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Review

Canine and feline intracranial meningiomas: An updated review

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ABSTRACT

Meningiomas are the most common primary brain tumours in dogs and cats. There are several morphological phenotypes of this extra-axial neoplasm and they show predilections for certain anatomical locations. There have been a number of attempts to apply the current World Health Organization (WHO) classification for human meningiomas to dogs and cats and to obtain a universal classification scheme for domestic animals. Recently, certain enzymes involved in tumour growth have been recognised as biological markers and have been related to degrees of malignancy. The secondary effects of meningiomas have also been investigated, and vascular endothelial growth factor and peritumoural oedema have been reported to reduce survival rate.

Breed and age predisposition are recognised in both dogs and cats and the presenting clinical signs are quite consistent. Magnetic resonance imaging and computed tomography are the techniques of choice for the presumptive diagnosis of meningiomas in domestic animals but advanced imaging techniques are constantly being developed and applied. Treatment methods for meningiomas involve a combination of de-bulking surgery, chemotherapy and radiotherapy, and detailed accounts of several treatment protocols have been reported.

Introduction

Meningioma is the most commonly reported primary brain tumour in dogs and cats (Troxel et al., 2003; Snyder et al., 2006). It arises from the cap cells covering the arachnoid granulations, particularly at the point where they project into the venous sinuses (Summer et al., 1995). In view of their development from mesenchyme and neural crest and of the wide array of functions performed by arachnoid cells (Kepes, 1986), it is not surprising that meningiomas exhibit highly variable morphological and immunophenotypic patterns. Nevertheless, the biological behaviour of meningiomas, except for the anaplastic type, is generally considered benign in humans (Louis et al., 2007) as is also the case in dogs and cats.

The aim of this review is to provide updated information both for clinicians and pathologists who may deal with canine and feline intracranial meningiomas. Clinical signs, diagnosis, gross anatomy, histopathological classification, treatment, prognosis and future potential studies of canine and feline meningiomas are reviewed.

In recent retrospective analyses of canine and feline primary intracranial neoplasia, meningioma has been diagnosed in 45% (Snyder et al., 2006) and 85% (Troxel et al., 2003) of cases, respectively; meningiomas account for about 22.3% (Snyder et al., 2006, 2008) and 59% (Troxel et al., 2003) of canine and feline brain tumours.

Meningiomas are extra-axial central nervous system (CNS) tumours growing within the dura mater but outside the brain and spinal cord parenchyma, although direct invasion of the nervous tissue can occur. In humans, most meningiomas occur over the cerebral convexities, often in parasagittal locations in association with the falx cerebri and the venous sinuses (Louis et al., 2007). Most canine meningiomas are adjacent to the calvarium and a significant number of these tumours involve the olfactory/frontal region, the floor of the cranial cavity, the optic chiasm or the suprasellar and parasellar regions (Patnaik et al., 1986; Snyder et al., 2006; Sturges et al., 2008) (Fig. 1). Other uncommon intracranial localisations include the cerebello-pontomedullary region (Bagley et al., 2000; Kaldrymidou et al., 2001; Kitagawa et al., 2004; Sturges et al., 2008; Holland et al., 2010), the retrobulbar space (Patnaik et al., 1986; Willis et al., 1997; Pérez et al., 2005) and the middle ear cavity (Owen et al., 2004).

In cats, common locations include the tela choroidea of the third ventricle, the supratentorial meninges (Troxel et al., 2003; Mandara et al., 2006) (Fig. 2) and, rarely, the cerebellar meninges (Quesnel and Parent, 1995; Kaldrymidou et al., 2000; Troxel et al., 2003; Tomek et al., 2008). Feline multiple meningiomas are common (Luginbohl, 1961; Zaki and Hurvitz, 1976; Nafe, 1979; Averill, 1987; Gordon et al., 1994; Lobetti et al., 1997; Troxel et al., 2003; Forterre et al., 2007; Tomek et al., 2008), occurring in approximately 17% of

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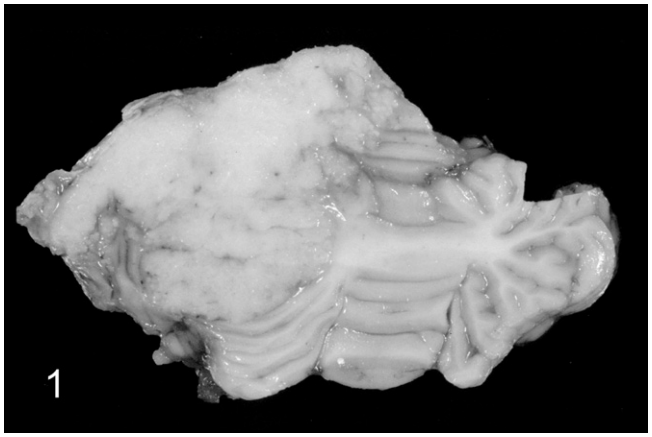

Fig. 1. Canine infratentorial meningioma (meningothelial histotype) in the left cerebellar hemisphere. Note the multilobular pattern and the granular aspect of the neoplastic tissue.

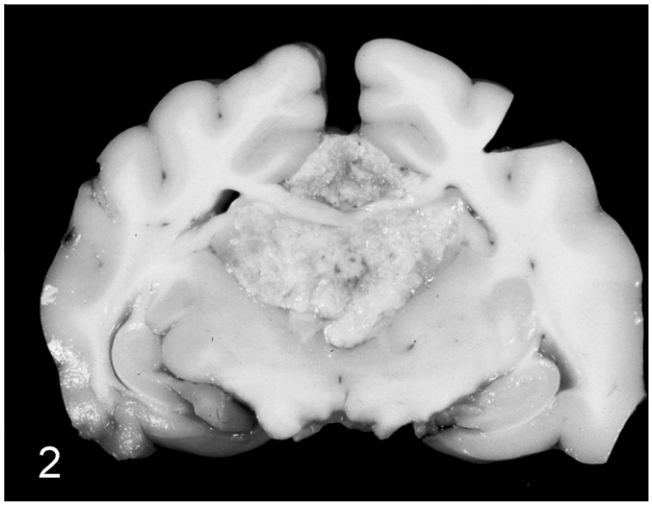

Fig. 2. Feline meningioma (granular cell histotype) extending from the third ventricle to the cingulate gyrus crossing the corpus callosum. This mass has a widely calcified and irregular cut surface.

meningioma cases (Nafe, 1979; Summer et al., 1995; Troxel et al., 2003) (Fig. 3) whereas it is very uncommon to detect more than one meningioma in dogs (McDonnell et al., 2007; Sturges et al., 2008).

Canine and feline intracranial meningiomas have been diagnosed with concurrent neural (Stacy et al., 2003; Troxel et al., 2003; Snyder et al., 2006; Ginel et al., 2009) or extra-neural disorders such as mucopolysaccharidosis type 1 (Haskins and McGrath, 1983), thymic lymphoma (Lobetti et al., 1997) and other unrelated neoplasia (Snyder et al., 2006). In particular, 13.9% of cats and 19% of dogs develop a meningioma in addition to another intracranial neoplasm (Stacy et al., 2003; Troxel et al., 2003; Snyder et al., 2006). Furthermore, cats may have concurrent benign and malignant multiple meningiomas (Lu et al., 2003).

Clinical findings and diagnosis

Signalment and neurological signs

Generally, meningioma occurs in dolichocephalic breeds, especially German Shepherds, Golden Retrievers and Labrador Retrievers, with no consistent sex predisposition (Snyder et al., 2006; Sturges et al., 2008). Boxers are known to have an increased prevalence (Snyder et al., 2006; Sturges et al., 2008). Domestic shorthaired cats seem to be predisposed to develop meningioma and no significant difference between sexes has been found (Troxel et al., 2003; Tomek et al., 2006). In most reports, meningioma has been diagnosed in dogs over 7 years of age and in cats over 9 years of age (Nafe, 1979; Troxel et al., 2003; Snyder et al., 2006; Tomek et al., 2006), although they have occasionally been observed in young cats <3 years old (Haskins and McGrath, 1983; Lobetti et al., 1997) and in young dogs <6 months (Keller and Madewell, 1992).

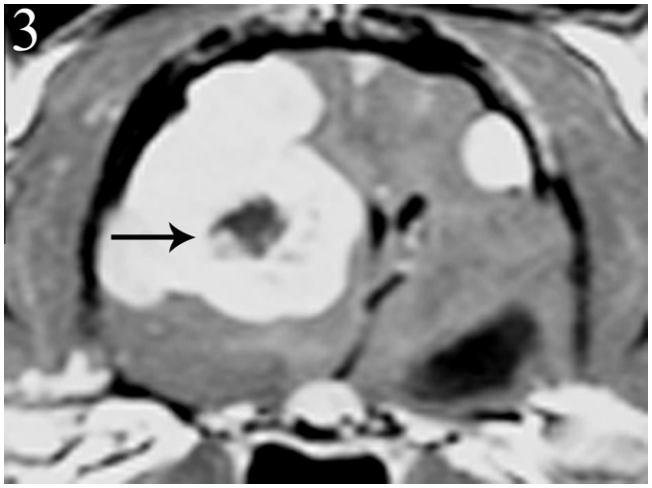

Fig. 3. Cat, 8 years old. Transverse post-contrast T1-weighted MR image at the level of the pituitary gland showing multiple mass-like lesions histopathologically confirmed as meningiomas. There is a severe shift of the falx cerebri. Note the hypointense cyst-like lesion within the tumour (black arrow) signifying necrosis.

Although the majority of animals affected by brain neoplasms present an array of mild or ill-defined neurological signs, the most common clinical signs in dogs and cats with intracranial meningioma are altered consciousness, seizures and vestibular dysfunction (Gordon et al., 1994; Troxel et al., 2003; Greco et al., 2006; Snyder et al., 2006; Tomek et al., 2006; Negrin et al., 2010). These clinical signs are likely to be related to the neuroanatomical distribution of canine and feline meningiomas. Epileptic seizures are generated in the cerebral cortex and in the diencephalon (Fisher et al., 2005); these are neuroanatomical areas frequently invaded by feline and canine meningiomas (Troxel et al., 2003; Snyder et al., 2006; Sturges et al., 2008). In addition, compression and/or damage of the diencephalon may result in altered consciousness because of the dysfunction of the ascending reticular activating system, a network of neurons responsible for maintaining the state of wakefulness (De Lahunta and Glass, 2009). Finally, diencephalic damage may lead to vestibular signs as the thalamus functions as a relay station for afferent vestibular inputs to the cortex (Dieterich et al., 2005).

Other specific neurological deficits associated with intracranial meningiomas, e.g. external and internal ophthalmoplegia, have been rarely reported (Larocca, 2000; Webb et al., 2005; Holland et al., 2010; Seruca et al., 2010).

Blood and cerebrospinal fluid analysis

There are no clinical studies evaluating the influence of the parameters of haematology, serum biochemistry, and urinalysis in dogs or cats with intracranial meningiomas. General anaesthesia may lead to clinically important hyperlactatemia in dogs with intracranial meningiomas (Sullivan et al., 2009) but the degree

and usefulness of this finding has not been established. Unfortunately, cerebrospinal fluid (CSF) analysis is neither a sensitive nor a specific investigative test for the diagnosis of canine and feline meningiomas (Troxel et al., 2003; Dickinson et al., 2006). Albuminocytological dissociation is found in about 30% of canine and feline intracranial meningiomas (Troxel et al., 2003; Snyder et al., 2006). In cats a mild to moderate predominantly neutrophilic pleocytosis may be observed along with increased total protein concentration (Troxel et al., 2003). In dogs CSF may reveal a neutrophilic pleocytosis (Bailey and Higgins, 1986; Dickinson et al., 2006) especially when the tumour is located within the caudal portion of the cranial fossa (Dickinson et al., 2006). However, a neutrophilic pleocytosis is characteristic of many other neurological diseases (Di Terlizzi and Platt, 2009). A significant elevation in uric acid in the CSF of dogs with confirmed intracranial meningioma has been reported (Platt et al., 2006a) but the clinical significance of this finding is unknown.

Imaging

Since intracranial meningiomas may metastasise to the lungs (Dahme, 1957; Geib, 1966; Schulman et al., 1992; Pérez et al., 2005) or may be found in association with primary pulmonary tumours (Snyder et al., 2006), thoracic radiographs should be obtained.

Computed tomography (CT) and magnetic resonance imaging (MRI) are considered the main diagnostic tools available for the ante-mortem investigation of the various histological types of brain neoplasms. However, histopathological evaluation of biopsy specimens remains the most reliable way to achieve a definitive diagnosis. Advanced imaging techniques may also be very helpful in identifying the precise anatomical location and intracranial relationships between brain tumours and the surrounding tissues. This information is important and useful especially whenever surgical excision is planned, during the surgery (Gallagher et al., 1995) and in the post-operative time (Bergman et al., 2000; Forterre et al., 2007). Ultrasonography has been shown to be a useful intra-operative diagnostic tool (Gallagher et al., 1995) that helps to localise deep-seated cerebral lesions that could not be seen following craniotomy and to delineate the extent of the tumour.

In humans and dogs, CT has a diagnostic accuracy of about 80% for detecting intracranial meningiomas (Polizopoulou et al., 2004; Assefa et al., 2006). The diagnostic accuracy of CT in the diagnosis of feline intracranial meningiomas is unknown. In humans, the predictive accuracy of diagnosing meningiomas based on their MRI characteristics is between 65% and 96% (McDermott and Wilson, 1996; De Monte et al., 2001; Engelhard, 2001). The sensitivity of MRI to correctly identify intracranial meningiomas varies between 66% and 100% in dogs (Thomas et al., 1996; Polizopoulou et al., 2004; Snyder et al., 2006; Ródenas et al., 2011) and has been estimated to be 96% in cats (Troxel et al., 2004).

Despite the relatively high sensitivity of MRI in diagnosing meningiomas, MRI features do not allow prediction of tumour subtype or grade in dogs (Sturges et al., 2008). In contrast, a recent study in human medicine showed that the intratumoural cystic change and extracranial tumour extension through the skull base foramina visualised on MRI might be potential markers of atypical/malignant meningiomas (Hsu et al., 2010). To the best of our knowledge there are no studies evaluating the MRI features that can be used to predict the meningioma type or grade in cats. In one limited study the CT diagnostic sensitivity was quite similar to that of MRI for the tentative diagnosis of canine meningiomas (Polizopoulou et al., 2004). In dogs, several lesions, including pituitary tumours (Pollard et al., 2010), lymphomas (Thomovsky et al., 2011), intracranial histiocytic sarcomas (Tamura et al., 2009) and intracranial germ cell tumours (Motta et al., 2011) may have similar MRI characteristics as meningiomas. In cats, the MRI features of cerebral toxoplasmosis (Falzone et al., 2008) and cryptococcosis (Sykes et al., 2010) may mimic those of meningioma.

After the intravenous administration of contrast medium, meningiomas may reveal the 'dural tail' sign. This is a linear enhancement of thickened dura mater continuous with an extra-axial mass; the degree of contrast uptake is equal to or greater than the associated lesion (Nagele et al., 1994; Graham et al., 1998). In humans, when a dural tail is seen, any associated mass is most likely to be a meningioma but this specific sign has also been observed in patients with glioblastoma, pituitary adenoma, and acoustic schwannoma (Rokni-Yazdi and Sotoudeh, 2006).

Signal void of the adjacent calvarium as a result of reactive hyperostosis is another sign associated with canine (Mercier et al., 2007), feline (Troxel et al., 2004) and human (Pieper et al., 1999) meningiomas. Tumour-related hyperostosis is a bone erosion caused by pressure atrophy with subsequent thickening due to invasion of the Haversian canals by tumour cells (Adamo et al., 2004). Recently, skull hyperostosis secondary to an intracranial meningioma with skull invasion by tumour tissue has been reported in a cat (Gutierrez-Quintana et al., 2011). The MRI and CT characteristics of meningiomas are summarised in Table 1 (Figs. 4 and 5). New imaging techniques may be used for better diagnosis of meningioma in animals (Table 2).

Pathological findings

Most meningiomas grow as well-demarcated, sometimes lobulated, firm, granular masses with a broad-based or pedunculated attachment to the overlying meninges (Summer et al., 1995). In some cases, canine meningioma shows a large cystic cavity as a consequence of ischaemic events or of aggregation of severely vacuolated neoplastic cells (Pinna et al., 1986; Salvadori et al., 2010).

Cytological examination carried out during de-bulking surgery or with stereotactic techniques can aid in the diagnosis of meningioma (Zimmerman et al., 2000; Long et al., 2002; Platt et al., 2002; Sharkey et al., 2004; De Lorenzi et al., 2006; Harms et al., 2009; Wills et al., 2009) and may reveal whorl formations with epithelial-like appearance or spindle cells arranged in a storiform pattern. The major advantages of this technique for intraoperative diagnosis are (1) the speed, (2) the ease of preparation, (3) the technical simplicity and need for minimal technical equipment, and (4) the high degree of cytological resolution. Limitations of the system include: (1) adequate smear preparations are difficult to make in some types of brain neoplasms (including meningiomas) and can lead to artefacts, (2) the smear preparations may differ from the familiar histological appearance of tissues, and (3) there may be sampling errors and tissue from necrotic areas within tumours or adjacent to the neoplasm can lead to an erroneous or non-diagnostic interpretation (Vernau et al., 2001).

Histopathological examination of biopsy specimens remains the best way to achieve a definitive diagnosis. On histological examination, meningiomas are characterised by: (1) a mixture of sheets of epithelioid cells showing abundant and homogeneous cytoplasm without defined borders. This lobular pattern is characterised by syncytial whorl-like formations (meningothelial pattern). (2) A number of spindle shaped cells that create intersecting bundles or streams separated by variably dense collagen fibres (fibroblastic pattern). Not infrequently, meningiomas have a mixture of meningothelial and fibroblastic patterns (transitional meningioma) or they may show a whorl formation with a core of central hyalinisation, necrosis and mineralisation (psammomatous pattern) (Koestner and Higgins, 2002) (Fig. 6).

In selected cases, it can be difficult to distinguish meningiomas from other neoplasms, such as astrocytomas, oligodendrogliomas,

Table 1
Magnetic resonance imaging (MRI) and computed tomography (CT) features of canine and feline intracranial meningiomas.[b]

	Dogs	Cats	References
Margins on CT and MRI images		Well-defined regular	Kraft et al. (1999), Jones (2004), and Troxel et al. (2004)
	Well-defined regular		Hathcock et al. (1996), Thomas et al. (1996), Kraft et al. (1997, 1999), Snyder et al. (2006), and Sturges et al. (2008)
	Less commonly ill-defined		Snyder et al. (2006) and Rodenas et al. (2011)
CT density on pre-contrast images	Isodense to hyperdense	Isodense to hyperdense	Kraft et al. (1999) and Jones (2004)
MRI T1-weighted features		Iso- to hypointensity	Kraft et al. (1999) and Troxel et al. (2004)
	Iso- to hypointensity		Hathcock et al. (1996), Thomas et al. (1996), Kraft et al. (1999), Snyder et al. (2006), Sturges et al. (2008), and Rodenas et al. (2011)
	Uncommonly hyperintensity		Hasegawa et al. (2008) and Sturges et al., 2008
MRI T2-weighted features		Hyperintensity	Kraft et al. (1999) and Troxel et al. (2004)
	Hyperintensity		Hathcock et al. (1996), Thomas et al. (1996), Kraft et al. (1999), and Sturges et al. (2008)
	Uncommonly isointensity, hypointensity and mixed signal		Hathcock et al. (1996), Thomas et al. (1996), Sturges et al. (2008), Rodenas et al. (2011), and Martin Vaquero et al. (2010)
Post-contrast enhancement on CT and MRI images		Commonly homogeneous moderate to marked. Less commonly heterogeneous. Ring enhancement rare	Kraft et al. (1999), Jones (2004), and Troxel et al. (2004)
	Commonly homogeneous moderate to marked		Kraft et al. (1997, 1999), Sturges et al. (2008), Snyder et al. (2006), and Rodenas et al. (2011)
	Less commonly heterogeneous		Hathcock et al. (1996), Thomas et al. (1996), Snyder et al. (2006), and Sturges et al. (2008)
	Ring enhancement rare		Kraft et al. (1997, 1999), Snyder et al. (2006), Rodenas et al. (2011)
Tumour associated oedema on CT and MRI images		Commonly mild	Kraft et al. (1999) and Troxel et al. (2004)
	Commonly mild/moderate		Hathcock et al. (1996), Kraft et al. (1997, 1999), Sturges et al. (2008), Rodenas et al. (2011)
Hyperostosis		73% cases (diffuse thickening of the calvarium)	Troxel et al. (2004)
	Rare (focal bony proliferation)		Mercier et al. (2007)
Dural tail[a]	May be visualised on CT images		Jones (2004)
		64% cases	Troxel et al. (2004)
	23%		Hathcock et al. (1996)
	60%		Graham et al. (1998)
	82%		Cherubini et al. (2005)
	27%		Sturges et al. (2008)
	22%		Rodenas et al. (2011)
Cysts[a]	Actual occurrence has not been reported in veterinary patients undergoing CT exam		
		6% cases	Troxel et al. (2004)
	23%		Hathcock et al. (1996)
	12.5%		Thomas et al. (1996)
	32%		Kraft et al. (1997)
	26%		Sturges et al. (2008)
	22%		Rodenas et al. (2009)
Visualisation of mass effect[a]	Usually visualised on CT images		Kraft et al. (1999) and Jones (2004)
		97%	Troxel et al. (2004)
	100%		Rodenas et al. (2011)

All MRI intensity are referred to the grey matter.
All CT density are referred to the rest of the brain parenchyma.
[a] Percentage available for MRI only.
[b] See Appendix A to view the references appearing in the table.

metastatic carcinomas, germ cell tumours, and peripheral nerve sheath tumours. In these cases, a basic immunohistochemical panel consisting of vimentin, CD34, and E-cadherin has been proposed for the characterisation of canine and feline meningiomas (Ramos-Vara et al., 2010).

Classification

The current WHO histological classification for meningiomas in domestic animals (Koestner et al., 1999) classifies them into two major groups: (1) benign slow-growing tumours of eight subtypes and (2) anaplastic tumours (Table 3). Further subtypes similar to those recognised in human meningioma (microcystic, chordoid, lipomatous, and secretory) (Louis et al., 2007) were later identified independently in dogs. However, a grading system is not applied to domestic animal meningiomas. By comparison, in humans a more detailed classification system was more recently applied by the WHO in 2007 (Louis et al., 2007) enabling a consistent correlation between histological findings, biological behaviour and outcome prediction (Table 4).

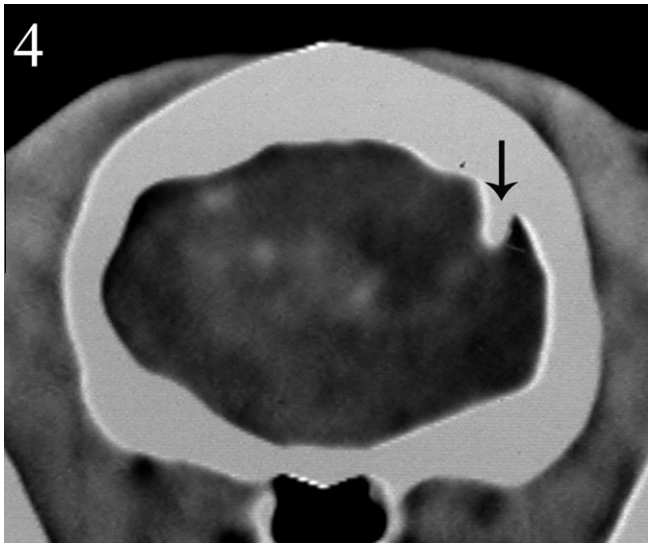

Fig. 4. Cat, 10 years old. Appearance of a histopathologically confirmed meningioma in a pre-contrast transverse CT image. An ill-defined mass-like lesion characterised by heterogenous densities can be seen corresponding to the frontal lobes. Note the severe shift of the falx cerebri (black arrow). Multiple small hyperdense areas are visualised within the tumour signifying acute haemorrhagic foci confirmed at histopathological analysis.

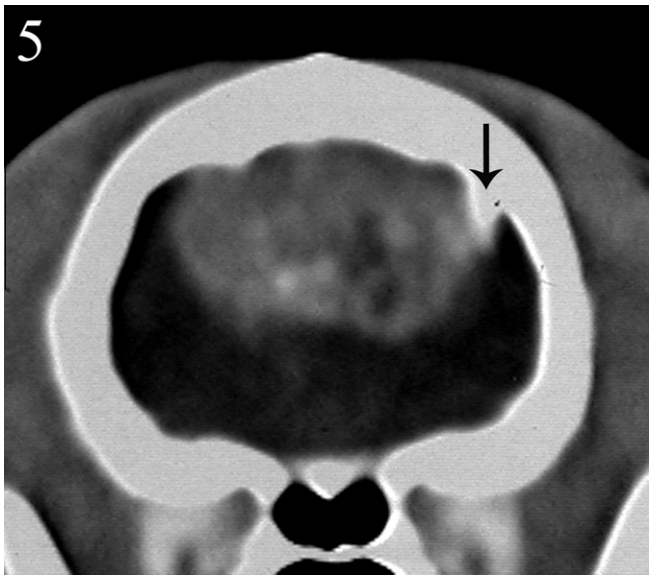

Fig. 5. Same cat as Fig. 4. A large well-defined broad-based mass-like lesion with homogeneous marked contrast enhancement is visualised adjacent to the frontal bone. Note the severe shift of the falx cerebri (black arrow). There are multiple hypodense and hyperdense lesions within the mass signifying necrosis and acute haemorrhagic foci, respectively (these findings were confirmed at histopathological analysis).

Because of the increasingly recognised limitations of the domestic animal classification scheme, there have been a number of attempts in recent years to establish an improved classification based on striking pathological, immunological, molecular and MRI similarities between human and canine meningiomas. There are reports in the literature pointing out the advantages of the human system of classification compared with the current WHO scheme for animals (Sturges et al., 2008; Mandara et al., 2009, 2010). In these studies it was confirmed that the prevalence of canine atypical (grade II) meningioma is much higher than in humans (Burger et al., 2002) (>40% vs. 8%), while canine benign meningioma occurs less frequently (from about 40% to 57% vs. 80%).

In addition, it has been reported that a mitotic index $\geqslant$4 mitoses/10HPF and brain invasion can be sufficient criteria to identify grade II meningiomas (Mandara et al., 2010), as already assumed in humans (Louis et al., 2007). Moreover, it has been suggested that the visualisation of patternless sheets alone can be assumed as a criterion to attribute a grade II to canine meningiomas (Mandara et al., 2010). Interestingly, in cats, meningiomas of grade III were not detected, confirming the less aggressive behaviour of feline meningioma and suggesting that no grading system is currently applicable to feline meningioma (Mandara et al., 2010).

The advantages of applying the human system to animals are that it includes a more comprehensive list of histological subtypes and it fixes a range of morphological criteria to assign the histological grade. This serves to reduce any subjective interpretation in evaluating the malignancy potential of the tumour and is designed to support a long-term prognosis based on clinical data.

Biological behaviour

Currently, the challenge is to define the biological potential of meningioma emphasising the differences between cytological and biological malignancy. But what does *biological malignancy* mean when applied to meningiomas?

Metastases are very uncommon and appear to be anecdotal events in domestic animal meningiomas. In dogs, metastases to the lungs and/or heart have been occasionally reported from intracranial meningiomas (Geib, 1966; Schulman et al., 1992; Dugan et al., 1993; Pérez et al., 2005). Metastases from a histopathologically confirmed meningioma have been found in the kidneys and uterus in a cat (Dahme, 1957). In humans, metastases from meningioma occur in <1% of cases and in up to 43% of malignant meningiomas (Enam et al., 2005). Although human meningiomas are 2–4 times more likely to occur in females, they develop metastases in men more often than in women (ratio, 3:2) (Som et al., 1987). In 0.1% cases, metastases have been reported in the presence of a meningioma classified as benign type at histological examination (Fulkerson et al., 2008).

To explain such a low prevalence of metastases for meningioma, different hypotheses have been put forward. Meningiomas are characterised by pronounced interdigitations and desmosomal interconnections of neighbouring cells; this would reduce the likelihood of exfoliation of tumour cells (Kepes, 1986). In addition, because most meningiomas are histologically benign, the few cells that may break off into the circulation lack the ability to colonise and form distant metastases (Kepes, 1986). However, it has been shown that pulmonary metastases have a higher mitotic rate than the primary tumour, suggesting the presence of a clone with a more aggressive behaviour that would be able to colonise distant organs (Schulman et al., 1992). In the absence of demonstrated metastases, peritumoural oedema and recurrence have to be taken into strong consideration when evaluating the biological malignancy of meningioma.

Novel potential therapeutic strategies

Because of its high prevalence and the wide number of morpho- and immunophenotypes it expresses (Bernhart et al., 2002; Louis et al., 2007), the meningioma is a very interesting tumour and has been extensively studied in both human and veterinary medicine. The broad aim of current research is to define the relationships between the biological behaviour of meningiomas, advanced therapeutic applications and prognosis.

Table 2
New imaging techniques that may improve characterisation of brain lesions.[a]

Imaging technique	Description	Usefulness
Brain perfusion CT	Provides information regarding the cerebral blood volume and the mean transit time (the ratio between cerebral blood volume and cerebral blood flow) of meningiomas in dogs	Potentially helpful for the diagnosis and grading of meningiomas (Kishimoto et al., 2008)
Magnetisation transfer imaging	Aides in both the detection and the characterisation of white matter abnormalities	May substantially increase tissue contrast and can improve sensitivity for the detection and characterisation of brain diseases (Vite and Cross, 2011)
Diffusion-weighted imaging	Useful in the detection of cytotoxic oedema	Limited use as a predictor of the histological type of canine intracranial disease; for example, low apparent diffusion coefficient values is identified in acute non-haemorrhagic infarcts, but is also seen in meningiomas, glial cell tumours, and granulomatous meningoencephalitis (Sutherland-Smith et al., 2011)
Magnetic resonance spectroscopy	Evaluates brain biochemistry by quantifying the concentrations of specific metabolites from spectra of metabolite distributions	May improve the assessment of neuronal loss, gliosis, and membrane turnover of tumours (Vite and Cross, 2011)
Dynamic contrast-enhanced MRI	Evaluate kinetic parameters of contrast enhancement between various brain lesions	Objective assessment of contrast enhancement is possible and may be able to assist with the differentiation of brain tumours (Zhao et al., 2010)

[a] See Appendix A to view the references appearing in the table.

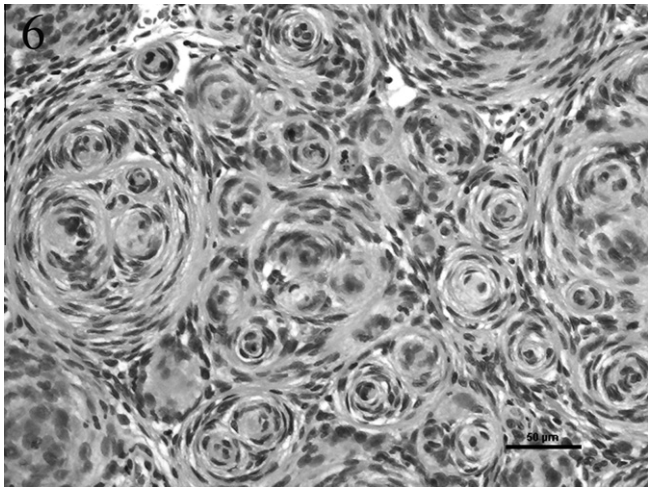

Fig. 6. Canine transitional intracranial meningioma. Island and whorl patterns of neoplastic meningothelial cells characterised by spindloid cells (Haematoxylin and eosin, bar = 50 µm).

Nowadays, advanced imaging diagnostic investigations make a great contribution in identifying primary (intratumoural oedema or cystic areas) and secondary effects (peritumoural oedema and infiltration, compression and midline shift, herniation and metastases) of meningioma preoperatively or before histological investigations. However, these advances are still not sufficient to characterise the biological malignancy of meningiomas.

Recently, a number of biological markers have been investigated for animal meningiomas strictly in relation to the rate of growth, mitotic activity, infiltration, peritumoural oedema and neovascularisation properties of the tumour. So far, the proliferative activity of meningiomas, assessed by immunohistochemistry using MIB-1-antibodies against Ki-67 antigen, has been successfully correlated with the histological grade of meningeal neoplastic cells, in both humans and domestic carnivores (Mandara et al., 2002; Devaprasath and Chack, 2003; Maes et al., 2005). At the same time, in humans Ki-67 expression has been found to be higher in recurrent benign intracranial meningioma than in the recurrence-free patients (Lanzafame et al., 2000; Takahashi et al., 2004). In contrast, no correlation has been found between Ki-67 expression and survival in dogs (Matiasek et al., 2009).

The proliferating cell nuclear antigen (PCNA) is considered another useful marker to both outline the proliferative index of canine and feline meningiomas (Mandara et al., 2009) and can be used to support the outcome prediction of this tumour in dogs (Theon et al., 2000). However, when compared with Ki-67, some potential problems can be found inherent in the technique of PCNA labelling, including a concentrated immunoreactivity in the S-phase cell cycle and/or the long half-life of the PCNA molecule (Matiasek et al., 2009).

Interestingly, for a long time the identification of steroid receptors in the meningeal neoplastic cells has suggested that the neoplastic growth is an expression of hormone stimulation. The first evidence of hormone-dependent growth of meningiomas in people was recognised by Cushing and Eisenhardt in 1938, following the observation that pregnant women showed high predisposition for the occurrence or recurrence of meningiomas. Despite discrepancies between different methods and results, it is now believed that the majority of meningiomas in humans demonstrate the presence of progesterone receptors (PR) in the absence of oestrogen receptors (ER) (Hsu et al., 1997). Furthermore, it appears that more aggressive and atypical meningiomas are less likely to express PR in humans (Hsu et al., 1997; Shayanfar et al., 2010) as well as in dogs (Theon et al., 2000; Mandara et al., 2002).

In veterinary medicine it is largely agreed that the majority of canine and feline meningiomas possess PR (Theon et al., 2000; Mandara et al., 2002; Adamo et al., 2003) but not ER. In addition, it has been shown that in dogs, cats and humans a high proliferative index in meningiomas is associated with a low PR concentration, suggesting that PR concentration might be a reliable prognostic factor (Mandara et al., 2002; Shayanfar et al., 2010). Loss of PR in tumours with an increase in proliferative index has been considered to indirectly affect prognosis after radiation therapy (Theon et al., 2000). These studies provide more information about the biological behaviour of meningiomas, especially for those in which the histological grading is not straightforward. In addition, the identification of PR in most meningiomas supports the possibility of the use of antiprogestinics that may be beneficial for unresectable or recurrent tumours (Serfaty, 1995).

More recently, a number of additional biological markers have been investigated in canine meningiomas and their expression has been compared with that occurring in humans. In particular, in both human and veterinary oncology there has been a considerable interest in studying telomerase (TL) and metalloproteinase (MMP) activities, which are involved in tumourigenesis, and

Table 3
Histological classification of tumours of the nervous system of domestic animals (WHO): Tumours of the meningothelial cells (Koestner et al., 1999).

Tumour type	Histological classification
Benign Meningioma	Meningotheliomatous Fibrous (fibroblastic) Transitional (mixed) Psammomatous Angiomatous (angioblastic) Papillary Granular cell Myxoid
Malignant Meningioma	Anaplastic (*malignant*) i.e. high mitotic rate, hypercellularity with uninterrupted patternless growth, extensive necrosis, nervous tissue invasion, and metastases

Table 4
Human WHO grading criteria for meningioma (Louis et al., 2007).

Tumour type	Grading criteria
Benign meningioma (grade I)	Histological variant other than clear cell, chordoid, papillary, and rhabdoid Lacks criteria of atypical and anaplastic meningioma
Atypical meningioma (grade II) (any of three criteria)	Mitotic index $\geqslant$4/10 high powered fields (HPF) At least 3/5 parameters: 1. Sheeting architecture (loss of whirling and/or fascicles 2. Small cell formation (high N/C ratio) 3. Macronucleoli 4. Hypercellularity 5. Spontaneous necrosis (i.e., not induced by embolism or radiation) Brain invasion
Anaplastic (malignant) meningioma (grade III) (either of two criteria)	Mitotic index $\geqslant$20/10HPF Frank anaplasia (sarcoma, carcinoma, or melanoma-like histology)

tumour invasion and metastases, respectively. In human meningiomas, the TL activity has been demonstrated high in malignant tumours, but low or completely absent in the benign type (Maes et al., 2007). Moreover, TL activity seems to be expressed more in recurring than in the non-recurring benign tumours (Maes et al., 2007).

TL activity has also been demonstrated in canine and feline meningiomas but the relationship between its expression and the proliferative index of the tumour still remains contradictory (Long et al., 2006; Mandrioli et al., 2007). Since telomerase is expressed in the majority of neoplastic processes and is not found in most normal tissues, this enzyme can be considered a useful target for therapeutic intervention. Currently, several potential cancer therapy applications, namely telomerase inhibition, telomerase promoter targeting and telomerase immunotherapy, are under development and may be beneficial for animal and human cancer patients (Nasir, 2008).

In human meningiomas controversy exists in the literature regarding the level of MMP expression in tumours of differing grades. In fact, while in some studies MMP-2 increases progressively from WHO grade I to grade II/III, MMP-9 shows an increased expression in grades I and II but is decreased significantly when progressing from WHO grade II to grade III (von Randow et al., 2006). Conversely, other studies reported that only MMP-9 shows a real tendency to increase with higher tumour grade (Panagopoulos et al., 2008). Currently, and contrary to human oncology (Okada et al., 2004), the data collected from canine and feline meningioma support the view that the MMP-expression is not correlated with morphological malignancy patterns (Mandara et al., 2009).

In human, canine and feline meningiomas, MMP-expression seems to be independent of the proliferative potential (Okada et al., 2004; Mandara et al., 2009). Moreover, the effort to find some significant correlation between MMP, TL and PR expression in canine and feline meningiomas was without success, probably indicating that all of these biological markers follow different and independent activation pathways (Mandara et al., 2009). Whatever the correlation between MMP and other biological marker expression, in human medicine it is now assumed that an increased ratio between MMPs and tissue inhibitors of MMP (TIMPs) plays an important role in the cancer malignancy progression and that TIMP may be a future additional instrument for novel therapeutic strategies against meningioma (Kachra et al., 1999).

There is inadequate evidence for involvement of adhesion molecules in the neoplastic progression of canine and feline meningiomas (Ramos-Vara et al., 2010). In fact, adhesion molecules have been tested as immunohistochemical markers instead of as actual biological markers (Ramos-Vara et al., 2010). On the other hand, in humans, it seems that the anaplastic type of meningioma does not express E-caderin (Panagopoulos et al., 2008).

The hypothesis that meningioma tumourigenesis may, in part, be driven by over-expression of cyclooxygenase-2 (COX-2) is well documented and supported in humans (Buccoliero et al., 2007). These results encourage novel promising therapeutic treatments with selective COX-2 inhibitors, such as celecoxib (Pfizer). Moreover, since celecoxib is well tolerated in humans, this makes its use for long-term therapy for meningiomas very attractive (Ragel et al., 2007). To date, whilst COX-2 over-expression has been demonstrated in multiple canine malignancies, it has not been significantly associated with tumour grade in canine meningiomas (Rossmeisl et al., 2009). No studies have evaluated COX-2 expression in feline meningiomas.

The most serious secondary effects that need to be considered for meningiomas are the perilesional oedema and infiltration of adjacent tissues. In order to better understand the malignancy potential of meningiomas and their relationship with the secondary effects, MMPs and vascular endothelial growth factor (VEGF) have been investigated in human and canine medicine. In humans, both MMP2 and MMP9 have been associated with perilesional oedema

Table 5
Survival (in months) for dogs and cats with intracranial meningiomas in relation to different therapy strategies.[b]

	No treatment	Corticosteroids and anticonvulsants	Chemotherapy	Surgery alone	Radiation therapy alone [a]	Surgery plus radiation therapy	De-bulking surgery via endoscopic technique	De-bulking surgery via surgical aspirator
Dogs	2.5, *n* = 13 (Foster et al., 1988)	2, *n* = 8 (Turrel et al., 1984)	Steroid and hydroxyurea – 14, *n* = 1 (Tamura et al., 2007)	4.5 (median), *n* = 4 (Kostolich and Dulisch, 1987); 6 (median), *n* = 10 (Niebauer et al., 1991); 7 (median), *n* = 14 (Axlund et al., 2002); 27 (median), *n* = 11 (Gallagher e al., 1993) 22 (median), *n* = 34 (Troxel et al., 2003)	8 (median), *n* = 22 (Spugnini et al., 2000); 12.2 (median), *n* = 35 (Brearley et al., 1999)	15.7 (median), *n* = 6 (Brearley et al., 1999) [a]	Forebrain meningiomas: 70.13 (median), *n* = 21 (Klopp and Rao, 2009); caudal brain meningiomas: 23.4 (median), *n* = 6 (Klopp and Rao, 2009)	41.8 (median), *n* = 17 (Greco et al., 2006)
			Steroid and lomustine – 13, *n* = 1 (Jung et al., 2006a,b)			30 (median), *n* = 20 (Theon et al., 2000)		
			Nitrosylcobalamin – complete remission of previously partially excised spinal meningioma, *n* = 1 (Bauer et al., 2010)			16.5 (median), *n* = 12 (Axlund et al., 2002)		
Cats	Unknown	Unknown	Hydroxyurea – In vitro evidence that hydroxyurea slows or arrests feline meningioma cells multiplication (Forterre et al., 2000)		Unknown	Unknown	Unknown	Unknown

n, number of animals included in each of the published studies.
[a] Radiation therapy carried out in dogs with extra-axial brain masses not histopathologically confirmed as meningiomas.
[b] See Appendix A to view the references appearing in the table.

(Panagopoulos et al., 2008) as well as with recurrence and infiltration (Mizoue et al., 1999; Okada et al., 2004). There are not sufficient data for canine and feline meningiomas.

More attention has been paid to the ability of VEGF to produce peritumoural oedema and to reduce the survival rate in dogs affected by meningioma. To date, no significant correlation has been demonstrated between VEGF expression and peritumoural oedema or histological grade of feline and canine meningiomas (Dickinson et al., 2008). In some cases, the over-expression of VEGF has been correlated with a shorter survival time in dogs (Platt et al., 2006b), suggesting that the angiogenesis may be a more important predictor of canine meningiomas than Ki-67. Despite the evidence that increased vascularisation is associated with higher proliferation index in human meningioma, no association between VEGF and Ki-67 expression has been found in canine intracranial meningiomas (Matiasek et al., 2009).

In humans, VEGF over-expression is now considered a marker for both recurrence of meningiomas after surgery and malignancy potential (Yamasaki et al., 2000). Although meningiomas do not show a clear angiogenic switch involving VEGF, as occur in gliomas, the biological activity of VEGF in meningiomas suggests that VEGF is a potential target for antiangiogenic therapy in all WHO grades of meningiomas (Lamszus et al., 2000).

No studies have been carried out on VEGF expression in feline meningiomas.

Medical treatment

In general, conventional treatment of brain tumours in people as well as in animals involves a combination of surgical debulking, chemotherapy and radiation therapy (Tables 5 and 6). Surgical intervention and/or radiotherapy are sometimes not feasible for canine and feline meningiomas due to a combination of factors such as deeply located tumours, patient age, financial constraints and ethical reasons, but medical treatment is appropriate to relieve clinical signs associated with brain neoplasms, to provide dogs and cats with a good quality of life and to prolong their survival time. The most common medical treatment strategies involve a combination of corticosteroids, antiepileptic medications and/or different chemotherapeutic agents. The efficacy of corticosteroids in reducing vasogenic oedema associated with tumours is well described (Papadopoulos et al., 2004; Barnes, 2005). Corticosteroids diffuse through the plasma membrane and bind to the cytoplasmic receptor, allowing the steroid-receptor complex to move to the nucleus where it affects transcription of genes and also interacts with other transcription factors (Barnes, 2005). Corticosteroids also decrease endothelial permeability causing dephosphorylation of the tight junction component proteins occludin and ZO1 (Papadopoulos et al., 2004).

There are no studies evaluating the use of antiepileptic drugs in dogs and cats with brain tumours. The main goal for using antiepileptic drugs in animals with tumour-associated seizures is to reduce the frequency and the severity of the seizure episodes. The problem of most concern in the use of antiepileptic drugs in human patients with brain tumours is the interaction of anticonvulsants and corticosteroid metabolism by the cytochrome P450 system ('enzyme-inducing anticonvulsants') with many common antineoplastic agents (Dropcho and Soong, 1991). In humans, prophylactic anticonvulsants are not effective and should not be used routinely (Sirven et al., 2004).

Surgery, radiotherapy and chemotherapy

The majority of meningiomas in humans are treated surgically and recurring tumours may be treated with radiotherapy and/or repeated surgical resection (Ropper and Brown, 2005). Different surgical techniques have been used to remove feline and canine meningiomas successfully (Parker and Cunningham, 1972; DeWet et al., 1982; Kostolich et al., 1987; Glass et al., 2000; Forterre et al., 2006, 2009; Barreau et al., 2010; Michal Altay et al., 2010). Recently, a suprazygomatic temporobasal approach has been used successfully to completely excise a rostro-temporal basal meningioma in a cat (Forterre et al., 2009). Feline medial tentorial meningiomas may be removed completely or partially using a unilateral temporal supracerebellar transtentorial approach (Forterre et al., 2006). The recently described 'trap door' technique has been used with success for complete removal of feline rostrotentorial meningiomas with dural and bone attachment (Michal Altay et al., 2010). In dogs descriptions of modified approaches to the olfactory bulb and frontal lobes have been described for meningioma removal (Parker and Cunningham, 1972; DeWet et al., 1982; Kostolich et al., 1987; Glass et al., 2000). A modified bilateral transfrontal sinus craniotomy has been shown to provide excellent access to the canine olfactory bulbs and frontal lobes for removal and biopsy of meningiomas in three dogs (Glass et al., 2000).

In dogs, only sporadic post-surgical complications have been reported, such as intraventricular tension pneumocephalus and cervical subarachnoid pneumorrhachis (Garosi et al., 2002; Cavanaugh et al., 2008). Post-operative complications related to surgical removal of meningiomas in cats include central blindness (Forterre et al., 2006), anaemia (Gordon et al., 1994) and acute renal failure (Gallagher et al., 1993). The immediate post-operative mortality rate varies between 19% (Gordon et al., 1994) and 17% (Gallagher et al., 1993) of cats that underwent de-bulking surgery.

Radiation therapy alone has been reported to be useful for the treatment of presumptive intracranial meningiomas in dogs (Brearley et al., 1999; Spugnini et al., 2000). It is a valid procedure for tumours that are inoperable and it may be preferable to surgical

Table 6
Characteristics of chemotherapeutic agents used to treat meningiomas.[a]

Chemotherapeutic agent	Characteristics	Adverse effects
Hydroxyurea	It is an antimetabolite that specifically affects the S stage of the cell cycle. It is a drug that inhibits the growth of tumours with low mitotic indices, such as meningiomas (Hoshino et al., 1986)	Toxicity in dogs common but usually not life threatening (Tamura et al., 2007) No adverse affects noted in cats (Forterre et al., 2006, 2007)
Lomustine (1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea)	Alkylating antineoplastic agent belonging to the nitrosourea group High lipid solubility of lomustine and its metabolites results in wide distribution to tissues and penetration across the blood–brain barrier (Carter and Newman, 1968)	Toxicity in dogs common but is usually not life threatening (Jung et al., 2006a,b) No studies in cats
Nitrosylcobalamin	Vitamin B12 analogue which includes nitric oxide as an axial ligand that uses receptor-mediated cobalamin uptake to target nitrosylcobalamin causing apoptosis of cancer cells (Bauer et al., 2002)	No adverse affects noted in dogs (Bauer et al., 2010) No studies in cats

[a] See Appendix A to view the references appearing in the table.

resection if the mass appears infiltrative. Mild acute radiation effects on normal tissue (e.g. keratoconjunctivitis sicca, otitis externa, pharyngeal mucositis and conjunctivitis) are common and do not seem to influence outcome (Spugnini et al., 2000). However, delayed radiation toxicity may occur and may be the cause of death or reason for euthanasia (Brearley et al., 1999). In addition, the study by Spugnini et al. (2000) reported that about 76% of dogs that underwent radiotherapy for treatment of intracranial masses died of recurrent progressive neuropathy suggestive of tumour regrowth or progression. In dogs, meningiomas treated with a combination of surgery and radiotherapy have a significantly better outcome than surgery alone (Table 5).

The usual treatment of choice for cats with meningiomas is surgical excision as in this species these tumours tend to be well encapsulated and easily delineated from normal brain (Fig. 7). The cat's age, location of intracranial meningioma and presence of multiple intracranial meningiomas have not been found to affect significantly the survival and outcome of cats that underwent debulking surgery (Gordon et al., 1994). In a retrospective analysis of cats that underwent surgical removal of intracranial meningiomas, the overall survival for 34 cats was 71% at 6 months, 66% at 1 year, and 50% at 2 years (Gordon et al., 1994). Other studies have determined a median survival interval after tumour resection to be 22 and 27 months (Gallagher et al., 1993; Troxel et al., 2003), compared to 18 days for cats that were treated medically (Gordon et al., 1994). Long-term remission of clinical signs associated with solitary or multiple meningiomas in cats may be achieved by surgical excision followed by treatment with hydroxyurea (Forterre et al., 2006, 2007; Tomek et al., 2008) (Table 5).

Post-operative recurrence of feline meningiomas has been reported to occur in about 20% of cases (Gallagher et al., 1993; Gordon et al., 1994; Troxel et al., 2003) and a large study has determined the tumour recurrence to be 9.5 months (median time) after surgery (Troxel et al., 2003). To the best of our knowledge there are no studies evaluating the post-operative recurrence of canine meningiomas. In addition, no data are available regarding the best therapeutic approach to apply in case of recurrence of feline and canine meningiomas.

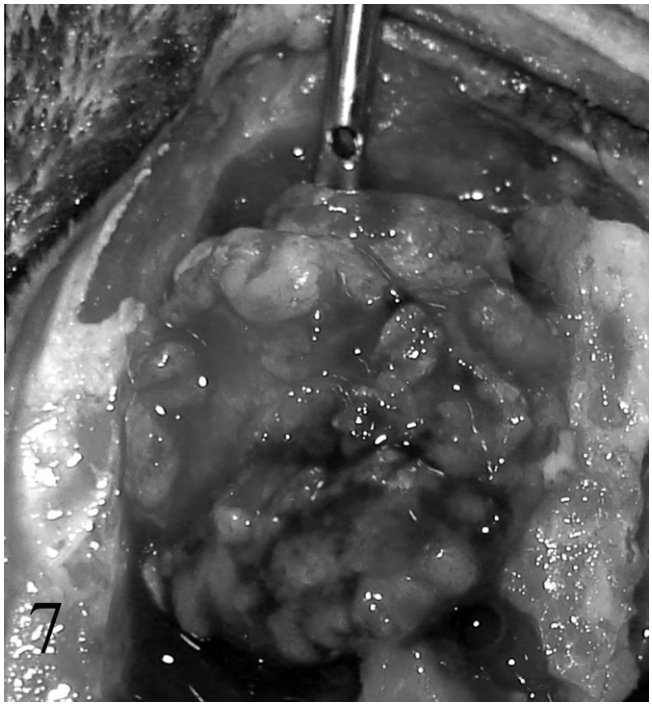

Fig. 7. Intra-operative photograph showing the appearance of a large histopathologically confirmed meningioma in a 9 year old cat. The mass appears well demarcated, firm and granular.

Conclusions and future directions

The application of clinical predictive and prognostic indicators currently used in people is limited in small animal medicine because insufficient data are available correlating biological tumour behaviour with the current WHO classification system in dogs as well as in cats.

Recent published information concerning the morphological and biological features of meningiomas in domestic animals indicates the need for an improved classification and grading, pertinent to the biological behaviour, so that prognostic and advanced therapeutic applications could be of benefit to veterinary oncology. Furthermore, the knowledge of molecular mechanisms responsible for progression of neoplastic processes is the basis for the development of future therapeutic strategies. The clinicopathological and immunophenotypic similarities between canine and human meningioma support the need for new comparative studies of canine meningioma as a possible animal model for the human neoplasm (Thomas et al., 2009).

Although a definitive diagnosis of meningioma requires histopathological examination of the neoplastic tissue, further studies based on the correlation between advanced diagnostic imaging and histopathology are necessary to provide objective parameters that can be used to (1) predict the type and grade of the meningioma, (2) create a scoring system that may be used to predict the extent of tumour removal, (3) create a scoring system that may reflect the surgical risk, and (4) predict the tumour recurrence after gross resection.

Advances in surgical technique have been shown to improve survival times in dogs and cats with intracranial meningiomas and further studies on large numbers of dogs and cats are needed to provide useful and standardised information about the best surgical techniques for these primary tumours and the usefulness of post-operative chemotherapeutics/ radiotherapy.

More complete and careful follow-up data needs to be collected to identify differences between morphological and biological malignancy and to strengthen the prognostic value of a new grading system applied to meningiomas of domestic animals. Close collaborations between clinicians and pathologists will facilitate this, as will the collection of a large number of tumour specimens from living animals, ideally using minimally invasive techniques (Greco et al., 2006; Klopp and Rao, 2009; Klopp and Ridgway, 2009).

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tvjl.2011.10.008.

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