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Stereotactic radiation therapy for the treatment of functional pituitary adenomas associated with feline acromegaly

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Background: Conventional fractionated radiotherapy has been shown to be partially effective for management of pituitary tumors in cats that cause acromegaly and diabetes mellitus (DM), but, the efficacy and safety of stereotactic radiation therapy (SRT) as a treatment for acromegalic cats has not been described.

Hypothesis: Stereotactic radiation therapy is an effective and safe treatment for controlling acromegaly associated with pituitary adenomas in cats. Additionally, SRT-treated acromegalic cats with DM will experience a decrease in insulin requirements after radiation therapy.

Animals: Fifty-three client-owned cats referred to Colorado State University for SRT to treat pituitary tumors causing poorly controlled DM secondary to acromegaly.

Methods: Retrospective study of cats treated for acromegaly with SRT between 2008 and 2016 at Colorado State University. Diagnosis of acromegaly was based on history, physical examination, laboratory results, and cross-sectional imaging of the pituitary. Signalment, radiation protocol, insulin requirements over time, adverse effects, and survival were recorded.

Results: Median survival time was 1072 days. Of the 41 cats for which insulin dosage information was available, 95% (39/41) experienced a decrease in required insulin dose, with 32% (13/41) achieving diabetic remission. Remission was permanent in 62% (8/13) and temporary in 38% (5/13) cats. Median duration to lowest insulin dose was 9.5 months. Of the treated cats, 14% developed hypothyroidism and required supplementation after SRT.

Conclusions: Stereotactic radiation therapy is safe and effective for treating cats with acromegaly. Cats treated with SRT have improved survival time and control of their DM when compared to previously reported patients treated with non-SRT.

KEYWORDS

cats, hypofractionated radiation therapy, megavoltage radiation, SRT

1 | INTRODUCTION

Acromegaly in cats is caused by a functional pituitary adenoma causing hypersecretion of growth hormone (GH) and consequently insulin-like growth factor 1 (IGF-1) from the liver.[1] Growth hormone has anabolic and catabolic effects. Anabolic effects are mediated by IGF-1, whereas catabolic effects contribute to insulin resistance and ultimately diabetes

Abbreviations: ARE, acute radiation effects; CBCT, cone beam computed tomography; CI, conformity index; CKD, chronic kidney disease; CT, computed tomography; CTV, clinical target volume; DM, diabetes mellitus; GH, growth hormone; GI, gradient index; GTV, gross tumor volume; HCM, hypertrophic cardiomyopathy; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; OAR, organ at risk; OBI, on board imaging; PTV, planned target volume; QA, quality assurance; SRT, stereotactic radiation therapy; TRH, thyrotrophin releasing hormone.

mellitus (DM).[2] Not only is the pituitary gland responsible for secretion of GH, but it is also responsible for maintaining thyroid homeostasis.

Clinical signs and laboratory results consistent with acromegaly in cats include polyphagia, polyuria, polydipsia, weight gain, insulin-resistant DM, enlargement of the head, paws and internal organs, stertorous breathing, and central nervous system signs.[2] A male sex predilection has been identified.[1–9] Diagnosis is based on clinical findings, serum IGF-1 concentrations, and cross-sectional imaging of the pituitary gland.[1,2] One study reported identifying a pituitary mass in cats with insulin resistance based on advanced imaging, suggesting these cats likely had acromegaly or pituitary-dependent hyperadrenocorticism, but the distinction between these conditions can be made using laboratory test results.[5]

Medical management, surgery, and radiotherapy options have been explored for this condition.[4–8,10–13] Medical management with pasireotide, a somatostatin receptor-ligand, has shown efficacy with a recent publication identifying diabetic remission in 3 of 8 cats treated with long-acting pasireotide.[4] However, this medication is prohibitively expensive and has some intolerable adverse effects including diarrhea, hypovolemia, hypoglycemia, and worsening polyphagia.[4] Successful treatment with transphenoidal hypophysectomy has been reported, but the surgery is technically challenging with limited availability.[11]

Early efforts using radiotherapy were directed at resolving neurological signs associated with intracranial masses in the pituitary fossa.[8] These studies evaluated fractionated protocols ranging from 2.7 to 4 Gy/fraction for a total of 36–54 Gy using either electrons or photons.[6,8,12] Reduction in insulin requirements for these cats ranged from 55 to 92%.[3,6–8,12] A single fraction technique utilizing 3-dimensional-conformal radiotherapy (3D-CRT) of 15–20 Gy also has been reported, decreasing insulin requirements in 56% (5/9) of treated patients with poorly controlled DM.[9] Advances in radiotherapy now allow administration of higher doses of targeted radiation to tumors using 1–5 fractions using a technique known as stereotactic radiation therapy (SRT).

Stereotactic radiation therapy is now an accepted treatment for many tumor types and locations in both human and veterinary medicine.[14–21] Stereotactic radiation therapy delivers an ablative dose of radiation to the tumor while avoiding normal tissues in the field.[14] Administration of high doses of radiation is possible because of the precision associated with immobilization, image-guidance, and a steep, conformal, dose drop-off.[14] For veterinary patients, SRT permits for fewer anesthetic episodes to deliver a curative intent protocol.

The purpose of our study was to report the clinical outcome of 53 acromegalic cats with presumed pituitary adenomas treated with SRT at Colorado State University. It was hypothesized that SRT would allow for superior control of acromegaly and associated DM. Patient response was characterized according to survival time, control of DM with respect to reduction in insulin requirements over time, and the incidence of presumed acute and late normal tissue adverse radiation effects.

2 | MATERIALS AND METHODS

2.1 | Case selection

Cats with acromegaly that were treated with curative-intent SRT at the Colorado State University Veterinary Teaching Hospital between February 2008 and November 2016 were included in our study. Inclusion criteria were developed by T. Wormhoudt, K. Lunn, and S. LaRue and consisted of cats diagnosed with acromegaly and concurrent DM. Medical records were reviewed and follow-up data was collected from referring veterinarians and clients regarding presenting clinical signs, clinical signs after treatment, prescribed insulin dose before and after treatment, thyroid hormone status, acute and late normal tissue adverse radiation effects, response to therapy and overall survival time. Data was collected from staging diagnostic tests which were performed before radiation therapy, including CBC, serum biochemical profile, urinalysis, serum IGF-1 concentration, thoracic radiographs, echocardiogram, abdominal ultrasound examination, computed tomography (CT) examination and magnetic resonance imaging (MRI) when available.

2.2 | CT examination

Computed tomography examination was performed using either a Picker PQ2000 CT single slice helical scanner (before November 2009; Picker Medical Systems, Cleveland, Ohio), or a Philips Gemini TF Big Bore 16-slice scanner (after November 2009; Philips Medical Systems, Nederland, B.V.). When obtaining CT images for radiation planning, all patients were placed in sternal recumbency in a foam trough with the forelimbs positioned caudally. Patients' heads were further immobilized using a previously described system including a carbon fiber stand, a fixed thermoplastic dental mold, and a facial mask (Figure 1).[22] A Styrofoam bead-style cushion was used to provide ventral support to the cervical region.[22]

A non-contrast volumetric (helical) dataset was obtained through the skull. Omnipaque 350 (GE Healthcare, Princeton, New Jersey) contrast media then was injected IV (2.2 mL/kg) before the postcontrast series. Images were reconstructed at 2.0 mm contiguous intervals with a 512 matrix, using the smooth algorithm.

2.3 | Radiation treatment planning

Both the 2-mm precontrast and postcontrast CT scan were used for inverse treatment planning performed using a Varian Eclipse treatment planning system (Varian Medical Systems, Inc Palo Alto, California). Organs at risk (OAR) and gross tumor volume (GTV) were identified and contoured. A 1–2 mm isotropic planned target volume (PTV) expansion encompassed the GTV to account for daily set-up positioning error. No clinical target volume was used. The OARs for the radiation treatment plans included brain, skin, palatine mucosa, ocular lenses, optic chiasm, pharynx, bone, esophagus, and cochlea. Normal brain tissue was defined as the contoured brain minus the GTV for radiation treatment planning. When MRI was available, the T1-weighted postcontrast was fused with the CT in the treatment planning software to aid in contouring of the tumor volumes.

Inverse-planning was employed using Eclipse planning software; all plans were designed using coplanar or noncoplanar, isocentrically placed 6 MV radiation beams. Radiation beams were modulated using sliding-window technique. The intent for each radiation plan was to deliver 100% of the radiation prescription to 99% of the GTV and 95% of the PTV. The volume constraint for the brain in these plans was that

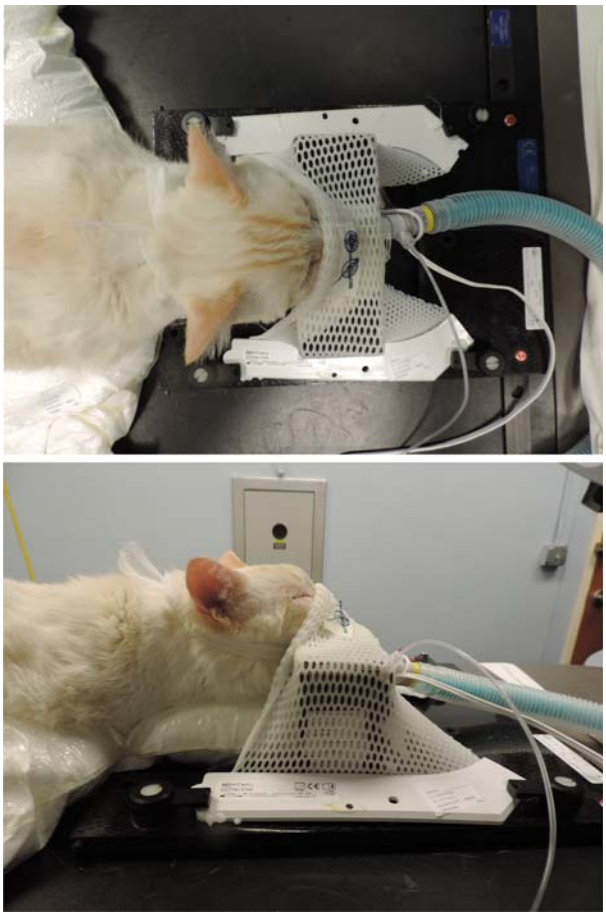

FIGURE 1 Patient shown in immobilization devices including a bead cushion ventrally, dental mold, bite block bridge, and thermoplastic mask over the bridge of the nose

no more than 1.0 cc of normal brain may receive 24Gy for 3 fractions and 27Gy for 4 fractions. Biological equivalent doses (BED) were calculated for comparison of plans based on the following formula: BED = $nd\ (1+\ [d/(\alpha/\beta)])$ where n is the number of fractions, d is the dose per fraction and the α/β was assumed to be 10 for a tumor.

Quality assurance (QA) was performed by gamma analysis using the Varian portal dosimetry system on individual fields. A minimum of 95% gamma for a 3 mm distance to agreement and a 3% absolute dose difference were defined as a passing QA score.

When retrospectively reviewing the radiation treatment plans, the following data was collected: dose to 99% of GTV, dose to 95% of PTV, maximum tumor dose, minimum tumor dose, mean doses to the PTV, conformity index (CI), and gradient index (GI). The GTV was recorded for each patient. Regarding radiation dose delivered to normal brain tissue, the dose of 1.0 cc of the normal brain was recorded.

The CI is a quantitative measurement evaluating the degree of conformity of the dose distribution to the size and shape of the target volume and can be calculated as $CI = TV_{PIV}^2/(TV \times PIV)$, where

TV_{PIV} = volume (in cubic centimeters) of the PTV that is covered by the prescription dose

TV = volume of the target (PTV)

PIV = prescription isodose volume

A CI of 1 indicates that the prescription isodose line cover the PTV without irradiation of any tissue outside of the PTV. The GI is an objective assessment that evaluates dose drop-off outside of the target and is evaluated by dividing the volume of the body receiving 50% of the prescription by the volume of the body getting 100% of the prescription.[23]

2.4 | Radiation treatment

Patients were anesthetized for the delivery of radiation therapy. Anesthetic protocols varied but in most cases consisted of an opioid premedication followed by propofol induction and maintenance with an isoflurane and oxygen admixture. Once anesthetized, cats were positioned in the same immobilization devices used for their initial CT imaging. Daily patient position verification was performed by online registration of the simulation CT with images of the daily setup obtained using an on-board cone beam CT (CBCT), or registration of a digitally reconstructed radiograph with setup images obtained using on-board imaging (OBI) with kilovoltage radiographs. Therapy was delivered using a Varian Trilogy linear accelerator.

2.5 | Follow-up

After completion of SRT, the recommended follow-up schedule included physical examination and evaluation of blood glucose concentration at 2 weeks and 4 weeks, and assessment of a serum thyroid panel at 4 weeks including total T4 and TSH performed through CSU Diagnostic Laboratory, IDEXX Laboratories (Westbrook, ME) or Antech Diagnostics (Fountain Valley, CA). Blood glucose monitoring at home with a glucometer calibrated for cats and adjusting insulin dose as necessary was recommended, under the guidance of the primary care veterinarian or veterinary specialist. It was recommended that any change in neurologic status or appetite should be investigated immediately by the referring veterinarian or veterinary specialist.

2.6 | Statistical analysis

Survival time was calculated as the time between the first day of treatment and death. Survival analysis was performed on an intent-to-treat basis; events included death of the patients. Cats were censored at the time of analysis if they were still alive or lost to follow-up. Kaplan-Meier survival curves were created depicting median survival time. Continuous variables including age, weight, plasma IGF-1 concentrations, and GTV were evaluated for correlation using Pearson's correlation coefficient. The data was described using means, medians, and 95% confidence limits of means. A *P*-value of .05 was considered for statistical significance. The software SAS v9.4 (SAS Institute Inc, Cary, North Carolina) was used for all statistical analyses.

3 | RESULTS

3.1 | Patient population

Fifty-six cats with pituitary tumors were considered for our study from case reviews. Three cats with pituitary tumors not causing signs

TABLE 1 Mean and range values for each protocol

	28 Gy 7Gy × 4fx	27 Gy 6.75Gy × 4fx	24 Gy 8Gy × 3fx	18 Gy 6Gy × 3fx	17 Gy 17Gy × 1fx
Number of Patients	5	3	44	1	1
Dose to 99% Of GTV	25.64 (22.0–28.3)	24.1 (22.8–24.8)	25.04 (22–26.6)	18.31	18.0
Dose to 95% Of PTV	24.8 (20.0–27.0)	23.67 (22.0–25.0)	23.89 (22.0–25.0)	17.16	17.0
Max Dose to PTV	30.6 (29.3–31.6)	27.77 (26.7–28.8)	27.29 (25.7–30.6)	19.13	19.0
Min Dose to PTV	16.9 (11.9–24.7)	15.97 (13.0–18.1)	20.95 (16.0–24.5)	14.77	14.8
Mean Dose to PTV	27.98 (26.5–28.7)	25.8 (25.3–26.5)	25.73 (24.7–27.8)	18.09	18.0
Median Dose To PTV	29.32 (28.7–29.7)	25.26 (23.5–26.8)	25.82 (24.9–27.1)	18.15	18.09
Modal Dose To PTV	30.32 (29.5–31.1)	26.04 (23.4–28.6)	26.26 (24.5–29.4)	18.19	19.1
Dose at Isocenter	30.93 (29.3–33.5)	26.55 (24.7–28.6)	26.98 (25.1–30.2)	18.92	18.99
Volume of GTV (cm^3)	0.226 (0.06-0.35)	0.23 (0.16-0.29)	0.43 (0.04-3.17)	0.08	0.04
Volume of PTV (cm^3)	0.898 (0.53-1.4)	0.97 (0.75-1.09)	0.87 (0.3–4.85)	0.47	0.2
CI	1.254 (0.82-2.26)	0.23 (0-0.45)	1.27 (0.89-2.09)	0.61	1.27
GI	0.67 (0.61-0.75)	0.88 (0.69-1.1)	0.62 (0.53-0.8)	0.72	0.53
PTV Expansion (mm)	1.8 (1–2)	2	1	2	1
Dose to 1 cm^3 of Normal Brain	23.8 (19.0–28.0)	20.67 (19.0–23.0)	19.57 (16.0–24.0)	18	9
Number of Beams	7	7	7.15 (5–11)	7	7

Dose refers to the radiation dose (in gray). CI = (prescription isodose volume)2/(total PTV volume) × (prescription isodose volume).[23]

associated with acromegaly or DM were excluded. In total, 53 acromegalic cats treated with SRT were included in our retrospective analysis. The median age of the cats at the time of treatment was 10 years (95% CI, 9.9–11.2 years). There were 43 neutered males and 10 neutered females. Forty-three cats were domestic shorthairs, 8 were domestic longhairs, and 2 were Maine Coon cats. The median weight of the patients was 5.85 kg (95% CI, 5.67–6.49 kg).

All cats were presented with signs consistent with acromegaly, including DM that was deemed poorly responsive to insulin (100%). All cats had ≥1 of the following clinical signs: polyuria, polydipsia, weight gain, enlargement of the head and paws, and polyphagia. Three cats (5.6%) also had neurologic signs, including seizures, light sensitivity, star gazing, and head pressing. Twenty cats (38%) had laboratory test results that were suggestive of chronic kidney disease (CKD) and 22 (42%) had echocardiogram findings consistent with hypertrophic cardiomyopathy (HCM). Thirteen cats (25%) had both CKD and HCM. Six cats had echocardiograms and did not have evidence of HCM. Insulin-like growth factor concentrations were available for 40 patients with a median concentration of 345 nmol/L (95% CI, 315.5–379; reference interval, 12–92 nmol/L).

3.2 | Imaging findings

A presumptive diagnosis of pituitary adenoma was made for all cats in the study (100%) according to the CT images and interpretation by board-certified veterinary radiologist. Four of the cats were diagnosed with suspected microadenoma (8%) based on clinical signs, laboratory results, and an otherwise normal appearing pituitary gland. The remaining 49 were diagnosed with macroadenoma (92%). Findings for most cats with the diagnosis of macroadenoma included an ovoid, soft tissue attenuating, homogenously contrast-enhancing mass in the sella turcica without lysis or proliferation of surrounding bone. Magnetic resonance imaging was available for 8 cats and supported the presumptive diagnosis of microadenoma (1/8, 12%) and macroadenoma (7/8, 88%).

3.3 | Radiation treatment protocol

Several SRT treatment protocols were utilized to treat the cats, but the dose per fraction generally was escalated as we became more experienced with normal tissue tolerance. Forty-four cats received 8Gy over 3 consecutive days for a total of 24Gy. Five cats received 7Gy over 4 days for a total of 28Gy. Three cats received 6.75Gy over 4 consecutive days for a total of 27Gy. One patient received 18Gy in 3 fractions of 6Gy. One of the cats that received 24Gy over 3 fractions of 8Gy, was re-treated with a single fraction of 17Gy. Consecutive days are defined by a Monday-Friday schedule. Table 1 presents the mean treatment values for the various treatment groups.[23]

The mean dose to 1 cc of normal brain for the patients that received 4 fractions of SRT was 22.6Gy (range, 19–28). The mean dose to 1 cc of normal brain for the patients that received 3 fractions of SRT was 19.5Gy (range, 16–24). The dose to 1 cc of normal brain for the patient that received a single fraction of 17Gy was 9.0Gy. Figure 2 presents a selected patient's dose volume histogram (DVH) and dose color wash from the treatment planning software.

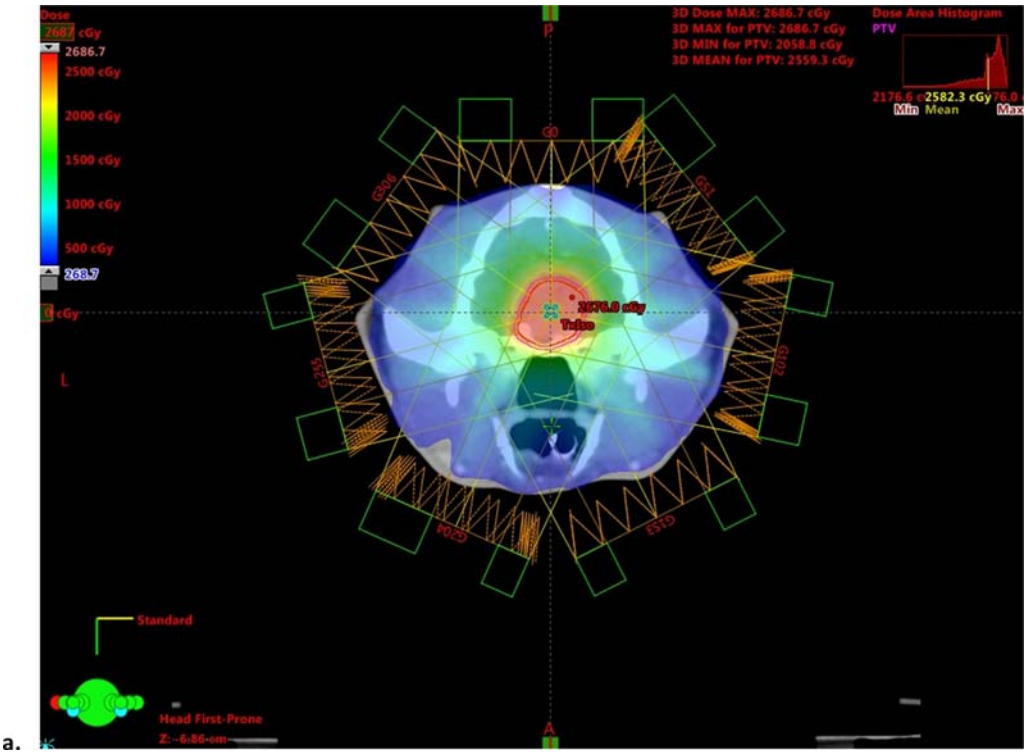

FIGURE 2 A, Dose color wash displaying the seven-angle beam arrangement that was used most commonly for patients in this study. Beams were typically arranged 51° apart as seen here. The angle numbers are listed at the top of each beam starting with "G0." Dose color interpretation is displayed on the left-hand side of the image with dose displayed in cGy. B, Dose color wash indicating that the orange/red portion is the area that received ≥2400 cGy. C, DVH displaying the GTV (red line) and PTV (pink line) curves with the red arrow and the OARs with the green arrow. Organ at risks in this DVH include optic chiasm (blue line), pharynx (brown line), and brain minus GTV (orange line). Y-axis displays the percentage of the total structure. The top X-axis displays the relative dose as a percentage. The bottom X-axis displays the absolute dose in cGy. In this case, 99% of the GTV received 25Gy, or 104% of prescription, and 95% of the PTV received 24Gy, or 100% of the prescription

3.4 | Survival

The median overall survival time for all patients after SRT, was 1072 days (95% CI, 845–1339 days; Figure 3). Sixteen patients were still alive at the time of censoring. Five cats were lost to follow-up. Inadequate numbers of patients in 4 of the different treatment protocol groups prevented meaningful comparison of the survival time among groups. Of the deceased cats, 7 deaths (13%) appeared to be neurologic in nature, 7 (13%) were attributed to heart failure or HCM complications, and 6 (11%) were related to CKD. Eight cats (15%) died of unrelated diseases including pancreatic neoplasia (n = 2), hepatic neuroendocrine neoplasia, tooth root abscess, oral neoplasia, leukemia, carcinoma of the thoracic wall, and nasal neoplasia. The cause of death of 4 cats (8%) was unknown. No statistically significant association was found between IGF-1 concentrations and survival time ($P = .81$) nor between volume of the pituitary tumor and survival time ($P = .56$). A significant negative correlation was observed between the patient age and survival time ($P = .03$).

3.5 | Diabetic regulation

Information regarding the insulin requirements of patients after SRT was available for 41 of 53 cats (77%). Of these 41 cats, 39 (95%) experienced a reduction in the insulin dose required to manage their DM, with 13 (32%) going into diabetic remission. Five of those 13 cats did have relapse of their DM 5, 11, 15, 17, and 46 months after the onset of remission. The median duration to lowest insulin dose was 9.5 months (95% CI, 9–15.3 months; range, 0–27 months). One patient experienced an increase in insulin dose of 150% of the starting dose. The mean decrease in insulin was 72% (median, 86%; range, −50%-100%).

3.6 | Radiation-induced adverse effects

Acute radiation effects were reported in 10 cats (18%) during radiation treatment, including mental dullness, light sensitivity, or mydriasis. In all cases, these effects were treated with prednisolone (0.5–1 mg/kg q24h for 1–6 weeks) and resolved without complication. One cat lost vision 2 years after treatment without development of cataracts. No other cats had reported vision changes. Two of the 3 cats (67%) that were presented with neurologic signs experienced neurologic improvement within 3 weeks after SRT.

Serum thyroid hormone concentrations after SRT were available for 50 cats (94%). Of those 50 cats, 7 cats (14%) developed hypothyroidism and supplemented. Five of the patients developed hypothyroidism between 4 and 6 months after SRT and the other 2 developed

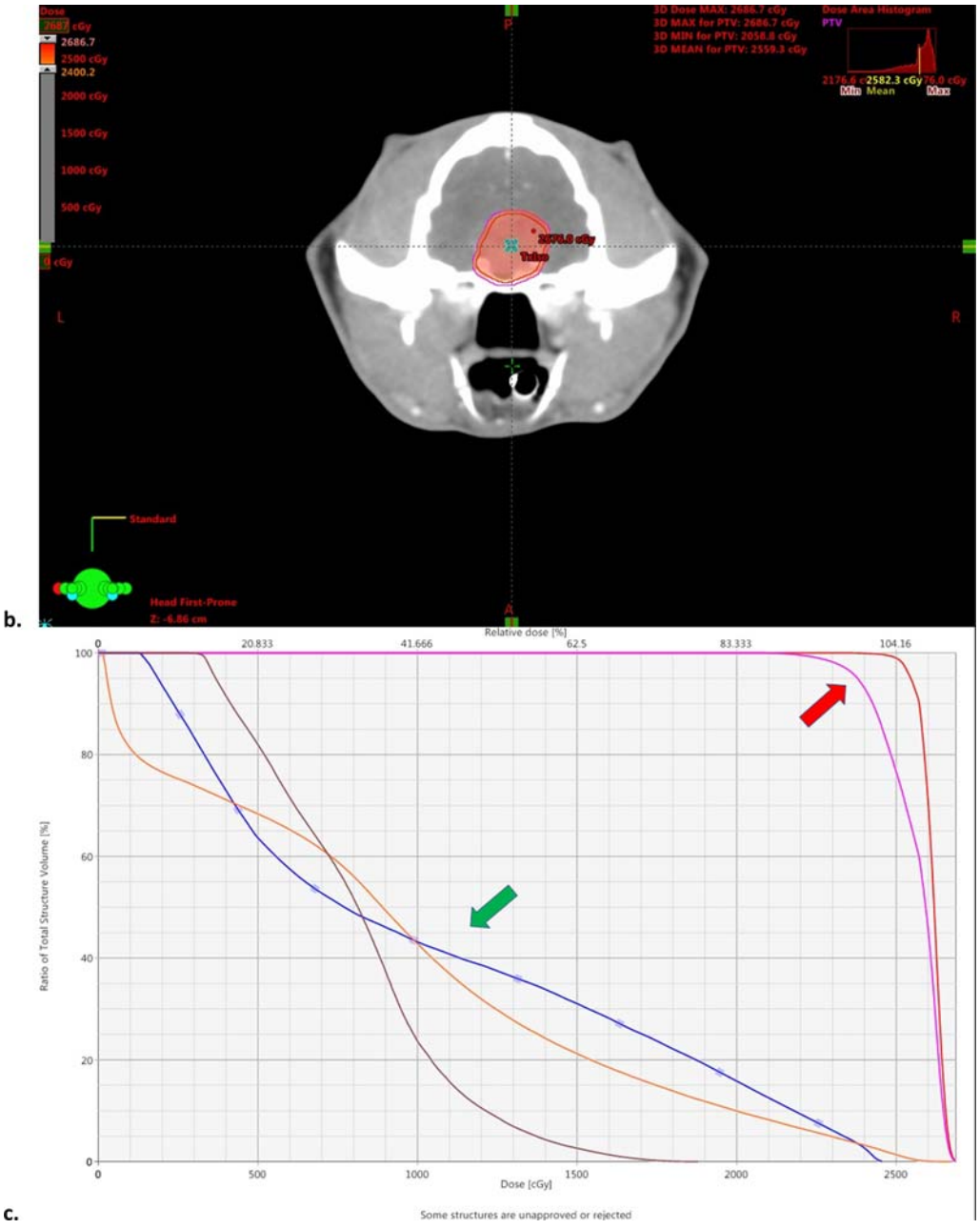

FIGURE 2 Continued

hypothyroidism 1.5 and 2 years after treatment. Figure 4 shows a cumulative risk curve that represents the timing for development of hypothyroidism.

3.7 | Necropsy findings

Necropsy was performed on 2 patients. One cat was euthanized for a thoracic wall adenocarcinoma with metastasis to the kidneys 277 days after SRT. On necropsy, an acidophil adenoma of the pituitary gland with cholesterol granuloma was noted. This patient experienced an 86% reduction in insulin dose. The second patient examined by necropsy had fibrosis of the pituitary gland 1461 days after radiation therapy. This patient had sustainable diabetic remission and developed hypothyroidism.

4 | DISCUSSION

Ours is the first study to evaluate the use of stereotactic radiation to treat pituitary tumors causing acromegaly in cats. The overall median survival time is longer than in other published studies evaluating conventionally fractionated, coarse fractionated and single fraction radiation treatments for acromegalic cats. Median survival in those studies ranged from 508 to 840 days, compared to 1072 days reported here.[6–9] This information, along with data from humans, suggests that a higher dose per fraction may be more biologically effective for this tumor type.[24] In addition to longer overall survival time, a higher proportion of the patients in our study had a more favorable response in terms of control of their DM. Previous studies reported a decrease in

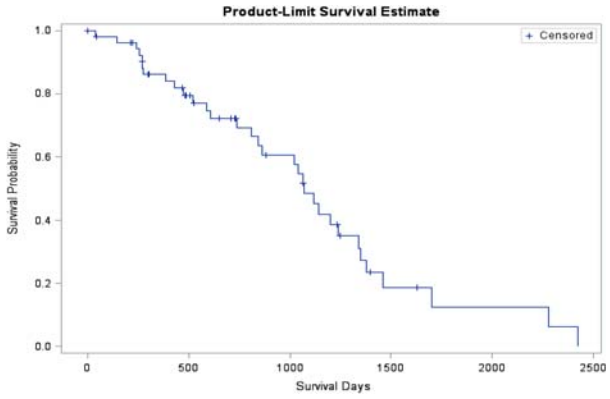

FIGURE 3 Kaplan-Meier curve depicting survival of cats that were treated with SRT for a pituitary tumor causing acromegaly. Cats censored from the analysis are depicted with a crosshair

exogenous insulin requirements in 55%-92% of treated patients compared with 95% reported here.[6–9] The information from our study is comparable to results of stereotactic radiosurgery for treatment of functional pituitary adenomas in humans.[24] In human patients, a single fraction of 35Gy resulted in shorter time to and higher rate of endocrine remission without an increase in radiation-induced adverse effects when compared to conventionally fractionated radiation.[24] In the previously described study, 70% of patients experienced endocrine remission with a median time of 17.7 months. Considering the improvement noted in our study and the reported human literature, evidence supports a higher dose per fraction to gain control of this disease.

The dose-limiting normal tissue in our study was the normal brain. The goal of the Radiation Oncology Service at CSU is to keep 1.1 cc of normal brain under 24Gy for 3 fractions and under 27Gy for 4 fractions.[17] Assuring that the brain was within tolerance constraints took precedence over total radiation dosage administered to the tumor volumes. Late radiation effects to the brain are irreversible and frequently

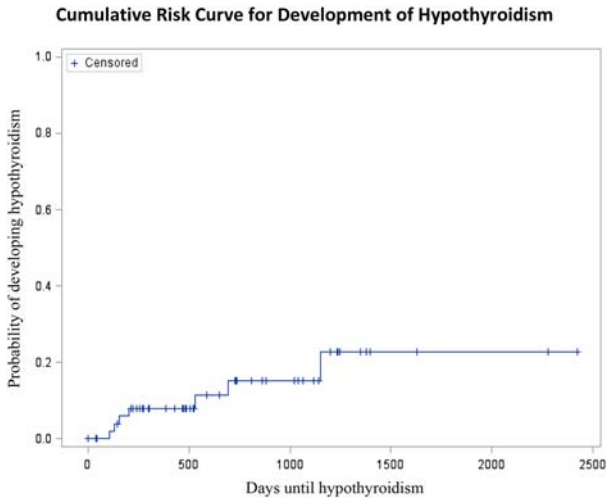

FIGURE 4 Cumulative risk curve. The x-axis shows days until diagnosis of hypothyroidism and the y-axis is the probability of developing hypothyroidism

incompatible with good quality of life. Neurologic changes were noted in 7 patients at the time of euthanasia. No advanced imaging was performed on these patients to confirm tumor recurrence or suggest possible late radiation effects. Necropsy in 2 cases did not show changes in the brain outside of the pituitary gland.

The other OAR considered in our study included the optic chiasm. Although the optic chiasm was consistently contoured in all patients treated, radiation dose to the tumor was not jeopardized to spare this tissue. Given the proximity of the optic chiasm to the sella turcica, in most cats the OAR dose was above the given constraint of 21Gy.[25] Owners were consistently warned about the potential of vision loss after radiation therapy given full dose to the optic chiasm in most patients. Despite this, only 1 patient reportedly lost vision in both eyes without development of cataracts 2.5 years after treatment. This finding was suspected to be a late radiation effect given that this patient went into diabetic remission approximately 22 months after treatment and the remission was sustained until euthanasia for a suspected nasal tumor. There was no evidence of tumor recurrence at the time of vision loss, suggesting that the vision loss could have been caused by radiation-induced optic neuropathy.

Our study supports a male sex predilection for the development of acromegaly in cats with approximately 80% of patients being male. Although 43 patients (81%) were listed as domestic shorthairs, this designation is a default at our institution for mixed breed cats with short hair coats. Given this information, no breed predilection was identified in our study.

One cat developed generalized osteopenia based on interpretation of thoracic radiographs 2.5 years after SRT. Thoracic radiographs disclosed healed vertebral and sternebrae fractures as well as multiple healed rib fractures. Laboratory testing including serum vitamin D, calcium, and parathyroid hormone concentrations was performed at Michigan State University and returned without abnormalities. The osteopenia was thought to be associated with the acromegaly. At the time of the radiography, the cat was suspected to have tumor progression, had come out of diabetic remission, and was exhibiting signs of polyuria, polydipsia, and polyphagia. This patient received SRT a second time, but was treated outside the time period to be included in the statistical analysis for our study. The pathogenesis of osteopenia in acromegaly is multifactorial, but is believed to be a result of GH hypersecretion causing high bone turnover, deterioration of bone microarchitecture, and high risk of vertebral fractures.[26] Although bone abnormalities have been noted in human patients with acromegaly, ours is the first study to report the development of acromegalic osteopathy in cats.

One cat underwent 2 treatments with SRT 39 months apart with the first protocol being 24Gy total over 3 fractions of 8Gy and the second being 17Gy total in a single fraction. Three months before presentation for the second treatment, the insulin requirements increased dramatically (0.7 IU q12h to 6.5 IU q12h). During this 3-month period, abnormal limb thickening and stridor also were reported. Anisocoria was noted for at least 8 months and confirmed on physical examination before radiation. The size of the GTV on the first treatment was 0.16 cc and 0.04 cc on the second. Stereotactic radiation therapy was

administered and this patient had a favorable response after both the first and second treatment with the insulin dose being decreased by 92% and 85%, respectively. This patient was well regulated with its insulin for 13 months after the second treatment until euthanasia was elected because of progression of CKD, HCM, and small cell gastrointestinal lymphoma.

The single patient that received a total of 18Gy in 3 fractions of 6 Gy initially was scheduled for 4 fractions, but during pre-anesthetic laboratory testing and physical examination, it was determined the cat was suffering an acute exacerbation of its previously diagnosed CKD, and the patient was hospitalized before anesthesia. After supportive care, the patient's renal test results, attitude and appetite improved. By the end of the third fraction, the cat developed bilateral mydriasis and weak pupillary light reflexes, but maintained its vision. These changes were attributed to edema of the brain within the radiation field and the final fraction was not given. The patient was treated with a tapering dose of prednisolone over the course of 2 weeks, and the clinical signs resolved. Despite the complications faced during the treatment protocol, this cat went on to have a 35% reduction in insulin requirements after 4 months. This patient lived for 1410 days after SRT.

Seven of 50 cats (14%) developed hypothyroidism after SRT. Clinical signs of the disease were mild and included hair coat changes, weight gain, and lethargy. Hypothyroidism required supplementation in all 7 patients. Spontaneous hypothyroidism in adult cats is very rare and its incidence in the feline population is unknown. The development of hypothyroidism in cats is more commonly iatrogenic as a result of the treatment of hyperthyroidism.[27–29] Development of hypothyroidism in our patients is believed to be related to therapy. Central hypothyroidism is caused by direct damage to the hypothalamic-pituitary axis and is characterized by decreased serum free T4 concentrations with normal or decreased TSH concentrations.[30] Radiation-induced hypothyroidism after pituitary tumor radiotherapy has not been reported previously in the veterinary literature. Reports in human medicine have evaluated thyroid function for patients receiving only conventionally fractionated radiotherapy, surgery followed by postoperative radiation therapy, and SRT to the pituitary gland and pharyngeal region.[30] These reports suggest a lower incidence of pituitary dysfunction in patients causing central endocrinopathies if they are treated with SRT.[30] Hormone function was disrupted in as few as 17% of patients treated with SRT when compared to 72–100% of patients treated with a fractionated protocol.[30,31] In the previously described study, it also was determined that the pituitary gland is capable of secreting sufficient TSH to maintain euthyroidism, but its concentration is lower than in normal non-irradiated individuals.[32] Although these individuals continue to have low-normal concentrations of TSH, l-thyroxine supplementation often is required for long term maintenance of euthyroidism.[30] Ours is the first study to report development of hypothyroidism in cats after pituitary irradiation. It is not clear whether development of hypothyroidism is a consequence of radiation-induced fibrosis of the pituitary gland or destruction of thyrotrophin-releasing hormone producing cells.

Several causes of death were identified in this population. Seven cats died or were euthanized because of neurologic disease. Of those cats, 1 had neurologic signs before radiation treatment with no improvement after SRT. It is unclear if the remaining 6 cats had progression of the pituitary tumor or if adverse effects in the normal brain caused the changes in neurologic status. The cats lost to CKD or HCM were diagnosed with these diseases before treatment of their pituitary tumors. This information suggests that although SRT may improve the insulin resistance associated with uncontrolled DM, it does not change the course of other diseases caused by acromegaly.

The primary limitations of our study are its retrospective nature and lack of consistent follow-up by the treating institution. Referring veterinarian records were reviewed for changes in physical examination findings and laboratory data after radiation, but the lack of consistency among clinicians was an important limitation. Necropsy results were available for 2 of the treated cats and provided encouraging information for successful treatment of the tumor, but the data would be stronger if more of the study population had undergone necropsy.

In conclusion, SRT is a safe and effective treatment for pituitary tumors causing acromegaly in cats. Acute radiation adverse effects are minimal in the treated population, mild in severity, limited in duration, and responsive to therapy. Late radiation effects include rare optic chiasm neuropathy, hypothyroidism, and potential for late stage neurologic progression. Based on the outcomes in our study, SRT should be considered for cats diagnosed with acromegaly.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

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REFERENCES

[1] Berg RIM, Nelson RW, Feldman EC, Kass PH, Pollard R, Refsal KR. Serum Insulin-Like Growth Factor-I Concentration in Cats with Diabetes Mellitus and Acromegaly. *J Vet Intern Med.* 2007;21:892–898.

[2] Feldman E, Nelson R. Acromegaly and hyperadrenocorticism in cats: a clinical perspective. *J Feline Med Surg.* 2000;2:153–158.

[3] Peterson M, Taylor RS, Greco D, et al. Acromegaly in 14 Cats. *J Vet Intern Med.* 1990;4:192–201.

[4] Gostelow R, Scudder C, Keyte S, et al. Pasireotide long-acting release treatment for diabetic cats with underlying hypersomatotropism. *J Vet Intern Med*. 2017;31:355–364.

[5] Elliott DA, Feldman EC, Koblik PD, et al. Prevalence of pituitary tumors among diabetic cats with insulin resistance. *J Am Vet Med Assoc*. 2000;216:1765–1768.

[6] Brearley MJ, Polton GA, Littler RM, Niessen SJ. Coarse fractionated radiation therapy for pituitary tumours in cats: a retrospective study of 12 cases. *Vet Comp Oncol*. 2006;4:209–217.

[7] Dunning MD, Lowrie CS, Bexfield NH, Dobson JM, Herrtage ME. Exogenous insulin treatment after hypofractionated radiotherapy in cats with diabetes mellitus and acromegaly. *J Vet Intern Med*. 2009; 23:243–249.

[8] Mayer M, Greco D, LaRue S. Outcomes of pituitary tumor irradiation in cats. *J Vet Intern Med*. 2006;20:1151–1154.

[9] Sellon RK, Fidel J, Houston R, Gavin PR. Linear-accelerator-based modified radiosurgical treatment of pituitary tumors in cats: 11 cases (1997–2008). *J Vet Intern Med*. 2009;23:1038–1044.

[10] Meij B, Auriemma E, Grinwis G, Buijtels JJ, Kooistra HS. Successful treatment of acromegaly in a diabetic cat with transsphenoidal hypophysectomy. *J Feline Med Surg*. 2010;12:406–410.

[11] Blois SL, Holmberg DL. Cryohypophysectomy used in the treatment of a case of feline acromegaly. *J Small Anim Pract*. 2008;49:596–600.

[12] Kaser-Hotz B, Rohrer CR, Stankeova S, Wergin M, Fidel J, Reusch C. Radiotherapy of pituitary tumors in five cats. *J Small Anim Pract*. 2002;43:303–307.

[13] Scudder CJ, Gostelow R, Forcada Y, Schmid HA, Church D, Niessen SJ. Pasireotide for the medical management of feline hypersomatotropism. *J Vet Intern Med*. 2015;29:1074–1080.

[14] Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J Clin Oncol*. 2014;32:2847–2854.

[15] Bloomfield R. Stereotactic radiation therapy in veterinary medicine. *Can Vet J*. 2015;56:95–97.

[16] Swift KE, McGrath S, Nolan MW, et al. Clinical and imaging findings, treatments, and outcomes in 27 dogs with imaging diagnosed trigeminal nerve sheath tumors: a multi-center study. *Vet Radiol Ultrasound*. 2017;58:679–689.

[17] Griffin LR, Nolan MW, Selmic LE, Randall E, Custis J, LaRue S. Stereotactic radiation therapy for treatment of canine intracranial meningiomas. *Vet Comp Oncol*. 2016;14:e158–e170.

[18] Dolera M, Malfassi L, Pavesi S, et al. Volumetric-modulated arc stereotactic radiotherapy for canine adrenocortical tumors with vascular invasion. *J Small Anim Pract*. 2016;57:710–717.

[19] Gieger TL, Nolan MW. Linac-based stereotactic radiation therapy for canine non-lymphomatous nasal tumors: 29 cases (2013–2016). *Vet Comp Oncol*. 2018;16:E68–E68.

[20] Swift KE, LaRue SM. Outcome of 9 dogs treated with stereotactic radiation therapy for primary or metastatic vertebral osteosarcoma. *Vet Comp Oncol*. 2017;2017:1–7.

[21] Leksell L. Stereotactic radiosurgery. *J Neurol Neurosurg Psychiatry*. 1983;46:797–803.

[22] Harmon J, Ufflen DV, Larue S. Assessment of a radiotherapy patient cranial immobilization device using daily on-board kilovoltage imaging. *Vet Radiol Ultrasound*. 2009;50:230–234.

[23] Paddick I. A simple scoring ratio to index the conformity of radio surgical treatment plans. Technical note. *J Neurosurg*. 2000;93: 219–222.

[24] Grant RA, Whicker M, Lleva R, Knisely JP, Inzucchi SE, Chiang VL. Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report. *World Neurosurg*. 2014;82:195–201.

[25] Adler JR, Gibbs IC, Puataweepong P, Chang SD. Visual field preservation after multisession CyberKnife radiosurgery for perioptic lesions. *Neurosurgery*. 2006;59:244–254.

[26] Mazziotti G, Maffezzoni F, Frara S, Giustina A. Acromegalic osteopathy. *Pituitary*. 2017;20:63–69.

[27] Rand JS, Levine J, Best SJ, Parker W. Spontaneous adult-onset hypothyroidism in a cat. *J Vet Intern Med*. 1993;7:272–276.

[28] Blois SL, Abrams-Ogg AC, Mitchell C, et al. Use of thyroid scintigraphy and pituitary immunohistochemistry in the diagnosis of spontaneous hypothyroidism in a mature cat. *J Feline Med Surg*. 2010;12: 156–160.

[29] Galgano M, Spalla I, Callegari C, et al. Primary hypothyroidism and thyroid goiter in an adult cat. *J Vet Intern Med*. 2014;28:682–686.

[30] Jereczek-Fossa BA, Alterio D, Jassem J, Gibelli B, Tradati N, Orecchia R. Radiotherapy-induced thyroid disorders. *Cancer Treat Rev*. 2004;30:369–384.

[31] Schulz-Ertner D, Frank C, Herfarth KK, Rhein B, Wannenmacher M, Debus J. Fractionated stereotactic radiotherapy for craniopharyngiomas. *Int J Radiat Oncol Biol Phys*. 2002;54:1114–1120.

[32] Lamberg B-A, Kivikangas V, Vartiainen J, Raitta C, Pelkonen R. Conventional pituitary irradiation in acromegaly. Effect on growth hormone and TSH secretion. *Acta Endocrinol*. 1976;82:267–281.

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