across the BBB is either

passive, driven by a concentration gradient from plasma to brain, with more lipid-soluble substances entering most easily, or may be facilitated by passive or active transporters in the endothelial cell membranes. Efflux transporters in the endothelium limit the CNS penetration of a wide variety of solutes (Abbot et al., 2006). Further information about BBB will be provided in a specific paragraph.

A second interface is formed by the epithelial cells of the choroid plexus facing the cerebrospinal fluid, which constitute the blood-cerebrospinal fluid barrier (BCSFB). The CSF is secreted across the choroid plexus epithelial cells into the brain ventricular system (Brown et al., 2004), while the remainder of the brain extracellular fluid, the interstitial fluid (ISF), is derived at least in part by secretion across the capillary endothelium of the BBB. ISF and CSF are free to communicate at several locations; different experimental studies have estimated the contribution of ISF to CSF as 10–60%. The third interface is provided by the avascular arachnoid epithelium, underlying the dura, and completely enclosing the CNS; this completes the seal between the extracellular fluids of the central nervous system and that of the rest of the body (Abbott et al., 2006).

Although the arachnoid also forms a barrier layer, its avascular nature and relatively small surface area mean that it does not represent a significant surface for exchange between the blood and the CNS (Fig. 1) (Abbott et al., 2006).

At all three interfaces, the barrier function results from a combination of physical barrier (tight junctions between cells reducing flux via the intercellular cleft or paracellular pathway), transport barrier (specific transport mechanisms mediating solute flux), and metabolic barrier (enzymes metabolizing molecules in transit). The barrier function is not fixed, but can be modulated and regulated, both in physiology and in pathology (Abbott et al., 2006).

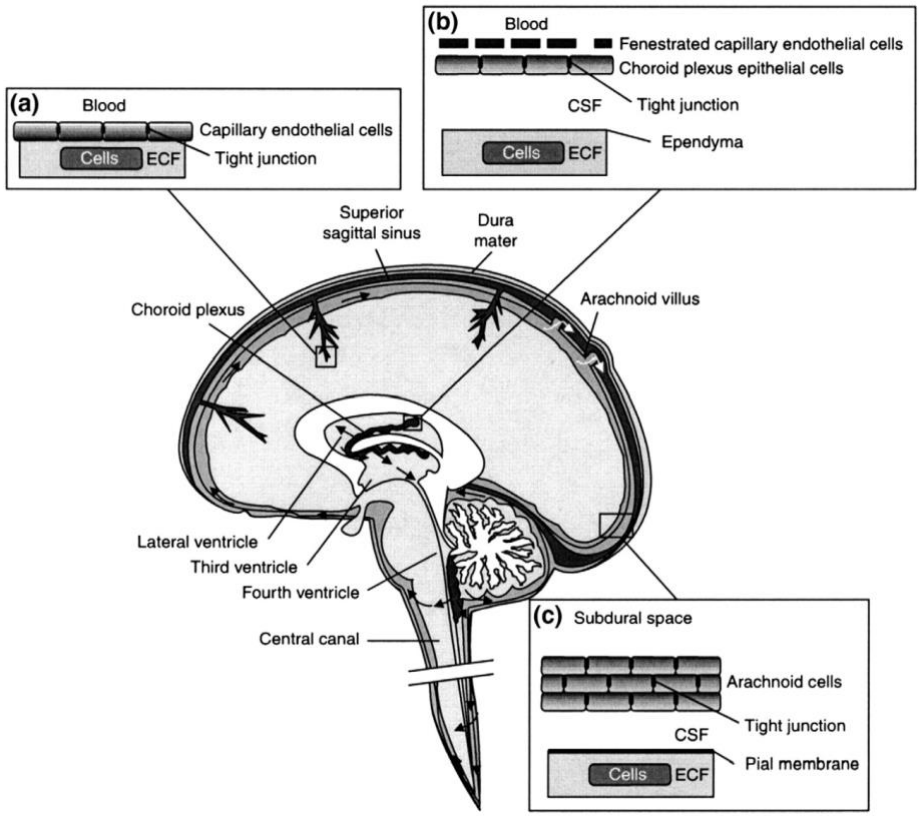

Figure 3. Barriers of the brain. There are three principal barrier sites between blood and brain. (a) The BBB proper, which is created at the level of the cerebral capillary endothelial cells by tight junction formation. (b) The blood–CSF barrier (BCSFB) lies at the choroid plexuses in the lateral, third, and fourth ventricles of the brain where tight junctions are formed between the epithelial cells at the CSF-facing surface (apical surface) of the epithelium. (c) The arachnoid barrier. The brain is enveloped by the arachnoid membrane lying under the dura. The arachnoid is avascular but lies close to the superior sagittal sinus and is separated from it by the dura. The arachnoid is a multi-layered epithelium with tight junctions between cells of the inner layer that form an effective seal. Arachnoid villi project into the sagittal sinus through the dura and a significant amount of CSF drains into the sinus through these valve-like villi which only allow CSF movement out of the brain to blood. Transport across the arachnoid membrane is not an important route for the entry of solutes into brain (Abbott et al., 2010).

3.3 The Blood-Brain Barrier: Structure, Function, and Role in Metastasis

The BBB is primarily formed by specialized cerebral endothelial cells that exhibit unique characteristics distinguishing them from peripheral endothelium (Ballabh et al., 2004). These endothelial cells are characterized by continuous intercellular tight junctions, absence of fenestrations, and extremely low rates of transcytosis, creating a formidable barrier to both paracellular and transcellular movement of molecules and cells (Figure 1).

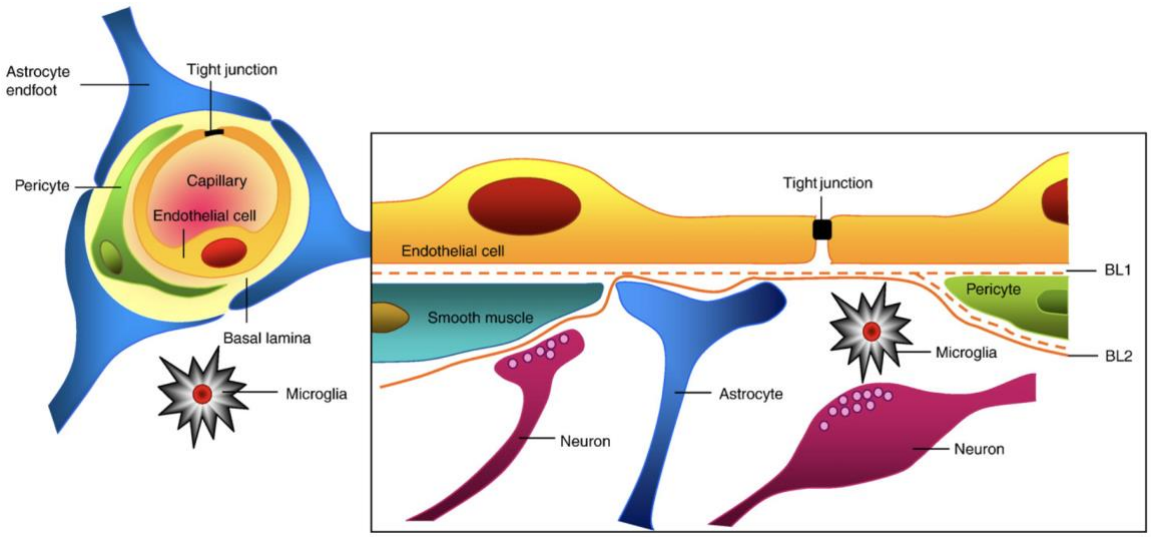

Figure 4. The cell associations at the BBB. The cerebral endothelial cells form tight junctions at their margins which seal the aqueous paracellular diffusional pathway between the cells. Pericytes are distributed discontinuously along the length of the cerebral capillaries and partially surround the endothelium. Both the cerebral endothelial cells and the pericytes are enclosed by, and contribute to, the local basement membrane which forms a distinct perivascular extracellular matrix (basal lamina 1, BL1), different in composition from the extracellular matrix of the glial endfeet bounding the brain parenchyma (BL2). Foot processes from astrocytes form a complex network surrounding the capillaries and this close cell association is important in induction and maintenance of the barrier properties. Axonal projections from neurons onto arteriolar smooth muscle contain vasoactive neurotransmitters and peptides and regulate local cerebral blood.

The molecular architecture of the BBB is defined by several key components that work in concert to maintain barrier integrity. Tight junctions, composed of transmembrane proteins including occludin, claudins (particularly claudin-5 and 3), and junctional adhesion molecules (JAMs), form the primary structural barrier regulating paracellular permeability (Stamatovic et al., 2008). Claudin-5 emerges as the most abundant claudin at the BBB, and its knockout in experimental models leads to size-selective leakage, demonstrating its critical role in barrier function (Nitta et al., 2003). However, claudin-5 expression alone is insufficient for complete barrier formation, as it is also expressed in peripheral vascular beds that lack BBB properties.

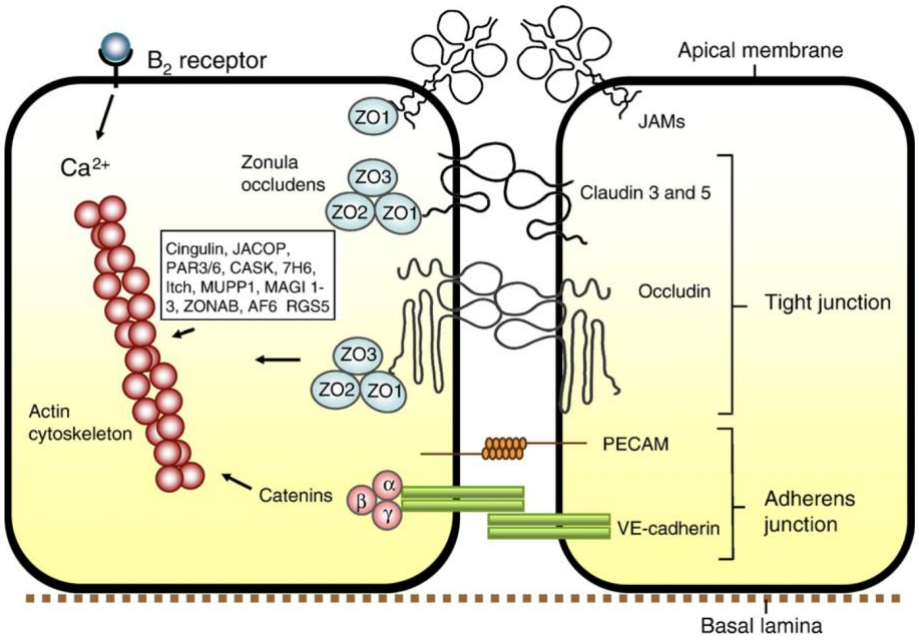

Figure 5. Structure of BBB tight junctions. The tight junctional complex comprises occludin, claudins 3 and 5, and possibly other claudins. Cadherins of the adherens junctions provide structural integrity and attachment between the cells and are necessary for the formation of tight junctions. The barrier to diffusion and the high electrical resistance of the BBB appear to be largely due to the properties of claudins 3 and 5. The claudins associate and bind to each other across the intercellular cleft. Occludin has similar associations across the cleft but does not form the restrictive pore to small ions. The claudins and occludin are linked to the scaffolding proteins ZO-1, ZO-2 and ZO-3, linked in turn via cingulin dimers to the actin/myosin cytoskeletal system within the cell. Activation of the actin cytoskeleton may be initiated by a rise in intracellular calcium, for example resulting from ligand binding to the B2 bradykinin receptor, and may change the configuration of claudins and occludin thus modifying the tight junctional properties. The role of the junction-associated molecules (JAMs, members of the immunoglobulin superfamily) is unclear, but they appear to act as cell-adhesion molecules for leukocytes.

The transcellular barrier is equally important, with CNS endothelial cells exhibiting remarkably low levels of transcytosis compared to peripheral endothelium. This restriction is mediated by MFSD2A, a transporter enriched in CNS endothelial cells that regulates endothelial cell lipid composition and restricts caveolin-dependent transcytosis (Ben-Zvi et al., 2014). The metabolic barrier component includes abundant efflux transporters such as MDR1/P-glycoprotein and breast cancer resistance protein, located on the luminal membrane, which actively pump xenobiotics and other potentially harmful substances back into the bloodstream.

3.4 The Neurovascular Unit and Cellular Interactions

The blood-brain barrier does not function in isolation but operates as part of the neurovascular unit (NVU), a complex multicellular structure that includes endothelial cells, pericytes, astrocytes, neurons, and microglia (Hawkins et al., 2005). This intricate cellular network coordinates to maintain CNS homeostasis and regulate barrier properties through dynamic intercellular communication.

Pericytes, embedded within the vascular basement membrane, play crucial roles in BBB development and maintenance. These cells regulate endothelial cell proliferation, contribute to vessel stability, and control blood flow through their contractile properties (Armulik et al., 2010). Pericyte coverage is particularly dense in brain capillaries compared to peripheral vessels, and pericyte dysfunction or loss leads to increased vascular permeability and microhemorrhages, compromising barrier integrity.

Astrocytes contribute to BBB function through their specialized perivascular end-feet that nearly completely end-sheath brain capillaries. These end-feet contain high concentrations of aquaporin-4 (AQP4) water channels and Kir4.1 potassium channels, facilitating ion and volume regulation (Nielsen et al., 1997). Astrocytes secrete numerous factors that influence BBB properties, including angiopoietin-1, which enhances barrier tightness, and transforming growth factor-β, glial-derived neurotrophic factor, and basic fibroblast growth factor, all of which can induce BBB phenotypic characteristics in endothelial cells. The extracellular matrix, particularly the vascular basement membrane, provides structural support and serves as a scaffold for organizing cellular interactions within the neurovascular unit. This specialized matrix contains collagen type IV, laminin, and fibronectin, along with cell adhesion molecules and immobilized signaling proteins that regulate cell positioning and intercellular communication during BBB development and maintenance (Sorokin, 2010).

The BBB is not static walls but **dynamic, regulatory interfaces** that:

- Maintain a precisely controlled ionic and chemical environment for neuronal activity;
- Protect the brain from neurotoxic plasma components and peripheral neurotransmitters;
- Regulate the selective uptake of nutrients and metabolites; and

- Depend on complex, intercellular signaling for their structural and functional integrity.

3.5 BBB Dysfunction in Disease Conditions

Under pathological conditions, the normally restrictive properties of the BBB can be significantly compromised, creating opportunities for cancer cell extravasation and brain colonization. BBB dysfunction involves multiple mechanisms, including tight junction disruption, increased transcytosis, elevated expression of leukocyte adhesion molecules, basement membrane degradation, and altered cellular coverage by pericytes and astrocytes (Zlokovic, 2008).

Tight junction disruption represents a primary mechanism of BBB compromise, often involving downregulation or internalization of junction proteins. In brain tumors, including primary neoplasm such as glioblastomas, the expression of claudin-1 and claudin-5 is frequently altered, and tight junction morphology becomes disrupted (Liebner et al., 2000). This disruption can be mediated by various factors, including proteolytic enzymes, inflammatory mediators, and growth factors secreted by tumor cells or activated by the tumor microenvironment.

Transcytosis, normally maintained at extremely low levels in healthy CNS endothelium, can be dramatically upregulated during injury and disease states, becoming a major component of BBB dysfunction. This increased vesicle-mediated transcellular transport provides an alternative pathway for molecules and potentially cells to cross the barrier, bypassing the tight junction-dependent paracellular route.

3.6 Mechanisms of Dissemination and Blood-Brain Barrier Crossing

3.6.1 The Metastatic Cascade and CNS Invasion

The formation of brain metastases requires cancer cells to successfully complete a complex multi-step process known as the metastatic cascade. This process begins with local invasion and intravasation at the primary tumor site, followed by survival in the circulation, arrest

within the CNS vasculature, extravasation across the blood-brain barrier, and finally, colonization and growth within the brain parenchyma (Fidler, 2003). Circulating tumor cells must first arrest within the brain's vascular network, a process that occurs primarily in capillaries and postcapillary venules where blood flow velocity is reduced and cellular interactions are facilitated. The brain receives approximately 15-20% of cardiac output, providing abundant opportunities for circulating cancer cells to encounter the CNS vasculature. However, successful arrest requires specific adhesive interactions between cancer cells and brain endothelium, mediated by adhesion molecules, integrins, and other cell surface receptors (Fidler, 2003).

3.6.2 Transcellular and Paracellular Crossing Mechanisms

Cancer cells can potentially cross the blood-brain barrier through both transcellular and paracellular routes, though the relative importance of each pathway in brain metastasis formation remains an area of active investigation. Transcellular crossing involves cancer cells traversing directly through endothelial cells, a process that may exploit existing transcytotic pathways or induce new transcellular routes (Wilhelm et al., 2013). This mechanism allows cancer cells to cross an apparently intact barrier without necessarily disrupting tight junctions. Paracellular crossing requires disruption of intercellular tight junctions, creating gaps between endothelial cells through which cancer cells can migrate. Studies using melanoma cells have demonstrated their ability to reduce transendothelial electrical resistance and disrupt tight junction proteins, leading to increased barrier permeability (Kienast et al., 2010). This disruption often involves proteolytic processes, with cancer cells secreting matrix metalloproteinases, serine proteases, and other enzymes that degrade junction proteins and extracellular matrix components.

Some research has identified specific molecular mechanisms underlying BBB crossing by metastatic cells. Brain-metastatic cells express particular cell-surface markers that facilitate extravasation, including ligands for endothelial receptors and proteases that modify the barrier. For example, the expression of ST6GALNAC5, a sialyltransferase, on circulating breast cancer cells facilitates paracellular crossing of the BBB through mechanisms involving cell surface glycosylation changes (Bos et al., 2009).

Cathepsin S, a cysteine protease expressed by brain-metastatic cells, degrades junctional adhesion molecule 2 (JAM2), contributing to BBB disruption and facilitating cancer cell extravasation (Sevenich et al., 2014). These findings highlight the active role of cancer cells in modifying barrier properties to enable their own extravasation, rather than simply exploiting pre-existing barrier dysfunction.

3.6.3 Temporal Dynamics of Extravasation

The process of cancer cell extravasation across the blood-brain barrier exhibits distinct temporal characteristics compared to extravasation in other organs. In vivo imaging studies have revealed that brain extravasation is significantly slower than in peripheral organs, with some cancer cells requiring up to 14 days to complete the extravasation process (Kienast et al., 2010). This extended timeframe suggests that the BBB presents a more formidable barrier than peripheral endothelium and that successful extravasation requires sustained interactions between cancer cells and the neurovascular unit (Wilhelm et al., 2013). During extravasation, cancer cells undergo dynamic morphological changes, including elongation, rounding, and stretching of vessel walls. Interestingly, brain endothelial cells exhibit retraction rather than covering tumor cells during transmigration, a response that differs from some other vascular beds (Arvanitis et al., 2020). While some studies demonstrate cancer cell-induced damage to endothelial monolayers, the barrier may retain the capacity for self-repair, though this repair may be incomplete or delayed. Intravascular proliferation represents an alternative mechanism by which cancer cells can establish brain lesions without necessarily completing extravasation (Deeken et al., 2007). Some cancer cells can proliferate within the vascular lumen, eventually obstructing vessels and disrupting local BBB integrity, creating secondary opportunities for invasion into the brain parenchyma (Kienast et al., 2010).

3.6.4 Brain Microenvironment and Metastatic Colonization (the Unique CNS Microenvironment)

The brain provides a highly specialized microenvironment that presents both challenges and opportunities for metastatic colonization. Unlike other organs, the brain lacks a conventional lymphatic drainage system, instead relying on the lymphatic system for interstitial fluid

clearance. This unique drainage pattern may influence the distribution and clearance of tumor-associated factors and therapeutic agents within the brain parenchyma. The brain's metabolic demands are extraordinary, consuming approximately 20% of total body glucose and oxygen despite representing only 2% of body weight (Zhang et al., 2024). This high metabolic activity is supported by a dense capillary network, with individual neurons rarely located more than 8-20 micrometers from a brain capillary (Zlokovic, 2008). This extensive vascularization provides numerous potential sites for cancer cell arrest and extravasation but also creates a metabolically demanding environment that colonizing cancer cells must successfully navigate.

3.6.5 Cellular Components and Their Roles in Metastasis

Once cancer cells successfully extravasate into the brain parenchyma, they encounter a complex cellular environment that can either support or inhibit their survival and growth (Deeken et al., 2007). Astrocytes, the most abundant glial cells in the brain, play particularly important roles in determining metastatic success. These cells can exhibit both protective and supportive functions toward metastatic cancer cells, depending on their activation state and the specific molecular context (Nag et al., 2011).

Reactive astrocytes, activated in response to brain injury or tumor presence, can protect cancer cells from chemotherapy-induced apoptosis through the secretion of survival factors and the creation of a protective microenvironmental niche (Lin et al., 2010). These activated astrocytes produce various neurotrophins, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which can promote cancer cell survival and invasion. Additionally, astrocytes secrete inflammatory cytokines such as interleukin-1β, tumor necrosis factor-α, and interleukin-6, which can stimulate cancer cell proliferation and modify the local immune environment (Lin et al., 2010)..

Paradoxically, astrocytes also contribute to BBB maintenance through the secretion of factors that enhance barrier tightness, creating a complex dual role in brain metastasis. The balance between astrocyte-mediated barrier protection and tumor support likely depends on the specific molecular signals present in the metastatic microenvironment and the activation state of the astrocytes themselves (Lin et al., 2010).

Microglia, the resident immune cells of the brain, represent another critical component of the metastatic microenvironment. These cells can exhibit both tumor-suppressive and tumor-promoting functions, depending on their polarization state and the molecular signals they encounter. Activated microglia can secrete cytotoxic factors and recruit additional immune cells to eliminate cancer cells, but they can also produce growth factors and create an immunosuppressive environment that facilitates tumor growth (Nag et al., 2011).

3.6.6 Vascular Interactions and Angiogenesis

The relationship between metastatic cancer cells and the brain vasculature extends beyond the initial extravasation event. Many brain metastases exhibit close associations with blood vessels through a process called vessel co-option, where cancer cells grow along existing vascular structures rather than inducing new blood vessel formation (Kienast et al., 2010). This co-option allows metastatic cells to access nutrients and oxygen from the existing vascular network while potentially avoiding the need for immediate angiogenesis (Kienast et al., 2010)..

The vascular basement membrane plays a crucial supportive role in this process, providing a scaffold for cancer cell attachment and migration. Breast cancer and melanoma metastases frequently exhibit vessel co-option, with cancer cells spreading along the abluminal surface of brain capillaries. This intimate association with the vasculature may also provide protection from immune surveillance and therapeutic interventions (Fidler, 2003).

As metastatic lesions grow, they eventually require additional vascular support, leading to angiogenesis and the formation of new blood vessels (Nag et al., 2011).

However, tumor-induced angiogenesis in the brain often results in abnormal vessel formation, with compromised barrier properties and increased permeability. This neovascularization creates a blood-tumor barrier that differs significantly from the normal BBB, often exhibiting increased permeability to some substances while maintaining restriction to others (Achrol et al., 2019).

3.6.7 Molecular Signaling and Metabolic Adaptations

Successful brain colonization requires cancer cells to adapt to the unique metabolic and signaling environment of the CNS. The brain's high glucose consumption and dependence on aerobic metabolism create specific metabolic demands that metastatic cells must accommodate. Cancer cells that successfully colonize the brain often exhibit enhanced glucose uptake and glycolytic capacity, allowing them to compete effectively with neurons and glial cells for available glucose (Achrol et al., 2019).

The brain microenvironment is rich in specific signaling molecules and neurotransmitters that can influence cancer cell behavior. Neurotrophins, originally identified for their roles in neuronal development and survival, can promote cancer cell survival, invasion, and proliferation. Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are particularly important, with their receptors frequently expressed on brain-metastatic cancer cells.

Chemokine signaling also plays crucial roles in brain metastasis formation and progression. The CXCR4/SDF-1 axis, important for normal neural development and function, can be exploited by metastatic cancer cells for migration, survival, and proliferation within the brain. Similarly, CCR4 and other chemokine receptors facilitate cancer cell migration across brain endothelium and subsequent colonization (Achrol et al., 2019).

3.7 Topographic Predilection of Metastases in Human Medicine

3.7.1 Regional Distribution Patterns

In human beings, brain metastases exhibit distinct patterns of anatomical distribution that reflect both hemodynamic factors and regional variations in the neurovascular environment (Fink et al., 2013). The majority of brain metastases occur in the cerebral hemispheres, particularly in watershed areas between major vascular territories where blood flow transitions between arterial distributions. The frontal and parietal lobes represent the most common sites of metastatic involvement, accounting for approximately 80% of supratentorial metastases (Delattre et al., 1988).

The posterior fossa, including the cerebellum and brainstem, accounts for approximately 15-20% of brain metastases, with the cerebellum being more commonly affected than the brainstem (Fink &

Fink, 2013). This distribution pattern correlates with regional blood flow patterns, as areas receiving higher blood flow volumes are more likely to encounter circulating tumor cells (Delattre et al., 1988). However, the relationship between blood flow and metastatic frequency is not strictly linear, suggesting that additional factors beyond hemodynamics influence metastatic localization (Kienast et al., 2010).

3.7.2 Vascular Architecture and Metastatic Susceptibility

Regional variations in vascular architecture and BBB properties contribute to differential metastatic susceptibility across brain regions (Zlokovic, 2008). The cerebral cortex, with its high capillary density and metabolic activity, provides numerous opportunities for cancer cell arrest and extravasation. The white matter, despite lower capillary density, can still support metastatic growth, particularly along major white matter tracts where blood vessels are aligned with fiber bundles (Bos et al., 2009). Certain brain regions exhibit specialized vascular characteristics that may influence metastatic susceptibility. The circumventricular organs (Fig. 3), including the area postrema, subfornical organ, and median eminence, lack typical BBB properties due to fenestrated capillaries that allow free exchange between blood and brain tissue (Ballabh et al., 2004). While these regions represent potential sites of enhanced cancer cell extravasation, they account for only a small fraction of total brain metastases, possibly due to their small volume and specific microenvironmental characteristics (Kiecker et al., 2018).

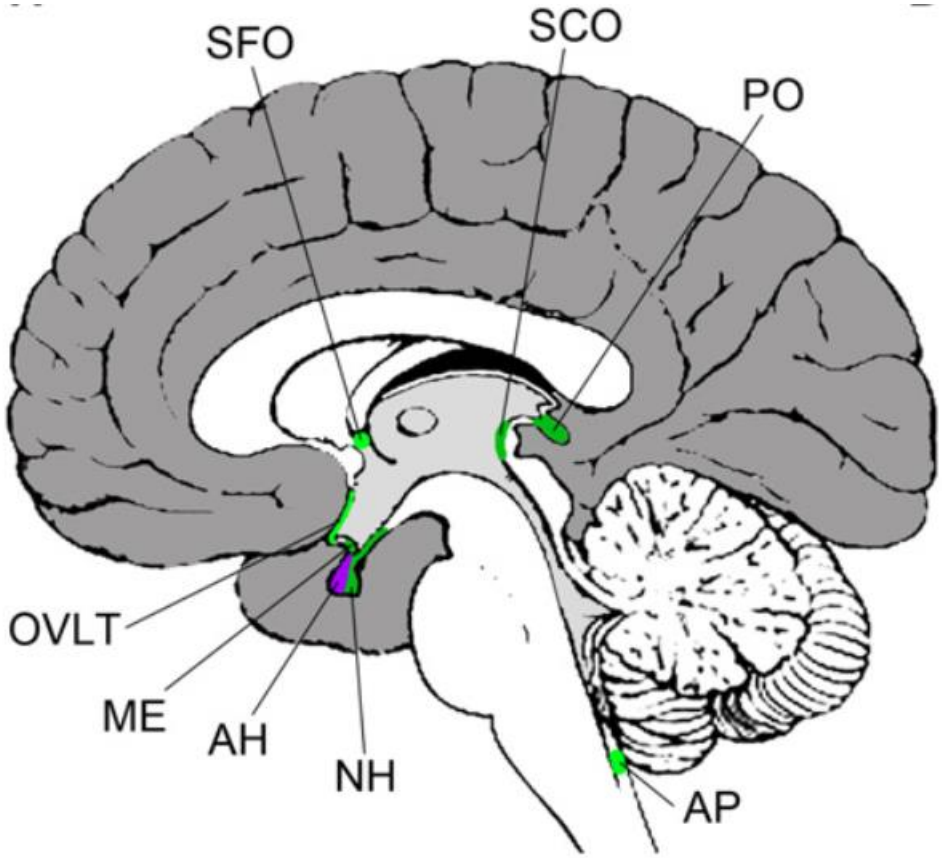

Fig. 5 Topographic anatomy of the circumventricular organs. Mid-sagittal section of a human brain, view of medial surface. The cerebral cortex is coloured in dark grey, the corpus callosum, septum pellucidum, fornix, dorsal and ventral diencephalon, brain stem and cerebellum are shown in white, and the walls of the ventricles in light grey. Circumventricular organs are highlighted in green. The adenohypophysis (AH) is shown in purple. AP, area postrema; ME, median eminence; OVLT, organum vasculosum of the lamina terminalis; PO, pinal organ; SCO, subcommissural organ; SFO, subfornical organ (From: Kiecker C. (2018). The origins of the circumventricular organs. Journal of Anatomy, 232(4):540-553.

The choroid plexus, responsible for cerebrospinal fluid production, exhibits a blood-CSF barrier rather than a typical BBB, with different permeability characteristics (Zlokovic, 2008). Metastases to the choroid plexus are relatively uncommon but can occur, particularly with certain tumor types such as renal cell carcinoma and melanoma (Delattre et al., 1988).

3.7.3 Primary Tumor-Specific Distribution Patterns

Different primary tumor types exhibit distinct patterns of brain metastatic distribution, reflecting both biological properties of the cancer cells and their interactions with specific brain regions (Bos et al., 2009). Lung cancer metastases, the most common source of brain metastases in humans, tend to distribute throughout the cerebral hemispheres with a slight predilection for frontal and parietal regions (Delattre et al., 1988). Small cell lung cancer, despite representing only 20% of lung cancers, accounts for approximately 50% of lung cancer brain metastases, demonstrating the particular neurotropism of this tumor subtype (Schouten et al., 2002).

Breast cancer brain metastases exhibit some regional preferences based on molecular subtype (Bos et al., 2009). HER2-positive breast cancers show enhanced propensity for brain metastasis formation and may exhibit different distribution patterns compared to hormone receptor-positive tumors (Mohammadi et al., 2023). These subtype-specific differences likely reflect distinct molecular mechanisms of BBB crossing and brain colonization.

Melanoma demonstrates one of the highest propensities for brain metastasis formation, with brain involvement found in 40-50% of patients at diagnosis and 70-90% at autopsy (Fife et al., 2004). Melanoma brain metastases can occur throughout the brain but show particular predilection for the frontal and temporal lobes (Stamatovic et al., 2008). The high frequency of melanoma brain metastases may reflect specific molecular characteristics of melanoma cells that facilitate BBB crossing and brain colonization.

3.7.4 Therapeutic Implications and Future Directions

Understanding the mechanisms of BBB disruption in brain metastases has opened new perspectives for therapeutic intervention (Arvanitis et al., 2020). Strategies aimed at restoring or maintaining BBB integrity could potentially prevent cancer cell extravasation while preserving the barrier's protective functions. However, this approach must be balanced against the need for therapeutic agents to reach established brain metastases, creating a complex therapeutic challenge.

Approaches to modulate BBB function include the use of tight junction stabilizers, anti-angiogenic agents to normalize tumor vasculature, and targeted inhibition of specific proteases involved in barrier disruption (Sevenich et al., 2014). The development of brain-penetrant therapeutic agents that can cross an intact BBB while maintaining efficacy against brain metastases represents a critical research priority (Arvanitis et al., 2020).

4. CLINICAL AND DIAGNOSTIC ASPECTS OF BRAIN METASTASES

4.1 Introduction

The clinical and diagnostic aspects of brain metastases represent a complex and evolving field requiring integration of clinical expertise, advanced imaging technology, and sophisticated differential diagnosis considerations. While significant advances have been made in human medicine, many challenges remain in achieving diagnostic accuracy and distinguishing metastases from other conditions in veterinary medicine (May et al., 2024).

4.2 Clinical Presentation

4.2.1 Human Clinical Presentation

The neurological manifestations of brain metastases in humans are diverse and largely dependent on tumor location, size, number of lesions, and the presence of associated vasogenic edema. Most patients initially present with neurological deficits or symptoms indicative of increased intracranial pressure, including headache, nausea, vomiting, epileptic seizure, or other neurological impairments (Mohammadi et al., 2023). The clinical presentation can range from very subtle cognitive changes to dramatic focal neurological deficits.

Seizures represent one of the most common presenting symptoms, occurring in approximately 20-40% of patients with brain metastases at initial diagnosis (Fink & Fink, 2013). These seizures can be focal or generalized and may be the first manifestation of metastatic disease in patients with previously undiagnosed primary cancers. The seizure semiology often provides valuable localization information, with temporal lobe seizures suggesting involvement of the temporal cortex, while motor seizures indicate involvement of the precentral gyrus (Fink & Fink, 2013).

Cognitive dysfunction and personality changes are also frequently observed, particularly with frontal lobe involvement. Patients may exhibit memory impairment, or behavioral alterations that can be subtle initially but progressively worsen as tumor burden increases.

These symptoms are often attributed to other causes, leading to delays in diagnosis (Mohammadi et al., 2023).

Motor deficits, including hemiparesis or hemiplegia, sporadically occur when metastases involve the motor cortex or subcortical motor pathways. Sensory disturbances, visual field defects, and language dysfunction (aphasia) can also occur depending on the specific brain regions affected. Cerebellar metastases typically present with cerebellar ataxia with dysmetria, and coordination difficulties, while brainstem involvement can cause cranial nerve deficits, altered consciousness, and vital sign instability (Fink & Fink, 2013).

4.2.2 Veterinary Clinical Presentations

Information regarding clinical presentation of brain metastases in veterinary medicine are rarely reported in literature. Generally, dogs with brain metastases commonly present with acute or subacute forebrain signs, with seizures being the most frequently reported clinical manifestation (Razmara et al. 2022; Souto et al., 2025; Snyder et al., 2008).

Cranial nerve abnormalities and altered mental status, while less common, can occur with metastases involving the brainstem (Snyder et al., 2008). A recent case report describe unusual presentations including obtundation and multiple cranial nerve deficits associated with cardiac hemangiosarcoma metastases to the brain (Bunn et al., 2021). The clinical course in veterinary patients is often rapid, with many animals being symptomatic at the time of detection and carrying a generally poor prognosis (Snyder et al., 2008).

4.3 Advanced Diagnostic Imaging: Role of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

4.3.1 CT Findings

In human medicine, most brain metastases appear hypodense on non-contrast CT but can be difficult to visualize amidst surrounding hypodense edema (Fink & Fink, 2013). Contrast administration significantly improves detection, even if CT remains less sensitive than MRI, particularly for small lesions. Hemorrhagic metastases are easily identified as hyperdense areas on acute imaging, with density decreasing over 7-10 days as blood products evolve

(Arnold et al., 2020). CT remains valuable for rapid assessment in acute clinical situations and is particularly useful for detecting complications such as hemorrhage, hydrocephalus, or mass effect requiring urgent intervention. In veterinary medicine, CT may be more readily available than MRI in some settings and can provide valuable information, though correlation with histopathology shows that imaging may detect tumors but can misclassify histologic type in some cases (Polizopoulou et al., 2004).

4.3.2 MRI features of Human Medicine Brain Metastases

In human medicine, MRI is unequivocally considered the gold standard for detecting and characterizing brain metastases due to its superior soft-tissue contrast and high-resolution depiction of tissue anatomy (Mohammadi et al., 2023). The standard MRI protocol for brain metastases evaluation typically includes pre- and post-contrast three-dimensional T1-weighted sequences, T2-weighted imaging with fluid-attenuated inversion recovery (FLAIR) to detect vasogenic edema, and increasingly, advanced sequences for problem-solving.

Brain metastases demonstrate characteristic imaging patterns that are remarkably consistent between human and veterinary medicine. On T1-weighted images, metastases are typically iso- to hypointense, while T2-weighted images show variable signal intensity depending on tumor composition and the presence of hemorrhage or necrosis (Fink & Fink, 2013). Different primary tumor types exhibit characteristic imaging features that can aid in differential diagnosis (Figure 6). Breast cancer metastases show variable enhancement patterns depending on molecular subtype, with HER2-positive metastases tending to occur in the occipital lobe and cerebellum, often presenting with smooth contours and solid composition (Mohammadi et al., 2023). Other breast cancer metastases are often evenly distributed throughout the brain with lobulated contours and cystic necrotic composition. Melanoma metastases may demonstrate T1 hyperintensity due to melanin content, though this finding is inconsistent and depends on the degree of melanin production.

Susceptibility-weighted imaging can help confirm melanoma metastases, as both melanin and blood products are paramagnetic and show characteristic susceptibility artifacts (Fink & Fink, 2013).

Lung cancer metastases, particularly from small cell lung cancer, may show restricted diffusion on DWI due to high cellularity. Renal cell carcinoma metastases are often highly vascular and may show prominent flow voids on T2-weighted sequences, indicating enlarged vessels and hypervascularity (Fink & Fink, 2013).

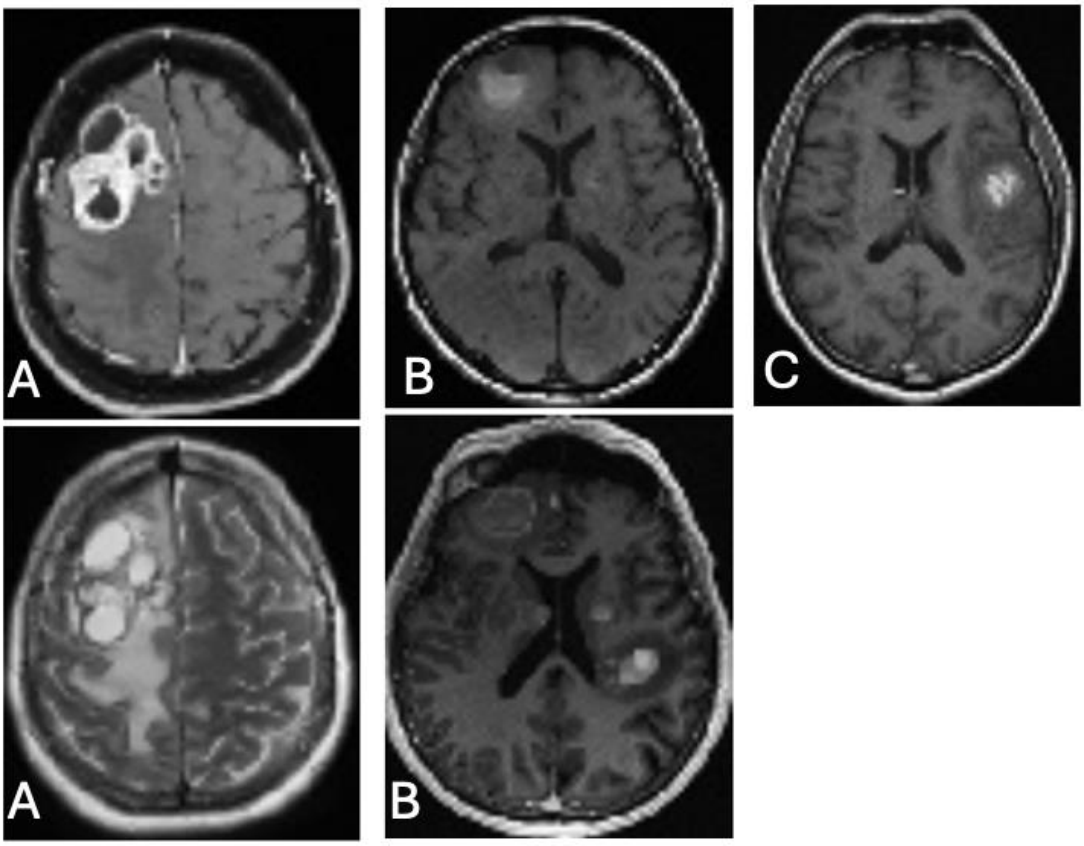

Figure 6: Brain metastases from Breast cancer (A); Melanoma (B); Renal carcinoma (C).
(A) Top: axial contrast-enhanced T1-weighted. Bottom: axial T2-weighted. Cystic components, with centrally low T1-weighted and high T2-weighted signal intensities and rim enhancement. (B) Top: axial pre-contrast T1-weighted revealing brain metastases through increased signal intensity (melanin). Bottom: axial contrast-enhanced T1-weighted revealing even more contrast-enhancing brain metastases. (C): Axial pre- contrast T1W: a single brain metastasis with signal hyperintensity, suggestive of blood products. From: Derks et al. Brain metastases: the role of clinical imaging. *The British journal of radiology* 2022:20210944.

Vasogenic edema is a hallmark feature of brain metastases, appearing as “finger-shaped” extensions of hyperintense signal on T2-weighted and FLAIR images (Mohammadi et al.,

2023). This edema pattern differs from the more infiltrative pattern seen with high-grade gliomas and can be a valuable discriminating feature. However, the amount of edema can be disproportionate to tumor size or may be completely absent in some cases (Derks et al., 2021). Contrast enhancement patterns vary with tumor size and composition. Smaller metastases often show homogeneous enhancement, while larger lesions frequently exhibit ring enhancement due to central necrosis (Fink & Fink, 2013). The enhancement pattern can provide clues about the primary tumor source, with certain primaries showing characteristic patterns.

The sensitivity of MRI for detecting brain metastases has been significantly enhanced by higher field strength systems (3 Tesla versus 1.5 Tesla), which increase sensitivity for small lesions (Mohammadi et al., 2023). Three-dimensional MPRAGE T1-weighted post-contrast imaging has proven more effective than two-dimensional spin-echo sequences for metastasis detection. The use of delayed post-contrast imaging and higher-dose contrast agents like gadobutrol has further improved detection rates (Mohammadi et al., 2023).

The differential diagnosis for brain metastases in human medicine is extensive and requires careful consideration of clinical context, imaging characteristics, and patient history. Solitary enhancing lesions present the greatest diagnostic challenge, as they can be virtually indistinguishable from high-grade gliomas on conventional imaging (Fink & Fink, 2013).

Primary brain tumors, particularly glioblastoma multiforme, represent the most important differential diagnosis for solitary metastases. While certain imaging features may suggest one diagnosis over another, definitive differentiation often requires advanced imaging techniques or histopathological confirmation. Glioblastomas typically show more infiltrative growth patterns with less discrete margins, while metastases tend to be more circumscribed with sharp demarcation from surrounding brain tissue (Fink & Fink, 2013). Infectious processes, particularly brain abscesses, can closely mimic metastases on conventional imaging. Both conditions can present as ring-enhancing lesions with surrounding edema. Diffusion-weighted imaging has proven invaluable in this differentiation, with abscesses typically showing restricted diffusion (low ADC values) due to high cellularity and viscous contents, while metastases generally show elevated ADC values (Fink & Fink, 2013). Inflammatory conditions, including demyelinating diseases and autoimmune disorders, can occasionally mimic metastases. Multiple sclerosis lesions may enhance and cause mass effect

during acute episodes, but the clinical history, lesion distribution, and cerebrospinal fluid analysis usually provide discriminating information (Ömerhoca et al 2018). Vascular lesions, including subacute infarcts and vascular malformations, can present as enhancing lesions with mass effect. The temporal evolution of these lesions and their distribution in vascular territories typically allows differentiation from metastatic disease (Fink & Fink, 2013).

4.3.3 Others MRI Techniques in Human Medicine

Advanced MRI techniques have revolutionized the evaluation of brain metastases beyond simple detection and localization. Diffusion-weighted imaging (DWI) provides information about tissue cellularity through apparent diffusion coefficient (ADC) measurements, helping differentiate metastases from other lesions such as abscesses (Fink & Fink, 2013). Metastases typically show elevated ADC values, while abscesses demonstrate restricted diffusion with low ADC values.

Perfusion-weighted imaging, including dynamic susceptibility contrast (DSC) and arterial spin labeling (ASL), provides valuable information about tumor vascularity and can help differentiate metastases from primary brain tumors. The peritumoral edema surrounding metastases typically shows lower relative cerebral blood volume (rCBV) compared to high-grade gliomas, where the edema contains infiltrating tumor cells with increased vascularity (Fink & Fink, 2013).

Magnetic resonance spectroscopy (MRS) offers metabolic information that can aid in differential diagnosis. Brain metastases often show elevated choline-to-creatine ratios and may demonstrate lipid peaks, particularly in necrotic regions (Mohammadi et al., 2023). The choline-to-creatine ratio can help distinguish between different primary tumor types, with specific patterns associated with non-small cell lung cancer, melanoma, and breast cancer metastases.

Susceptibility-weighted imaging (SWI) has proven particularly valuable for detecting hemorrhagic metastases, which occur in approximately 20% of cases (Fink & Fink, 2013). Melanoma, small cell lung cancer, thyroid cancer, choriocarcinoma, and renal cell carcinoma are the most common sources of hemorrhagic metastases. SWI can detect blood products for extended periods and may reveal lesions not visible on conventional sequences.

4.3.4 Veterinary Medicine Imaging Approaches

In veterinary medicine, MRI with contrast administration is considered the reference standard for evaluating brain pathology due to its superior contrast resolution for soft tissues (May et al., 2024). The diagnostic approach in veterinary medicine closely parallels human protocols, with T1-weighted pre- and post-contrast sequences, T2-weighted imaging, and FLAIR sequences forming the foundation of evaluation.

The challenge of distinguishing metastases from primary brain tumors or inflammatory conditions based solely on imaging characteristics is particularly pronounced in veterinary medicine. Solitary metastases can be indistinguishable from gliomas on conventional MRI, even when their location is unusual (May et al., 2024). Multifocal lesions raise suspicion for metastatic disease, but lymphoma and other conditions can produce similar appearances. Metastatic hemangiosarcomas frequently present as poorly defined, heterogeneous lesions in all sequences, with many lesions containing susceptibility artifact on T2* or SWI associated with moderate to severe perilesional edema and demonstrate moderate to strong heterogeneous or ring-type contrast enhancement (May et al., 2024; Mallol et al., 2022). Metastatic carcinomas also appear as ill-defined lesions that may be T1-weighted hypo- to iso-intense, T2-weighted andFLAIR hyperintense, and are typically contrast enhancing, although the degree and patterns of contrast enhancement can vary significantly. Unlike hemangiosarcoma, metastatic carcinoma lesions are not usually associated with imaging evidence of intratumoral hemorrhage. As melanin is a paramagnetic substance, melanomas may appear as hyperintense lesions on T1W sequences (May et al., 2024).

Advanced MRI techniques are increasingly available in veterinary medicine, though their utilization remains more limited than in human practice. Diffusion-weighted imaging, perfusion MRI, and magnetic resonance spectroscopy are being investigated for their potential to improve diagnostic accuracy in veterinary patients (May et al., 2024). Early results suggest these techniques may provide similar benefits to those observed in human medicine, but more research is needed to establish veterinary-specific protocols and interpretation criteria.

In veterinary medicine, the differential diagnosis for suspected brain metastases includes both neoplastic and non-neoplastic conditions. Primary brain tumors, particularly gliomas, represent major diagnostic considerations especially for single brain metastases. Inflammatory diseases constitute a significant portion of the differential diagnoses in veterinary medicine. Granulomatous meningoencephalitis (GME), necrotizing encephalitis, and infectious conditions including fungal or protozoal disease, can all produce multifocal enhancing lesions that mimic metastatic disease (Cherubini et al., 2005).

Lymphoma deserves special consideration in veterinary medicine as it can present as either primary central nervous system lymphoma or secondary involvement from systemic disease. The imaging characteristics of central nervous system lymphoma often overlap with other metastatic diseases, and the distinction may require additional diagnostic testing including cerebrospinal fluid analysis and systemic staging with abdominal ultrasound and chest X-rays (May et al., 2024).

Vascular lesions, including infarcts and hemorrhages, can occasionally mimic neoplastic disease, particularly in the acute phase when enhancement and mass effect may be present. The temporal evolution and clinical course usually help distinguish these conditions from metastatic disease (Cherubini et al., 2005).

4.3.5 Advanced Diagnostic Approaches

The limitations of conventional imaging in differentiating between various causes of brain lesions have driven the development of advanced diagnostic approaches. In human medicine, hybrid PET/MRI imaging, particularly with amino acid tracers like 18F-fluoroethyltyrosine (FET), has shown remarkable accuracy in distinguishing metastases from other conditions and in differentiating tumor progression from treatment-related changes (Mohammadi et al., 2023). Fluoroethyltyrosine demonstrates high diagnostic accuracy in differentiating radiation injury from tumor progression, a critical distinction in the management of treated brain metastases. Combined PET/MRI analysis has shown improved diagnostic accuracy (95%) compared to either modality alone (63% for PET, 82% for MRI) (Mohammadi et al., 2023).

In veterinary medicine, the integration of advanced imaging techniques with clinical information and diagnostic testing is essential for optimal diagnostic accuracy. The

combination of signalment, neurological localization, whole-body staging for primary tumors, high-quality contrast MRI, cerebrospinal fluid analysis where appropriate, and targeted biopsy when necessary, provides the most comprehensive diagnostic approach (May et al., 2024).

4.3.6 Diagnostic Challenges and Limitations

Several factors complicate the differential diagnosis of brain metastases in both human and veterinary medicine. Treatment-related changes, particularly following radiation therapy, can be extremely difficult to distinguish from tumor progression or recurrence. Both conditions may present with enlarging enhancing masses and surrounding edema, leading to diagnostic uncertainty and potential treatment delays (Mohammadi et al., 2023). The phenomenon of pseudoprogression, defined as an increase in radiological abnormalities months after therapy that does not reflect actual tumor progression, represents a significant diagnostic challenge. Advanced imaging techniques including perfusion MRI and amino acid PET have shown promise in making this distinction but overlap in imaging characteristics can still occur (Mohammadi et al., 2023).

In veterinary medicine, the frequent unavailability of histopathological confirmation is a major limitation in diagnostic accuracy. Many cases rely on presumptive diagnoses based on imaging characteristics and clinical context, which may lead to misclassification in some instances (May et al., 2024).

The effect of corticosteroid therapy on imaging appearance represents another important consideration. Steroids can rapidly reduce contrast enhancement and vasogenic edema, producing “pseudoregression” that can complicate interpretation if imaging is performed after steroid administration (Rossmeisl & Garcia-Mora, 2025).

4.3.7 Prognostic Implications, Future Directions and Emerging Technologies

The diagnostic evaluation of brain metastases carries significant prognostic implications influencing treatment decisions and patient counseling. In human medicine, factors such as number of lesions, size, location, primary tumor type, and patient performance status all contribute to prognosis and treatment selection (Mohammadi et al., 2023). Advanced

imaging techniques can provide additional prognostic information, including assessment of treatment response and early detection of progression.

The field of brain metastasis imaging continues to evolve with emerging technologies showing promise for improved diagnostic accuracy especially in human medicine. Artificial intelligence and machine learning algorithms are being developed to assist in lesion detection, characterization, and differential diagnosis. These systems may eventually provide automated analysis of imaging studies with accuracy comparable to or exceeding human interpretation (Mohammadi et al., 2023).

Advanced MRI techniques continue to be refined, with new sequences and analysis methods being developed. In human medicine, chemical exchange saturation transfer (CEST) imaging has shown potential for detecting treatment-induced metabolic changes and may improve the ability to distinguish tumor progression from treatment effects (Mohammadi et al., 2023).

Liquid biopsy techniques, analyzing circulating tumor cells or cell-free DNA in blood or cerebrospinal fluid, represent a promising approach for non-invasive tumor characterization and monitoring. These techniques may eventually complement imaging studies and provide molecular information to guide treatment decisions.

5. THERAPIES AND PROGNOSIS

5.1 Introduction

The treatment and prognosis of brain metastases represent one of the most challenging aspects of modern oncology (Nieblas-Bedolla et a., 2020), with marked disparities between the sophisticated therapeutic approach available in human medicine and the absence of evidence-based options in veterinary practice. While human medicine has witnessed remarkable advances in targeted therapies, immunotherapies, and precision radiation techniques (Soffietti et al., 2020), veterinary medicine continues to grapple with fundamental knowledge gaps regarding optimal treatment protocols, prognostic factors, and therapeutic outcomes for brain metastases in companion animals. Unlike human medicine, where large-scale clinical trials provide robust evidence for treatment recommendations (Vogelbaum et al., 2021), veterinary medicine lacks the infrastructure and patient populations necessary to conduct definitive studies on brain metastases treatment. This chapter examines the current state of brain metastases treatment across in human medicine, highlighting the sophisticated multimodal approaches available for human patients while emphasizing the critical limitations and knowledge deficits that characterize veterinary practice. The stark contrast between these fields underscores the urgent need for dedicated research in veterinary neuro-oncology to improve outcomes for companion animals with metastatic brain disease.

5.2 Treatments in Human Medicine

5.2.1 Corticosteroids and Symptomatic Management

Corticosteroids are a fundamental part of brain metastases management in human medicine, providing rapid symptomatic relief through reduction of peritumoral edema and stabilization of the blood-brain barrier (Suh et al., 2020; Ryken et al., 2019). Dexamethasone is the preferred agent due to its minimal mineralocorticoid activity and excellent central nervous system penetration. The typical dosing regimen involves 4-8 mg daily. For patients with more

severe symptoms due to increased levels of intracranial pressure, doses of ≥16 mg/day should be considered. If clinically indicated, steroid doses should be tapered within 1 week of initiation and discontinued within 2 weeks in order to avoid the untoward effects of chronic steroid use. The use of corticosteroids must be carefully balanced against potential side effects, including immunosuppression, hyperglycemia, and long-term complications such as osteoporosis and muscle weakness (Suh et al., 2020). Seizures are the presenting symptom in amost 10% of patients with brain metastases. Antiepileptic agents (such as levetiracetam, carbamazepine or lamotrigine) are both widely used for the management of symptoms in patients with brain metastases (Suh et al., 2020). Prophylactive antiepileptic treatment in human being with brain metastases is controversial (Suh et al., 2020). The conclusions of two meta-analyses and a systemic review indicate that prophylactic use of antiepileptic drugs in patients without a previous history of seizures provides no immediate or long-term benefit in patients with brain metastases (Sirver et al., 2004; Tremont-Lukats et al., 2008; Kong et al., 2015). The use of anticonvulsants after surgery is also controversial given the results of a prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumours, which found no statistically significant differences in the incidence or severity of seizures in the anticonvulsant prophylaxis versus control groups (Wu et al., 2013).

5.2.2 Systemic chemotherapies

Traditional cytotoxic drugs have had a limited role in the management of brain metastases owing to their lack of penetration of the blood-brain barrier (BBB) and the presence of efflux pumps (Fortin, 2012). The blood-tumour barrier also poses a challenge to the distribution of systemically administered chemotherapies, although this structure is often compromised in patients with brain metastases. In an analysis of >2,000 brain metastases in two different preclinical models of brain-metastatic breast cancer, a partial compromise in blood-tumour barrier permeability was detected in >89% of lesions; however, the concentration of drugs only reached cytotoxic levels in a relatively small subset (10%) of the most permeable metastases (Lockman et al., 2010). Traditionally, most chemotherapies are used in patients

with refractory disease, once all surgical and radiotherapy options are exhausted. Several trials exploring the use of systemic agents in patients with brain metastases, including commonly used chemotherapies such as cisplatin and pemetrexed, cisplatin and vinorelbine, paclitaxel and cisplatin, pemetrexed and cisplatin, and temozolomide, have failed to show impressive response rates (Suh et al., 2020).

5.2.3 Surgical Interventions

Surgery is an important treatment option for patients with brain metastases. Surgical interventions can provide immediate and effective relief from symptomatic mass effects that are refractory to corticosteroids, enable the removal of large brain tumours that require |decompression, and help to confirm or establish a diagnosis, which is important for patients with no prior history of cancer (Suh et al., 2020). Surgery improves the survival outcomes of patients with a single brain-metastatic lesion and a limited number of extracranial metastases (Noordijk et al., 1994). Furthermore, in selected patients, the removal of multiple brain metastases might be beneficial.

Various surgical approaches have been investigated; enbloc resection, which involves circumferential dissection of the tumour capsule along the brain–tumour interface, rather than piecemeal resection is recommended in order to decrease the risk of local recurrence, particularly in the posterior fossa (Nahed et al., 2019). The risk of leptomeningeal dissemination also seems to be higher after piecemeal rather than en bloc resection of metastases, although larger tumours (>3 cm diameter) cannot always be removed without some internal decompression (Patel et al., 2015).

Modern neurosurgical techniques have significantly improved the safety and efficacy of brain metastasis resection, with gross total resection being the preferred goal when achievable without permanent neurological deficits.

The surgical approach has evolved to incorporate advanced technologies including intraoperative neuronavigation, cortical mapping, and real-time imaging guidance (Vogelbaum et al., 2021).. En bloc resection is recommended when feasible to reduce local recurrence rates, particularly in the posterior fossa location. For patients with multiple

metastases, the removal of symptomatic lesions can provide significant benefit even when complete treatment of all lesions is not possible.

Laser interstitial thermal therapy (LITT) has emerged as a minimally invasive alternative to traditional surgical resection, particularly for deep-seated lesions or recurrent tumors following previous radiation therapy. This technique uses MRI-guided laser energy to achieve tumor ablation while minimizing damage to surrounding normal brain tissue (Vogelbaum et al., 2021).

5.2.4 Radiotherapy

Whole-Brain Radiotherapy

Whole-brain radiotherapy was first described by Chao et al. in the ‘50s demonstrated that external beam X-ray therapy delivered to the whole brain could palliate symptoms in patients with cerebral metastases, with improvement in neurological symptoms in about 60-70% of cases

Whole-brain radiotherapy involves irradiating the entire brain, typically including the leptomeninges, and continues to be an important treatment option owing to the simplicity of delivery and the ability to treat both local and distant intracranial disease (Welsh et al., 2013). Whole-Brain radiotherapy is often considered for patients in whom surgery or stereotactice radiotherapy is not recommended, for example, those with leptomeningeal disease, innumerable metastases, or medical contraindications. However, the role of whole-brain radiotherapy might be ambiguous compared with that of supportive care alone, given the poor survival outcomes typically expected in patients with these characteristics (Yang et al., 2017).

The standard whole-brain radiotherapy dose of 30 Gy in 10 fractions remains the most commonly used regimen when this treatment is selected (Mehta et al., 2003). However, the indications for whole-brain radiotherapy have become more restrictive, typically reserved for patients with multiple metastases not amenable to stereotactic approaches, leptomeningeal disease, or poor performance status (Soffietti et al., 2020).

Acute adverse effects of whole-brain radiotherapy include skin erythema, alopecia, fatigue, serous otitis and an altered sense of smell and taste while late-onset adverse effects, including memory loss, confusion and leukoencephalopathy, are often the most concerning to patients

and physicians. While whole-brain radiotherapy has historically been a mainstay of brain metastases treatment, concerns about neurocognitive toxicity have led to more selective use and the development of strategies to minimize cognitive impact (Soffietti et al., 2020). Modern approaches include hippocampal-avoidance whole-brain radiotherapy and the use of memantine as a neuroprotective agent (Vogelbaum et al., 2021).

Stereotactic Radiotherapy

Stereotactic radiosurgery has revolutionized the treatment of brain metastases, becoming the standard of care for patients with 1-4 intact brain metastases and good general status (Vogelbaum et al., 2021). This technique delivers highly conformal, high-dose radiation in a single fraction or few fractions, achieving excellent local control while minimizing exposure to normal brain tissue (Tsao et al., 2012). The evolution of stereotactic techniques has included the development of frameless systems, improved imaging guidance, and advanced treatment planning algorithms that optimize dose distribution. Single-fraction stereotactic radiosurgery typically delivers 15-24 Gy, depending on tumor size and location, while fractionated stereotactic radiotherapy may deliver 24-35 Gy in 3-5 fractions for larger lesions (Chao et al., 2018).

Neoadjuvant stereotactic radiotherapy, delivered 24-72 hours before surgical resection, represents an innovative approach that combines the benefits of both modalities while potentially reducing complications such as radiation necrosis and leptomeningeal metastases (Tsao et al., 2012).

External-beam radiation therapy is regarded as the standard treatment for non-resectable or incompletely excised intracranial tumors in dogs, with increasing availability in veterinary practice (Geiger, 2025).

Figure 7 illustrates the differences between whole-brain radiotherapy, stereotactic radiotherapy, and whole-brain radiotherapy with hippocampal avoidance.

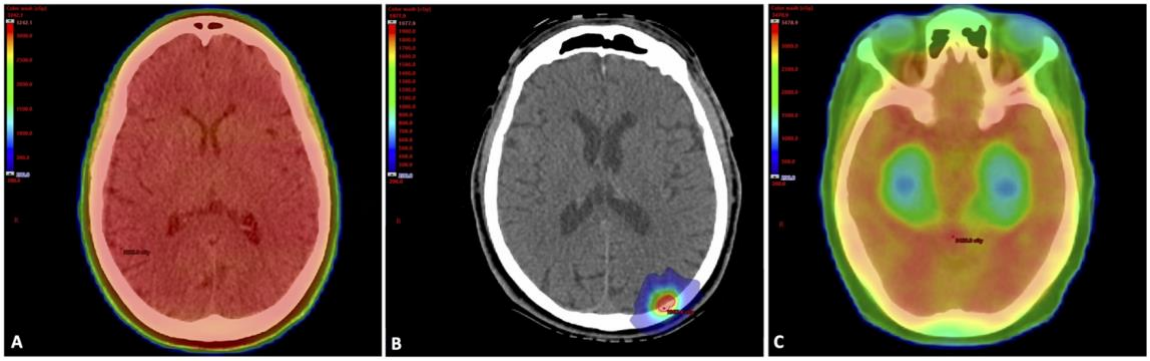

Figure 7 (A) Whole Brain Radiation Therapy Treatment Plan in which the entire brain including areas that play a major role in neurocognition receive the prescription radiation dose. (B) Stereotactic Radiosurgery Treatment Plan for metastatic melanoma who developed a left occipital lobe metastasis. (C) Whole Brain Radiation Therapy with Hippocampal Avoidance Treatment Plan for metastatic breast cancer. Areas in red received the prescription dose, while areas in green and blue represent lower dose areas. Note the sparing of the bilateral hippocampi (from: Lehrer EJ, et al., The Cognitive Effects of Radiotherapy for Brain Metastases. *Front Oncol.* 2022 30;12:893264).

5.2.5 Immunotherapies

The introduction of immune checkpoint inhibitors has transformed the treatment landscape for brain metastases from specific primary tumor types, particularly melanoma and non-small cell lung cancer in human medicine. These agents work by blocking inhibitory pathways that prevent T-cells from attacking cancer cells, thereby enhancing the immune system's ability to recognize and eliminate tumor cells (Nieblas-Bedolla et al., 2020).

Ipilimumab, targeting CTLA-4, was among the first checkpoint inhibitors to demonstrate efficacy in melanoma patients with brain metastases. Subsequent studies with PD-1 inhibitors (pembrolizumab, nivolumab) have shown significant intracranial response rates and improved overall survival. Combination therapy with ipilimumab plus nivolumab has achieved particularly impressive results, with intracranial response rates of 46% in some cohorts (Nieblas-Bedolla et al., 2020).

Information in veterinary medicine regarding immunotherapy treatment for brain metastases is still lacking.

5.2.6 Targeted Therapies

The development of targeted therapies has provided unprecedented treatment options for patients with brain metastases harboring specific molecular alterations. These agents are designed to interfere with specific molecular pathways essential for tumor growth and survival, often achieving superior central nervous system penetration compared to traditional chemotherapy agents (Set al, 2020).

For patients with EGFR-mutant non-small cell lung cancer, third-generation tyrosine kinase inhibitors like osimertinib have demonstrated superior blood-brain barrier penetration and improved CNS objective response rates compared to earlier-generation agents (Vogelbaum et al., 2021).

ALK-rearranged non-small cell lung cancer patients benefit from second and third-generation ALK inhibitors, including alectinib, brigatinib, and lorlatinib, which offer enhanced blood-brain barrier penetration and greater intracranial activity compared to first-generation agents like crizotinib (Vogelbaum et al., 2021).

HER2-positive breast cancer patients with brain metastases have access to targeted therapies, including tucatinib, which has demonstrated improved progression-free and overall survival in combination with trastuzumab and capecitabine. This oral tyrosine kinase inhibitor was specifically designed for enhanced central nervous system penetration (Vogelbaum et al., 2021).

BRAF-mutant melanoma patients can benefit from combination BRAF and MEK inhibition using agents like dabrafenib and trametinib, which have shown improved intracranial response rates compared to single-agent therapy (Vogelbaum et al., 2021).

5.3 Prognosis and Clinical Implications

Information regarding the prognosis for dogs with brain metastases is scarce.

A retrospective study of canine melanoma with central nervous system metastases found that the median survival time after the onset of neurological symptoms was 9.5 days (Razmana et al., 2022).

In cases of canine nasal carcinoma that has spread to the brain, a shift in brain structures, as detected by imaging, is an indicator of a poor prognosis (Wada et al., 2018).

In human medicine, the median survival for individuals with untreated brain metastases was less than six months (Stelzer et al., 2013). Survival varies considerably, depending on multiple factors, and select patient subgroups today can achieve significantly improved outcomes with personalized, multidisciplinary management (Stelzer, 2013).

Several prognostic models have been developed to facilitate individualized patient assessment and treatment selection.

The Karnofsky Performance Status (KPS) is a 0-to-100 scale used by clinicians to evaluate a cancer patient's ability to carry out daily activities and perform ordinary tasks. A higher KPS score indicates a better functional state and a greater ability to perform daily activities. The scale is used to determine a patient's prognosis, assess the effectiveness of therapies, monitor changes in a patient's condition, and decide on a patient's eligibility for clinical trials. The Graded Prognostic Assessment (GPA) is widely used and incorporates factors such as KPS, age, extracranial disease status, and number of BMs. These models can help clinicians estimate survival time and select appropriate therapies (Sperduto et al., 2013).

A patient's prognosis in the setting of brain metastases is depending on many different determinants as described below.

5.3.1 Epidemiological and clinical parameters

- Performance status (Karnofsky Performance Status, KPS): This is probably the single most consistent predictor of outcome and is included in virtually all prognostic indices and scoring systems (Stelzer, 2013).
- Number and volume of brain metastases: Patients with solitary or a limited number of small lesions have substantially better prognosis compared to those with multiple intracranial disease (Gupta et al., 2022).
- Extent of extracranial disease: The presence of active, uncontrolled systemic metastases or progressive extracranial cancer at the time of BM diagnosis portends a shorter survival (Fuchs et al., 2021)
- Age and sex: Younger age is generally favorable. Some evidence suggests women may have a slight survival advantage, potentially linked to underlying tumor biology (Mangesius et al., 2024).

- Interval from primary diagnosis to brain metastasis: A longer interval usually indicates a less aggressive tumor biology and more indolent disease course (Esmaeilzadeh et al., 2024).

5.3.2 Tumor-Specific Variability

Outcomes in braim metastases can also differ substantially according to the type of primary tumor. In non-small cell lung cancer (NSCLC) the median overall survival (OS) after brain metastases diagnosis commonly ranges from 7 to 18 months, with the higher end seen in patients with favorable molecular profiles such as ALK or EGFR mutations, or those treated with extensive local and systemic therapy (Fuchs et al., 2021). In patient with brain metastases due to melanoma prognosis is poor with median OS under 6 months, but patients eligible for immunotherapy, targeted therapies, and stereotactice radiotherapy may live significantly longer (Tan et al., 2022). Renal cell carcinoma is challenging due to radioresistance, yet the advent of novel agents and multimodal approaches has yielded modest improvements (Hasanov et al., 2022).

5.3.3 Treatment Impact

Surgical resection offers a meaningful survival benefit for those with single accessible lesions and is especially effective when combined with adjuvant radiotherapy. Achieving maximal cytoreduction is an independent positive prognostic factor. Stereotactic radiosurgery allows precise targeting, resulting in high local control rates and inferior cognitive toxicity compared to whole-brain radiotherapy (Fuch et al., 2021).

Advances in targeted and immune therapies (systemic therapies) have reshaped the landscape for certain patient populations. For example, the availability of central nervous system-penetrant tyrosine kinase inhibitors and immune checkpoint inhibitors has markedly improved outcomes in melanoma. Conversely, standard cytotoxic chemotherapy generally has limited efficacy due to the blood-brain barrier, except in chemosensitive tumors (Tan et al., 2022).

The treatment and prognosis of brain metastases reveal a striking disparity between the sophisticated, evidence-based approaches available in human medicine and the limited, largely empirical methods employed in veterinary practice. While human patients benefit from an expanding array of targeted therapies, immunotherapies, and precision radiation techniques, veterinary patients face uniformly poor outcomes with limited therapeutic options (Josè-Lopez, 2023).

The fundamental challenge in veterinary medicine is not merely the lack of advanced treatments but the absence of basic knowledge about optimal treatment approaches, prognostic factors, and expected outcomes. This knowledge deficit prevents the development of evidence-based treatment guidelines and complicates clinical decision-making for veterinary practitioners.

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PART II – EXPERIMENTAL STUDY

Okonji S, Rossi F, Sabattini S, Baroni M, Poli F, Zaccone R, Perfetti S, Gandini G, Marconato L. Brain Metastases From Solid Cancers in 58 Dogs. Veterinary Medicine and Science. 2025 Jul;11(4):e70441. *doi: 10.1002/vms3.70441.*

1. Introduction

Metastasis is the leading cause of cancer-related death worldwide, representing the most demanding challenge in modern human medicine (Seyfried and Huysentruyt 2013).

In people, the incidence of brain metastases (BM) has increased, largely due to an ageing population, the advent of targeted therapies that have extended the survival of cancer patients and improvement in early cancer detection (Singh et al. 2022; Kamar and Posner 2010). Approximately 20% of human cancer patients are reported to develop BM; however, necropsy studies suggest the true incidence may reach up to 40% (Nayak et al. 2012; Tabouret et al. 2012; Tsukada et al. 1983). Patients with lung cancer (40%–50%), breast cancer (15%–25%) and melanoma (5%–20%) have the highest prevalence (Singh et al. 2022).

BM are often associated with severe neurologic and cognitive impairment, along with disappointing survival rates. Computed tomography (CT) is typically performed in the acute setting for rapid intracranial assessment and detection of potential neuro- surgical emergencies (Pope 2018). CT is also a useful tool to detect haemorrhage, calcifications, and evaluate osseous structures (J. R. Fink et al. 2015). However, magnetic resonance imaging (MRI) remains the preferred modality for BM detection (Kaufmann et al. 2020). This imaging technique provides excellent soft tissue contrast, allowing for detailed and high-resolution visualization of brain anatomy (Kaufmann et al. 2020). BM pose a treatment dilemma due to the poor permeability of the blood-brain barrier to systemic therapy and their frequent occurrence in advanced-stage disease, indicating significant spread beyond the primary site (Kamar and Posner 2010).

Historically, patients with BM have a poor prognosis, with survival typically measured in weeks if left untreated and months with a multidisciplinary approach (Singh et al. 2022; Kamar and Posner 2010).

Brain metastases also occur in dogs, but their true incidence is difficult to estimate due to limited data, mostly derived from older studies made before the widespread use of advanced imaging. Many of these studies rely on autopsy reports that may relevantly underrepresent the actual number of cases (Song et al. 2013; Kishimoto et al. 2020). Overall, their prevalence is considered low, ranging from 0.2% to 2.2%, with haemangiosarcoma, metastatic carcinomas of various primaries and melanoma historically accounting for the majority of BM (Song et al. 2013; Kishimoto et al. 2020; Snyder et al. 2006). While this trend may reflect the general prevalence of these tumours, certain subgroups of primary malignancies may have a higher biological propensity towards metastatic spread to the brain, as documented in human patients (Nayak et al. 2012; Habbous et al. 2020). The rate of BM may also vary according to primary tumor size, presence of nodal or distant metastases and histologic malignancy (Habbous et al. 2020; Waqar et al. 2018; Koniali et al. 2020).

The aim of this retrospective study was to report the clinical characteristics, primary non-lymphomatous solid cancer histology, advanced imaging findings, treatment modalities and potential prognostic factors in dogs with presumed BM that occurred either at the time of the initial diagnosis or during the follow-up.

2. Materials and Methods

The study did not fall within the application areas of the Italian legislative decree 26/2014, which governs the protection of animals used for scientific or educational purposes; therefore, ethical approval was waived for this study. Dogs were treated according to the current standards. All owners provided written informed consent for the use of their animals' data for scientific purposes.

Electronic medical records of three Italian referral veterinary facilities (Veterinary Teaching Hospital «G. Gentile», Clinica Veterinaria dell'Orologio, Veterinary Clinic Valdinievole) were retrospectively reviewed to identify dogs diagnosed with histologically proven non-lymphomatous solid cancer and suspected BM over a 13-year period (2011-2024), either at the time of the initial diagnosis or during the follow-up. Search terms included: 'metastases', 'metastatic', 'brain', 'cerebral', 'cerebellar' and 'central nervous system'.

Cases were ultimately included if they were diagnosed with BM using one of the following modalities:

1) Total-body computed tomography (TBCT) performed for staging purposes of a primary cancer. Both dogs undergoing TBCT for staging a tumor at its initial presentation and those undergoing TBCT at a later stage due to progression of the known cancer were included. A further 5-minutes delayed scan was added to the standard protocol if a brain lesion was suspected in the first post-contrast series. Brain metastases was diagnosed in the presence of round/oval single or multiple cerebral or cerebellar, as previously described or brain stem space-occupying lesions with variable enhancement, occurring in combination with primary extracerebral cancer, and potentially associated with other sites of metastatic spread (Hecht and Adams 2010; Wisner et al. 2011; Wisner and Zwingenberger 2015; Kraft and Gavin 1999), .
2) Brain MRI performed on dogs with primary extracerebral cancer presenting with clinical signs of intracranial disease. BM were diagnosed based on the presence of intra-axial rounded to oval space-occupying lesions, which appeared isointense to hypointense on T1-weighted images (T1W) and hyperintense on T2-weighted images (T2W), showing homogeneous, heterogeneous or peripheral contrast enhancement. Additional features supporting the diagnosis of BM were the presence of perilesional oedema and a predilection for the grey–white matter junction and vascular border zones (Hecht and Adams 2010). Haemangiosarcoma BM was suspected in cases showing a heterogeneous appearance, particularly when susceptibility effects were present on GET2*-weighted images due to intratumoural haemorrhage (Wisner et al. 2011; Wisner and Zwingenberger 2015). If suspected BMs were identified in dogs initially undergoing brain MRI, additional imaging was conducted to determine the primary origin of the tumor.
3) Necropsy performed on dogs with solid cancer, either with or without neurologic signs.

Overall, dogs with single brain lesions were included if necropsy and histopathology confirmed the metastatic origin, if TBCT revealed concurrent multifocal visceral or nodal secondary lesions, or if MRI features suggested metastatic disease in the presence of an extracerebral solid tumor (Hecht and Adams 2010; Wisner et al. 2011).

Dogs were excluded if an extracranial primary cancer was not identified or if they had multiple synchronous primaries (i.e., two or more different malignant tumor types). Regardless of the method of identification, we chose an arbitrary threshold of 30 days to define the timeframes for classifying BM. Synchronous BM were defined as those detected during the initial diagnosis of the primary neoplasm, while metachronous BM were those identified more than 30 days after the primary cancer diagnosis.

The following clinical and pathologic variables were analysed: signalment (breed, age, sex, weight), primary cancer histotype, date of initial diagnosis of primary cancer, date of BM diagnosis, number, size and location of BM, patterns on TBCT or MRI, neurologic signs, presence/absence and location of extracranial metastases, treatment for BM (none vs. symptomatic vs. antitumoral), date of progression of BM, date and cause of death. The availability of all the above information was not mandatory for inclusion.

All TBCT and MRI studies were reviewed by four authors (two European College of Veterinary Neurology residents, one experienced European College of Veterinary Neurology diplomate, and one experienced European College of Veterinary Diagnostic Imaging diplomate) to identify morphologic TBCT or MRI patterns consistent with BM (Bentley 2015; Mallol et al. 2022; K. R. Fink and Fink 2013). All necropsy studies were conducted by a board-certified veterinary pathologist.

The presence of neurologic signs was gathered from the clinical records and was determined through neurologic examination or, in the case of epileptic seizures, from anamnestic details provided by the owners. Survival data were obtained from the medical records and, if required, through telephone interviews with the owners or referring veterinarians.

2.1 Statistical Analysis

Categorical variables were summarized as frequency (percentage), while numerical variables were summarized as median (range).

Binary logistic regression was applied to assess the influence of potential prognostic variables on the likelihood of developing synchronous BM. Evaluated variables included purebred, sex, age, weight, primary cancer location, tumour histotype, presence of nodal metastases at first presentation and at BM onset, presence of distant metastases at first

presentation and at BM onset, number of BM (solitary or multiple lesions), BM longest diameter (≤ or > 1 cm), and BM location (prosencephalon, brainstem, cerebellum).

Differences in BM characteristics, including lesion number, size and location, among the main tumour histotypes (haemangiosarcoma, carcinoma, melanoma) were also evaluated using binary logistic regression. The effect size of the variables was expressed as odds ratios (ORs) with their corresponding 95% confidence interval (CI).

Survival post-BM (SPBM) was defined as the duration, in days, from the date of BM diagnosis or the onset of neurologic signs or the dogs with BM diagnosed post-mortem to either the date of death or the closure of data collection. Dogs deceased from any cause were considered as events. Death due to tumor-related causes included cases where death or euthanasia was attributed to the primary tumor, extracranial metastases, and/or BM, as it was not always possible to determine the predominant cause.

The influence of the above variables on SPBM was evaluated through univariable and multivariable Cox proportional hazards regression analysis. Continuous variables such as age and body weight were dichotomized using the median value as the cut-off point. Covariates that exhibited a significant *p* value in univariable tests were subsequently incorporated into a multivariable regression model. Data were analysed with SPSS v.26 (SPSS, Inc., IBM, Chicago, IL, USA). $p \leq 0.05$ were considered significant.

3. Results

3.1 Dogs' and Tumors' Characteristics

The database search revealed 78 dogs with presumed BM, all of which were assessed for eligibility. A total of 12 dogs were excluded due to the absence of histologic confirmation of the primary tumor and 8 because imaging was limited to the head only. A total of 58 dogs met the inclusion criteria. There were 45 (77.6%) pure-breed dogs and 13 (22.4%) mixed-breed dogs. The most represented breed was the Boxer (n = 7; 12.1%), followed by the German Shepherd (n = 4; 6.9%), whereas 20 breeds were represented once or twice. A total of 35 (60.3%) dogs were males (10 neutered), and 23 (39.7%) were females (14 neutered). The median age was 11 years (range, 6–16), and the median weight was 27.6 kg (range, 3.7–46.0). The most common primary cancer histotypes were

haemangiosarcoma (*n* = 31; 53.4%) and carcinoma (*n* = 16; 27.6%), followed by melanoma (*n* = 7; 12.1%), undifferentiated sarcoma (*n* = 3; 5.2%) and stromal sarcoma (*n* = 1; 1.7%).

Overall, BM were diagnosed at initial presentation in 37 (63.8%) dogs (synchronous metastases), while in the remaining 21 (36.2%) dogs, BM were diagnosed during the course of the disease (metachronous metastases) after a median time of 339 days (53–1021) from initial primary cancer diagnosis. Dogs and tumour features are listed in Table 1.

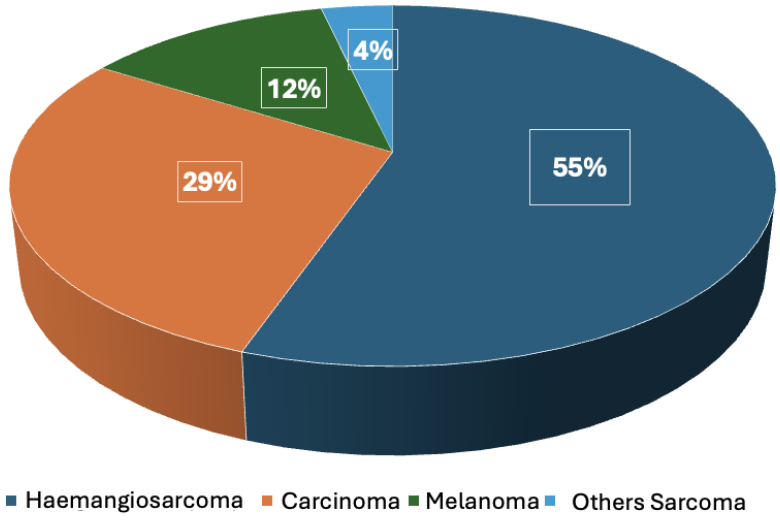

Figure 1: subdivision of brain metastases classified by histotype.

	Haemangiosarcoma (*n* = 31)	Carcinoma (*n* = 16)	Melanoma (*n* = 7)
Age (median [range])	11 (7–14) years	11 (6–16) years	11 (10–15) years
Sex			
Male	20 (64.5%)	8 (50.0%)	5 (71.4%)
Female	11 (35.5%)	8 (50.0%)	2 (28.6%)
Primary tumour location	spleen (*n* = 11), heart (*n* = 8), skin/subcutis (*n* = 3), liver (*n* = 2), lung (*n* = 2), retroperitoneum (*n* = 2), muscle (*n* = 1), kidney (*n* = 1), bone (*n* = 1)	mammary gland (*n* = 4), lung (*n* = 4), nasal cavity (*n* = 1), skin (*n* = 1), liver (*n* = 1), anal sac (*n* = 1), prostate (*n* = 1), kidney (*n* = 1), digit (*n* = 1), thyroid gland (*n* = 1)	oral (*n* = 5), digit (*n* = 2)
Nodal metastasis at presentation	1 (3.2%)	7 (43.8%)	2 (28.6%)
Distant metastasis at presentation	27 (87.1%)	7 (43.8%)	3 (42.9%)
Timing of BM			
Synchronous	26 (83.9%)	8 (50%)	0 (0.0%)
Metachronous	5 (16.1%)	8 (50%)	4 (100.0%)
Presence of neurologic signs	17/23 (73.9%)	10/13 (76.9%)	6 (85.7%)
BM location			
Prosencephalon	29 (93.5%)	16 (100.0%)	6 (85.7%)
Brainstem	4 (12.9%)	0 (0.0%)	0 (0.0%)
Cerebellum	6 (19.4%)	3 (18.8%))	1 (14.3%)
BM maximum diameter (median [range])	13 (2–40) mm	15 (8–26) mm	11 (6–30) mm
Number of BM			
Single	11 (35.5%)	11 (68.8%)	7 (100.0%)
2–10	17 (54.8%)	5 (31.2%)	0 (0.0%)
> 10	3 (9.7%)	0 (0.0%)	0 (0.0%)
Nodal metastasis at BM diagnosis	5 (16.1%)	10 (62.5%)	1 (14.3%)
Distant metastasis at BM diagnosis	29 (93.5%)	11 (68.8%)	5 (71.4%)

Table 1 Main demographic and clinical findings observed in a cohort of dogs with brain metastasis, stratified by primary tumour histotype

3.2 Dogs With Haemangiosarcoma

Regarding the 31 dogs with haemangiosarcoma, the presence of BM was documented through TBCT in 20 (64.5%), MRI in 5 (16.1%), and necropsy in 6 (19.4%) dogs. The necropsy was also performed on two of the dogs diagnosed via TBCT and on one

diagnosed through MRI. In all these nine cases undergoing necropsy, the diagnosis of BM from haemangiosarcoma was confirmed.

The primary tumour was localized in the spleen (*n* = 11, 35.5%), heart (*n* = 8, 25.8%), skin/subcutis (*n* = 3, 9.6%), liver (*n* = 2, 6.5%), lung (*n* = 2, 6.5%), retroperitoneum (*n* = 2, 6.5%), muscle (*n* = 1, 3.2%), kidney (*n* = 1, 3.2%) and bone (*n* = 1, 3.2%).

At the initial diagnosis, 26 (83.9%) dogs had synchronous BM, and the remaining 5 (16.1%) developed metachronous BM after a median time of 240 days (range, 142–392). At the time of BM diagnosis, all but two dogs had either distant (*n* = 24; 77.4%) or nodal and distant (*n* = 5; 16.1%) metastases.

A total of 11 (35.5%) dogs had a single brain lesion, while in the remaining dogs, the median number of BM was 7 (range, 2– 100). Lesions were located in the prosencephalon (*n* = 22, 70.9%), prosencephalon and brainstem (*n* = 3, 9.7%), prosencephalon and cerebellum (*n* = 3, 9.7%), cerebellum only (*n* = 2, 6.5%), and prosencephalon, cerebellum and brainstem (*n* = 1, 3.2%). The median maximum diameter was 13 mm (range, 2–40). The imaging characteristics are listed in Tables 2 and 3. Information regarding the presence of neurologic signs was available for 23 (74.2%) dogs at the time of BM diagnosis. Neurologic signs were documented in 17 (73.9%) dogs. Forebrain clinical signs were described in 8 dogs, including seven patients with only epileptic seizures and one case with left pleurothotonus and bilateral reduction in menace response. Obtundation, suggestive of brainstem involvement or increased intracranial pressure, was observed in seven dogs. In two dogs, it was associated with mild to moderate tetraparesis. Six (26.1%) dogs had no neurologic signs. Four out of the 26 dogs with synchronous BM underwent antitumoural treatment, consisting of metronomic therapy in 3 dogs and splenectomy due to a ruptured tumour in 1 dog. Two dogs received palliative care.

The 5 dogs with metachronous BM had also received treatment at the time of their primary cancer diagnosis, consisting of surgery and doxorubicin (*n* = 3), surgery and toceranib (*n* = 1), or surgery only (*n* = 1). At the onset of BM, none of them received additional treatment. All dogs died due to tumour-related causes with a median SPBM of 1 day (range, 1–131).

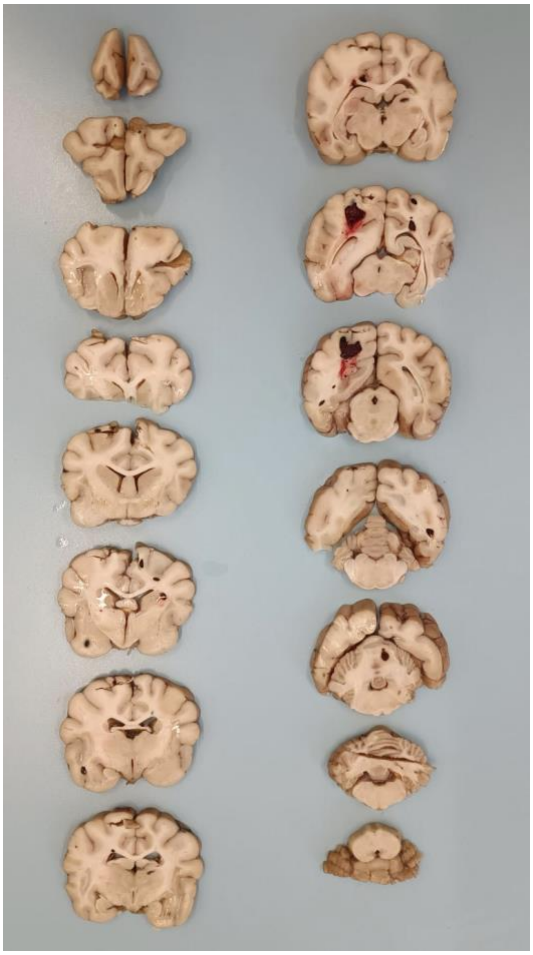

Image 1: Multiple transverse sections of formalin-fixed of the brain of a dog from our study population showing the presence of multiple lesions in the forebrain and cerebellum. Histological examination has confirmed a heamangiosarcoma.

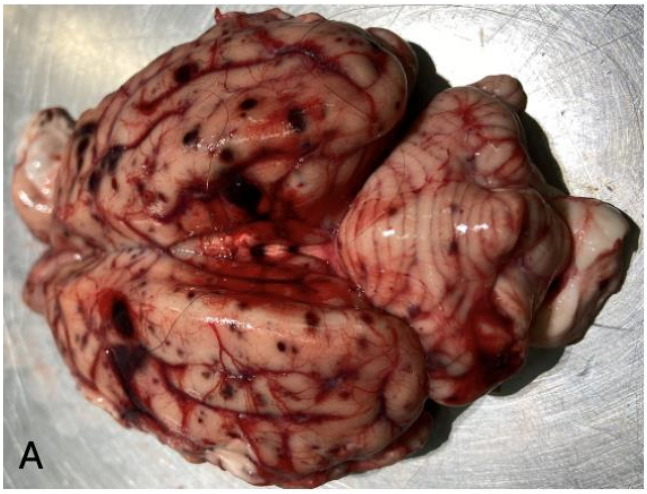

Image 2: Fresh, unfixed (A) and formalin-fixation, transverse section (B) of the brain of a dog of our study showing multiple and millimetric brain metastase from heamangiosarcoma localized throughout the brain.

3.3 Dogs with carcinoma

Among the 16 dogs with carcinoma, the presence of BM was documented through TBCT in all cases. The following primary sites were described: mammary gland (*n* = 4, 25%), lung (*n* = 4, 25%), and one (6.3%) each of nasal cavity, skin, liver, anal sac, prostate, kidney, digit and thyroid gland. Eight (50%) dogs had synchronous BM, and the remaining eight (50%) dogs developed metachronous metastases after a median time of 399 days (range, 53–657). Metachronous metastases occurred in 3 (75%) dogs with mammary carcinoma, whereas all (100%) lung cancer cases had synchronous metastases.

At the time of BM diagnosis, seven (43.8%) dogs had nodal and distant metastases. Four (25%) dogs had only distant metastases, and three (18.8%) dogs only had nodal metastases.

A total of 11 (68.8%) dogs had a single brain lesion, while the remaining 5 (31.3) had a median number of 5 lesions (range, 2–7). Lesions were located in the prosencephalon (*n* = 13, 81.3%) and prosencephalon and cerebellum (*n* = 3, 18.7%). The median maximum diameter was 15 mm (range, 8–26). The imaging characteristics are listed in Table 2.

Information regarding the presence of neurologic signs was available for 13 (81.3%) dogs at the time of BM diagnosis.

Neurologic signs were documented in 10 (76.9%) dogs. Forebrain clinical signs were observed in eight dogs, including three dogs with only epileptic seizures, disorientation in three cases, and epileptic seizures associated with compulsive aimless gait and disorientation in two patients. One dog exhibited a hypermetric gait followed by progressive tetraparesis, indicative of cerebellar involvement, while one dog showed obtundation. Three (23.1%) dogs showed no neurologic signs. Only one of the eight dogs with synchronous metastases received treatment consisting of toceranib.

Seven out of the 8 dogs diagnosed with metachronous BM had received treatment at the time of their primary cancer diagnosis. Treatments included surgery alone (n = 3), surgery and metronomic therapy (n = 1), surgery and toceranib (n = 1), radiation therapy and toceranib (n = 1) and radiation therapy alone (n = 1). At the onset of BM, two dogs continued to receive toceranib and metronomic therapy, respectively, and two dogs received palliative care. All dogs died due to tumour-related causes with a median SPBM of 7 days (range, 1–137).

3.4 Dogs with melanoma

Among the seven dogs included in this cohort, five (71.4%) had oral melanoma, and two (28.6%) had digit melanoma. The presence of BM was documented through TBCT in three (42.9%) dogs, MRI in one (14.3%), and necropsy in three (42.9%) dogs. The necropsy was also performed on one of the dogs diagnosed via TBCT, histologically confirming the diagnosis.

All dogs developed metachronous metastases after a median time of 339 days (range, 247–1021) from the initial primary cancer diagnosis. At the time of BM diagnosis, four (57.1%) dogs had only distant metastases and one (14.3%) dog had distant and nodal metastases.

All dogs had a single lesion, located in the prosencephalon in six (85.7%) and in the cerebellum in one (14.3%); the median maximum diameter was 11 mm (range, 6–30). The imaging characteristics are listed in Tables 2 and 3.

At the time of the BM diagnosis, neurologic signs were documented in six (85.7%) dogs. These signs included forebrain signs (n = 4), such as compulsive aimless gait and disorientation in two dogs and epileptic seizures in the other two. One dog exhibited reduced menace response in the left eye, while another showed obtundation. One (14.3%) dog showed no neurologic signs. All dogs received treatment for the primary cancer, consisting of surgery (n = 4) or radiation therapy (n = 3); six dogs were also treated with chemotherapy. At the onset of BM, four (57.1%) dogs received treatment: symptomatic care in two cases and investigational immunotherapy in the other two. All dogs died due to tumour-related causes with a median SPBM of 21 days (range, 1–255).

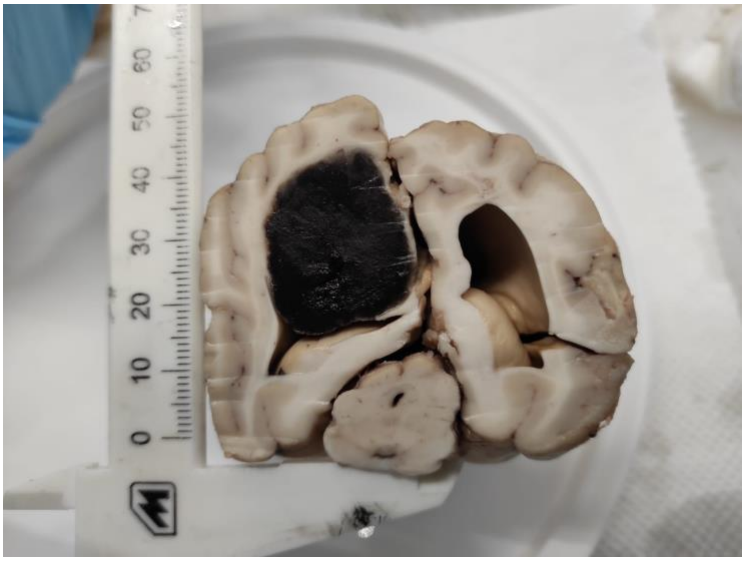

Image 3 formalin-fixed, transverse section of brain tissue showing a single space occupying lesion at the level of the forebrain. Histological examination has confirmed a melanoma.

3.5 Dogs With Sarcoma Other Than Haemangiosarcoma

Among these 4 dogs, three had an undifferentiated sarcoma involving, respectively, the subcutis, gastric wall and scapula, whereas one dog had a splenic stromal sarcoma. The presence of BM was documented through TBCT in two (50%) dogs at the time of initial cancer staging, MRI in one (25%) at the onset of neurologic signs, and necropsy in one (25%) dog. Three (75%) dogs had synchronous BM, while the remaining dog with gastric wall sarcoma developed metachronous metastases after 461 days. At the time of the BM

diagnosis, three (75%) dogs had distant and nodal metastases, and one (25%) only had distant metastases.

One (25%) dog had a single brain lesion, and the other three (75%) had a median number of 5 BM (range, 2–10). In all dogs, BM were located in the prosencephalon and had a median maximum diameter of 7 mm (range, 2–15). Based on TBCT, BM were well-defined in both dogs, had intense contrast enhancement, and exhibited ring enhancement. In no case was there evidence of mass effect or perilesional oedema. The single lesion in the dog undergoing MRI was ill-defined, had intense contrast enhancement, and showed homogeneous enhancement. There was no evidence of mass effect or perilesional oedema. At the time of the BM diagnosis, neurologic signs were documented in one (25%) dog only, presenting with obtundation. The three dogs with synchronous BM received no treatment. The dog with gastric wall sarcoma initially received chemotherapy (carboplatin) but did not undergo additional treatment at the onset of BM. All dogs were dead due to tumour-related causes with a median SPBM of 1 day (range, 1–49).

	Haemangiosarcoma (*n* = 20)	**Carcinoma (*n* = 16)**	**Melanoma (*n* = 3)**
Margins			
Well-defined	12 (60.0%)	10 (62.5%)	2 (66.7%)
Poorly demarcated	8 (40.0%)	6 (37.5%)	1 (33.3%)
Contrast enhancement			
Mild	0 (0.0%)	0 (0%)	0 (0.0%)
Moderate	5 (25.0%)	1 (6.2%)	1 (33.3%)
Intense	15 (75.0%)	15 (93.8%)	2 (66.7%)
Type of enhancement			
Homogeneous	9 (45.0%)	9 (56.2%)	2 (66.7%)
Heterogeneous	2 (10.0%)	0 (0.0%)	0 (0.0%)
Ring	9 (45.0%)	7 (43.8%)	1 (33.3%)
Mass effect	10 (50.0%)	15 (93.8%)	1 (33.3%)
Perilesional oedema	4 (20.0%)	11 (68.8%)	0 (0.0%)

Table 2 Main computed tomography findings observed in a cohort of dogs with brain metastasis, stratified by primary tumour histotype.

	Haemangiosarcoma (n = 5)	Carcinoma (n = 0)	Melanoma (n = 1)
Margins			
Well-defined	4 (80.0%)	—	1 (100.0%)
Poorly demarcated	1 (20.0%)	—	0 (0.0%)
Contrast enhancement			
Mild	0 (0.0%)	—	0 (0.0%)
Moderate	2 (40.0%)	—	0 (0.0%)
Intense	3 (60.0%)	—	1 (100.0%)
Type of enhancement			
Homogeneous	5 (100.0%)	—	0 (0.0%)
Heterogeneous	0 (0.0%)	—	0 (0.0%)
Ring	0 (0.0%)	—	1 (100.0%)
Mass effect	4 (100.0%)	—	1 (100.0%)
Perilesional oedema	4 (100.0%)	—	1 (100.0%)

TABLE 3 Main magnetic resonance imaging findings observed in a cohort of dogs with brain metastasis, stratified by primary tumour histotype.

3.6 Outcome and Statistical Analysis

At data analysis closure, all dogs had died. In 38 (65.5%) dogs, the cause of death was attributable to BM. The overall median SPBM was 3 days (range, 1–255). The 3- and 6-month survival rates were 8.6% and 1.7%, respectively. Among the 16 dogs receiving treatment for their BM, either antitumoural or symptomatic, 5 (31.3%) had a clinical benefit, defined as an temporary improved quality of life according to the owners. None of the investigated variables was significantly associated with a shorter SPBM.

Dogs with primary cancer locations in the heart, lung and bone (OR: 5.1; 95% CI, 1.0–25.6; $p = 0.046$), dogs with haemangiosarcoma (OR: 7.6; 95% CI, 2.2–25.8; $p = 0.001$) and those with distant metastases at presentation (OR: 16; 95% CI, 4.2–60.9; $p < 0.001$) had an increased likelihood of developing synchronous BM.

Dogs with haemangiosarcoma were more likely to have multiple BM (OR: 4.2; 95% CI, 1.3–13.3; $p = 0.015$). No other significant relationships were observed between tumour histotype and BM characteristics. Dogs with carcinoma were more likely to have nodal

metastases both at first presentation (OR: 4.7; 95% CI, 1.3– 17.3; p = 0.021) and at BM diagnosis (OR: 6.1; 95% CI, 1.7–21.4. p = 0.005).

4. Discussion

Brain metastases develop following the haematogenous spread of cells from a primary tumour to the brain microvasculature. This complex process unfolds over several stages and requires cancer cells with specific genetic traits that enable them to breach the blood-brain barrier and adapt to the brain's unique microenvironment (Liotta and Kohn 2003). Cancer cells invade blood vessels by degrading the extracellular matrix and enter circulation, where they form protective clusters or suppress immune responses to survive hostile conditions. Upon reaching the brain microvasculature, they arrest capillaries and extravasate by adhering to the endothelium and disrupting the blood-brain barrier through enzymatic degradation or co-opting leukocyte pathways. Once in the brain, metastatic cells exploit local growth factors and modulate glial and immune responses to establish a supportive, tumour-permissive microenvironment. To sustain growth, they induce angiogenesis, forming new blood vessels for oxygen and nutrients (Izadi et al. 2025).

In this study, we analysed 58 dogs with histologically confirmed primary solid tumours and BM documented via advanced imaging (TBCT/MRI) or necropsy findings. Strict inclusion criteria were applied to minimize potential misclassification and enhance diagnostic accuracy.

In line with previous literature, haemangiosarcoma was the most prevalent histotype, accounting for 53% of cases (Song et al. 2013; Snyder et al. 2006). Haemangiosarcoma, originating from pluripotent bone marrow progenitor cells, quickly reaches the circulatory system, which makes it prone to metastasis in virtually any organ, including the brain. Among the 31 haemangiosarcomas, 11 (35.5%) originated from the spleen and 8 (25.8%) from the heart.

We also found that dogs with haemangiosarcoma were more likely to develop synchronous BM compared to other malignancies; additionally, BM were more likely to be multiple. It is likely that haemangiosarcoma, due to its origin, can hijack pre-existing

blood vessels through the mechanism of vascular co-option, resulting in diffuse brain colonization after having crossed the blood-brain barrier (García-Gómez and Valiente 2020). Vascular co-option occurs when cancer cells integrate into the architecture of pre-existing blood vessels instead of inducing the formation of new ones. This process is particularly advantageous for tumors like haemangiosarcoma, as it allows for rapid establishment in well-vascularized tissues such as the brain. By adhering to and migrating along the endothelial lining of host vessels, tumor cells can gain access to nutrients and oxygen necessary for survival and proliferation without the time and resource-intensive process of angiogenesis (Harris et al. 2024).

These results suggest the need for increased awareness regarding the possibility of intracranial spread in dogs with haemangiosarcoma.

Carcinoma (27.6%) and melanoma (12.1%) were also common types of cancer presenting with BM, in line with previously reported data (Song et al. 2013). Among carcinomas, four (25.0%) dogs had a primary mammary malignancy, and four (25.0%) additional dogs had a primary lung tumor. The finding in the lung is noteworthy, as it has not been reported previously and because it mirrors what has been described in humans (Siegel et al. 2020).

Overall, in the current study, 63.8% of dogs had synchronous BM. However, this result should be interpreted with caution, as it may reflect the greater likelihood of performing advanced diagnostics and/or necropsy at the time of initial presentation rather than the true prevalence of synchronous BM. Notably, all dogs with melanoma in this study developed metachronous BM, compared with 8 out of 16 (50%) cases of carcinoma and out of 31 (16.1%) cases of haemangiosarcoma. Within the carcinoma group, 75% of mammary cancers had metachronous BM, while 100% of lung carcinomas had synchronous BM. This pattern may, in part, be due to how these tumors are typically detected: mammary cancer and melanoma are often identified during physical examination, allowing for timely treatment. As survival rates improve for dogs with treated malignancies, the likelihood of BM development over time may also increase. In contrast, malignancies originating from internal organs, such as lung carcinoma and haemangiosarcoma, are frequently diagnosed at advanced stages, potentially explaining the higher incidence of synchronous BM in these dogs.

The prosencephalon was more frequently involved, regardless of the histotype, which is in line with previous reports (Song et al. 2013; Snyder et al. 2006). In human medicine, the distribution of BM varies depending on the type of primary cancer, suggesting that different tumor histotypes may follow distinct metastatic pathways (Cardinal et al. 2021). This pattern of dissemination has been used to help predict the primary tumor site in human patients. Unfortunately, in our study, we were unable to establish any correlation between tumor histotype and the specific brain region affected, likely due to the limited sample size, which restricted our ability to detect potential associations. However, it remains possible that similar histotype-specific metastatic patterns exist in dogs, warranting further investigation in larger studies. Another noteworthy finding is that 30 (51.7%) dogs had a single BM, consistent with human data (Nayak et al. 2012). Additionally, all (100%) dogs with melanoma had a solitary lesion. The diagnosis was obtained via TBCT in 23 (76.7%) dogs, necropsy in 4 (13.3%), and through MRI in 3 (10%). Although we cannot exclude that the number of BM depends on the specific cancer type, as some malignancies are more likely to metastasize to the brain in a multifocal pattern rather than forming solitary lesions, it is also possible that the number of BM was underestimated if CT was used as the imaging technique. In the current study, 36.6% of patients undergoing CT showed multiple lesions, while MRI conducted on seven dogs revealed multiple lesions in 71.4% of them. This difference may underscore the greater sensitivity of MRI in detecting BM. Similarly, in human medicine, the limitations of CT in detecting the number of BM are well recognized. Approximately 19% of patients with a solitary metastasis on contrast-enhanced CT are found to have multiple metastases on a contrast-enhanced MRI (Schellinger et al. 1999). The number of BM may also have been underestimated in cases diagnosed through necropsy alone, particularly if only gross examination was performed without extensive histopathological sampling. While the majority of dogs showed neurologic signs, 21% of dogs had asymptomatic BM, suggesting that intracranial pathology may be underreported in historical data. Interestingly, all asymptomatic dogs had forebrain metastases. This intriguing finding reflects the ability of the canine forebrain to ‘mask’ brain involvement and produce obvious clinical signs only in the most severe cases. These results suggest a potential role for surveillance brain imaging in dogs with solid cancers

displaying neurotropism. However, it is currently unclear whether detecting occult BM provides a survival benefit by enabling treatment of the brain.

In our patient group, the presence of BM was associated with multiple distant and/or nodal metastases in 89.7% of cases, and BM was the sole site of tumour spread in only 10.3% of dogs. This information is crucial for clinicians and radiologists and supports the use of combined brain MRI and TBCT for comprehensive staging if BM are suspected.

There is no established treatment of choice against BM reported in veterinary medicine. Here, over 70% of dogs did not receive any treatment, whereas 15.5% of dogs underwent various medical antitumoural treatments. Although survival was not extended, some clinical benefit was reported in a small subset of treated dogs. Due to the small sample size and the heterogeneity of treatments, no definitive conclusions can be drawn.

The prognosis was poor, and the majority of dogs (65.5%) died due to BM, indicating that brain spread probably represents a final event in the course of the disease. The median survival after BM diagnosis was 3 days, and the 6-month survival rate was 1.7%. The reason can be attributed to the severe clinical condition, the lack of effective therapies and/or the poor control of extracranial disease, considering that nearly all dogs had distant metastases at the time of diagnosis of BM. It is important to note, however, that this figure includes both spontaneous deaths and euthanasia. Therefore, the high proportion of BM-related deaths may be influenced by a decision-making bias: many owners may opt for euthanasia upon the onset of neurologic signs or following the diagnosis of BM based on anticipated deterioration and limited treatment options. This potential bias should be considered when interpreting the data.

This study carries all the limitations and biases of a retrospective design. The number of dogs was small, given the rarity of the diagnosis, which limited the statistical analysis. Not all dogs underwent specialized neurologic examination, which may have led to an underestimation of mild neurologic deficits, particularly in dogs that were not initially evaluated at a neurology referral clinic. However, all dogs underwent a detailed anamnesis to assess for seizures or other behavioural abnormalities, as well as a thorough physical examination that included key neurologic parameters such as mental status and gait assessment. These parameters are frequently altered in patients with intracranial pathology and provide valuable clinical insight, even in the absence of a complete

neurologic evaluation. Similarly, not all dogs underwent standardized diagnostic work-up. The majority were evaluated using CT, with only seven undergoing MRI. Additionally, only a small subset of dogs received antitumoural therapy, which was exclusively pharmacologic. Therefore, it is not even possible to speculate on whether local therapies, such as surgery and radiotherapy, commonly used in human patients with BM, may have any efficacy in dogs. Additionally, only 14 dogs underwent necropsy, definitively confirming the presence of metastases and their origin. Unfortunately, ante-mortem biopsies are rarely proposed, both due to technical difficulties and because it would be unethical in fragile patients with a short life expectancy.

Due to the study design and the fact that one centre is referred for neurology cases only, it was not possible to calculate the prevalence by comparing demographics with dogs without BM. Therefore, it remains currently unknown how frequently dogs with haemangiosarcoma and carcinoma exhibit or develop BM.

Lastly, due to the retrospective nature of the study and variability in MRI unit types and magnet strengths, MRI protocols were not standardized. As a result, certain specialized sequences, such as susceptibility-weighted imaging, were not consistently included. These sequences could have been useful in better characterizing the observed lesions (Delmaire et al. 2015).

5. CONCLUSION

Our study found that haemangiosarcoma, carcinoma and melanoma accounted for the majority of all BM. Although this is largely due to the prevalence of these tumors, it also reflects the organotropism of certain malignancies toward the brain. BM were more often synchronous and symptomatic; nevertheless, a subset of dogs exhibited no neurologic signs. MRI more frequently revealed multiple BM, while CT demonstrated extracranial metastatic spread, supporting the diagnosis of BM. The prognosis was poor, regardless of the primary cancer type. Collaborative multi-institutional studies, including cooperation between the oncologist, the neurologist and the radiologist, are warranted to improve the knowledge and early detection of BM, which would lead to the development of efficacious treatments.

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