Neoplasms of the central nervous system of dogs and cats

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Contents

Introduction

The mammalian central nervous system (CNS) consists of the brain, spinal cord, and retina. The peripheral nervous system (PNS) is composed of all the cranial and spinal nerves and associated ganglia that arise from the brain and spinal cord. In veterinary medicine, neoplasms of the CNS (affecting the brain and/or spinal cord) and PNS (affecting cranial and/or spinal nerves and ganglia) have been consistently described in dogs and cats but are less commonly reported in other animal species.[11,15,25,34] The diagnosis of CNS and PNS neoplasms in companion animals depends initially on the clinical and/or postmortem determination of the neurolocalization of the neoplasm, with diagnostic confirmation relying on histologic examination of autopsy or biopsy samples aided by the use of immunohistochemistry (IHC).[15] Most current tumor classification and

grading systems in veterinary medicine are heavily based on the World Health Organization guidelines developed for human neuropathology, which also uses histology and IHC as the basis for diagnosis, but leans heavily on molecular diagnostic tools to provide a more objective tumor diagnosis.[20,21] Although efforts have been made to develop and apply updated classification and grading systems for specific groups of canine neoplasms,[4,19] further clinical studies are necessary to correlate tumor type and grade with clinical outcome and to establish their capacity to predict tumor behavior and prognosis.

Although numbers vary according to different institutions, the incidence rate of primary CNS neoplasia in dogs and cats is estimated to be up to 14.5 and 3.5 per 100,000 cases, respectively.[1] Most primary CNS neoplasms have meningeal or neuroepithelial origin (including stem cells or immature progenitor cells), but the exact cell of origin of many tumors remains poorly characterized.[16,37] The majority of primary CNS neoplasms of dogs and cats consist of meningiomas and gliomas (primarily oligodendrogliomas and astrocytomas).[13,17,22,24,28-30,32,33,36] In dogs, approximately 50% of primary brain tumors are meningiomas and 35% are gliomas.[25] In cats, meningiomas and gliomas account for nearly 85% and 12% of all primary brain neoplasms, respectively.[33] Spinal meningiomas and gliomas are less frequently described.[22] Less common primary CNS neoplasms of dogs include choroid plexus tumors,[6,7,9,27] ependymomas,[24] and embryonal tumors.[2,8,15,31] Uncommonly reported primary CNS neoplasms of cats consist mainly of ependymomas and lymphomas.[32,33,36] A variety of other primary neoplasms affecting the brain and spinal cord are rarely reported.[15] Secondary CNS neoplasms consist of metastatic tumors that spread hematogenously to the CNS (such as mammary carcinoma and melanoma), those that are part of a disseminated neoplasia (such as hemangiosarcoma, lymphoma, and histiocytic sarcoma), and those that compress or invade the CNS by direct extension from adjacent tissues (sinonasal, pituitary, cranial, and vertebral neoplasms, among others).[14,15]

Neoplasms of the PNS consist mainly of neoplasms arising from neurolemmocytes (Schwann cells), perineurial cells, and intraneural fibroblasts. Due to their uncertain

histogenesis and difficult classification on routine examination, these neoplasms are typically referred to as benign or malignant nerve sheath tumors.[15] Nerve sheath tumors are widely mentioned in the veterinary literature as peripheral nerve sheath tumors. However, since all nerves are peripheral and there are no central nerves, the term "peripheral" is redundant.[10] For that reason, the use of the term nerve sheath tumor (NST) is highly encouraged.

This protocol will focus primarily on CNS neoplasms of dogs and cats, including meningioma, glioma (oligodendroglioma, astrocytoma, and ependymoma), and choroid plexus tumors. Neoplasms of the PNS will be discussed in a separate protocol.

General guidelines for tumor neurolocalization and sampling

Patient signalment

Animal species

- ☐ Dog
- ☐ Cat
- ☐ Other (specify):

Age:

Sex

- ☐ Male
- ☐ Castrated male
- ☐ Female
- ☐ Spayed female
- ☐ Unknown

Breed:

Anatomic site

Regardless of the nature of a particular CNS neoplasm (primary versus secondary), a detailed description of the clinical neuroanatomic diagnosis coupled with the diagnostic neuroimaging findings allows pathologists to better interpret the histologic and IHC

findings of each tumor. This protocol aims to provide standards for a simplified but systematic determination of the neuroanatomic localization and local or remote effects of primary and secondary neoplasms of the CNS. The description of the affected anatomic site or sites and compartments in the brain, spinal cord, and/or adjacent tissues must be considered by the pathologist writing the autopsy or surgical biopsy report, as the tumor location provides important information regarding the diagnosis, prognosis, and potential treatment protocol. In addition, this protocol could be useful as a standardized tool for researchers involved in clinical studies focusing on neuro-oncology. Although focused primarily on neoplasms of companion animals (dogs and cats), readers are encouraged, when possible, to adapt this protocol to other mammalian species.

Skull and vertebral bones (Fig. 1)

- ☐ Skull
  - ☐ Supratentorial
    - ☐ Calvaria
    - ☐ Rostral skull base (sella turcica and rostral areas)
  - ☐ Infratentorial
    - ☐ Cerebellar
    - ☐ Caudal skull base (caudal to the sella turcica)

- ☐ Vertebrae
  - ☐ Cervical (specify):
  - ☐ Thoracic (specify):
  - ☐ Lumbar (specify):
  - ☐ Sacral (specify):
  - ☐ Vertebral canal (specify):

Meninges

Dura mater and leptomeninges (arachnoid and pia mater)

- ☐ Telencephalic meninges

- ☐ Falx
- ☐ Tentorium
- ☐ Olfactory bulb
- ☐ Olfactory peduncle
- ☐ Frontal lobe
- ☐ Parietal lobe
- ☐ Temporal lobe
- ☐ Occipital lobe
- ☐ Piriform lobe
- ☐ Hippocampus

☐ Diencephalic meninges

- ☐ Thalamus
- ☐ Hypothalamus
- ☐ Epithalamus (pineal area)

☐ Mesencephalic meninges

- ☐ Rostral colliculus
- ☐ Caudal colliculus
- ☐ Ventral mesencephalon

☐ Metencephalic meninges

- ☐ Pons
  - ☐ Cerebellar peduncle
    - ☐ Rostral
    - ☐ Middle
    - ☐ Caudal
- ☐ Cerebellar meninges
  - ☐ Tentorium
  - ☐ Vermis
  - ☐ Hemisphere
  - ☐ Cerebellopontine angle

☐ Myelencephalic (medulla oblongata) meninges

☐ Skull base meninges (meningeal neoplasms attached to the skull base)

- ☐ Paranasal area
- ☐ Rostral cranial fossa
- ☐ Central cranial fossa
- ☐ Caudal cranial fossa
- ☐ Sellar area

☐ Other (specify):

☐ Spinal cord

- ☐ Cervical (specify segment):
- ☐ Thoracic (specify segment):
- ☐ Lumbar (specify segment):
- ☐ Sacral (specify segment):
- ☐ Vertebral canal (specify segment):

Overall relationship of the neoplasm to the meninges

- ☐ Extradural or epidural (lesion outside the dura mater)
- ☐ Intradural (lesion between the dura mater and neuroparenchyma)

Brain (Fig. 2–9)

Telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon

☐ Telencephalon

- ☐ Olfactory bulb
- ☐ Olfactory peduncle
- ☐ Frontal lobe
- ☐ Parietal lobe
- ☐ Temporal lobe
- ☐ Occipital lobe
- ☐ Piriform lobe

- ☐ Corpus callosum
- ☐ Basal nuclei
- ☐ Internal capsule
- ☐ Hippocampus

☐ Diencephalon

- ☐ Interthalamic adhesion
- ☐ Thalamus
- ☐ Epithalamus (pineal area)
- ☐ Hypothalamus
- ☐ Optic tract

☐ Mesencephalon

- ☐ Rostral colliculus
- ☐ Caudal colliculus
- ☐ Tegmentum
- ☐ Cerebral crus

☐ Metencephalon

- ☐ Pons
  - ☐ Cerebellar peduncles
    - ☐ Rostral
    - ☐ Middle
    - ☐ Caudal
  - ☐ Pontine tegmentum (dorsal pons)
  - ☐ Ventral pons
- ☐ Cerebellum
  - ☐ Vermis
  - ☐ Hemisphere (paravermis, outer hemisphere, and paraflocculus)
  - ☐ Cerebellopontine angle (including flocculus)

☐ Myelencephalon (medulla oblongata)

☐ Other (specify):

- ☐ Ventricles
  - ☐ Lateral ventricles
  - ☐ Third ventricle
  - ☐ Mesencephalic aqueduct
  - ☐ Fourth ventricle
  - ☐ Lateral apertures (including cerebellopontine angle)

Adjacent structures: Benign and malignant neoplasms arising from these tissues can compress or invade the CNS

- ☐ Cranial nerve (please specify nerve):
- ☐ Pineal gland
- ☐ Sellar area, suprasellar and parasellar area
- ☐ Pituitary gland
  - ☐ Adenohypophysis
  - ☐ Neurohypophysis

Spinal cord

Cervical, thoracic, lumbar, and sacral spinal cord

- ☐ Cervical (specify segment and which nerve roots are involved):
- ☐ Thoracic (specify segment and which nerve roots are involved):
- ☐ Lumbar (specify segment and which nerve roots are involved):
- ☐ Sacral (specify segment and which nerve roots are involved):
- ☐ Central canal

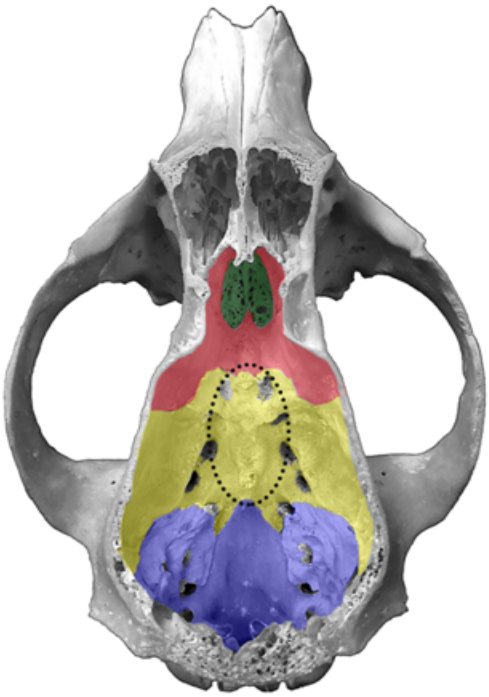
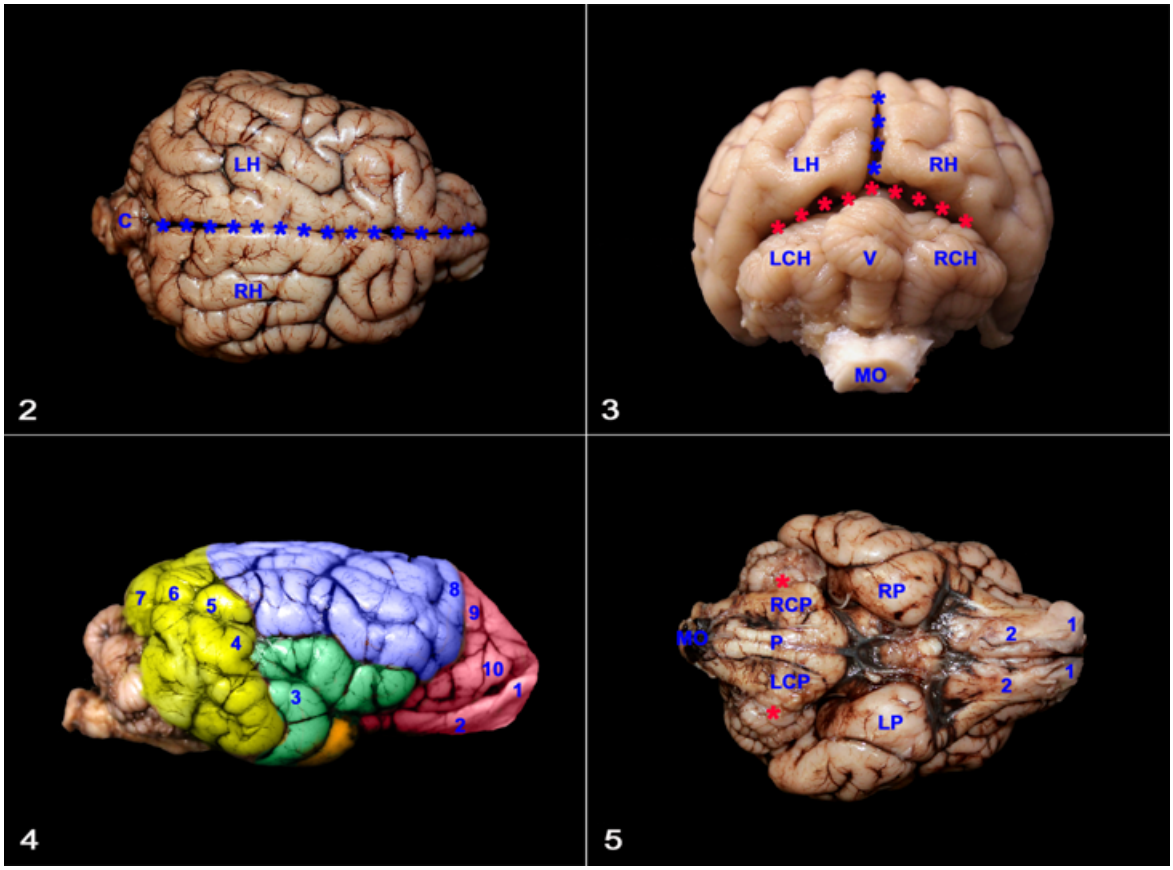
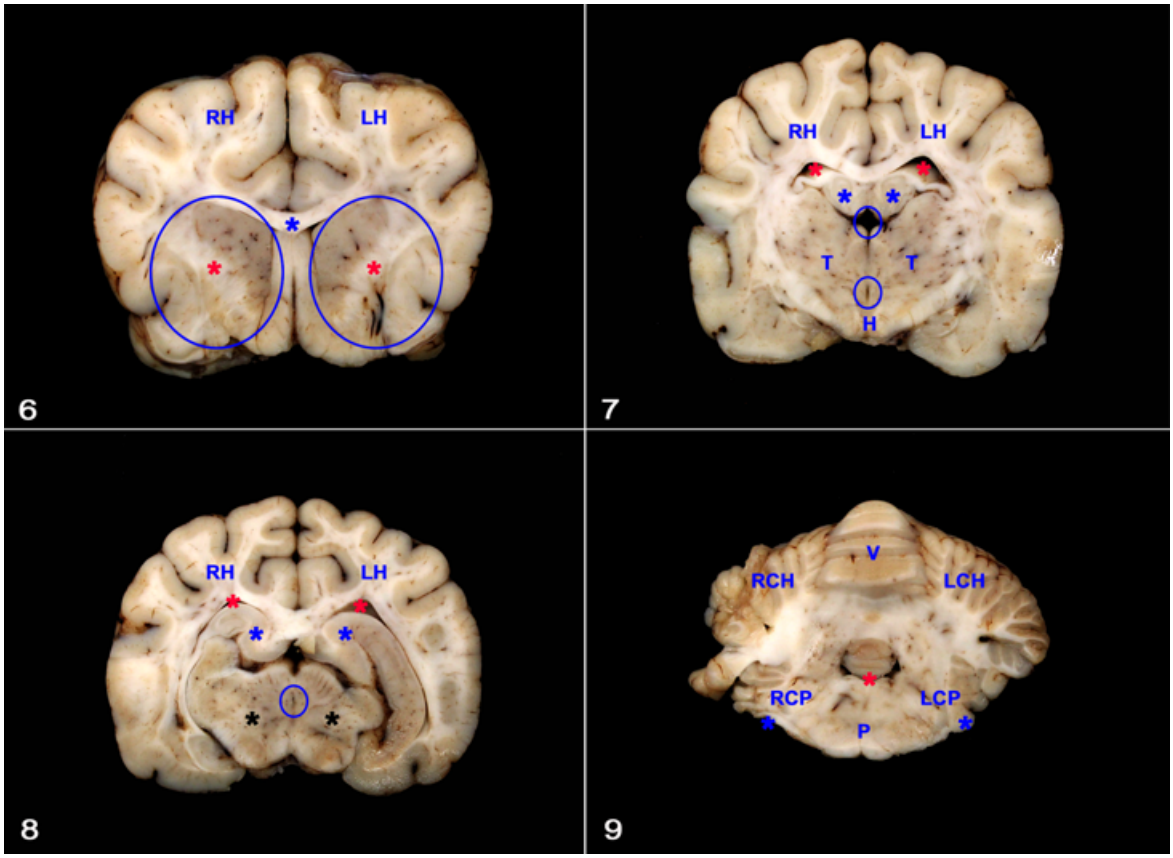


Figure 1. Dorsal view of a canine skull after removal of the skull cap revealing the anatomic subdivisions of the rostral skull base (paranasal region = green; rostral cranial fossa = red; central cranial fossa = yellow), caudal skull base (caudal cranial fossa = blue), and sellar region (dashed lines). Adapted from Rissi DR. J Vet Diagn Invest 27:743-748, 2015.



Figures 2–5. Main neuroanatomic hallmarks for tumor neurolocalization in the canine brain. **Figure 2.** Longitudinal cerebral fissure (blue asterisks), left cerebral hemisphere (LH), right cerebral hemisphere (RH), and cerebellum (C). **Figure 3.** Left cerebral hemisphere (LH), right cerebral hemisphere (RH), longitudinal cerebral fissure (blue asterisks), tentorium (red asterisks), cerebellar vermis (V), right cerebellar hemisphere (RCH), left cerebellar hemisphere (LCH), and medulla oblongata (MO). **Figure 4.** Olfactory bulb (1), olfactory peduncle (2), sylvian gyrus (3), ectosylvian gyrus (4), suprasylvian gyrus (5), ectomarginal gyrus (6), marginal gyrus (7), prostcruciate gyrus (8), precruciate gyrus (9), and prorean gyrus (10). These structures are helpful when defining the boundaries of the frontal lobe (red), piriform lobe (orange), temporal lobe (green), parietal lobe (blue), and occipital lobe (yellow). **Figure 5.** Olfactory bulb (1), olfactory peduncle (2), left piriform lobe (LP), right piriform lobe (RP), pons (P), right cerebellar peduncle (RCP), left cerebellar peduncle (LCP), cerebellopontine angle (red asterisks), and medulla oblongata (MO).



Figures 6–9. Main neuroanatomic hallmarks for tumor neurolocalization in the canine brain. **Figure 6.** Left cerebral hemisphere (LH), right cerebral hemisphere (RH), basal nuclei (blue circles), internal capsule (red asterisks), and corpus callosum (blue asterisk). **Figure 7.** Left cerebral hemisphere (LH), right cerebral hemisphere (RH), thalamus (T), hypothalamus (H), hippocampus (blue asterisks), lateral ventricles (red asterisks), third ventricle (blue circle). **Figure 8.** Left cerebral hemisphere (LH), right cerebral hemisphere (RH), hippocampus (blue asterisks), lateral ventricles (red asterisks), mesencephalon (black asterisks), and mesencephalic aqueduct (blue circle). **Figure 9.** Cerebellar vermis (V), right cerebellar hemisphere (RCH), left cerebellar hemisphere (LCH), right cerebellar peduncle (RCP), left cerebellar peduncle (LCP), cerebellopontine angle (blue asterisks), and fourth ventricle (red asterisk).

Laterality

- ☐ Unilateral
  - ☐ Right
  - ☐ Left
- ☐ Midline
- ☐ Bilateral

Neuroimaging findings (brief description, if applicable):

Procedure

- ☐ Biopsy
  - ☐ Incisional biopsy
  - ☐ Excisional biopsy
  - ☐ Other (specify):
- ☐ Not specified
- ☐ Autopsy

Specimen size*

Greatest dimension (cm): cm

Additional dimensions (cm): x cm

Cannot be determined (explain):

*For fragmented tissue, an aggregate size may be given.

Tumor invasion

- ☐ Not identified
- ☐ Equivocal
- ☐ Present
  - ☐ Adjacent neuroparenchyma
  - ☐ Meninges

☐ Ventricular system

☐ Cerebrospinal fluid

☐ Adjacent bones

☐ Other (specify):

Please refer to Lymphovascular Invasion Guideline:

https://vcgp.org/documents/2022/03/lymphovascular-invasion.pdf/

Mitotic count (Note A)

☐ None identified

☐ Number of mitoses in 2.37 mm^2:

☐ Cannot be determined (explain):

Please refer to Mitotic Count Guideline:

https://vcgp.org/documents/2022/03/mitotic-count-2.pdf/

Margins (Note B)

How were margins assessed?

☐ N/A (explain)

☐ Tumor extends to tissue margins histologically

☐ Clean: Histologic tumor-free margins (HTFM) measurement: mm

Please refer to Margin Evaluation Guideline:

https://vcgp.org/documents/2021/05/margin-evaluation.pdf/

Ancillary tests (IHC, genomics, etc.)

The most common and reliable immunomarkers routinely utilized for the diagnosis of primary CNS neoplasms are summarized in **Table 1**.

Table 1. Common diagnostic immunomarkers utilized for canine and feline CNS neoplasms.

	Dogs		Cats	
Neoplasm	**Consistent immunolabeling**	**Variable immunolabeling**	**Consistent immunolabeling**	**Variable immunolabeling**
Meningioma	Vim	CK, E-cad	Vim, E-cad	CK
Oligodendroglioma	Olig2, CNPase	GFAP	Olig2	GFAP
Astrocytoma	GFAP	Olig2	GFAP	Olig2
Ependymoma	GFAP, CK	Olig2	GFAP, CK, Olig2	-
Choroid plexus tumor	Kir7.1	CK	-	-

Treatment

☐ Yes (specify):

☐ No

Patient outcome

☐ Alive

☐ Dead

☐ Natural death

☐ Tumor-related death (CNS spread, metastasis)

How was it determined?

☐ Clinically

☐ Autopsy

☐ Other (specify):

☐ Length of time between diagnosis and death:

☐ Non-tumor related death

☐ Euthanasia

☐ Unknown

Please refer to Outcomes Assessments Guideline:
https://vcgp.org/documents/2022/03/outcome-assessments.pdf/

Histologic diagnosis and grading (if applicable) of CNS neoplasms

The classification and grading of most canine and feline CNS neoplasms is heavily based on the Histological Classification of Tumors of the Nervous System of Domestic Animals[20] and the World Health Organization (WHO) Classification of Tumors of the Central Nervous System.[35] However, the veterinary guidelines for domestic animals were published in 1999 and are outdated. The current human WHO guidelines rely on molecular diagnostics as an aid to for the classification and grading of neoplasms,[35] a routine diagnostic technology that is not yet routinely available in veterinary medicine. In veterinary medicine, these neoplasms are diagnosed based on morphology, which can be subjective (Notes A and C-E), and IHC.

Canine and feline meningioma

Canine and feline meningiomas are subjected to the available veterinary and human classification and grading systems (**Table 2**).[20,21] Most canine and feline meningiomas are WHO grade 1 tumors, including meningothelial, transitional, psammomatous, and fibrous meningiomas, but WHO grade 2 neoplasms (atypical, chordoid, and clear cell meningiomas) and WHO grade 3 neoplasms (papillary and rhabdoid meningiomas or anaplastic meningiomas) are also reported (Note F). Many of these distinct morphologic patterns can be present in one neoplasm and a particular neoplasm should be subtyped according to the dominant morphologic pattern (typically consisting of around 70% of the neoplasm). In most cases, the diagnosis can be achieved based on histology. The diagnostic IHC profile of canine and feline meningiomas has not been well established, but positive immunolabeling for vimentin, CD34, laminin, E-cadherin, and N-cadherin, among others, support a diagnosis of meningioma.[26]

Canine and feline meningioma (Figs. 10–27)

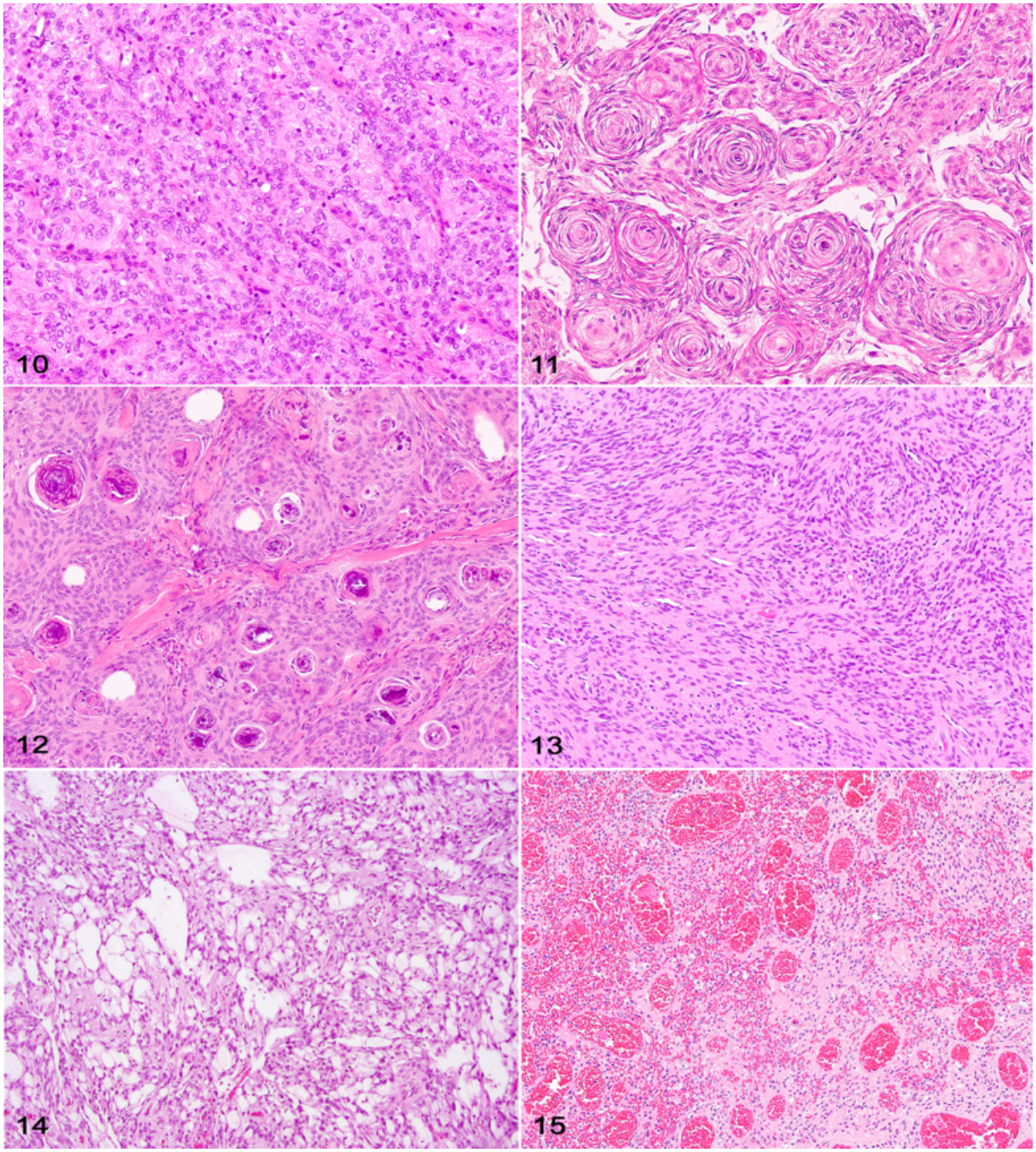
☐ Meningothelial (WHO grade 1)
☐ Transitional (WHO grade 1)
☐ Psammomatous (WHO grade 1)
☐ Fibrous (WHO grade 1)
☐ Microcystic (WHO grade 1)

☐ Angiomatous (WHO grade 1)
☐ Atypical (WHO grade 2)
☐ Chordoid (WHO grade 2)
☐ Clear cell (WHO grade 2)
☐ Papillary (WHO grade 3)
☐ Rhabdoid (WHO grade 3)
☐ Anaplastic (WHO grade 3)
☐ Other (specify):

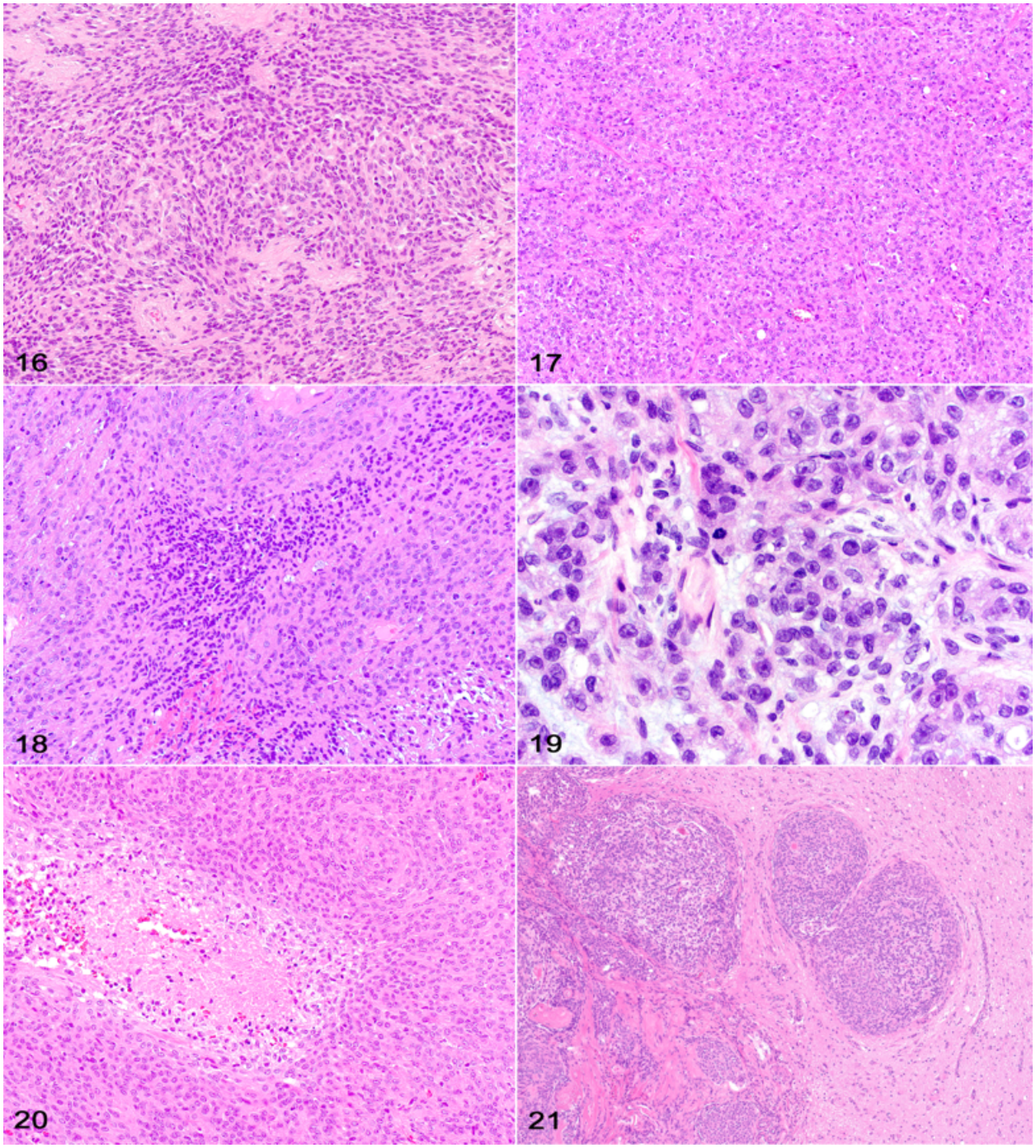
Table 2. Morphologic features for routine classification and grading of canine and feline meningiomas (adapted from Koestner et al. 1999. Histological Classification of Tumors of the Nervous System of Domestic Animals).

Tumor type	Grade	Key morphologic features
Meningothelial, transitional, psammomatous, fibrous	1	Low to moderate cellularity with low cell and nuclear atypia, absent or low mitotic activity, geographic necrosis can be present
Atypical, chordoid, clear cell*	2	Mitotic activity (4 or more mitoses in 2.37 mm^2), or invasion into the neuroparenchyma, or at least 3 of the following criteria: Hypercellularity Sheeting of neoplastic cells Small cell formation Nuclear atypia and macronucleoli Geographic necrosis
Papillary, rhabdoid, anaplastic	3	High cellularity, marked cell and nuclear pleomorphism, high mitotic activity (more than 20 in 2.37 mm^2), geographic necrosis, invasion into the neuroparenchyma

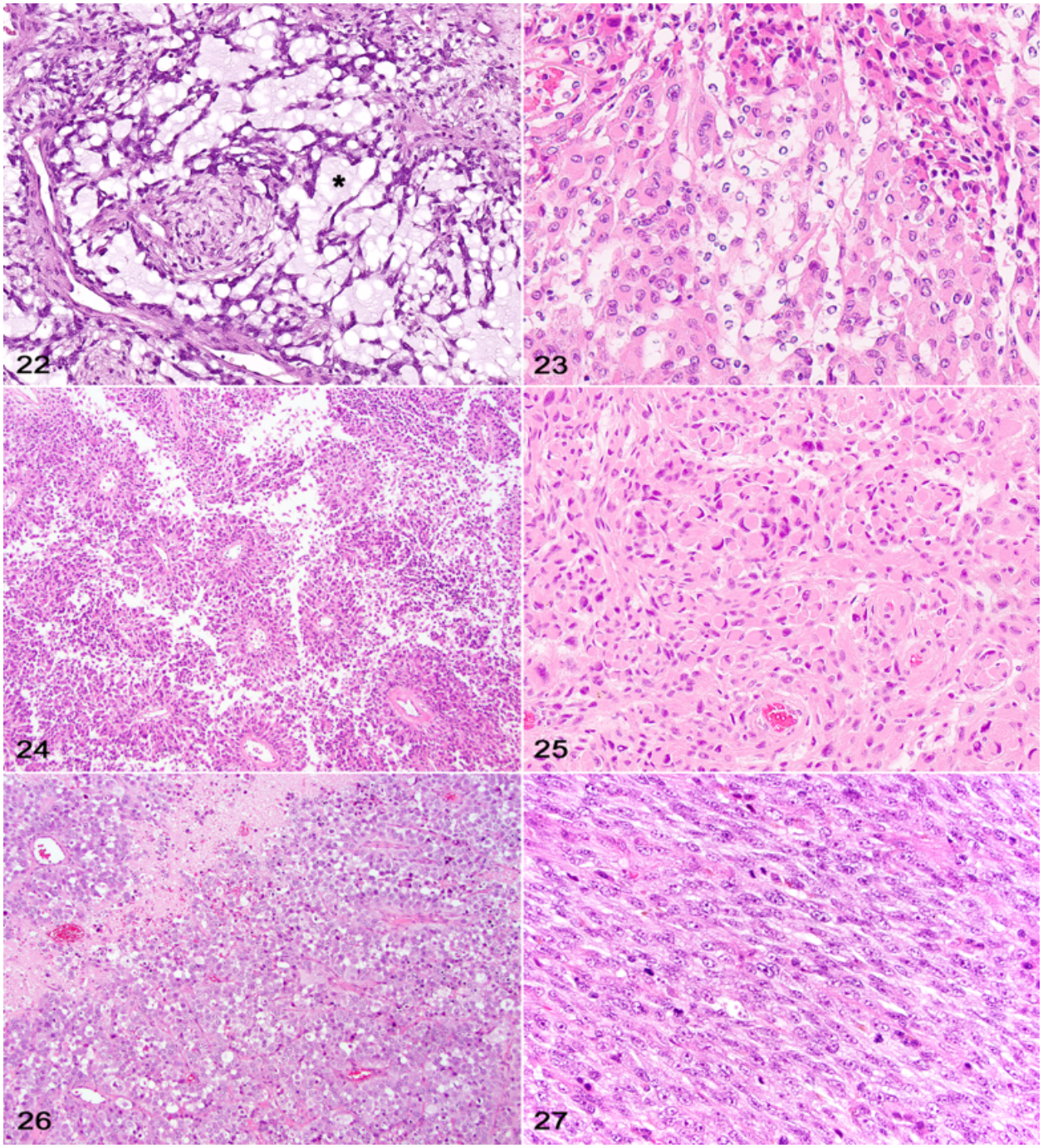
*Chordoid and clear cell meningioma are WHO grade 2 by default.



Figures 10–15. WHO grade 1 canine meningioma. Figure 10. Meningothelial meningioma consists of lobules of polygonal neoplastic cells with low cellular and nuclear pleomorphism. **Figure 11**. Transitional meningioma with the typical concentric whorls of neoplastic cells interspersed with spindle neoplastic cells. **Figure 12.** Psammomatous meningioma with whorls of neoplastic cells containing central mineralized concretions. **Figure 13.** Fibrous meningioma consists of interlacing fascicles of spindle neoplastic cells. **Figure 14.** Microcystic meningioma. Neoplastic cells are separated by accumulations of extracellular fluid that produces a lacy meshwork of microcysts. **Figure 15.** Angiomatous meningioma. Neoplastic cells are separated by numerous blood vessels.



Figures 16–21. Atypical (WHO grade 2) canine meningioma. Figure 16. Atypical meningioma with hypercellularity. **Figure 17.** Atypical meningioma with neoplastic cells arranged in sheets. **Figure 18.** Atypical meningioma with small cell formation (center). **Figure 19.** Atypical meningioma with nuclear atypia and macronucleoli. **Figure 20.** Atypical meningioma with an area of necrosis. **Figure 21.** Atypical meningioma with focal invasion into the neuroparenchyma.



Figures 22–27. WHO grade 2 and 3 canine meningioma. Figure 22. Chordoid meningioma (WHO grade 2). Neoplastic cells arranged in cords embedded in a mucinous stroma. **Figure 23.** Clear cell meningioma (WHO grade 2). Neoplastic cells have finely vacuolated cytoplasm. **Figure 24.** Papillary meningioma (WHO grade 3). Neoplastic cells form papillary projections throughout. **Figure 25.** Rhabdoid meningioma (WHO grade 3). Neoplastic cells are round and have hypereosinophilic, glassy cytoplasm. **Figure 26.** Anaplastic meningioma (WHO grade 3). Neoplastic cells have marked pleomorphism with extensive necrosis. **Figure 27.** Anaplastic meningioma (WHO grade 3). There is high mitotic activity.

Canine and feline glioma

The histologic examination of canine and feline glial neoplasms is based on a set of morphologic criteria (**Table 3**) aimed to classify and grade a glioma as oligodendroglioma, astrocytoma, undefined glioma, or ependymoma (and their distinct subtypes, when applicable). Although a revised diagnostic grading system for canine glioma has been developed as an alternative to the outdated veterinary guidelines (**Fig. 28 and Table 4**),[19] feline gliomas are still subjected to the available veterinary and human classification and grading systems (**Table 5**).[20,21] Ependymoma is a ventricular or rarely neuroparenchymal glioma that is thought to arise from radial glia. The classification and grading of ependymomas is also based on the veterinary and human classification and grading systems (**Table 6**).[20,21]

Table 3. Morphologic features for routine assessment of gliomas (adapted from Koehler, Miller, Miller, Porter et al. J Neuropathol Exp Neurol 77:1039-1054, 2018).

Histologic classification	Key morphologic features
Oligodendroglioma (when more than 80% of neoplasm meets these criteria)	Scant to moderate eosinophilic or lost cytoplasm (honeycomb or fried-egg appearance) Small, round nuclei with coarse chromatin, with nuclear rowing or molding Mucinous matrix with branching capillaries Pseudorosettes (Note G) Secondary structures Mineralization
Astrocytoma (when more than 80% of neoplasm meets these criteria)	Abundant eosinophilic cytoplasm or elongate cells Oval to elongate nuclei (angular) with open-faced chromatin and occasional large nucleoli; multinucleate cells Eosinophilic stroma (fibrillary) Rare mucinous microcysts Mineralization
Undefined (both phenotypes present in the same neoplasm, 30-40% each)	Undifferentiated cellular morphology Biphenotypic or biphasic morphology

Table 4. Morphologic features for routine classification and grading of canine gliomas (adapted from Koehler, Miller, Miller, Porter et al. J Neuropathol Exp Neurol 77:1039-1054, 2018).

Tumor grade	Key morphologic features
Low-grade glioma	Low to moderate cellularity, low cell and nuclear pleomorphism, absent or low mitotic activity
High-grade glioma	Extensive intratumoral geographic necrosis with or without palisading, microvascular proliferation, high mitotic activity, morphologic features of malignancy (cell and nuclear pleomorphism, anisocytosis, anisokaryosis)

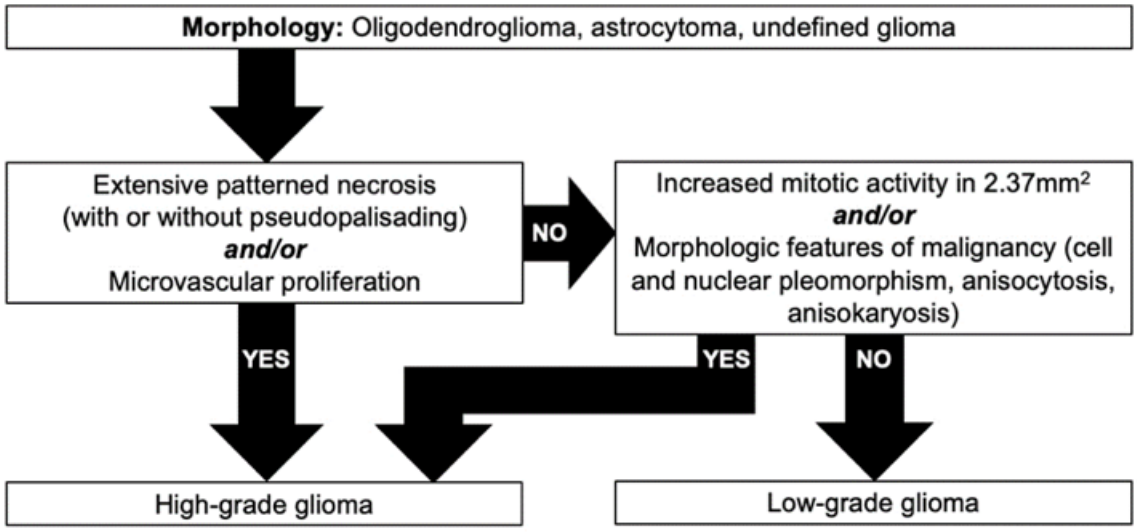


Figure 28. Flow-chart for grading of canine glioma. Adapted from Koehler JW, Miller AD, Miller R, Porter B et al. J Neuropathol Exp Neurol 77:1039-1054, 2018.

Please refer to **Note A** for more information about reporting mitotic activity.

Canine oligodendroglioma, astrocytoma, and undefined glioma (Figs. 29–36)

☐ Low-grade oligodendroglioma

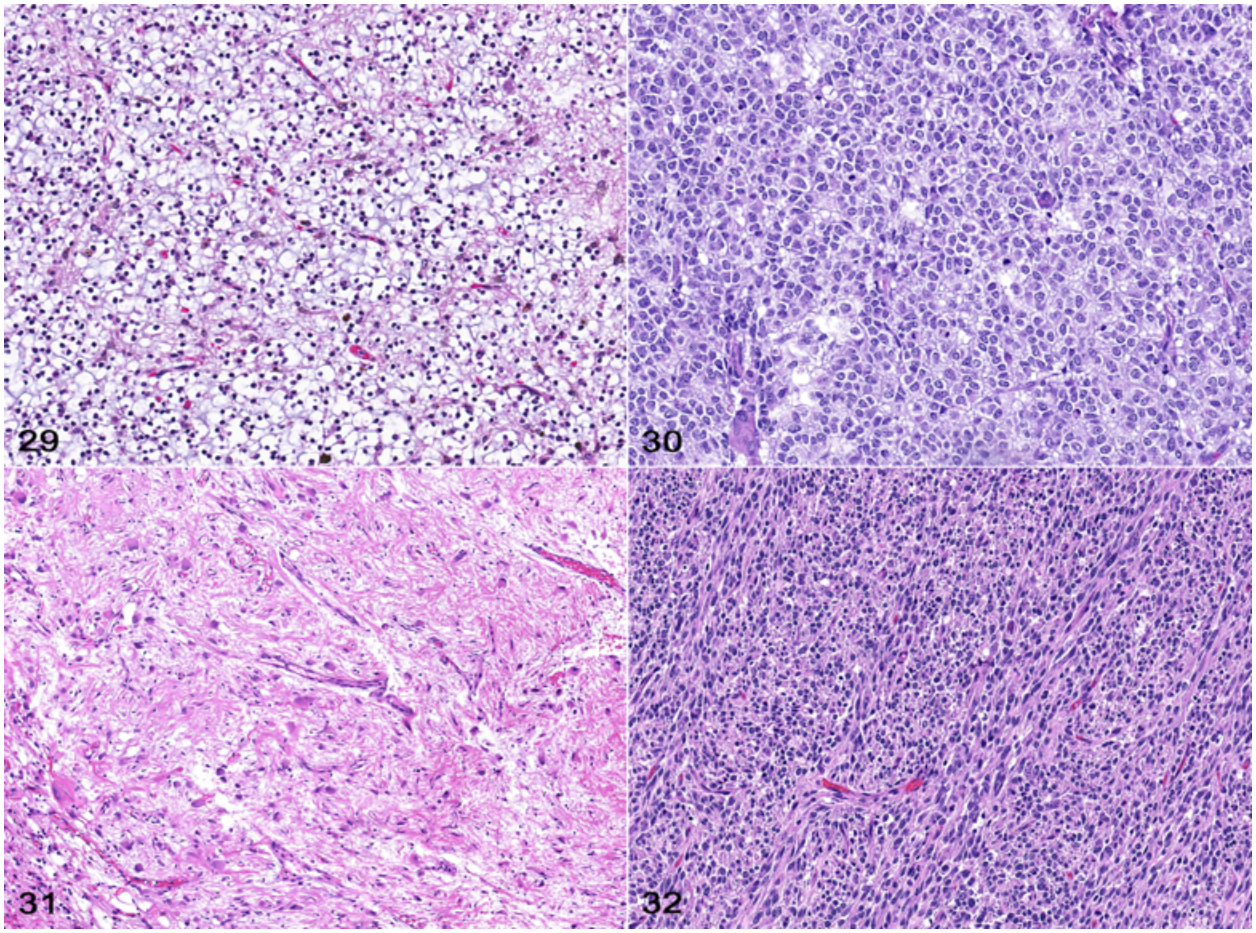
☐ High-grade oligodendroglioma

☐ Low-grade astrocytoma

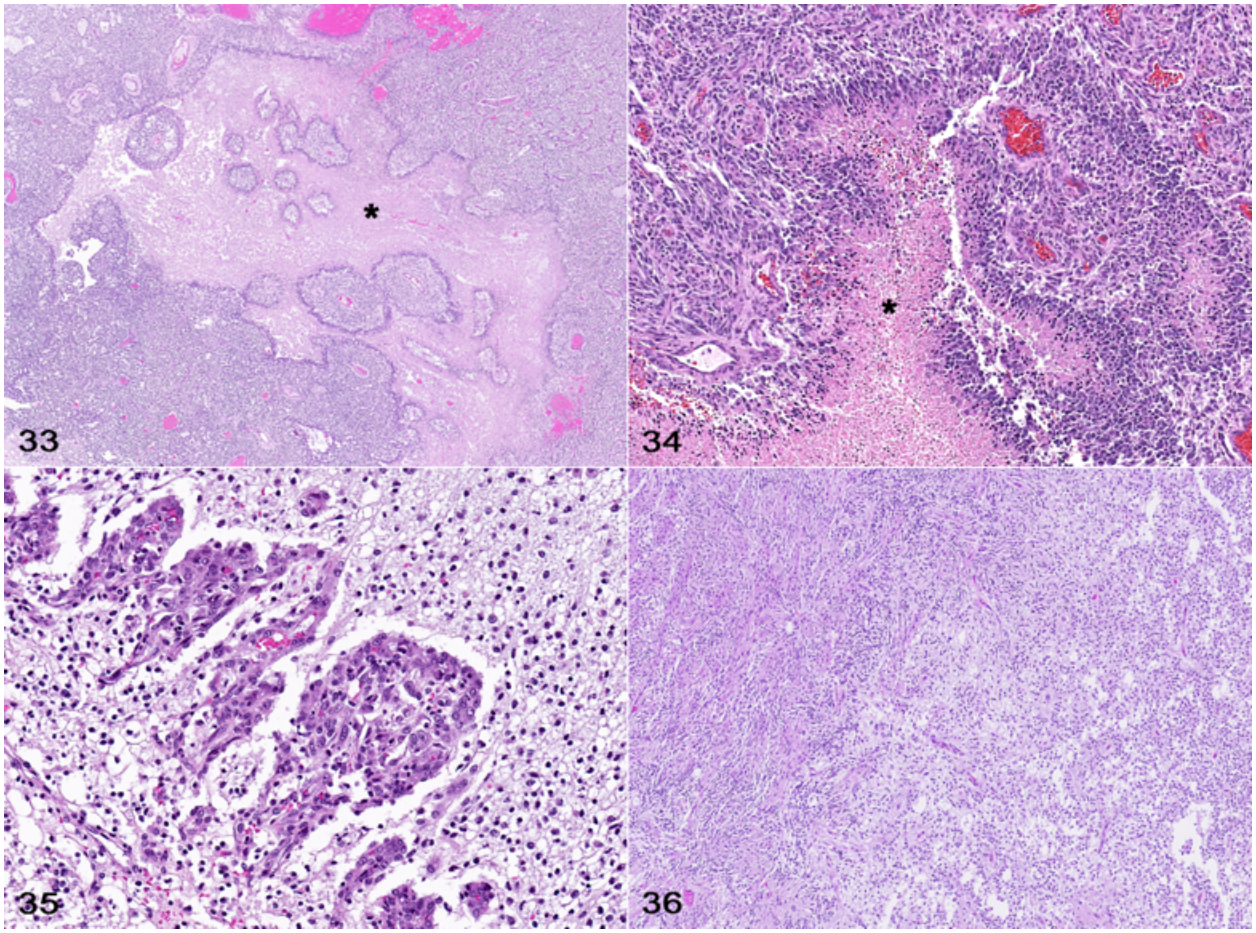
☐ High-grade astrocytoma

☐ Low-grade undefined glioma

☐ High-grade undefined glioma



Figures 29–32. Cellular and nuclear features of canine glioma. Figure 29. Low-grade oligodendroglioma. Neoplastic cells have eosinophilic or lost cytoplasm (honeycomb appearance) and small, round nuclei with dense chromatin. The mucinous stroma contains branching capillaries. **Figure 30.** High-grade oligodendroglioma. Neoplastic cells have large, slightly elongate, irregular nuclei with coarse chromatin. The neoplasm is densely cellular and has marked cellular and nuclear pleomorphism. **Figure 31.** Low-grade astrocytoma. Neoplastic cells have abundant eosinophilic cytoplasm and oval to elongate nuclei with dense chromatin. There is abundant fibrillary eosinophilic stroma. **Figure 32.** High-grade astrocytoma. Neoplastic cells form bundles and have irregular nuclei with coarse chromatin. The neoplasm is densely cellular and has marked cellular and nuclear pleomorphism.



Figures 33–36. High-grade canine glioma. Figure 33. High-grade oligodendroglioma. There is extensive geographic necrosis within the neoplasm (asterisk). **Figure 34.** High-grade astrocytoma. Necrotic areas (asterisk) are surrounded by palisading neoplastic cells. **Figure 35.** High-grade oligodendroglioma. Areas of microvascular proliferation are characterized by capillaries lined by multiple layers of plump endothelial cells forming distinct clusters. **Figure 36.** High-grade undefined glioma. The neoplasm consists of equal proportions of neoplastic cells with oligodendroglioma morphology (bottom right) and astrocytoma morphology (top left).

Feline oligodendroglioma and astrocytoma (Figs. 37–42)

☐ Astrocytoma (WHO grade 1 or 2)

☐ Anaplastic astrocytoma (WHO grade 3)

☐ Glioblastoma (WHO grade 4 astrocytoma)

☐ Oligodendroglioma (WHO grade 2)

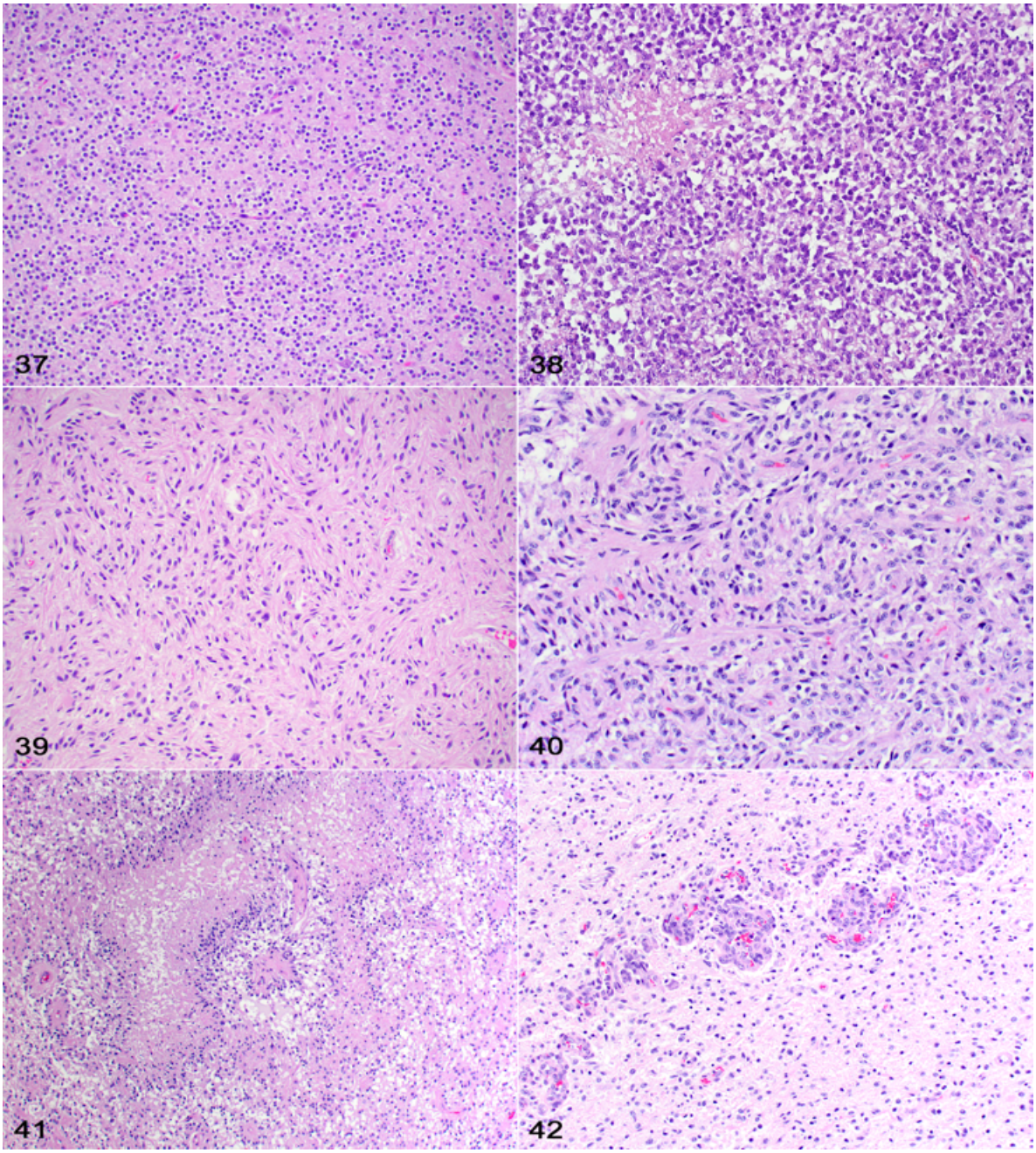
☐ Anaplastic oligodendroglioma (WHO grade 3)

☐ Other (specify; for example: subependymal giant cell astrocytoma, angiocentric astrocytoma):

Table 5. Morphologic features for routine classification and grading of feline gliomas (adapted from Koestner et al. 1999. Histological Classification of Tumors of the Nervous System of Domestic Animals).

Tumor type	Grade	Key morphologic features
Oligodendroglioma	2	Low to moderate cellularity, low cell and nuclear atypia, absent or low mitotic activity, rare geographic necrosis
Anaplastic oligodendroglioma	3	Moderate to high cellularity, moderate to marked cell and nuclear atypia, frequent mitoses (more than 6 in 2.37 mm^2),[a] geographic necrosis with or without palisading of neoplastic cells, microvascular proliferation
Astrocytoma	1	Low to moderate cellularity, low cell and nuclear atypia, absent or low mitotic activity
Astrocytoma	2	Moderate cellularity, low to moderate cell and nuclear atypia, absent or low mitotic activity
Anaplastic astrocytoma	3	High cellularity, moderate to marked cell and nuclear atypia, frequent mitoses, rare geographic necrosis
Glioblastoma	4	High cellularity, marked cell and nuclear atypia, high mitotic activity, geographic necrosis with or without palisading of neoplastic cells, microvascular proliferation

[a]Not validated in cats.



Figures 37–42. Feline glioma. Figure 37. WHO grade 2 oligodendroglioma. Neoplastic cells have eosinophilic or lost cytoplasm and small, round nuclei with dense chromatin. **Figure 38.** Anaplastic (WHO grade 3) oligodendroglioma. Neoplastic cells have irregular nuclei with coarse chromatin. The neoplasm is densely cellular and pleomorphic. **Figure 39.** WHO grade 2 astrocytoma. Neoplastic cells have eosinophilic cytoplasm and elongate nuclei in a fibrillar stroma. **Figure 40.** Anaplastic (WHO grade 3) astrocytoma. Neoplastic cells have irregular nuclei with coarse chromatin. The neoplasm is densely cellular. **Figure 41.** Glioblastoma (WHO grade 4 astrocytoma). There is high cellularity and nuclear atypia with geographic necrosis and palisading of neoplastic cells. **Figure 42.** WHO grade 4 astrocytoma (glioblastoma). Microvascular proliferation.

Canine and feline ependymoma (Figs. 43–48)

☐ Subependymoma (WHO grade 1)

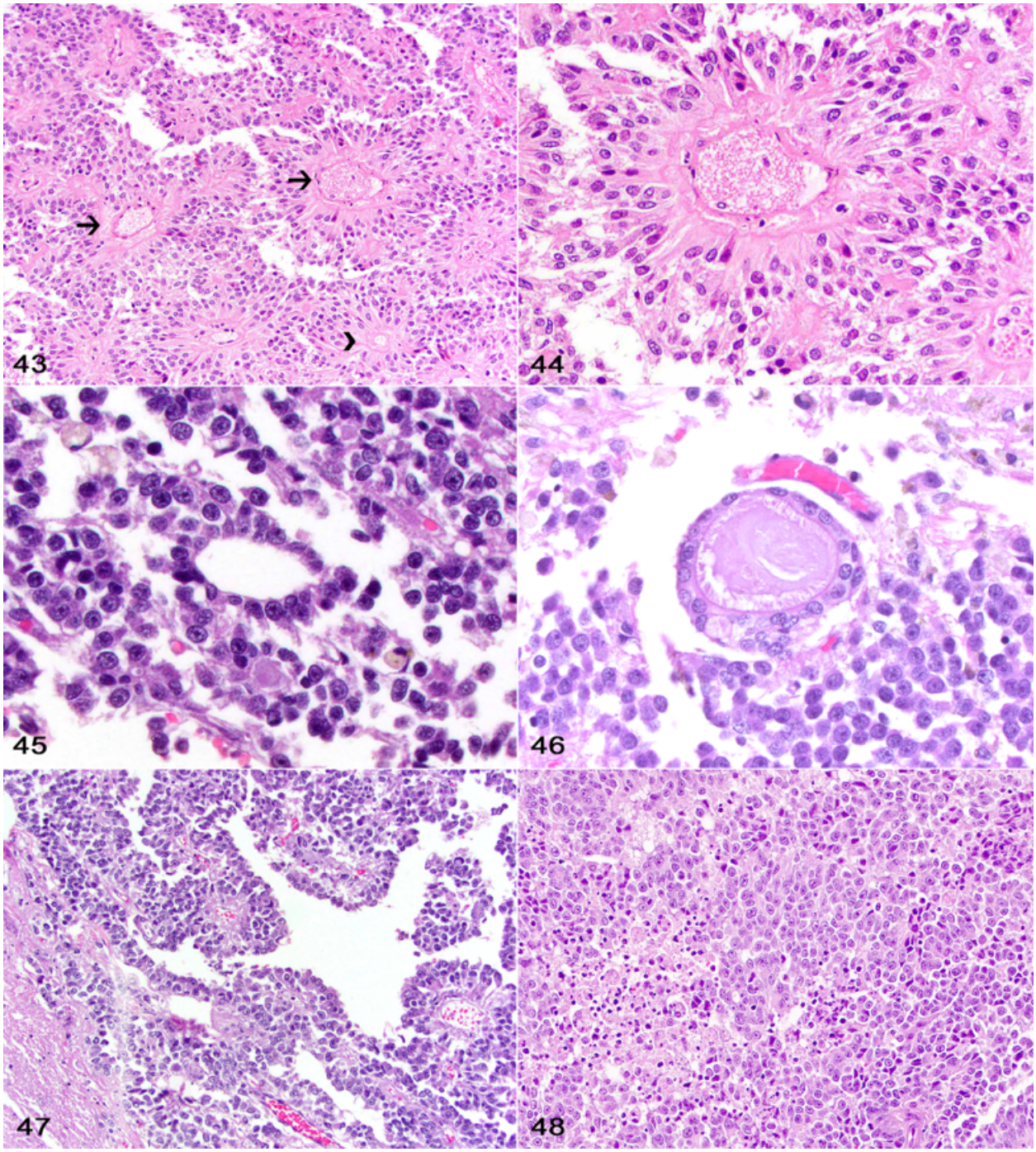
☐ Ependymoma (WHO grade 2)

☐ Anaplastic ependymoma (WHO grade 3)

☐ Other (specify):

Table 6. Morphologic features for routine classification and grading of canine and feline ependymomas (adapted from Koestner et al. 1999. Histological Classification of Tumors of the Nervous System of Domestic Animals).

Tumor type	Grade	Key morphologic features
Subependymoma	1	Periventricular clusters of glial cells embedded in a fibrillary stroma
Ependymoma (classic, papillary, tanycytic)	2	Sheets of round to polygonal neoplastic cells, ependymal canals, rosettes (Note G) and pseudorosettes, low to moderate cellularity and nuclear atypia, absent or low mitotic activity, no necrosis or microvascular proliferation, no invasion into the neuroparenchyma
Anaplastic ependymoma	3	Sheets of neoplastic cells with scattered rosettes and pseudorosettes, high cellularity and nuclear atypia, moderate to high mitotic activity, necrosis, microvascular proliferation, invasion into the neuroparenchyma, intraventricular metastasis



Figures 43–48. Ependymoma. Figure 43. Canine ependymoma. Neoplastic cells form rosettes (arrowheads) and pseudorosettes (arrows). **Figure 44.** Canine ependymoma. Pseudorosette (neoplastic cells palisading around a blood vessel). **Figure 45.** Canine ependymoma. Rosette (neoplastic cells palisading around a central lumen). **Figure 46.** Canine ependymoma. Rosette (ciliated neoplastic cells palisading around a central lumen with pale basophilic material). **Figure 47.** Canine ependymoma. Ribbons of neoplastic cells lining ependymal canals. **Figure 48.** Feline ependymoma. Higher-grade ependymomas tend to lack the typical rosettes and pseudorosettes and form sheets of neoplastic cells with necrosis. Figs. 43-47 from Miller AD et al. Vet Pathol 27:743-748, 2015.

Choroid plexus neoplasms

Choroid plexus tumors are intraventricular neoplasms that arise from the choroid plexus epithelium. These neoplasms are reported almost exclusively in dogs and are subjected to the veterinary and human classification and grading systems (**Table 6**).

Canine choroid plexus neoplasms (Figs. 49–52)

☐ Choroid plexus papilloma (WHO grade 1)

☐ Atypical choroid plexus papilloma (WHO grade 2)

☐ Choroid plexus carcinoma (WHO grade 3)

☐ Other (specify):

Other neoplasms (not listed above)

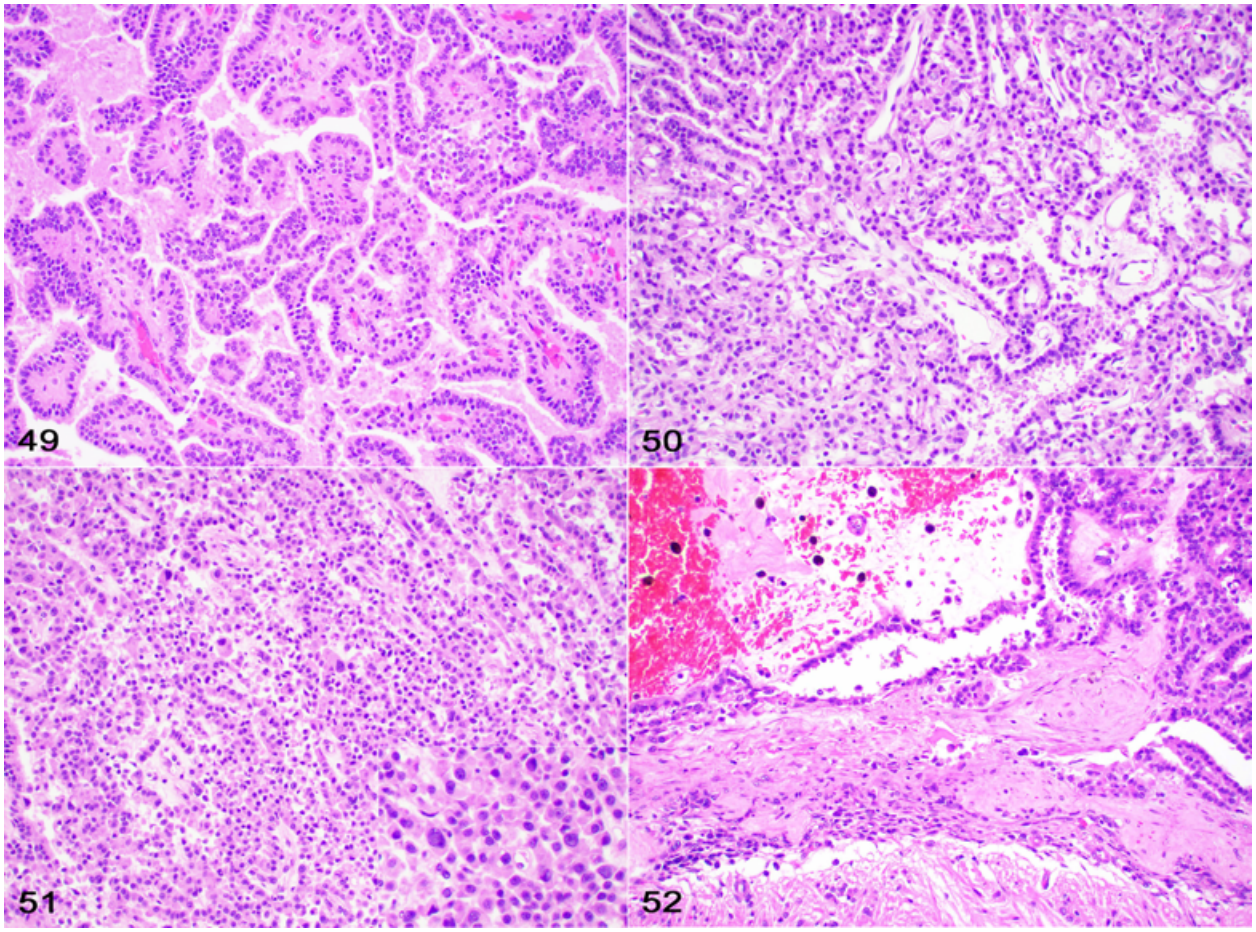
☐ Other (specify):

Table 7. Morphologic features for routine classification and grading of choroid plexus neoplasms (adapted from Koestner et al. 1999. Histological Classification of Tumors of the Nervous System of Domestic Animals).

Tumor type	Grade	Key morphologic features
Choroid plexus papilloma	1	Papillary proliferations of neoplastic cells, low cellularity and nuclear atypia, absent or low mitotic activity (less than 2 in 2.37 mm^2),[a] rare necrosis or invasion into the neuroparenchyma
Atypical choroid plexus papilloma	2	Papillary proliferations of neoplastic cells, low cellular and nuclear atypia, low mitotic activity (more than 2 in 2.37 mm^2),[a] at least two atypical morphologic criteria: hypercellularity, loss of papillary arrangement, and necrosis; rare invasion into the neuroparenchyma
Choroid plexus carcinoma	3	Solid and less often papillary proliferations of neoplastic cells, high cellularity and moderate cellular and nuclear atypia, frequent mitoses (more than 5 in 2.37 mm^2),[a] necrosis, microvascular proliferation, invasion into the neuroparenchyma, intraventricular metastasis

[a]Not validated in cats.

Please refer to **Note A** for more information about reporting mitotic activity.



Figures 49–52. Canine choroid plexus neoplasms. Figure 49. WHO grade 1 choroid plexus papilloma. Papillary proliferations of neoplastic cells with low cellularity and nuclear atypia, absent or low mitotic activity, and no necrosis or microvascular proliferation. **Figure 50.** WHO grade 2 atypical choroid plexus papilloma. Papillary proliferations are less distinct and there is increased cellularity. **Figure 51.** WHO grade 3 choroid plexus carcinoma. Disorganized and often solid proliferations of neoplastic cells with increased cellular and nuclear atypia (inset). **Figure 52.** WHO grade 3 choroid plexus carcinoma. Invasion into the neuroparenchyma with desmoplasia is a common finding in grade 3 tumors.

Discussion

The diagnostic characterization of CNS neoplasms of dogs and cats relies on routine histologic examination and IHC of biopsy and autopsy tumor samples. For this reason and until molecular diagnostic tools are available in veterinary medicine, there is an urgent need for more objective and precise means to morphologically classify and grade CNS neoplasms that would reduce intra and interobserver disagreement when examining tumor samples.

Although new or newly adapted classification and grading systems have been developed for canine glioma and meningioma, respectively, most of the diagnostic and phenotypic characterization of CNS neoplasms in veterinary medicine is still based on the human WHO guidelines.[4,19] Although the WHO recommendations have been useful for diagnostic purposes of canine and feline CNS neoplasms, their capacity to predict tumor behavior, prognosis, and response to treatment remains vastly unknown because of the lack of clinical outcome data in veterinary medicine.

Current and future species-specific tumor grading systems need to be validated by clinical studies. Modification to the grading systems should be based on correlation with clinical outcomes so that they provide relevant prognostic information for affected canine and feline patients. Some investigations have already evaluated the revised grading system for canine glioma and have found no associations between tumor type or grade and survival.[18] More studies are needed to confirm or refute these findings to improve reproducibility, accuracy, and ultimately patient care.

Notes:

A. Current veterinary classification and grading systems for CNS tumors are still vague in terms of quantification of mitotic activity and its possible correlation, if any, with clinical outcome. The mitotic count (MC) has been used as a reliable tool in many tumor classification and grading systems.[23] However, the MC used for grading of CNS neoplasms may be either vague (listed as low, high, or increased),[19,20] extrapolated from human grading systems (meningioma),[4] or not obtained with standardized approaches. Imprecise guidelines can result in variation of interpretation, impacting diagnosis, potential treatment and patient care. Therefore, as part of the standardization of tumor mitotic activity evaluation, we recommend that the number of mitoses should be counted in areas with the highest mitotic activity, including contiguous tumor fields and covering a total tumor area of 2.37 mm^2, while avoiding edema, inflammation, necrosis, hemorrhage, fibrosis, or artifacts.[23] Once standardized methods are applied to counting mitoses in CNS tumors, the resultant MC should be correlated with outcome data using statistical analysis to establish whether a cutoff (either a MC number or range) or cutoffs

can be used for predictive or prognostication purposes. Researchers are encouraged to perform MCs in different areas of the neoplasm to help determine which region's MC, if any, is better correlated to clinical outcome(s). If applicable, this information can be used alone or in a grading system. More details are provided in the Development, Reporting and Validation of Histologic Tumor Grading (see below).

Please refer to Mitotic Count Guideline:
https://vcgp.org/documents/2022/03/mitotic-count-2.pdf/

Please refer to Morphologies of Mitotic Figures Guideline:
https://vcgp.org/documents/2021/05/morphologies-of-mitotic-figures.pdf/

Please refer to Development, Reporting and Validation of Histologic Tumor Grading Systems Grading Guideline: www.vcgp.org

B. Margins: Brain biopsy is becoming more common in our veterinary patients. Establishment of margin designations can be performed in these cases, and criteria for these should be clearly defined.

C. Cellularity: Precise methods to qualify other tumor morphologic features such as degree of cellularity (hypocellular vs hypercellular) are still poorly defined and rely mostly on the experience and expertise of pathologists. Hypercellularity has been shown to have only slight to fair interobserver agreement among pathologists in a study evaluating canine meningiomas.[4] This is likely due to the lack of a clear and objective definition of hypercellularity (and hypocellularity) in veterinary medicine. Efforts to more objectively quantify this parameter should be undertaken in future studies, with methods of quantification clearly detailed and described.

D. Nuclear atypia and pleomorphism: The definition of these terms is subjective, and if used, they need to be detailed. We recommend that nuclear atypia should be clearly defined (e.g., anisokaryosis with irregular nuclei and chromatin patterns). When studies

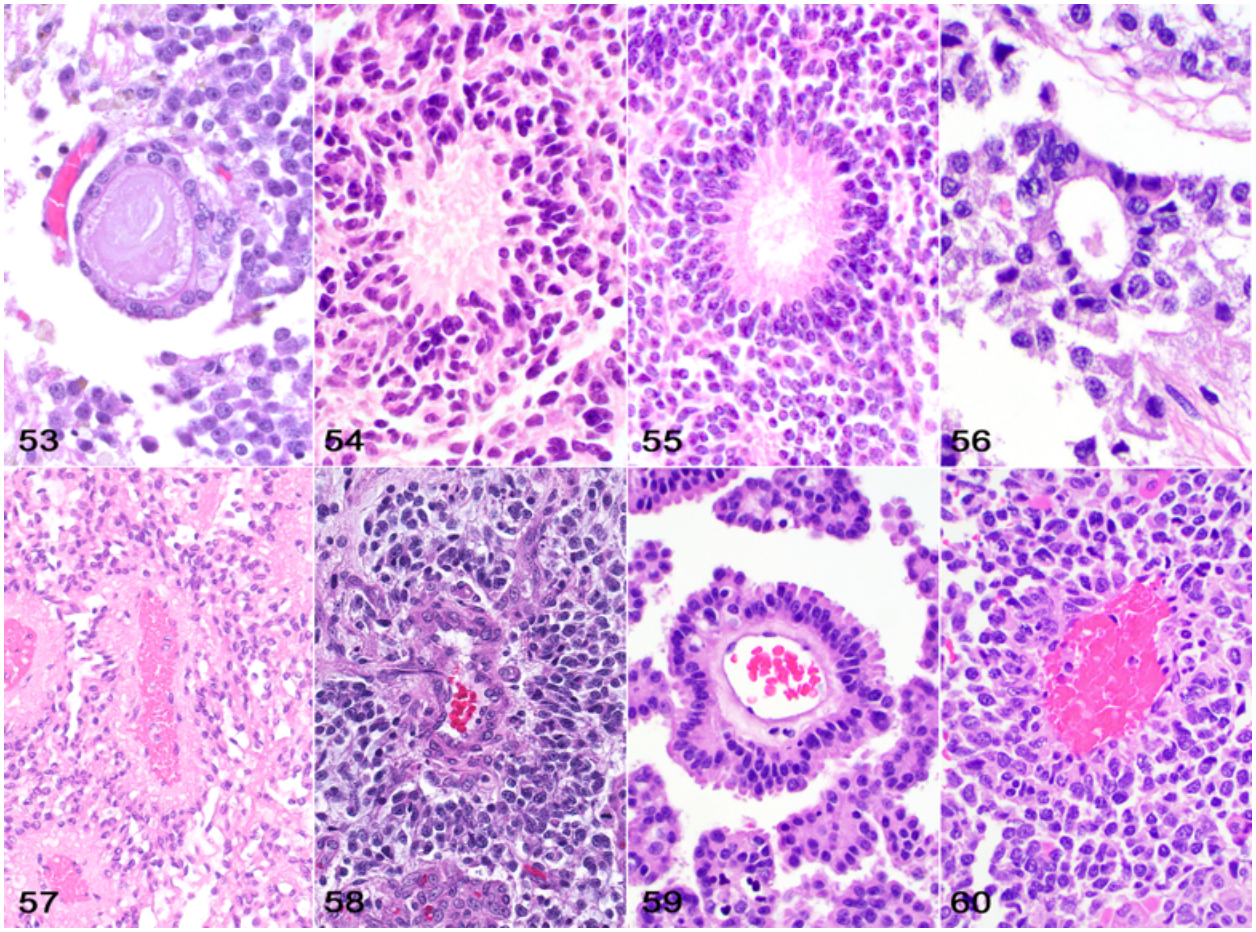
are performed using these parameters, the characteristics of nuclear atypia must be clearly defined such that others can reproduce and validate this parameter in other studies. Illustrations may be helpful in describing morphologic characteristics.

E. Tumor necrosis: It is no longer acceptable to write necrosis without description. The morphologic pattern (e.g., palisading, geographic) and type of necrosis (e.g., coagulative, liquefactive, etc.), as well as the amount of necrosis must be clearly defined and described within the methods section. If necrosis is quantified, the method must be described (estimated, morphometry, and gross and/or histologic assessment).[3]

Please refer to Tumor Necrosis Guideline:
https://vcgp.org/documents/2021/11/tumor-necrosis.pdf/

F. In veterinary medicine, it is currently unknown whether all rhabdoid meningiomas are truly WHO grade 3 tumors. In human medicine, additional ancillary tests are used (e.g. loss of BAP1) to support a poorer prognosis for this meningioma subtype. Thus, focal or multifocal rhabdoid change must be interpreted with caution until additional information regarding this subtype is obtained.

G. Rosettes and pseudorosettes (see Figs. 43–46 and Figs. 53–60) are a common histologic feature of different types of neoplasms and should not be relied upon for diagnostic confirmation of a particular tumor. In the CNS, rosettes are a hallmark of ependymomas, in which palisading neoplastic cells surround a central lumen that may contain pale basophilic material. Although rosettes can also occur in other CNS or adjacent neoplasms (such as embryonal and pituitary tumors), ciliated neoplastic cells lining the rosettes are typical of ependymomas (hence the term ependymal rosettes). Pseudorosettes consist of palisading neoplastic cells surrounding a central blood vessel. In the CNS, pseudorosettes have been reported mainly in ependymomas, but also meningiomas, oligodendrogliomas, choroid plexus tumors, and pituitary tumors.



Figures 53–60. Rosettes and pseudorosettes. Figure 53. Canine ependymoma. A rosette characterized by ciliated neoplastic cells palisading around a central lumen with pale basophilic intraluminal material. From Miller AD et al. Vet Pathol 27:743-748, 2015. **Figure 54.** Bovine medulloblastoma. A Homer Wright rosette characterized by neoplastic cells palisading around a central lumen filled with cell processes. **Figure 55.** Canine medulloblastoma. A Flexner-Wintersteiner rosette characterized by neoplastic cells palisading around a central empty lumen with scant cytoplasmic extensions. **Figure 56.** Canine pituitary carcinoma. A rosette characterized by neoplastic cells palisading around a central empty lumen. **Figure 57.** Canine meningioma. Pseudorosette characterized by neoplastic cells palisading around a central blood vessel. **Figure 58.** Canine oligodendroglioma. Pseudorosette characterized by neoplastic cells palisading around a central blood vessel. **Figure 59.** Canine choroid plexus papilloma. Pseudorosette characterized by neoplastic cells palisading around a central blood vessel. **Figure 60.** Canine pituitary carcinoma. Pseudorosette characterized by neoplastic cells palisading around a central blood vessel.

Future considerations:

1. Precisely define morphologic parameters for more standardized evaluation of CNS tumors, with or without computational assistance.[5,12,23]
    a. Mitotic activity should be standardized and reported as mitotic count within a specified area.
    b. Define and quantify cellularity within CNS tumors.
    c. Define and quantify nuclear pleomorphism and atypia for each tumor type.
    d. Define tumor necrosis and standardize terminology for different types of necrosis within CNS tumors.
2. Correlate standardized, well-described parameters with clinical outcome data for common CNS tumors (meningioma, glioma).
3. Correlate molecular tests obtained from CNS tumors with clinical outcome data.
4. Create grading systems with adequate prognostic and/or therapeutic relevance.
    a. These grading systems should be reproducible within and across observers and laboratories and applicable in a routine diagnostic setting.

    Please refer to Grading Guideline: www.vcgp.org

    Please refer to Development, Reporting and Validation of Histologic Tumor Grading Systems Grading Guideline: www.vcgp.org

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