NEOPLASIA

Central nervous system neoplasia

Francois-Xavier Liebel, Peter M. Smith

Seizures can be the first sign noticed by owners of animals with intracranial neoplasia. This article looks at the key features that should prompt consideration of neoplasia as a differential diagnosis. Signalment plays an important role in this, with age and breed both key predictors of particular types of tumour; clinical findings should also arouse the suspicion of structural brain disease. We discuss the tools that are needed to reach a diagnosis and highlight some of the pitfalls that should be considered, particularly in those with raised intracranial pressure. Although the prognosis is necessarily guarded in affected animals, carefully selected patients can respond remarkably well to treatment.

INTRACRANIAL neoplasia is seen relatively frequently in companion animals, with a reported prevalence of between 0.14 and 4.5 per cent in dogs (Snyder and others 2006; Song and others 2013) and between 2 and 3 per cent of cats (Troxel and others 2003). Although these figures are derived from referral populations of animals and likely over-represent the prevalence in the general population, they nonetheless emphasise the importance of considering neoplasia in patients presenting with brain disorders.

Clinical presentation of animals with brain neoplasia

Signalment

Breed is an important factor in dogs with brain neoplasia – there can be few practitioners, presented with an elderly boxer experiencing seizures for the first time, who have not made the assumption that there is a sinister underlying cause. Brachycephalic breeds in general, particularly boxers, Boston terriers and bulldogs, have a predisposition for glial neoplasms (Snyder and others 2006, Song and others 2013). In contrast, there is a higher incidence of meningiomas in dolichocephalic breeds, with a recent study reporting the incidence of meningiomas in dolichocephalic and others 2013). Both, however, are much less common across all breeds than glioma and meningioma.

Age is also an important factor in brain neoplasia, with a clear correlation between age and increased risk of intracranial neoplasia (Song and others 2013). However, it is important to recognise that younger animals can also be affected, with primary neuroectodermal tumours, gliomas and lymphoma having a relatively higher incidence in younger animals. One report has documented an oligodendroglioma in a dog only 2.4 months old (Song and others 2013).

Clinical signs

Seizures are one potential manifestation of intracranial neoplasia. In many cases, they might be the only indication of a problem, which reflects the fact that it is possible to develop sizeable forebrain lesions without developing obvious neurological deficits. Even in human patients, where cognitive assessments can supplement basic physical examination, tumours can be large before patients show any clear localising signs.

In those cases showing signs other than seizures, there can be both historical features and abnormal findings on clinical examination. Forebrain dysfunction can cause behavioural abnormalities, such as the development of aggression in previously placid dogs or a progressive loss of interest in play and/or exercise. Of course, these are non-specific and occur with a variety of other conditions. In others, sleep patterns can be disrupted, house training patterns altered and in more severe cases, owners might report a tendency for their pet to pace restlessly around rooms, frequently in circles; patients occasionally appear to become trapped or lost in unusual places, under furniture and in the corners of rooms.

Findings on clinical examination will reflect the site of the lesion. Solitary neoplasia of the forebrain will typically affect one side of the brain more than the other, which causes deficits that affect one side of the body more than the other. Due to the crossover of sensory and motor pathways, deficits are typically contralateral to the side of the lesion (Box 1). Postural deficits are not unusual and can be detected by testing paw positioning, hopping and hemiwalking – these can be relatively obvious, even in dogs that appear to walk without marked gait abnormalities. Vision might also be impaired, again with contralateral deficits, so that right-sided lesions typically impair the menace response and tracking of moving objects in the left eye. Facial sensation can be similarly affected – not to the extent that the palpebral reflex is affected but in the way that patients react to an irritating or painful stimulus, such as tickling the nostrils with artery forceps.

Table 1: Division of intracranial neoplasia seen in dogs and cats according to site of origin

<table>
<thead>
<tr>
<th>Primary intracranial neoplasia</th>
<th>Secondary neoplasia</th>
<th>Metastatic neoplasia</th>
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</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>Nasal neoplasia</td>
<td>Haemangiosarcoma (dog)</td>
</tr>
<tr>
<td>Glioma</td>
<td>Ocular neoplasia</td>
<td>Mammary carcinoma</td>
</tr>
<tr>
<td>Choroid plexus tumour (dog)</td>
<td>Skull neoplasia</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Pituitary neoplasia</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Nerve sheath tumour</td>
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</tbody>
</table>

Box 1: Neurological deficits in animals with unilateral forebrain diseases

- Contralateral proprioceptive deficits with normal spinal reflexes
- Contralateral vision loss
- Contralateral nasal +/- body sensation deficits
- Altered mental status
- Circling toward the side of the lesion
It is also important to remember that neoplasia can be multifocal, leading to clinical signs that are impossible to explain with a single focal lesion. Moreover, large focal lesions can cause secondary changes that cause additional neurological abnormalities. For example, a lesion affecting the brainstem can impair cerebrospinal fluid (CSF) flow, leading to secondary hydrocephalus and signs of forebrain disease, including seizures. Conversely, a large forebrain lesion can squash the brain against the bony limits of the skull, leading to signs of brainstem dysfunction where the brain herniates beneath the tentorium or at the foramen magnum (Fig 1).

### Types of brain neoplasia

#### Histological classification

Neoplasia can be classified as either primary or secondary. The former represents tumours of the various tissue components that comprise the brain and are listed in Table 1. Secondary neoplastic lesions are those that do not arise from the brain but damage the brain through local extension from surrounding tissues or by metastatic spread of neoplastic cells from a distant site (Table 1). Pituitary tumours are classified sometimes as primary and sometimes as secondary neoplasia – most arise from the adenohypophysis, which develops from outside the neuraxis and, strictly speaking, makes them secondary tumours. However, many authors classify pituitary tumours as primary brain neoplasia.

#### Radiographic classification

It is common not to achieve a definitive histological confirmation of brain neoplasia – many animals are euthanased without postmortem examination and brain biopsy remains a rarely performed technique. In cases that undergo advanced neuroimaging, it is common to classify lesions based on the location relative to the brain parenchyma and the ventricular system. Thus, intra-axial neoplasia arises within the neuraxis (ie, within the central nervous system parenchyma), extra-axial lesions are on the surface or adjacent to the brain and intraventricular tumours are within the ventricular system (Table 2). The most common intra-axial tumour is a glioma, a tumour of either astrocytes or oligodendrocytes, and the most common extra-axial tumour is a meningioma; choroid plexus tumours are the most common intra-ventricular tumours (Fig 2). Round cell tumours including lymphoma (most commonly) or histiocytic sarcomas can present as either an intra-axial, extra-axial, and, less commonly, as an intraventricular mass; they can therefore resemble many other neoplasms.

#### Differential diagnosis

The other articles in this supplement highlight the range of underlying conditions in dogs presenting with seizures. It is important to remember that although many elderly dogs presenting with seizures have underlying neoplasia, meningoencephalitis is also common and a variety of other conditions is also possible. Many of these conditions are identifiable on advanced neuroimaging.

### Table 2: Intracranial neoplasia classified according to radiographic location in relation to the brain parenchyma and ventricular system

<table>
<thead>
<tr>
<th>Intra-axial</th>
<th>Extra-axial</th>
<th>Intraventricular</th>
</tr>
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<tbody>
<tr>
<td>Glioma</td>
<td>Meningioma</td>
<td>Choroid plexus tumour</td>
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<td>Lymphoma</td>
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<td>Ependymal tumour</td>
</tr>
<tr>
<td>Histiocytic sarcoma</td>
<td>Histiocytic sarcoma</td>
<td>Neurocytoma</td>
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<tr>
<td>Primary neuroectodermal tumour</td>
<td>Pituitary neoplasia</td>
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**Fig 1:** Extra-axial right-sided meningioma compressing the right parietal and temporal lobes: sagittal T2-weighted (a) and transverse T2-weighted (b), T1-weighted pre-contrast (c) and T1-weighted post-contrast (d) images. This large lesion is causing herniation of the forebrain caudally at the tentorium (a, plain arrow) and of the cerebellum at the foramen magnum (a, dashed arrow). This causes compression of brainstem structures and can lead to clinical signs of brainstem dysfunction, complicating the neurological examination. Critically, however, many animals with radiologically identifiable herniation do not have clinical signs and those with significantly raised intracranial pressure might be missed.

**Fig 2:** Transverse T1-weighted post-contrast images (a, b and d) and T2*-weighted image (c) demonstrating the typical MRI appearance of a choroid plexus tumour (contrast enhancing mass in the lateral ventricles [a]), a glioma (well-defined mass with ring enhancement in the left frontal lobe [b]), metastatic tumours (arrows, multiple intra-axial haemorrhagic lesions [c]) and a cystic nerve sheath tumour (arrow, cavitated mass affecting the left middle cranial fossa [d]).
Box 2: Why do tumours cause seizures? Pathophysiology of seizures in intracranial neoplasia

Intracranial neoplasia causes physical distortion of the brain parenchyma by local invasion or direct and indirect compression of the surrounding brain. The impact of the mass depends not only on its location (neurological deficits will depend on which parts of the brain are affected) but also its rate of growth (slow growing tumour being more commonly silent or showing mild neurological deficits initially), and the presence of intracranial hypertension (see below). In addition, neoplasms are frequently surrounded by a zone of oedema, likely the result of leaky, immature blood vessels in the vicinity of the tumour that lack normal tight junctions. This increases the impact of the tumour on the adjacent structures.

While neurological deficits are readily explained by invasion and/or compression of brain tissue, the reason that seizures develop is more complex and remains poorly understood. Metabolic disturbances (decrease in inhibitory and increase in excitatory neurotransmitters), cerebral ischaemia, synaptic alterations and both biochemical and immunological derangements are some of the proposed mechanisms (Schwartz and others 2011). In human patients, there is a tendency for tumours in particular regions of the brain to be more likely to trigger seizures; for example, tumours of the temporal cortex are more likely to cause epilepsy than those in the frontal lobe. Similar studies in animals also indicate an association of location, with those in the frontal lobe more likely to cause seizures; those showing marked contrast enhancement and/or subfalcial or transtentorial herniation are also more likely to cause seizures, although this might simply reflect their large size and slow growth (Schwartz and others 2011). In human studies, tumour type affects seizure frequency, with glioma compared with 30 to 60 per cent of those older than six years old had an identifiable structural brain disease on MRI and, of these, 75 per cent were considered likely to be neoplastic (Smith and others 2008).

On neurological examination of the abdomen is also useful. In most cases, however, advanced neuroimaging – either CT or MRI – is likely to be needed to achieve a diagnosis of brain neoplasia.

In both human and veterinary medicine, CT remains useful due to its ability to identify mass effect and oedema but lacks sensitivity and specificity. MRI is now considered the modality of choice for the diagnosis of brain neoplasia due to its superior contrast resolution compared with CT. The disadvantages of MRI are the availability of the MRI machines, the cost of the procedure and the need of general anaesthesia. Moreover, although very sensitive for diagnosing intracranial neoplasia, MRT still lacks specificity, with a correct identification rate of only 70 per cent in one recent study (Rodenas and others 2011). The problem lies in the varied appearance of many types of neoplasia. For example, glial neoplasms can share imaging features with haemorrhagic stroke (intra-axial intracranial haemorrhage) and with meningoencephalitis, whereas certain features of meningiomas can be mimicked by lymphoma or by histiocytic sarcoma (Troxel and others 2004, Sturges and others 2008, Winsner and others 2011). Although MRI is often viewed by the public as the ultimate diagnostic test, definitive diagnosis is often impossible, which can be frustrating for clinicians and owners alike.

**Box 3: Neoplasia and intracranial pressures**

One of the potential consequences of an intracranial lesion is raised intracranial pressure. This is a direct effect of the tumour but is potentially exacerbated by peritumoral oedema and, in some cases, obstructive hydrocephalus (i.e., hydrocephalus caused by blockage of the cerebrospinal fluid pathway).

Intracranial pressure depends on the volume of the contents of the cranial cavity—the brain parenchyma, the CSF and blood. Pressure is carefully regulated, such that an increase in the volume of the brain parenchyma—so happens when a tumour develops—can be compensated, initially by a shift in CSF out of the skull and later by a reduction in the volume of venous blood. However, as the tumour continues to grow, this adaptive mechanism is eventually exhausted, and a point is reached when a relatively small increase in tumour volume can no longer be accommodated and pressure begins to rise. This forces the brain against the various bony prominences of the cranial cavity and ultimately leads to brain herniation—most commonly, the occipital lobes herniate beneath the tentorium or the cerebellum herniates through the foramen magnum. Neurological deficits can develop through herniation, most commonly through cerebellar herniation at the foramen magnum, leading to compression of the caudal brainstem and the development of vestibular dysfunction; in severe cases, pressure on the respiratory centres can trigger respiratory arrest. However, in many patients with MRI-confirmed herniation, clinical signs of herniation are not apparent. Great caution should therefore be exercised in making the decision to take a sample of CSF in patients considered likely to have brain neoplasia, since this might precipitate an acute deterioration in animal on the brink of or just beginning to herniate.

**Diagnosis**

**Diagnostic imaging**

The cornerstone of diagnosing brain neoplasia is radiology. While a complete blood profile, including haematology and serum biochemistry, is always recommended to rule out metabolic causes of seizures (especially in older dogs presenting with symmetrical or no neurological deficits), it would be rare for this to achieve a diagnosis of brain neoplasia.

Primary brain neoplasia metastasizes infrequently, so obtaining a presumptive diagnosis of meningioma or glioma by imaging the thorax and/or abdomen in these cases is very unlikely to be effective. However, thoracic radiographs should still be considered in older animals or in those with previously diagnosed neoplasia, to rule out the possibility of metastatic lung disease. Ultrasound examination of the abdomen is also useful. In most cases, however, advanced neuroimaging—either CT or MRI—is likely to be needed to achieve a diagnosis of brain neoplasia.

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There is no evidence of tumour regrowth but postoperative changes are evident left extra-axial parietal lobe meningioma before (a and b) and three months after surgery (c and d). Fig 4: Transverse T2-weighted (a and c) and T1-weighted, post-contrast (b and d) images showing a

| Table 3: Drugs that we commonly use for the palliative treatment of intracranial neoplasia in dogs and cats |
|--------|-------------------------------------------------|----------------------------------|----------------------------------|
| Drug   | Dosage                                          | Indication                       | Adverse effects                  |
| Phenobarbital | 2 to 3 mg/kg PO every 12 hours                  | Seizure management               | Sedation, PUPD, ataxia, paraparesis, liver toxicity |
| Leviracetam* | 20 to 30 mg/kg PO every 8 hours                 | Seizure management               | Mild sedation                    |
| Prednisolone | 0.5 to 1 mg/kg PO every 24 hours               | Reduction of peritumoural oedema, decreased angiogenesis | PUPD, polyphagia, vomiting, diarrhoea, small risk of infection |

* This is not a veterinary licenced product

CSF Cerebrospinal fluid, PO Orally, PUPD Polyuria, polydipsia

Cerebrospinal fluid

During the investigation of intracranial neoplasia, the clinician may be faced with the decision whether or not to collect CSF. A typical analysis of CSF includes a cell count and differential analysis, with measurement of protein concentration. In many dogs and cats with tumours this is unrewarding, with either no change or only a slight elevation in protein concentration, suggestive of disruption to the blood brain barrier. Occasionally, in round cell tumours (lymphoma in particular) or in particularly exfoliative tumours, neoplastic cells might be identified, providing a definitive diagnosis. More often, however, the aim of CSF analysis is to distinguish a solitary inflammatory or, rarely in the UK, an infectious lesion from a neoplasm.

A critical consideration in taking a CSF sample is whether the procedure creates undue risk for the patient, specifically whether brain herniation might occur through the release of fluid from the cisterna magna or whether the brainstem might be damaged if the cerebellum is already herniated. CSF collection is contraindicated in the presence of severely raised intracranial pressure, especially if clinical or radiological signs of herniation are present (Fig 1).

**Biopsy**

Brain biopsy is widely practiced in human medicine and is increasingly mooted as a useful procedure in dogs and cats. The process involves stereotactic targeting of the tumour, permitting precise sampling and definitive diagnosis before any decision regarding treatment is made. Both CT- and MRI-guided frame-guided or frameless devices are now available. However, cost is a significant limiting factor, while the risk of complications during the procedure should be discussed carefully with the owners (these include seizures, clinical deterioration through damage to adjacent neural structures and, more alarmingly, death).

**Treatment**

Treatment of brain neoplasia has to take into account the nature of the tumour, its location, size and the presence of concurrent disease. Costs, ethical considerations and cosmetic concerns are also important factors to discuss with owners.

As with tumours elsewhere in the body, the options for treatment include surgery, chemotherapy and radiation therapy – or a combination of all three. However, these treatments pose particular problems in managing brain neoplasia and many clients opt for simple palliative medical treatment, using corticosteroids and anti-seizure medication (Table 3).

**Corticosteroids**

Corticosteroids are the most commonly used medication for the palliative treatment of brain neoplasia. They are beneficial for several reasons: through a reduction in CSF production, by reducing angiogenesis and, perhaps most importantly, by reducing vasogenic oedema, which can be significant in patients with brain neoplasia (Fig 3). The benefits of glucocorticoids were first noted in the late 1950s and early 1960s, when human patients with glioma were found to dramatically improve following administration of dexamethasone, most likely through reduced peritumoural oedema. In a small number of cases, steroids can also have a direct cytopathic effect on tumour cells, for example, in patients with lymphoma. In most cases, however, corticosteroids should be considered palliative and clinicians should aim to use the lowest effective dose. An anti-inflammatory dose of prednisolone (0.5 to 1 mg/kg orally once a day) is most commonly used, tapered to the lowest effective dose without causing debilitating side effects.

**Seizure management**

Seizure management in animals with brain neoplasia involves the same range of drugs used to control seizures in other conditions (see accompanying articles in the supplement). Diazepam (0.5 to 1 mg/kg intravenously to effect) remains the first-line medication for the emergency management of status epilepticus, while a phenobarbital loading dose (18 to 24 mg/kg intravenously by small 3 mg/kg boluses) or levetiracetam (20 mg/kg intravenously every eight hours) offer additional treatment options. A constant rate infusion of a benzodiazepine or propofol may be necessary in refractory cases (see idiopathic epilepsy article, pp 17-23).
For the longer term management of epilepsy secondary to intracranial neoplasia, our preference is to use phenobarbital (2 to 3 mg/kg orally every 12 hours) or, should the patient’s level of consciousness already be significantly obtunded, levetiracetam (20 mg/kg orally every eight hours); this medicine minimises the additional sedative effect of anti-seizure medication.

**Surgery**

Surgery is the treatment of choice for extra-axial neoplasms (most commonly meningiomas) in both dogs and cats, although this depends on their precise location. It can be curative if the tumour is benign, non-invasive and if clean surgical margins are achieved (Fig 4). However, an extensive approach and skull reconstruction might be necessary for extensive lesions. The surgical management of intra-axial or intraventricular tumours is considered palliative at best. These tumours are very difficult to locate and remove and involve manipulation of normal and abnormal brain tissue, increasing the risk of complications and prolonging recovery.

The long-term outcome after surgery of extra-axial meningiomas is considered good in dogs and fair to good in dogs, especially if they are slow growing and if the surgical intervention is followed by radiotherapy (Axlund and others 2002). Postoperative imaging studies are very useful to assess the effectiveness of tumour removal and can help to guide radiotherapy by permitting more accurate targeting of residual neoplastic tissue (Fig 4).

**Radiation therapy**

Radiation therapy can be used as a sole therapy for extra-axial, intra-axial and intraventricular tumours. Careful planning is necessary to allow correct targeting of neoplastic tissue and treatment involves multiple doses, typically spread over four to five weeks, with anything from one to five sessions per week. Each treatment requires the patient to be immobilised, so repeated general anaesthetics are necessary. These can generally be carried out on an out-patient basis, although it still requires a significant investment of time by owners. Reported outcome varies, with one study reporting a median survival time of approximately 11 months (Brearley and others 1999).

While cats with meningioma tend to have a protracted remission following surgery, making radiation therapy difficult to justify, dogs with meningioma demonstrate a significantly extended survival following combined surgery and radiation therapy (median 16.5 months versus seven months for surgery alone) (Axlund and others 2002).

Radiation therapy is also used commonly for the management of pituitary tumours. While surgery via a trans-sphenoidal approach is practiced in a limited number of institutions, radiotherapy allows treatment of even larger tumours and may not only alleviate neurological signs but might also improve management of the endocrine complications associated with functional pituitary tumours (central diabetes insipidus, acromegaly, pituitary-dependent adrenocorticism).

**Chemotherapy**

Chemotherapy is uncommonly used for the treatment of intracranial neoplasia in dogs and cats. The primary reason for this is the restricted range of drugs that will penetrate the blood-brain barrier and permit therapeutic concentrations of drugs to be achieved within the tumour. Despite this, a variety of chemotherapeutic protocols, using a restricted range of drugs, have been used in the management of intracranial neoplasia, both alone and in combination with surgery.

There is little convincing evidence that chemotherapy improves the outcome in animals with brain neoplasia, with one recent study showing no improvement in outcome when treating dogs with anti-seizure medication and prednisone versus a group also receiving lomustine (van Meervenne and others 2014). However, an exception to this is in the treatment of intracranial lymphoma, for which chemotherapy is the treatment of choice. Treatment protocols published have been associated with variable outcomes, but a prolonged survival can be obtained in a number of cases.

**Other therapies**

Immunotherapy, intratumoural drug delivery, oncolytic viral therapy, gene therapy and non-thermal irreversible electroporation are more recent innovative approaches that need further clarification before being used at a larger scale in veterinary or human patients.

**Prognosis**

Multiple factors have an impact on the prognosis of dogs or cats presenting with intracranial neoplasia. The nature of the tumour, its size and location, are crucial, as are the age and general wellbeing of the animal and the attitudes and concerns of the owner. In general, all treatments should be considered palliative, since complete surgical removal and/or remission are not realistic targets. The exception to this rule is meningiomas in cats, which carry a very good prognosis following surgical resection, with protracted survival times. Surgery for meningiomas in dogs is less effective, although survival times in excess of a year remain possible, particularly when accompanied by radiotherapy. Intra-axial tumours, such as gliomas, are less commonly considered as surgical candidates, though can respond favourably to radiation therapy alone. However, all decisions for treatment need to be balanced against the risk of side effects and the cost of treatment, neither of which are trivial. The commonest approach to management of dogs with brain tumours in practice is to use anti-seizure medication and glucocorticoids. While such treatment is clearly short term, with median survival times of around zero to two months reported, individual cases can still retain a good quality of life for several weeks – and even months in some cases (Rossmeisl and others 2013).

**Summary**

Seizures are a common clinical manifestation of intracranial neoplasia, present in about half of dogs with brain tumours (Bagley and others 1999) and about 25 per cent of cats (Tomek and others 2006). In many cases, seizures can be the first sign noticed by owners. Achieving a diagnosis is centred on advanced neuroimaging (conventionally MRI), and despite the scant availability of brain biopsy, it is often possible to reach a likely – if not definitive – diagnosis. The prognosis must always be guarded, particularly if there is a significant increase in intracranial pressure. However, surgery, radiotherapy and chemotherapy are realistic options for many patients, which can lead to remarkably good outcomes. For owners who choose not to attempt definitive treatment, palliation of clinical signs is best achieved by a combination of glucocorticoids and anti-seizure medication; although this can have a dramatic effect, restoring a good quality of life, the effect is relatively short lived and clients should be counselled to expect a deterioration in the near future.

**References**


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