CHAPTER 3

Efficacy of transsphenoidal hypophysectomy in treatment of dogs with pituitary-dependent hyperadrenocorticism

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Abstract

The long-term survival, disease-free fractions, and the complications of hypophysectomy in 150 dogs with pituitary-dependent hyperadrenocorticism (PDH) were examined in a prospective study. Long-term survival and disease-free fractions in relation to pituitary size were analyzed by the Kaplan-Meijer estimate procedure.

The 1-, 2-, 3-, and 4-year estimated survival rates were 84% (95% confidence interval [CI], 76-89%), 76% (67-83%), 72% (62-79%), and 68% (55-77%), respectively. Treatment failures included procedure-related mortalities (12 dogs) and incomplete hypophysectomies (9 dogs). The 1-, 2-, 3-, and 4-year estimated relapse-free fractions were 88% (CI: 80-93%), 75% (64-83%), 66% (54-76%), and 58% (45-70%), respectively. Postoperative reduction of tear production (58 eyes in 47 dogs) was often reversible but remained low until death in 11 eyes of 10 dogs. Central diabetes insipidus (CDI) occurred more frequently (62%) in dogs with enlarged pituitaries than in dogs with nonenlarged pituitaries (44%). Survival and disease-free fractions after hypophysectomy were markedly higher in dogs with nonenlarged pituitaries than in dogs with enlarged pituitaries.

Transsphenoidal hypophysectomy is an effective treatment for PDH in dogs. The survival and disease-free fractions after hypophysectomy decrease, and the incidence of CDI increases with increasing pituitary size. Therefore, early diagnosis of PDH is important and transsphenoidal hypophysectomy is expected to have the best outcome when used as primary treatment for dogs with nonenlarged or moderately enlarged pituitaries.

Hyperadrenocorticism, or Cushing's syndrome, is the complex of physical and biochemical changes resulting from chronic exposure to glucocorticoid excess. In pituitary-dependent hyperadrenocorticism (PDH), excess ACTH is produced by pituitary corticotropic adenomas that may range in size from microadenomas to large tumors.[16,25] The most common treatment in dogs has been the selective or non-selective elimination of the glucocorticoid excess by chemotherapy with the adrenocorticolytic drug o,p'DDD (mitotane), which has a relative high recurrence rate.[7,15] Recently, treatment with a competitive inhibitor of adrenal 3β-hydroxysteroid dehydrogenase has been introduced.[6,24,30,38] Results of long-term follow-up are not yet available.

Although effective, these treatments are not directed at the elimination of the primary lesion, the ACTH-producing pituitary adenoma. The pituitary tumor may continue to expand, leading to neurological signs due to an intracranial mass effect.[2,8] Pituitary-tumor growth may even be promoted by treatment that eliminates the suppressive negative feedback of glucocorticoids on pituitary tumor growth. Bilateral adrenalectomy in humans with Cushing's disease may result in markedly high ACTH concentrations, and aggressive invasive pituitary-tumor growth.[14] There are few treatment options once a pituitary macroadenoma has resulted in neurological signs.

Early diagnosis, pituitary imaging, and treatment at the pituitary level should be the hallmarks of a treatment protocol for canine PDH. Selective pituitary microsurgical adenomectomy by the transsphenoidal approach is considered the treatment of choice for pituitary tumors of the sellar region causing Cushing's disease in humans.[26] In 1993, in Utrecht, The Netherlands, hypophysectomy was reintroduced as treatment of PDH in dogs. Short-term (≤3 years) results were reported in a group of 52 dogs,[21] and since then, the study has progressed.[19] In the present study long-term survival, disease-free fraction, complications and the relation between pituitary size and the long-term results in 150 dogs with PDH are described.

Materials and Methods

Animals

One hundred and fifty dogs with PDH, referred to the Utrecht University Clinic for Companion Animals, over a 10-year (1993–2003) period underwent transsphenoidal hypophysectomy. Crossbred dogs and purebred dogs were represented (Table 1). Head shapes varied from brachycephalic (eg, French bulldog, Dogue de Bordeaux) to mesaticephalic (the majority of the dogs) to dolichocephapic (eg, collie type). Sixty-eight dogs were male and 82 were female. The age at the time of surgery ranged from 3 to 14 years (median 9 years), and the body weight of the dogs ranged from 4 to 61 kg (median 15 kg).

Apart from the characteristic clinical signs, such as polyuria, skin atrophy, and increased abdominal size, the diagnosis of hyperadrenocorticism was based upon biochemical changes[27] and high ($\geq 10 \times 10^{-6}$) urinary corticoid-to-creatinine ratios (UCCR) measured in 2 consecutive morning urine samples collected by the owner.[29,33] Immediately after collection of the 2nd urine sample, the animals received 3 doses of 0.1 mg dexamethasone/kg PO at 8-hour intervals. The next morning, a 3rd urine sample was collected. When the UCCR in the 3rd sample was less than 50% of the mean in the 1st 2 samples, the dog was categorized as being responsive to dexamethasone suppression, and PDH was diagnosed. In 123 dogs, the

combination of high UCCRs and dexamethasone suppression allowed the diagnosis of PDH. In 27 dogs, there was resistance to dexamethasone suppression and pituitary-dependency was demonstrated by measurements of plasma-ACTH concentrations and further supported by visualization of the adrenals by ultrasonography and pituitary imaging.[5,28,37] In 149 dogs, the basal UCCR exceeded the upper limit of the reference range, ranging from 10 x 10^{-6} to 598 x 10^{-6}. In 1 dog UCCR was not available. Diagnosis was made at another institution based on ACTH stimulation and the low-dose dexamethasone suppression test.

Table 1
Breeds of 150 dogs with pituitary-dependent hyperadrenocorticism

Breed	No.
Wire-Haired Dachshund	12
Minature Poodle	11
Jack Russell Terrier	6
Maltese	6
Yorkshire Terrier	5
English Cocker Spaniel	4
Labrador Retriever	4
Beagle	3
Bouvier des Flandres	3
Dalmatian	3
German Shepherd	3
Medium-sized Poodle	3
Crossbred	31
Other breeds	56

Pituitary imaging

The pituitary size and the localization of the gland in relation to surgical landmarks were assessed with computed tomography (CT) in 130 dogs, and with magnetic resonance imaging (MRI) in the remaining 20 dogs. CT was performed in anesthetized dogs with a 3rd generation CT scanner (Tomoscan CX/S, Philips NV, Eindhoven, The Netherlands), using a protocol described previously.[19, 36] The height and width of the pituitary were measured on transverse images (Figure 1A). The length of the pituitary was estimated from the number of images containing a section of the gland.

MRI was performed in anesthetized dogs with a 0.2-Tesla open magnet (Magnetom Open Viva, Siemens AG, Germany) using a multipurpose coil. Contiguous 1-mm-thick transverse slices of the pituitary gland were obtained using a 3-dimensional flash (T1-weighted gradient echo) sequence both before and after the intravenous administration of 0.3 ml of contrast medium per kg of body weight (Dotarem, Guerbet Nederland BV, Gorinchem, The Netherlands, containing 279.32 mg gadoterate/ml as meglumine salt). The height and width of the pituitary were measured on transverse images and the length was measured on sagittal reconstructions of the transverse images (Figure 1B).

The maximum pituitary size was defined as the maximum value of pituitary height, width, or length. Enlarged pituitaries were distinguished from nonenlarged pituitaries by the ratio between the height of the pituitary gland and the area of the brain (P/B ratio), as

described previously.[16] Enlarged pituitaries have a P/B ratio greater than 0.31 and non-enlarged pituitaries have a ratio equal to or less than 0.31.

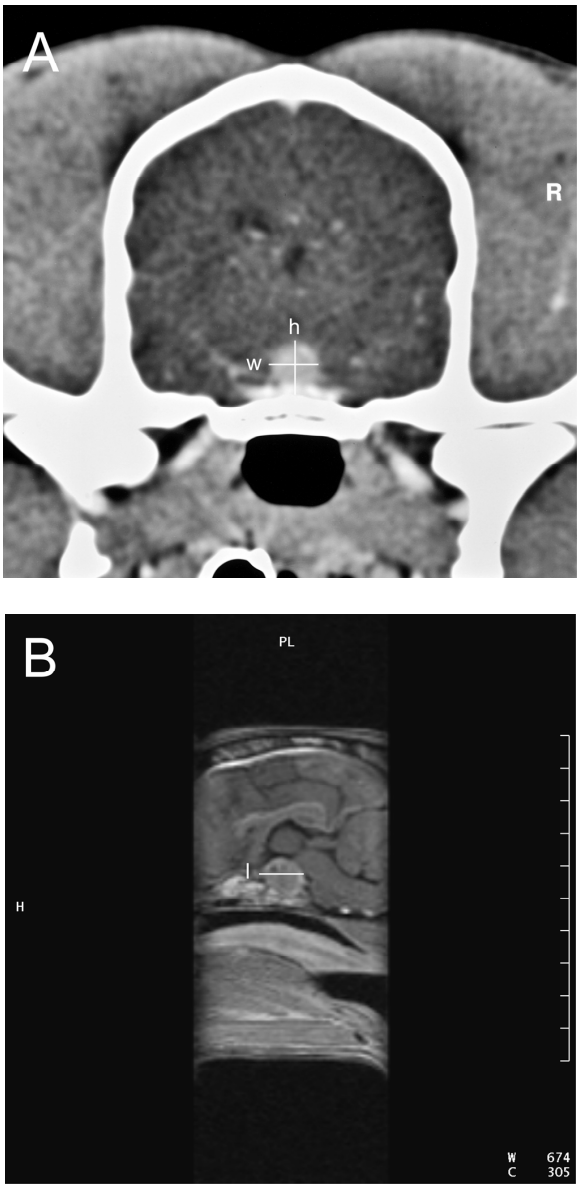

Figure 1. Measurements of pituitary dimensions (height, width, and length) in contrast-enhanced computed tomography (CT) (A) and magnetic resonance (MR) (B) images. (A) Transverse CT image: measurement of the pituitary height (h) and width (w) on transverse images. (B) Sagittal MR image: measurement of the pituitary length (l).

Surgical procedure and medication

Transsphenoidal hypophysectomy, and peri- and postoperative monitoring and medication were performed according to the protocol described earlier.[21,22] Usually, the dogs resumed drinking on the day of hypophysectomy, and were discharged from the hospital within 3 days after surgery. Hormone substitution consisted of life-long administration of cortisone acetate (Cortisoni acetas, Genfarma, Maarssen, The Netherlands) and thyroxine (L-thyroxine, Aesculaap, Boxtel, The Netherlands). Desmopressin (Minrin, Ferring, Hoofddorp, The Netherlands) was administered for 2 weeks routinely, and continued if polyuria due to central diabetes insipidus (CDI) persisted.[21] In case of postoperative decreased Schirmer tear test (STT) (Clement Clarke International Ltd, Harlow Essex, UK) values (≤5 mm wetting/min), dogs were treated according to a protocol as described earlier.[21]

Follow-up

After hypophysectomy, 136 dogs were reevaluated within 8 weeks, which included physical examination, routine blood chemistry, measurement of basal plasma T_4 concentration 10-12 hours after last thyroxine medication, and basal UCCR in duplicate at 24 hours after cortisone medication. After this 1st follow-up examination, UCCRs were measured at 6 months after surgery and thereafter once a year, unless a relapse was suspected in between. Urine samples were mailed to our laboratory, and follow-up reports were obtained from routine follow-up examinations in the hospital, and during telephone conversations with the owner, and/or the referring veterinarian. Postoperative mortality was defined as death within 4 weeks after surgery irrespective of the cause of death. Remission was defined as UCCR $<10 \times 10^{-6}$ and resolution of clinical signs of hyperadrenocorticism. Residual disease was defined as early postoperative (<8 weeks) UCCR $\geq 10 \times 10^{-6}$ and/or remnant pituitary tumor tissue on early postoperative (<2 months after surgery) CT or MRI scans. Recurrence was defined as UCCR $\geq 10 \times 10^{-6}$, return of clinical signs of hyperadrenocorticism or both after initial complete remission was achieved as defined above.

Statistical Analysis

Results are presented as median and ranges (UCCR, pituitary sizes). Survival and disease-free fractions were analyzed by the Kaplan-Meijer estimate procedure[10] as described previously.[21] Kaplan-Meijer curves for survival and disease-free fractions were plotted for dogs with a nonenlarged pituitary (P/B ≤0.31) and for dogs with enlarged pituitary tumors (P/B >0.31). In addition dogs with maximum pituitary dimension <10 mm were compared with dogs with maximum pituitary dimension ≥10 mm. Differences between Kaplan-Meier curves were tested for significance ($P < 0.05$) by the log rank test. The chi-square test was used to analyze the occurrence of keratoconjunctivitis sicca (KCS) and DI in relation to pituitary size.

Results

CT and MRI - preoperative scans

The pituitary glands, as measured on contrast-enhanced CT and MRI images, ranged in height (n=150) from 2.1 to 15 mm (median, 5.1 mm), in width (n=148) from 3.3 to 17 mm (median, 6.1 mm), and in length (n=143) from 2 to 18 mm (median, 5.0 mm). Pituitary

glands of 74 dogs were not enlarged, the P/B ratios ranged from 0.15 to 0.31 (median, 0.24). The pituitary glands of 76 dogs were enlarged with P/B ratios ranging from 0.32 to 0.76 (median, 0.43). The maximum dimension of the pituitary gland, ranged from 3.3 to 18.0 mm (median, 6.9 mm). The maximum diameter was <10 mm in 130 dogs ≥10 mm in 20 dogs.

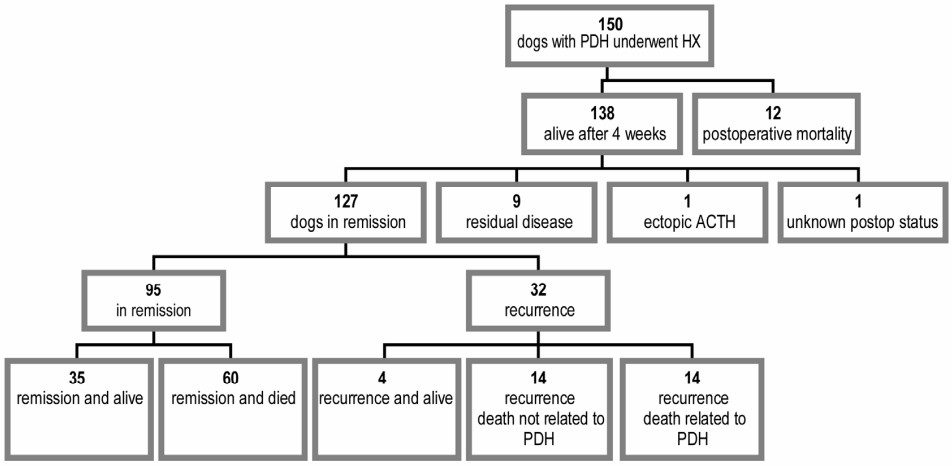

Figure 2. Organigram of 150 dogs with pituitary-dependent hyperadrenocorticism (PDH) that underwent transsphenoidal hypophysectomy (HX) in the period 1993-2003.

Postoperative mortality

Twelve dogs died within 4 weeks after surgery. Two dogs (dogs 3 and 27) with an enlarged pituitary (P/B ratios, 0.48 and 0.53, respectively) developed an arterial hemorrhage from the arterial cerebral circle during exploration of the fossa for pituitary remnants. Two dogs (dogs 115 and 132) died within 6 hours after surgery; postmortem examination in 1 dog (dog 132) revealed thromboendocarditis of the right atrium, concentric myocardial hypertrophy of the left ventricle and lung edema due to circulatory failure. Four dogs (dogs 8, 21, 105, 141), in which surgery was uneventful, died 1 day after surgery: 2 of these dogs (dogs 8, 105) became dyspneic, 1 dog (dog 21) with glucocorticoid-associated myotonia died of unknown cause, and 1 dog (dog 141) had hypernatremia due to insufficient oral fluid intake. This dog had been released prematurely to the surgical ward and died shortly after return to the intensive care unit. One dog (dog 148) died 5 days after surgery due to accidental IV injection of oral potassium solution. Two dogs had a prolonged stay in the ICU for 2 weeks because of severe hypernatremia (dog 5), and diabetic ketoacidosis (dog 65) and were eventually euthanized. One dog (dog 14) developed severe bronchopneumonia, had a prolonged stay in the hospital (10 days) and died at home 4 weeks after surgery.

Long-term survival and disease-free fraction

One-hundred-thirty-eight dogs were alive 4 weeks after surgery. Hyperadrenocorticism went into remission in 127 dogs (Figure 2). In 9 dogs, there was residual disease (Figure 2) based on early high UCCR ($\geq 10 \times 10^{-6}$) and/or remnant pituitary tissue on postoperative pituitary

imaging within 8 weeks after surgery. Five of the 9 dogs with residual disease were euthanatized or died within 5 months after surgery for reasons associated with hyperadrenocorticism, 3 dogs were treated with o,p'DDD (Lysodren; Bristol-Meyers, Syracuse, NY) 3 to 6 months after surgery and, at the time of evaluation, survival times were 17, 26, and 32 months. In 1 dog with residual disease bilateral adrenalectomy was performed. The dog survived 34 months until it developed seizures and was euthanatized. In 1 other dog, clinical signs worsened and UCCR further increased after surgery (Figure 2). In this dog, complete hypophysectomy was confirmed with postoperative CT (empty sella) and at histopathological examination of the complete pituitary, no pituitary adenoma was found. Based on persistent high plasma ACTH concentrations it was suspected that this dog had an extrapituitary source of ACTH-secretion. Following total body CT scanning and laparotomy for abdominal masses, a metastasized neuroendocrine pancreatic tumor was found.[11] One dog died at home 7 weeks after surgery because of renal failure; no postoperative UCCR was available (Figure 2).

In 124 dogs in which hyperadrenocorticism went into remission, basal UCCR values within 8 weeks after hypophysectomy were $<1 \times 10^{-6}$ in 50 dogs, ≥ 1 - $<5 \times 10^{-6}$ in 55 dogs, and ≥ 5 - $<10 \times 10^{-6}$ in 19 dogs. In 3 dogs, there was late remission, signs of hyperadrenocorticism resolved, and low basal UCCR values (5.1, 4.5, 3.9 x 10^{-6}) were achieved or available later than 8 weeks, at, respectively, 3, 6, and 36 months after hypophysectomy.

The long-term follow-up results are presented by curves of estimated survival and disease-free fraction (Figures 3A, 4A). The 1-year estimated survival rate was 83.5% (95% confidence interval [CI], 76-89%). The 2-year estimated survival rate was 76.1% (95% CI, 67-83%). The 3-year estimated survival rate was 71.5% (95% CI, 62-79%). The 4-year estimated survival rate was 67.8% (95% CI, 55-77%)(Figure 3). The 1-year estimated relapse-free fraction was 87.9% (95% CI, 80-93%). The 2-year estimated relapse-free fraction was 74.9% (95% CI, 64-83%). The 3-year estimated relapse-free fraction was 66.3% (95% CI, 54-76%). The 4-year estimated relapse-free fraction was 58.5% (95% CI, 45-70%)-(Figure 4).

In 95 of 127 dogs (75%), hyperadrenocorticism remained in remission (Figure 2). Over time 60 of these 95 dogs died (9 dogs) or were euthanatized (51 dogs) because of non-Cushing-related causes after a median interval of 28 months after hypophysectomy (range, 2-87 months). The causes of death were: old age (13 dogs), carcinoma (11 dogs), heart failure (9 dogs), preexisting primary epilepsy (5 dogs), gastrointestinal problems (5 dogs), preexisting diabetes mellitus (4 dogs), passive urinary incontinence (4 dogs), anterior or posterior paralysis (3 dogs), pancreatitis (1 dog), pre-existing copper-associated hepatitis (1 dog), chronic renal failure (1 dog), lung failure (1 dog), skin problems (1 dog) and behaviour problems (1 dog). In the 35 dogs alive at the time of evaluation, the period of remission ranged from 2 to 89 months (median, 15 months). In these 35 dogs, median P/B ratio was 0.29 (range, 0.15-0.71); in 20 dogs, the pituitaries were nonenlarged (P/B ratio ≤ 0.31); and in 15 dogs, the pituitaries were enlarged (P/B ratio >0.31). The median value of the last available UCCR was 0.6 x 10^{6}, which was not significantly different from the median value 0.8 x 10^{-6} within 2 months after hypophysectomy.

In 32 of 127 dogs (25%) (Figure 2), signs of hyperadrenocorticism recurred with high UCCR ($\geq 10 \times 10^{-6}$) at 6 weeks to 56 months after surgery (median, 18.3 months). In the 32 dogs in which hyperadrenocorticism recurred, the median basal UCCR at time of initial

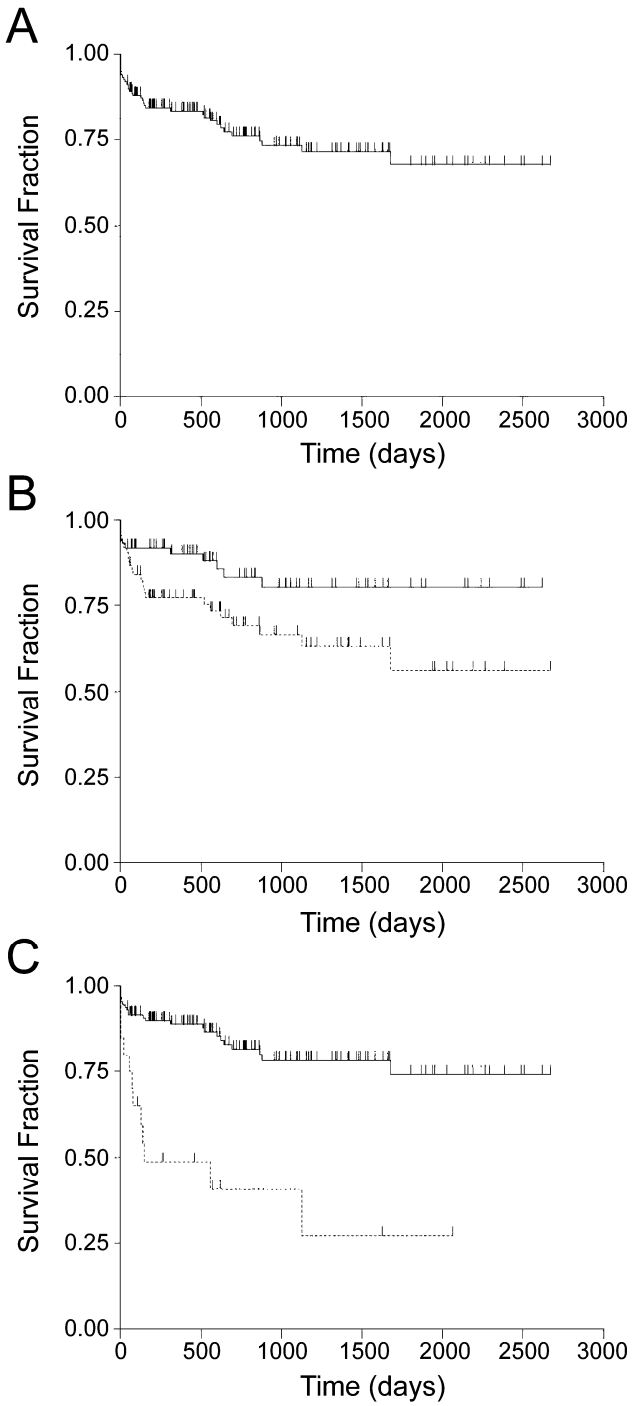

Figure 3. (A) Survival curve after transsphenoidal hypophysectomy for 150 dogs with pituitary-dependent hyperadrenocorticism. Censored cases (i.e., dogs that died from unrelated causes or were still alive at the time of follow-up) are represented by vertical bars. (B) Survival curves for dogs with pituitary/brain ratio (P/B) ≤0.31 (—) and dogs with P/B >0.31 (---) (Log rank test, P=0.023). (C) Comparison of survival curves for dogs with pituitary diameter <10 mm (—) and dogs with pituitary diameter ≥10 mm (---) (Log-rank test, P <0.001).

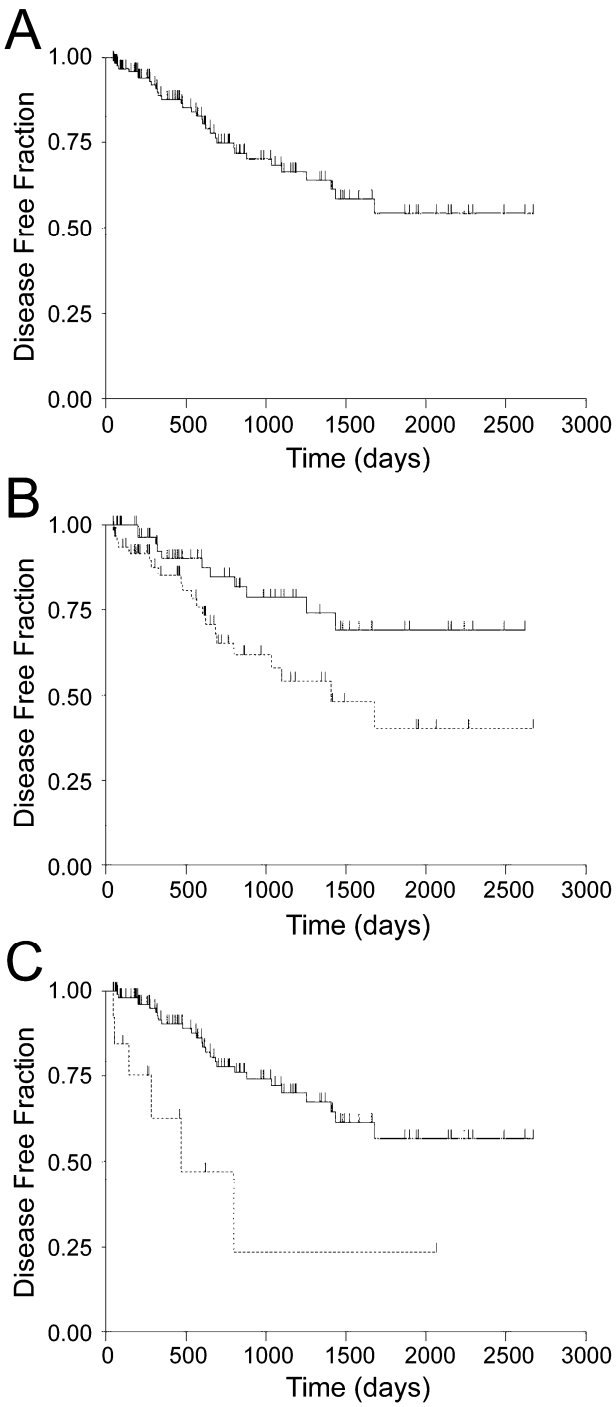

Figure 4. (A) Disease-free fraction curve after transsphenoidal hypophysectomy for 127 dogs with pituitary-dependent hyperadrenocorticism. Censored cases (i.e., dogs that died from unrelated causes or were still alive at the time of follow-up) are represented by vertical bars. (B) Comparison of disease-free fraction curves for dogs with pituitary/brain ratio (P/B) ≤0.31 (—) and dogs with P/B >0.31 (---) (log rank test, P=0.020). (C) Comparison of disease-free fraction curves for dogs with pituitary diameter <10 mm (—) and dogs with pituitary diameter ≥10 mm (---) (log rank test, P <0.001).

remission was 3.7 x 10^{-6}. The UCCR were <1 x 10^{-6} in 6 dogs, ≥1 and <5 x 10^{-6} in 14 dogs, and ≥5 and <10 x 10^{-6} in 12 dogs. The median P/B ratio before surgery in these 32 dogs was 0.40 (range, 0.19-0.76), in 11 dogs the pituitaries were nonenlarged (P/B ratio ≤ 0.31); and in 21 dogs the pituitaries were enlarged (P/B ratio >0.31). One dog (dog 124) developed a recurrence 16 months after hypophysectomy and went in remission spontaneously two months later. Nevertheless the dog was categorized in the recurrence group. Fifteen of the 32 dogs with recurrence were subsequently treated with o,p'DDD , and 5 dogs received no further therapy at the owners request. At the time of evaluation, 14 of the 32 dogs were euthanatized or died because of recurrent signs of hyperadrenocorticism, 14 died of unrelated causes and 4 dogs were still alive.

Survival and disease-free fractions of dogs with enlarged pituitaries (P/B >0.31) were significantly (log rank test, P=0.023 and P=0.020, respectively) lower than in dogs with nonenlarged pituitaries (Figures 3B, 4B). Survival and disease-free fractions of dogs with pituitary dimension ≥10mm were significantly (P <0.001) lower than those of the dogs with pituitary dimension <10 mm (Figures 3C, 4C).

Keratoconjunctivitis sicca (KCS)

In 58 eyes in 47 dogs of the total of 150 dogs (31%), there was no (STT = 0 mm in 26 eyes) or decreased (STT values >0 and ≤ 5 mm wetting/min in 32 eyes) tear production on the 1st postoperative day. The dogs had blepharospasm and conjunctivitis and were treated according to a KCS. KCS developed significantly more frequently (chi-square test, P <0.001) in the left eye (38 eyes) than in the right eye (20 eyes). STT values became normal in 29 left eyes and in 18 right eyes. In 11 eyes in 10 dogs (6.7%), tear production remained low until death. Ophthalmologic treatment was needed for 3-547 days in recovered left eyes (median 70 days) and for 3-717 days in recovered right eyes (median 58 days). In the 1st series (dog 1 through 75), 32 eyes in 26 dogs (35%), and in the 2nd series (dogs 76-150), 27 eyes in 21 dogs (28%) developed KCS. There was no relation between the frequency of KCS and pituitary size.

Central Diabetes Insipidus (CDI)

In 67 of 127 dogs (53%) in which there was remission of hyperadrenocorticism, prolonged (more than 2 weeks) treatment with desmopressin was needed to control polyuria. In 28 of 127 dogs (22%), CDI was present until death or until the latest available follow-up date and treatment with 1 or 2 drops desmopressin was required. In the other 39 of 127 dogs (31%), desmopressin was discontinued after 28-1,329 days (median, 133 days). Of the dogs in remission, CDI occurred in 29 dogs (47%) of the 1st series (*n*=62), and in 38 dogs (58%) of the 2nd series (*n*=65), and CDI occurred significantly more frequently (chi-square test, P=0.04) in dogs with a P/B ratio >0.31 (39 of 63 dogs =62%) than in dogs with P/B ratio ≤0.31 (28 of 64 dogs = 44%).

Discussion

Since our report on the results of transsphenoidal hypophysectomy in 52 dogs with PDH,[21] the number of operated dogs has increased to 150 dogs. The extended follow-up on these dogs confirms that transsphenoidal surgery is an effective treatment of PDH in dogs. The

results were obtained as a joint effort of the disciplines endocrinology, diagnostic imaging, and neurosurgery, with all hypophysectomies performed by 1 neurosurgeon (BPM). Also in human medicine, transsphenoidal surgery is the treatment of choice for Cushing's disease,[23] and pituitary surgeries at a center should best be performed by 1 surgeon to ascertain enough volume and to maintain the surgical skills.[1,26]

In the present study there were 12 deaths within the 1st month after surgery and 7 of these were in the 1st series of 75 dogs and 5 in the 2nd series of 75 dogs. All 5 dogs in the 2nd series died in the ICU, and 2 deaths were related to errors in the ICU. The reduction in surgical mortality (death within 4 weeks after surgery irrespective of cause of death) in the previous study on 52 dogs was attributed to the initial learning curve for the surgical procedure and to improvements in postoperative care.[21] In the present study, the post-operative mortality in the 2nd 75 dogs is restricted to the immediate postoperative period in the ICU. Further reduction in postoperative mortality may be expected from a more stringent ICU protocol for hypophysectomies. The results in the 2nd 75 dogs approach the mortality rate (1-4%) reported for transsphenoidal surgery for Cushing´s disease in humans.[4,17,26]

Depending on the definition of remission criteria, the remission rate varies between 42-93% after pituitary surgery in humans with Cushing's disease.[26,32] In humans, the corticotroph adenomas are usually microadenomas and may be so small that they may be difficult to localize with pituitary imaging or during pituitary surgery.[32] Recurrence is most likely to be caused by regrowth of adenoma cells left in situ.[21] After transsphenoidal hypophysectomy in healthy dogs, the pituitary fossa was usually found to contain micro-scopic nests of pituitary cells.[22]

In the present study, remission was achieved in 127 dogs of 150 dogs (85%). Remission was defined as UCCR $<10 \times 10^{-6}$ and resolution of clinical signs of hyperadrenocorticism. Recurrence rate was 25% (32 of 127 dogs). In two other studies, 11 and 78 dogs with PDH were treated with trilostane, a competitive inhibitor of adrenal 3β-hydroxysteroid dehydro-genase. Remission of polyuria/polydipsia occurred in 100% and 70% of the dogs, res-pectively; skin abnormalities improved in 82% and 62%, respectively.[24,30] In another study with 30 dogs, trilostane treatment reduced plasma cortisol concentrations, and clinical signs improved.[6] However, follow-up periods for trilostane have not been long enough to allow comparison with the results of hypophysectomy. The remission and recurrence rates in the present study compare favorably with those of 129 dogs with PDH treated at the same institution with o,p'DDD for nonselective destruction of the adrenal cortex.[7] Using similar criteria, remission in that study occurred in 111 dogs (86%) of which 43 (39%) had a relapse (UCCR $>10 \times 10^{-6}$).

If all procedure-related mortalities (12 dogs), incomplete hypophysectomies (9 dogs), and recurrences after remission (32 dogs) are considered to be treatment failures, the overall success rate in this study was 65% (97 of 150 dogs). These results compare favorably with those of 129 dogs treated in the same institution with o,p'DDD.[7] The overall success rate in the o,p'DDD study was 61% (68 of 111 dogs), the estimated 1-, 2-, and 3-year survival fraction were 80%, 69%, and 61%, respectively.[7] In the present surgical study the 1-, 2-, and 3-year survival fraction were 84%, 76%, and 72 %, respectively. The estimated 1-, 2-, and 3-year disease-free fraction in the o,p'DDD study were 77%, 53%, and 44%, respectively. In the present surgical study the 1-, 2-, and 3-year disease-free fraction were 88%, 75%, and 66%, respectively. Thus, with longer follow-up time hypophysectomy leads to better results than o,p'DDD treatment. However, there may have been a bias for selection of dogs for

surgery (smaller tumors) or for o,p'DDD treatment (larger tumors). Still, in this study 76 dogs (50%) had enlarged pituitaries with increased P/B ratio.

Comparison with the results of studies performed in other institutions is more difficult. In a study of o,p'DDD treatment in 54 dogs, the 1-, 2-, and 3-year survival fractions were 80%, 59%, and 45%, respectively.[9] This study included dogs with adrenocortical tumors. In another study including 200 dogs with PDH, 72% of the dogs were alive after 1 year, 47% after 2 years and 30% after 3 years of chronic (non-selective) treatment with o,p'DDD.[15] In a study of 78 dogs treated with trilostane, the median survival time of the 26 dogs which died was 549 days.[24] The experience with radiotherapy as a treatment for dogs with PDH is limited. In a study using cobalt 60 radiotherapy in 6 dogs with PDH, the clinical signs resolved in 3 dogs but recurred in 2 dogs within 10 months. There was a substantial decrease in tumor size 1 year after radiotherapy.[12] Megavoltage irradiation in dogs has also been shown to reduce tumor size.[35]

There is a significant influence of pituitary tumor size, reflected in the maximum pituitary dimension and P/B ratio, on survival and disease-free fraction after hypophysectomy in dogs with PDH. The larger the pituitary tumor, at time of surgery, the shorter survival and disease-free fraction after surgery. In humans with pituitary adenomas the incidence of dural invasion increases with pituitary size, and dural invasion is correlated to a decreased survival rate.[20] In other studies on transsphenoidal surgery in humans with Cushing's disease, the remission rate of cases with suprasellar lesions has been found to be lower than cases of intrasellar lesions,[26,31,34] with a correlation of remission rate and size of the pituitary.[26] The influence of the size of microadenomas on remission rate has been studied by Shimon et al.[32] The patients were divided into three groups; no detectable tumor on MRI, tumor size 2-5 mm and tumor size 6-10 mm. All pituitary tumors were restricted to the sellar compartment which, in humans, measures 10 mm in diameter. There was no difference in remission rate between the groups.[32] These findings demonstrate the importance of early diagnosis of a corticotroph adenoma. The period of remission after surgery is expected to be the longest when the pituitary adenoma is still contained in the sellar compartment.

After complete hypophysectomy, there is a sudden cessation of arginine vasopressin (AVP) secretion by the neurohypohysis. Usually, after a few days, AVP released by the hypothalamic paraventricular and supraoptic nuclei reaches the systemic circulation sufficiently to restore antidiuresis.[21] The transient CDI normalizes 5 days after hypophysectomy in healthy dogs, but may persist up to 2 weeks in dogs with PDH,[12, 13] and severe hypernatremia after hypophysectomy in dogs has been reported.[18] After transsphenoidal pituitary surgery in humans, transient CDI lasting 1-3 days occurs in 38% of the patients.[17,26] Desmopressin, a synthetic AVP analog, is administrated to substitute for the postoperative impairment of AVP release. The prophylactic efficacy of desmopressin after hypophysectomy in healthy dogs, has been studied by Hara et al.[13] Administration of 4 µg desmopressin acetate in the conjunctival sac twice daily effectively prevented hypernatremia that otherwise occurred 24 hours after surgery. However, mild immediate postoperative hypernatremia was frequently observed after hypophysectomy in dogs with PDH that were routinely treated with desmopressin postoperatively for a period of 2 weeks.[21] This may be explained by the vasopressin resistance in dogs with hyperadrenocorticism.[3] Therefore, to prevent hypernatremia, low sodium fluids (0.45% sodium chloride + 2.5% glucose) are best started before and continued during and after surgery.[21] Thirty-nine dogs in the present study developed chronic CDI, which required desmopressin administration for relatively long

periods until it could be discontinued. The damage to the axons of pituitary stalk may be such that neuronal degeneration ensues, leading to permanent CDI.[22] In our study, permanent CDI developed in 28 of 127 dogs, which is more frequent than in humans after transsphenoidal surgery.[23] The explanation for this is that, in humans with Cushing's disease, selective adenomectomy is performed, whereas in the present study total hypophysectomy was performed, which includes removal of the neurointermediate lobe. The frequency of permanent CDI in the present study is also higher than that in the previous study (10%, 5 of 52 dogs).[21] Pituitary tumor extension usually occurs in dorsal direction and prolonged mass effect by the tumor on the hypothalamic nuclei may result in (irreversible) damage to these nuclei. Indeed, the incidence of CDI was significantly higher in the group of dogs with an enlarged pituitary than that in the group of dogs with a nonenlarged pituitary. Also, efforts to completely remove dorsally located tumor tissue in cases with large pituitary tumors may lead to damage of the median eminence, leading to more frequent CDI than in dogs with small pituitary tumors.

KCS is a severe complication after transsphenoidal hypophysectomy in dogs if left untreated. Decreased tear production was detected in 47 of 150 dogs in the present study, which is similar to what was found in the previous study, 18 of 52 dogs.[21] With early detection, KCS develops less severely. Routine postoperative check of the STT values and immediate ophthalmologic treatment prevent the development of lesions in the cornea. Complete recovery occurred in 47 eyes after intensive treatment, but in 11 eyes of 10 dogs, the tear production remained low until death. There was no correlation between pituitary size and development of KCS.

KCS after hypophysectomy has been ascribed to direct (traumatic) or indirect (ischemic) neuropraxia of the major petrosal nerves, resulting in a secretomotoric deficit in the lacrimal glands.[22] Decreased tear production occurred more frequent in the left than in the right eye, a finding consistent with earlier studies.[21,22] It may be that a right-handed surgeon deviates the burr slot slightly to the left side of the dog, leading to more unilateral petrosal nerve damage. Another explanation for occurrence of KCS is ischemic damage to the pterygopalatine ganglion from longstanding pressure of the mandibular coronoid process in the retrobulbar area due to the open mouth approach. This theory is supported by the fact that the degree of lower jaw retraction has successively been reduced with time, and the incidence of KCS in the latest dogs seems to decrease (data not shown). This theory, however, cannot fully explain the predominance of decreased tear production in left eyes.

The lacrimal gland has been shown to be dependent on pituitary hormones. Reduced tear production has been reported in association with endocrine diseases such as hyperadrenocorticism (Peirce VE, Williams DL. Reduced tear production in 50 dogs with endocrine disease [abstract]. In Proceedings of British Small Animal Veterinary Association Congress, Birmingham, England, 2004:517), which may also have affected the occurrence of KCS after hypophysectomy. Although the pathogenesis of the decreased tear production after transsphenoidal hypophysectomy in dogs remains uncertain, it may be concluded that the STT should be performed on the 1st day after hypophysectomy. Early detection and treatment of a reduction in tear production prevents the development of KCS. In most cases tear production recovers with time.

It is concluded that hypophysectomy is an effective long-term treatment for PDH in dogs directed at elimination of the pituitary origin of the disease. With increasing pituitary dimensions, the survival and disease-free fractions after hypophysectomy decrease, and the inci-

dence of DI increases. Therefore, early diagnosis of a corticotroph adenoma is important and transsphenoidal hypophysectomy is expected to have the best outcome when installed as primary treatment for dogs with nonenlarged or moderately enlarged pituitaries.

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