



# Canine Pituitary Macrotumors

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**ABSTRACT:** Pituitary macroadenomas and macroadenocarcinomas are being increasingly recognized in veterinary medicine. The term *macroadenoma* is poorly defined in veterinary medicine. Because pituitary imaging is not routinely performed in dogs with pituitary-dependent hyperadrenocorticism (PDH), the true incidence of pituitary macroadenomas is unknown but may range from 15% to 75% of dogs with PDH. Recent advances in endocrine testing and pituitary imaging have facilitated the detection of pituitary macrotumors, leaving routine imaging of affected patients as the last hurdle to early detection, treatment, and an improved quality of life.

**P**ituitary macroadenomas/adenocarcinomas (PMAs) are large, glandular tumors of the pars intermedia or pars distalis of the pituitary. A strict definition of what constitutes a pituitary microtumor versus a macrotumor is somewhat controversial; however, most clinicians consider masses greater than 1 cm in diameter to be PMAs.<sup>1-3</sup> PMAs may be functional or nonfunctional, malignant (25%) or benign (75%),<sup>4</sup> and often cause neurologic signs consistent with intracranial disease.<sup>1</sup> PMAs may also be an incidental finding at necropsy; however, with the increased availability of computed tomography (CT) and magnetic resonance imaging (MRI) for veterinary use, the frequency of antemortem diagnosis is increasing.

The most clinically recognized pituitary macrotumor is the functional pituitary macroadenoma.<sup>4</sup> These tumors usually secrete adrenocorticotropic hormone (ACTH) and result in pituitary-dependent hyperadrenocorticism (PDH). The incidence of PMAs in dogs diagnosed with PDH is estimated to be 15% to 50%<sup>2,5</sup>; however, this incidence may be as high as 75% when all visible pituitary masses are included.<sup>6</sup>

## CLINICAL SIGNS

The typical signalment for a dog with a PMA is an older patient (mean age at onset of clinical signs: 11 years, with a reported range of 7 to 16 years) with a 1- to 2-year history of treatment for hyperadrenocorticism.<sup>4</sup> Most subsequent neurologic signs are referable to intracranial disease; however, the onset of these signs is often insidious and nonspecific and may initially be attributed to other causes, such as hypercorticism, hypocorticism, mitotane toxicosis, or simply old age. Lethargy, anorexia, stupor, and symmetric tetraparesis are most common, and ataxia, circling, and behavioral changes also occur frequently.<sup>4</sup> Although blindness is a common manifestation of PMAs in humans, it is uncommon in dogs due to incomplete dural adhesion to the pituitary and frequent involvement of the pars distalis. These anatomic differences favor dorsal expansion of the tumor, leading to compression of the diencephalon and hypothalamic destruction in advanced disease states rather than impingement on the optic chiasm. Signs related to hypothalamic invasion include interference with the reticular activating system and, less commonly, adipsia. Disorders of water metabolism and of thermoregulation may also occur.

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Seizures, while often associated with other intracranial neoplasms, are an uncommon manifestation of PMAs.<sup>4</sup>

### ENDOCRINE TESTING

Diagnosis of a PMA before development of neurologic signs has been historically challenging and requires a high index of suspicion. Several authors have investigated the use of endocrine testing as a means of differentiating pituitary microtumors and macrotumors in cushingoid dogs. Unfortunately, no difference has been consistently observed between responses to low- or high-dose dexamethasone suppression or ACTH stimulation testing in these two groups.<sup>1,5,7</sup>

Recently, plasma concentrations of ACTH precursors have been measured and highly correlated with tumor size in animals with PDH.<sup>8,9</sup> Pro-opiomelanocortin (POMC) is a high molecular weight polypeptide precursor to pro-ACTH, an ACTH precursor. Plasma con-

centrations of POMC/pro-ACTH are consistently higher in dogs with PDH and large pituitary tumors.<sup>8,9</sup> Because a commercially available assay for human POMC levels has recently been validated in dogs,<sup>9</sup> measurement of ACTH precursors may represent a promising means of determining whether advanced imaging of the pituitary should be pursued *before* neurologic signs develop.

### IMAGING TECHNIQUES

Until availability and acceptance of alternative endocrine testing become widespread, pituitary imaging by means of CT or MRI will remain the mainstay of diagnosing PMAs. CT has been more frequently used in veterinary medicine<sup>5,6,10</sup>; however, increased availability of MRI has led to its use in evaluating the canine brain and pituitary tumor.

The normal magnetic resonance (MR) appearance of the canine pituitary has been described.<sup>11</sup> The height of the pituitary is variable (approximately 3 to 7.5 mm), and the image should enhance rapidly after administration of intravenous contrast. It is also common for the normal canine pituitary to exhibit an area of central hyperintensity on T1-weighted images before contrast

medium administration; however, the gland should enhance uniformly after contrast medium is administered<sup>11</sup> (Figure 1). Microadenomas of the pituitary are composed of abnormal glandular tissue that may enhance more slowly and less intensely than the normal surrounding pituitary tissue, leading to nonuniform contrast enhancement. This may allow identification of small pituitary tumors that are otherwise indiscernible from the surrounding tissue.<sup>11</sup> PMAs are more easily identified and can be consistently visualized on standard MR images<sup>10</sup> (Figure 2).

Dynamic CT is another protocol for imaging the human pituitary; complex time-dependent contrast enhancement patterns of the pituitary have been well described in humans.<sup>12-14</sup> Changes in these patterns may elucidate even very small intrahypophyseal lesions. The normal enhancement pattern of the canine pituitary using dynamic CT has also been described<sup>15,16</sup> and pro-

*The incidence of pituitary macroadenomas is unknown but may range from 15% to 75% of dogs with pituitary-dependent hyperadrenocorticism.*

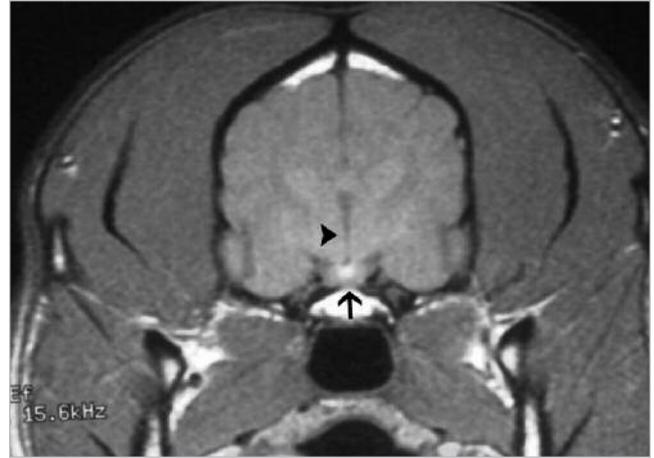
vides the opportunity to screen for pituitary tumors that may otherwise be indistinguishable from normal pituitary tissue.<sup>17</sup>

A standard definition of what should be classified as a PMA based on imaging characteristics does not exist. The previously accepted measurement of larger than 1 cm in diameter was adopted from the human literature but seems inappropriate for veterinary medicine because of the great variation in canine sizes, breeds, and conformation. While variation in the size of the pituitary among individuals and breeds has been reported,<sup>18,19</sup> there seems to be relatively little correlation between the size of the animal and the size of the pituitary.<sup>11</sup> A ratio of pituitary tumor height to brain area has been used as a more accurate way to assess the relative size of pituitary tumors and to correct for differences in body weight among animals<sup>8,9,18</sup>; however, a lack of correlation between body weight and normal pituitary size may make the pituitary tumor height:brain area ratio an unreliable way to account for differences in patient size and weight.<sup>11</sup> Other standards have been used to classify microadenomas versus macroadenomas; in these standards, anything that extends out of the sella turcica is included in the category of macroadenoma.<sup>11,18</sup>

**Figure 1. MR images of the normal canine brain.** The arrows indicate the pituitary located below the third ventricle (arrowheads) and within the sella turcica. The appearance of normal canine pituitary is enhanced by the use of contrast medium. (Courtesy of Dr. Todd Axlund)



Midline sagittal view.



Transverse T1-weighted image with contrast.

## MEDICAL MANAGEMENT

The treatment of canine PDH has previously been limited to the use of chemotherapeutic agents regardless of microtumor or macrotumor status. *o,p'*-DDD (mitotane) has been used almost exclusively in cases of PDH because of its reliability and general efficacy. Mitotane works by inducing progressive necrosis of the zona fasciculata and zona reticularis of the adrenal cortex, effectively reducing cortisol production by the adrenal gland.<sup>20</sup>

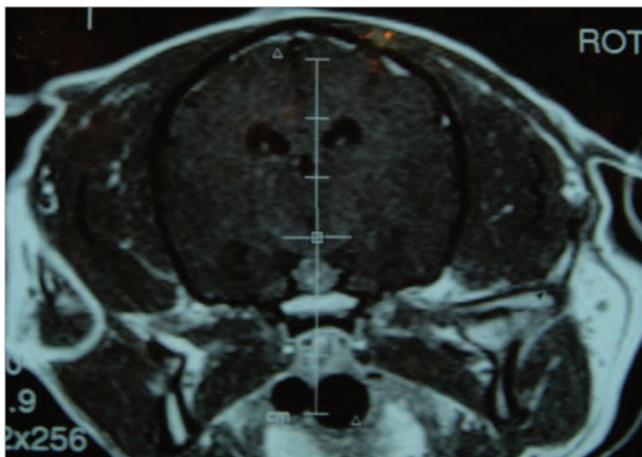
Other chemotherapeutics, such as ketoconazole and L-deprenyl, have also been used historically to treat canine PDH.<sup>3</sup> L-Deprenyl is the only commercial medication for PDH that acts directly on the pituitary. The mechanism of action of L-deprenyl is complex but primarily involves the inhibition of dopamine metabolism by monoamine oxidase B.<sup>20</sup> Dopamine acts to inhibit the release of ACTH from the pars intermedia of the pituitary.<sup>21</sup> Because most dogs with PDH have a tumor of the pars distalis, not the pars intermedia, L-deprenyl has been shown to be largely ineffective in treating canine PDH.<sup>21</sup>

Trilostane is another chemotherapeutic agent that is gaining favor in treating hyperadrenocorticism. Trilostane is an orally available steroid analogue that inhibits the production of cortisol and other steroids.<sup>22</sup> No significant difference in survival time has been noted for dogs with PDH that are treated with trilostane versus mitotane.<sup>22</sup> The effectiveness of these two drugs is suggested to be comparable.<sup>23</sup>

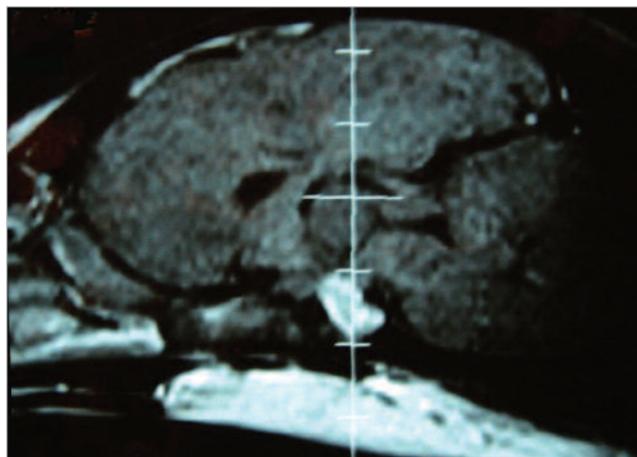


Transverse T2-weighted image.

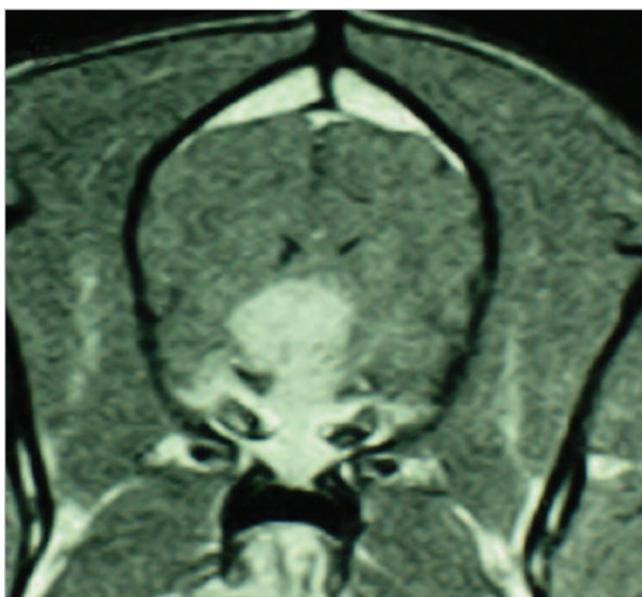
Because most chemotherapeutic agents have no effect on the pituitary itself, they do not inhibit ACTH secretion, which may actually increase with therapy. This phenomenon, known as *Nelson's syndrome*, has been well documented in humans with pituitary tumors treated with bilateral adrenalectomy.<sup>24,25</sup> Nelson's syndrome refers to rapid enlargement of a pituitary mass that occurs after loss of negative feedback from adrenal cortisol production, which has an inhibitory effect on ACTH release. While this phenomenon has been suggested to occur in dogs,<sup>26,27</sup> studies have shown no correlation between treatment with mitotane and pituitary size or rate of pituitary tumor growth.<sup>4,6</sup> However, because the exact mechanism behind the development of Nelson's syndrome is not completely understood, the potential for

**Figure 2.** T1-weighted MR images with contrast of pituitary tumors. (Courtesy of Dr. Todd Axlund)

Transverse image of a microadenoma showing a contrast-enhancing pituitary tumor measuring less than 1 cm in diameter (gridlines = 1 cm).



Midline sagittal image of a pituitary tumor measuring 1 cm in diameter (gridlines = 1 cm). Tumors 1 cm or larger are classified as macroadenomas.



Transverse image of a large pituitary macroadenoma compressing the hypothalamus and thalamus.

tumor expansion as a result of adrenal corticolytic or decreased cortisol production seems plausible.

## SURGICAL TREATMENT

In humans with PMAs, surgical resection via the transsphenoidal approach to the pituitary is the well-accepted standard of care.<sup>28</sup> Hypophysectomy was first described in treating canine PDH in 1968.<sup>29</sup> Variants of transsphenoidal hypophysectomy are the most frequently

described surgical approaches to the pituitary in veterinary medicine.<sup>30–33</sup> The procedure is difficult, but the clinical outcome is generally successful. An average remission rate of 82% has been reported with this procedure, with a 2-year survival rate of 80% and a 1-year estimated relapse-free fraction of 92%.<sup>31</sup> Reported complications of this procedure range from a temporary decrease in tear production and mild postoperative hyponatremia to permanent diabetes insipidus in a small number of cases.<sup>31</sup> More recently, a novel ventral paramedian approach to the canine pituitary has been described, with comparable success and a similarly low rate of serious complications.<sup>34</sup> Regardless of the approach to the pituitary, the goal of surgery is complete removal of the pituitary with minimal damage to the surrounding tissue and peripheral structures. Complete removal of all pituitary tissue is difficult, and residual corticotrophic cells are often present after surgery.<sup>32,34</sup> These ACTH-secreting cells may help maintain eucortisolism after surgery; however, remaining adenoma cells may lead to tumor recurrence. Surgery may be a curative therapy for functional pituitary tumors and avoids potential tumor enlargement as a consequence of medical therapy directed solely at suppression of adrenal function.

Hypophysectomy to treat pituitary tumors has most often been performed in dogs without pituitary enlargement (i.e., to treat PDH caused by a microadenoma). There is certainly a limit to the size of a mass that can be removed by standard transsphenoidal hypophysec-

tomy, but Meij et al<sup>31</sup> reported the removal of pituitary tumors up to 11 mm in width. Surgical removal of large pituitary tumors offers a promise of definitive treatment; however, surgical expertise is required and may not be available in all cases.

## RADIATION THERAPY

As radiation therapy becomes a more practical option in veterinary medicine, its viability as a noninvasive definitive treatment of PMA is being explored. A dramatic clinical response to radiation therapy in dogs with neurologic signs caused by a PMA has been observed. Several studies have found a near-100% positive patient response in tumor size reduction and return to normal or near-normal neurologic status during or within several months after treatment,<sup>27,35-37</sup> with continued shrinkage of tumors for more than 1 year after treatment in some cases.<sup>35</sup> In patients in which hypersecretion of ACTH is

therapy, the median survival time of dogs with PMA and neurologic signs has reportedly been 140 days.<sup>4</sup> Thus, radiation therapy appears to be valid and promising for animals with nonresectable tumors or in which invasive procedures are undesirable due to an owner's wishes or concerns or a clinician's lack of surgical expertise.

## CONCLUSION

Pituitary macrotumors represent an interesting clinical dilemma in that multiple treatment modalities are effective in producing extended median survival times when clinical neurologic signs develop. However, these tumors are rarely diagnosed before this point, making it difficult to evaluate whether survival times can be extended if early diagnosis and treatment are rendered. Medical treatment alone is often satisfactory to eliminate clinical signs due to hyperadrenocorticism but does not address the primary tumor, does not relieve neurologic signs

*Dramatic clinical response to radiation therapy has been observed in dogs with neurologic signs caused by a pituitary macroadenoma.*

a component of the clinical signs, excessive ACTH secretion may persist after full-course radiation therapy<sup>35</sup>; however, Dow and LeCouteur<sup>27</sup> reported that radiation therapy may decrease excessive ACTH secretion while preserving normal pituitary function.

In 1990, Mauldin and Burk<sup>2</sup> established guidelines regarding potential radiation therapy for patients with PDH with or without a PMA. They recommended radiation as the primary therapy for dogs with poorly controlled PDH, even if no neurologic signs were present. Radiation therapy with a minimum of 50 Gy was also recommended as the primary therapy in patients with PMA and mild to moderate neurologic signs, but these guidelines stated that a grave prognosis should be conveyed regarding dogs with severe neurologic deficits.<sup>2</sup> More recently, Bley et al<sup>37</sup> found little correlation between tumor size, type, or neurologic signs and median survival time for an assortment of intracranial neoplasms, including PMAs. The median survival time for dogs regarding all intracranial tumors treated solely with radiation therapy was 699 days; patients with pituitary tumors had a slightly longer median survival time of 750 days. Similar median survival times for dogs with PMAs after radiation therapy have been previously demonstrated.<sup>29</sup> With no

caused by tumor expansion, and may lead to rapid tumor growth in some cases. Surgical resection of the tumor and surrounding normal pituitary tissue has been shown to be definitive and successful but requires surgical expertise. Radiation therapy is a promising modality that has shown dramatic results in shrinking tumors, controlling tumor-associated vascular edema, and rapidly resolving neurologic signs. Tumor growth does not cease after radiation therapy; however, this therapy is associated with vast improvement in the patient's quality of life, greater owner satisfaction, and median survival times that are comparable with those for dogs that undergo surgical excision of their tumors.

Because multiple approaches to therapy are available and have been thoroughly assessed for efficacy in treating PMA, early diagnosis is the next step in evaluating whether early treatment can dramatically improve survival times. A high index of suspicion for the existence of or subsequent development of a PMA should be maintained in all animals diagnosed with PDH. At the very least, serial neurologic examinations should be performed on these animals to identify early, subtle neurologic deficits that may indicate increased tumor size and the need for further intervention. Advanced imaging

should be conducted for any animal showing neurologic signs referable to an intracranial lesion and should be offered to all owners when PDH is initially diagnosed. At this time, potential development of a large pituitary tumor should be discussed with owners. While advanced endocrine testing shows promise regarding the evaluation of pituitary tumor size, CT and MRI are the mainstays in assessing pituitary size and the presence of detectable pituitary tumors. Because routine pituitary imaging is not currently performed in animals with diagnosed PDH, the true incidence of PMAs is unknown. Early diagnosis and treatment may improve the understanding of pituitary tumor growth patterns and rates and the prognosis for patients with PMAs.

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- 1. The incidence of PMAs in patients with PDH is**
  - a. 5% to less than 10%.
  - b. 10% to less than 15%.
  - c. 15% to 50%.
  - d. greater than 75%.
  
- 2. Which statement(s) regarding functional pituitary macroadenomas in dogs is/are correct?**
  - a. Most functional tumors secrete ACTH.
  - b. Most dogs have a history of treatment for PDH before the development of neurologic signs.
  - c. Most dogs are middle aged or older at the time of diagnosis.
  - d. all of the above
  
- 3. One of the most common manifestations of a pituitary macrotumor is**
  - a. seizures.
  - b. blindness.
  - c. lethargy.
  - d. polydipsia.
  
- 4. Which endocrine test can distinguish a PMA from a small pituitary tumor?**
  - a. the low-dose dexamethasone suppression test
  - b. the high-dose dexamethasone suppression test
  - c. the ACTH precursor assay
  - d. the endogenous ACTH level test
  
- 5. When MRI is used, the normal canine pituitary**
  - a. does not contrast enhance.
  - b. enhances uniformly with administration of contrast medium.
  - c. enhances variably with contrast medium.
  - d. is not visible.
  
- 6. Complications after transsphenoidal hypophysectomy include**
  - a. permanent diabetes insipidus.
  - b. decreased tear production.
  - c. Addisonian crisis.
  - d. a and b
  
- 7. Approximately \_\_\_\_ of large pituitary tumors shrink in response to radiation therapy.**
  - a. 40%
  - b. 60%
  - c. 80%
  - d. 100%
  
- 8. The median survival time for dogs in which large pituitary tumors were treated with radiation therapy was \_\_\_\_ days.**
  - a. 140
  - b. 420
  - c. 699
  - d. 750
  
- 9. With no therapy, the median survival time for dogs with neurologic signs due to a large pituitary tumor was \_\_\_\_ days.**
  - a. 140
  - b. 420
  - c. 699
  - d. 750
  
- 10. Which statement regarding the prognosis for dogs with large pituitary tumors treated with radiation therapy is correct?**
  - a. It is worse than that for dogs with most other intracranial neoplasms.
  - b. It is slightly better than that for dogs with most other intracranial neoplasms.
  - c. There is no information regarding the prognosis for canine pituitary tumors.
  - d. It is the same as that for dogs that do not receive treatment.