Long-term outcome of domestic ferrets treated surgically for hyperadrenocorticism: 130 cases (1995–2004)

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Objective—To determine the long-term survival rate and factors that affect survival time of domestic ferrets treated surgically for hyperadrenocorticism.

Study Design—Retrospective case series.

Animals—130 ferrets with hyperadrenocorticism that were treated surgically.

Procedures—Medical records of ferrets surgically treated for hyperadrenocorticism were reviewed. Data recorded included signalment, duration of clinical signs prior to hospital admission, CBC values, serum biochemical analysis results, anesthetic time, surgical time, concurrent diseases, adrenal gland affected (right, left, or both [bilateral]), histopathologic diagnosis, surgical procedure, caudal vena caval involvement (yes or no), postoperative melena (yes or no), days in hospital after surgery, and whether clinical signs of hyperadrenocorticism developed after surgery.

Results—130 ferrets were entered in the study (11 of 130 ferrets were admitted and underwent surgery twice). The 1- and 2-year survival rates were 98% and 88%, respectively. A 50% survival rate was never reached. Combined partial adrenal gland resection with cryosurgery had a significantly negative effect on survival time. No other risk factors were identified. Survival time was not significantly affected by either histopathologic diagnosis or specific affected adrenal gland (right, left, or bilateral).

Conclusions and Clinical Relevance—Ferrets with adrenal gland masses that were treated surgically had a good prognosis. Survival time of ferrets with hyperadrenocorticism undergoing surgery was not affected by the histologic characteristic of the tumor, the adrenal glands affected (right, left, or bilateral), or complete versus partial adrenal gland resection. Debulking was a sufficient surgical technique to allow a favorable long-term outcome when complete excision was not possible. (*J Am Vet Med Assoc* 2008;232:1338–1343)

The current pet ferret (*Mustela putorius furo*) population in the United States is estimated to be between 8 and 10 million. Hyperadrenocorticism in ferrets was first reported in 1987. Prevalence of the disease has been reported to range from 0.55% to 25%.[1,2]

This disease commonly occurs in middle-aged ferrets with no sex predilection. The most common clinical sign associated with hyperadrenocorticism is pruritic or nonpruritic alopecia.[3] Other clinical signs may vary but include vulvar enlargement, aggression, return of sexual behavior in neutered males, and urinary blockage secondary to prostatic cysts.[4]

A diagnosis is usually made on the basis of clinical signs, findings on abdominal radiography and ultrasonography, CBC values, and findings on serum biochemical analysis.[5–7] Complete blood counts are often within reference range limits. Results of serum biochemical analysis are also generally within reference range limits; however, high serum alanine aminotransferase activities are occasionally observed. Serum concentrations of estradiol, androstenedione, or 17-hydroxyprogesterone are usually high in ferrets with hyperadrenocorticism.[5]

Ferrets with hyperadrenocorticism are treated surgically or medically.[8] Medical treatment is generally recommended for ferrets unable to withstand anesthesia and surgery or that have owners who are reluctant to pursue surgery. Surgical intervention is the preferred treatment and consists of removal of affected adrenal glands. Partial resection, partial resection plus cryosurgery, and complete resection of affected adrenal glands have been recommended.[2,9,10] Following subtotal bilateral adrenalectomy in a study,[11] approximately 5% of the ferrets developed hyperadrenocorticism.

The purpose of the study reported here was to evaluate the long-term outcome, prognosis, and risk factors that affect survival time of ferrets with hyperadrenocorticism following surgical treatment. Our hypothesis was that ferrets treated surgically for hyperadrenocorticism have a good long-term prognosis.

Materials and Methods

Case selection—Medical records of ferrets examined at Colorado State University Veterinary Medical

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Center between 1995 and 2004 were reviewed. Ferrets were included in this retrospective study if they were treated surgically for hyperadrenocorticism. Ferrets that did not survive surgery were excluded.

Medical records review—Information extracted from the medical records included history, primary clinical sign at the time of admission, findings on physical examination, hematologic and serum biochemical analysis, and abdominal ultrasonography as well as information on surgical findings and technique, postoperative complications, and results of histologic evaluation. At the time of surgery, affected adrenal glands were completely removed, partially resected, or partially resected followed by cryosurgery of the remaining tissue. Assessment of completeness of resection was made on the basis of surgical descriptions. Any other abnormalities detected at surgery were treated as necessary.

Medical records were reviewed for information on survival times. Phone interviews with owners and referral veterinarians were performed to acquire additional information on resolution of clinical signs, development of other disease, survival time, and cause of death.

Statistical analysis—Analyses were performed by use of a software program.[a] The χ^2 test was performed to evaluate distribution of categoric data. Univariate Cox analysis was performed to identify whether hematologic and serum biochemical data were risk factors that affect survival time. Ferrets that required 2 surgeries were entered twice in the univariate Cox analysis with the date of the second surgery as a failure point for the first procedure (uncensored). Kaplan-Meier survival analysis was performed to determine median survival time and 1-, 2-, and 5-year survival rates. Survival time was defined as time from the first surgery to time of death or as time from the first surgery to the time that patients were lost to follow-up. Ferrets alive, lost to follow-up, or that died from reasons other than adrenal gland disease were censored in the analysis, whereas ferrets that died from the disease were uncensored. Data are presented as mean ± SD values. Values of $P < 0.05$ were considered significant.

Results

Signalment and clinical findings—Between 1995 and 2004, 141 surgeries were performed on 130 ferrets for treatment of hyperadrenocorticism. The mean age at the time of initial evaluation was 4.10 ± 1.30 years. Females comprised 55% (69/130 spayed, 3/130 sexually intact) and males comprised 45% (54/130 castrated, 4/130 sexually intact) of the study population. At the time of admission, 61% (86/141 [11 of the 130 ferrets were admitted twice]) of ferrets had a primary clinical sign of alopecia; 30% (26/86) of these ferrets were also pruritic. Fifty-seven percent (41/72) of females had vulvar enlargement as a primary clinical sign. Less than 5% of our ferret population had additional clinical signs at the time of admission (**Table 1**).

The mean follow-up time was 256 ± 410 days. Three ferrets were alive at the time of this study, and 8 ferrets died or were euthanized because of hyperadrenocorticism. Seventy-nine ferrets were lost to follow-up at 505 ± 92 days. The 1- and 2-year survival rates were 98% and 88%, respectively. Five-year survival rate was 70% (**Figure 1**).

Laboratory findings—Complete blood counts and results of serum biochemical analysis were available for 97 of 141 admitted ferrets (11 of the 130 ferrets were admitted twice). None of the values were identified as significant risk factors that affected long-term survival (**Table 2**).

Ultrasonography—Results of abdominal ultrasonography were available for 18 ferrets. Of these, 7 ferrets had the correct affected adrenal gland identified on ultrasonography, 6 ferrets had a large adrenal gland identified but not on the correct side, and 5 ferrets that had adrenal glands that were classified as normal in appearance on ultrasonography had 1 or both adrenal glands identified as affected during surgery.

Surgical procedures—Surgical procedures performed included 88 complete resections, 33 partial resections, and 4 partial resections followed by cryo-

Table 1—Primary clinical signs and findings of 130 ferrets admitted for hyperadrenocorticism. Eleven ferrets were admitted to the hospital twice.

Clinical sign or finding	No. of occurrences*	Frequency (%)
Alopecia	86	61
Vulvar enlargement	41†	57
Weight loss	6	4
Hypoglycemia	5	3
Lethargy	4	3
Diarrhea	3	2
Stranguria	2	1
Polyuria or polydipsia	2	1
Adrenal gland tumor	1	1
Aggression	1	1
Anorexia	1	1
Palpable abdominal mass	1	1
Vaginal discharge	1†	1
Inappropriate urination	1	1
Large prostate	1‡	1

*Number of times found during 141 admissions of ferrets (male and female). †Number of times found during 72 admissions of female ferrets. ‡Number of times found during 69 admissions of male ferrets.

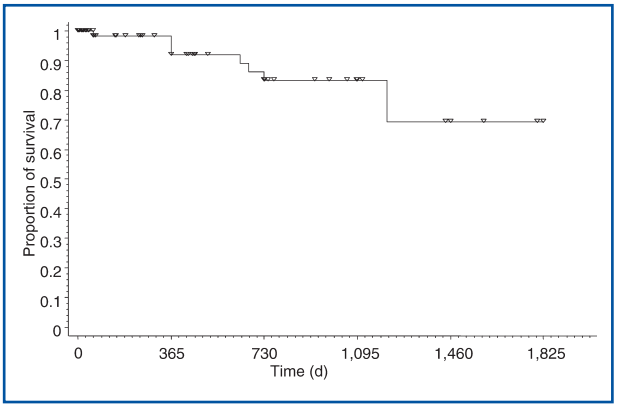

Figure 1—Overall Kaplan-Meier survival curve of 130 ferrets surgically treated for adrenal gland mass.

Table 2—Hazard ratios calculated from results of CBC determination and serum biochemical analysis to determine risk factors that affected long-term survival of 97 ferrets surgically treated for hyperadrenocorticism.

Measurements	Hazard ratio (95% CI)	*P* value: Univariate Cox analysis	*P* value: Likelihood ratio
Serum biochemical analysis			
CK (U/L)	1.001 (0.997–1.004)	0.71	0.73
AST (U/L)	1.006 (0.997–1.035)	0.70	0.72
ALT (U/L)	1.004 (0.994–1.014)	0.39	0.41
ALP (U/L)	1.014 (0.979–1.050)	0.43	0.45
GGT (U/L)	1.017 (0.951–1.088)	0.62	0.64
Total bilirubin (mg/dL)	0.000 (0.000–2.927)	0.08	0.07
BUN (mg/dL)	0.963 (0.886–1.048)	0.39	0.37
Creatinine (mg/dL)	0.398 (0.004–41.760)	0.70	0.69
Glucose (mg/dL)	0.999 (0.986–1.013)	0.94	0.94
Calcium (mg/dL)	0.550 (0.107–2.817)	0.47	0.47
Phosphate (mg/dL)	1.211 (0.635–2.310)	0.56	0.56
Total protein (g/dL)	1.450 (0.319–6.615)	0.63	0.63
Albumin (g/dL)	1.367 (0.178–10.622)	0.78	0.77
Albumin to globulin ratio	0.659 (0.70–6.172)	0.71	0.71
Globulin (g/dL)	1.156 (0.315–4.242)	0.83	0.83
Bicarbonate (mEq/L)	1.074 (0.844–1.367)	0.56	0.55
Sodium (mEq/L)	1.081 (0.829–1.410)	0.56	0.56
Potassium (mEq/L)	1.583 (0.184–13.603)	0.68	0.67
Chloride (mEq/L)	1.087 (0.885–1.336)	0.43	0.43
CBC determination			
Band cells ($\times 10^3/\mu L$)	0.000 (NA)	NA	NA
Neutrophils ($\times 10^3/\mu L$)	1.009 (0.625–1.629)	0.97	0.97
Lymphocytes ($\times 10^3/\mu L$)	0.445 (0.158–1.252)	0.12	0.06
Monocytes ($\times 10^3/\mu L$)	0.736 (0.017–31.941)	0.87	0.87
Eosinophils ($\times 10^3/\mu L$)	0.354 (0.017–7.451)	0.50	0.37
Basophils ($\times 10^3/\mu L$)	0.002 (0–2.289 $\times 10^7$)	0.60	0.58
PCV (%)	1.043 (0.957–1.135)	0.34	0.34

CI = Confidence interval. CK = Creatine kinase. AST = Aspartate aminotransferase. ALT = Alanine aminotransferase. ALP = Alkaline phosphatase. GGT = γ-Glutamyltransferase. NA = Not applicable.

surgery. The surgical technique used could not be determined for 16 surgeries. These 16 patients were not included for evaluation of the effect of surgical technique on survival time. The caudal vena cava was involved grossly in 33 affected adrenal glands; only 7 of these adrenal glands were completely removed, and the other adrenal glands were partially resected. The type of surgical procedure had a significant ($P = 0.005$) effect on survival time (**Figure 2**). If ferrets treated by cryosurgery were removed from the analysis, survival times were not significantly ($P = 0.77$) different between ferrets that underwent partial resection and complete removal. Complete adrenal gland resection was achieved for 68 left adrenal gland masses, 10 right adrenal gland masses, and 10 bilateral adrenal gland masses, whereas partial resection was performed for 3 left adrenal gland masses, 14 right adrenal gland masses, and 16 bilateral adrenal gland masses. Complete adrenal gland resection was performed significantly ($P = 0.001$) more often than partial resection. Partial resection and cryosurgery were implemented for 2 right adrenal gland masses and 2 bilateral resections. Mean survival time for these 4 patients was 60 days, compared with 1,097 and 666 days for ferrets that died of their disease and that underwent complete or partial resection, respectively.

Histologic evaluation revealed that 70 adrenal gland masses were benign; 54 had been completely resected, 14 were partially resected, and 2 were partially resected followed by cryosurgery. Fifty-five masses were malignant. Of those, 34 had been completely resected, 19 were partially resected, and 2 were partially resected followed by cryosurgery. The distribution of complete and partial resections for benign and malignant masses was not significantly ($P = 0.248$) different. The caudal vena cava was involved in 33 adrenal gland masses with

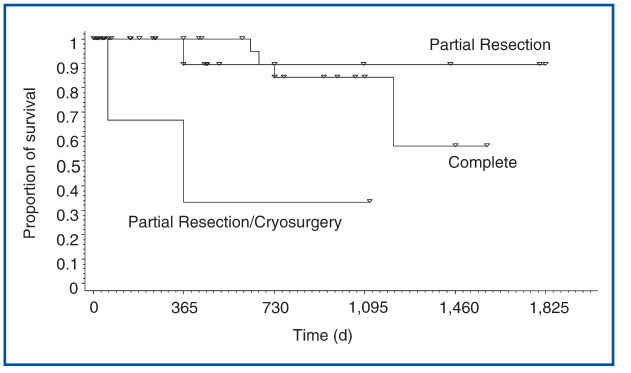

Figure 2—Kaplan-Meier survival curves of 130 ferrets treated for adrenal gland mass with partial adrenal gland resection, partial adrenal gland resection plus cryosurgery, or complete adrenal gland resection. The type of surgical procedure had a significant ($P = 0.005$) effect on survival time.

partial resection of the mass performed in 26 of these adrenal glands. Complete resection was achieved in 7 adrenal glands with resection of the prehepatic vena cava and tumor removal in 2 instances and dissection away from the caudal vena caval wall in 5 instances. In these 5 adrenal glands, small rents in the vena caudal caval wall that occurred during dissection were primarily repaired.

Affected adrenal glands—The left adrenal gland was affected in 76 ferrets, whereas the right adrenal gland was affected in 26 ferrets. Seventy-five left adrenal glands and 26 right adrenal glands were removed at the first surgery. Twenty-eight ferrets had bilateral adrenal glands affected; 18 ferrets had a bilateral adrenalectomy during the first surgery. The 11 ferrets that required a second surgery had both adrenal glands removed by the end of the second surgery. During the first surgery, 4 ferrets had the right adrenal gland removed and 3 had the left adrenal gland removed. For 4 ferrets, we could not determine what side was removed during the first surgery or the second surgery. Two ferrets had the left adrenal gland removed by the referring veterinarian and had a second surgery at the Colorado State University Veterinary Medical Center for a right side adrenalectomy.

Postoperative assessment—Of the 86 patients that had alopecia as a primary clinical sign at the time of admission, 28 had hair regrowth after surgery and an assessment of hair regrowth was not recorded for 58 patients. Four of 28 (14.3%) ferrets with bilateral adrenalectomy developed signs of hypoadrenocorticism, including excessive lethargy and anorexia after surgery. These signs resolved once medical treatment was instituted. Of these 4 patients that developed hypoadrenocorticism, 1 had a complete resection, 2 had partial resections, and 1 had an undetermined surgical procedure. The adrenal gland affected (right or left) had no significant ($P = 0.749$) effect on survival time (**Figure 3**). The number of surgical interventions was not a significant (hazard ratio, 1.46; 95% confidence interval, 0.615 to 6.35; $P = 0.43$) risk factor that affected survival time. Survival rate was not significantly ($P = 0.22$) affected by caudal vena caval involvement (**Figure 4**).

Histologic evaluation was performed on 131 masses. Seventy masses were benign (50 adenomas, 15 hyperplastic adrenal glands, 2 cysts, 1 cortical vacuolation, 1 normal adrenal gland, and 1 teratoma). Sixty-one masses were malignant (53 carcinomas, 5 pheochromocytomas, 2 leiomyosarcomas, and 1 fibrosarcoma). When pheochromocytoma, leiomyosarcoma, and fibrosarcoma are removed from the analysis, histologic characteristic was still not significantly ($P = 0.842$) different between benign and malignant masses. The histologic characteristic of the tumor had no effect ($P = 0.843$) on survival time (**Figure 5**). Twenty-eight malignant tumors were on the left adrenal gland and 12 on the right adrenal gland, whereas 48 benign tumors were on the left adrenal gland and 14 were on the right adrenal gland. The distribution (left vs right) was not significantly ($P = 0.169$) different between groups. Sixteen ferrets that underwent bilateral adrenal gland resection had malignant tumors. Twelve ferrets that underwent bilateral adrenal gland resection had benign tumors. Age was not a significant ($P = 0.12$) risk factor in regard to tumor classification of benign or malignant.

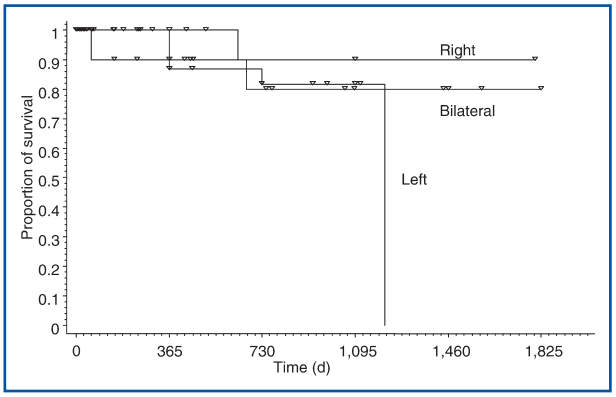

Figure 3—Kaplan-Meier survival curves of 130 ferrets surgically treated for adrenal gland mass on the right, left, or both (bilateral) adrenal glands. The adrenal gland affected (right or left) had no significant ($P = 0.749$) effect on survival time.

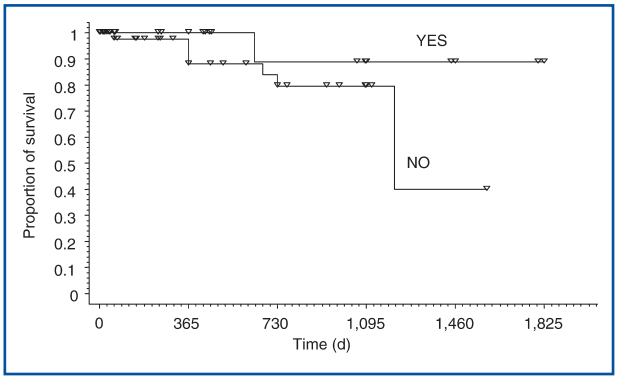

Figure 4—Kaplan-Meier survival curves of 130 ferrets surgically treated for adrenal gland mass with (yes) or without (no) vena caval involvement. Survival rate was not significantly ($P = 0.22$) affected by caudal vena caval involvement.

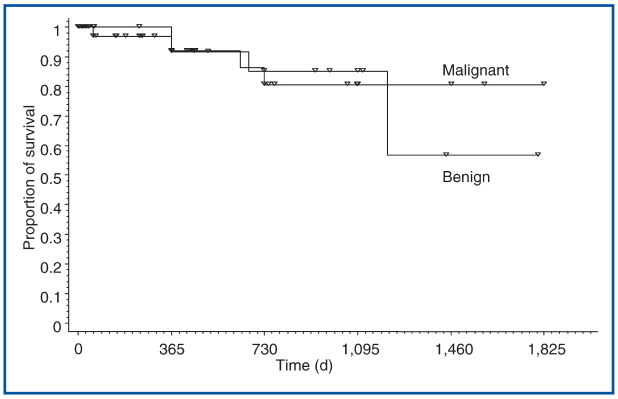

Figure 5—Kaplan-Meier survival curves of 130 ferrets surgically treated for benign and malignant adrenal gland masses. The histologic characteristic of the tumor had no significant ($P = 0.843$) effect on survival time.

Discussion

Domestic ferrets treated surgically for adrenal gland disease have a good prognosis with 98% and 88%

survival rates at 1- and 2-years, respectively. Complete resection of the affected adrenal gland was not required; however, partial resection followed by cryosurgery was associated with a shorter survival time. The adrenal gland affected and the histologic characteristic of the tumor did not have an effect on survival rate.

Primary clinical signs at the time of admission in the ferrets of our study were similar to previous reports[12] of ferrets with hyperadrenocorticism. The diagnostic procedures performed varied by clinician preference. In this population, serum alanine aminotransferase activity was not increased, as previously reported for ferrets with hyperadrenocorticism.[12] This difference may be a result of the large SD; however, 90% of our population had serum alanine aminotransferase activity within our reference range limits, so this is unlikely. Another possible explanation is that the reference range limits at the laboratory we used are higher than the reference range limits used in the previous report.[13]

In our population of ferrets, 18 had abdominal ultrasonography performed as a diagnostic tool. Because of the number of false negative findings (5/18 ferrets) and incorrect identification of the adrenal gland affected (6/18 ferrets), abdominal ultrasonography may not be a definitive diagnostic tool. However, because of our small sample size, statistical analysis was not possible. Expertise of the ultrasonographer may influence the results obtained with this diagnostic tool.

In our population, the histologic characteristic of the adrenal gland was not associated with prognosis. Tumors were classified as benign versus malignant. Tumors with a reported low rate of metastasis (pheochromocytoma, leiomyosarcoma, and fibrosarcoma) were included in the malignant group. This finding may have influenced the overall favorable prognosis for ferrets with malignant tumors in our study. However, no significant effect of tumor type (benign vs malignant) was found once ferrets with pheochromocytoma, leiomyosarcoma, and fibrosarcoma were removed from the survival analysis. In addition, completeness of tumor resection could not be assessed histologically because of the retrospective nature of the study. More left than right adrenal glands were affected. Seemingly, left adrenal glands are more often completely resected than right adrenal glands because of their anatomic location relative to the caudal vena cava. The distribution of malignant tumors between right and left adrenal glands could have been a confounding factor. However, this distribution was not significantly different in our study.

In the study presented here, the addition of cryosurgery with partial resection was a negative prognostic indicator for long-term survival rate. Six of 141 patients (11/130 ferrets were admitted twice) had cryosurgery performed after partial resection. Though this small number of ferrets had a significantly decreased survival time, if larger numbers of patients are evaluated, this finding may not be significant. Additionally, experience may play a role in outcome with cryosurgery. Case bias may play a role in the decreased survival rate associated with having a partial resection and cryosurgery. These ferrets may have had affected adrenal glands that were more difficult to resect, and cryosurgery was performed in an attempt to remove remaining tumor. Cryosurgery has been reported for adrenalectomy in ferrets[10]; however, no long-term studies have been performed to determine its efficacy in treating the tumor and preventing recurrences. More importantly, partial adrenal gland resection has a similar outcome in terms of survival rate, compared with complete adrenal gland resection to remove the adrenal gland mass. Partial resection was most commonly performed for right adrenal gland tumors, whereas complete resection was most commonly achieved for left adrenal gland tumors. Partial resection and complete resection were evenly distributed between malignant and benign tumors. Although complete tumor resection is the goal of surgical treatment, partial resection seems to be sufficient to achieve a long-term survival rate, especially for tumors involving the right adrenal gland. Because invasion of the caudal vena cava was not a risk factor with a significant effect on survival time in our study and partial resection seems to be a sufficient surgery, venotomy of the caudal vena cava during adrenal gland resection may not be warranted.

This study was retrospective in nature and therefore limited by the information contained in the record and the information that could be acquired from owners and referral veterinarians. Sixty percent of the cases were lost to follow-up at 505 days. Since we censored these ferrets in the study at the time they were lost to follow-up, it should have no impact on the Kaplan-Meier analysis. As well, factors in the diagnosis, surgical treatment, or follow-up of these ferrets could not be controlled. Multiple surgeons, ultrasonographers, and pathologists were involved in the management of these ferrets, which was another variable that could not be controlled. Disease-free intervals could not be assessed from medical records; therefore, survival time was used to assess the outcome of our patients in this study.

In conclusion, ferrets treated surgically for adrenal gland disease had a 98% 1-year survival rate and 70% 5-year survival rate. Long-term outcome of ferrets with hyperadrenocorticism undergoing surgery was not affected by the histologic characteristic of the tumor. Additionally, long-term outcome was not affected by which adrenal gland was involved (right vs left) or complete versus partial adrenal gland resection. Complete adrenal gland resection should be the surgical aim; however, when this adds substantial risk, partial adrenal gland resection may be used. Combined partial resection and cryosurgery is not recommended according to our findings.

a. JMP statistical analysis, SAS Institute Inc, Cary, NC.

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