Title

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Journal

Veterinary radiology & ultrasound : the official journal of the American College of Veterinary Radiology and the International Veterinary Radiology Association, 60(2)

ISSN

1058-8183

Authors

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Publication Date

2019-03-01

DOI

10.1111/vru.12708

Peer reviewed

Title:

Long-term Survival With Stereotactic Radiotherapy for Imaging-Diagnosed Pituitary Tumors in Dogs

Authors:

Katherine S. Hansen[1], Allison L. Zwingenberger[1], Alain P. Théon[1], Michael S. Kent[1]

[1]Department of Surgical and Radiological Sciences, UC Davis School of Veterinary Medicine, Davis, CA, USA

Corresponding author:

Katherine S. Hansen; One Shields Avenue, Davis, CA 95616; kshansen@ucdavis.edu

Key Words:

SRS, photon therapy, stereotaxis, Cushing's disease, hyperadrenocorticism

Running head:

Pituitary Stereotactic Radiotherapy

Funding Sources:

None

Previous presentations or abstracts:

None

Abstract:

Published results for stereotactic radiotherapy (SRT) of canine pituitary tumors are limited. In this UC Davis Veterinary Medical Teaching Hospital retrospective observational study, 45 dogs with imaging-diagnosed pituitary tumors were identified from December 2009-2015. SRT was delivered in one 15 Gray (Gy) fraction or in three 8 Gy fractions. At analysis 41 dogs were deceased. Four were alive and censored from all survival analyses; one dog received 8 Gy every other day and was removed from protocol analyses. The median overall survival (MS) from first treatment was 311 days (d) (95% CI 226-410 d [range 1-2134 d]. Thirty-two dogs received 15 Gy (MS 311 d; 95% CI [range 221-427 d]), and 12 received 24 Gy on three consecutive days (MS 245 d, 95% CI [range 2-626 d]). Twenty-nine dogs had hyperadrenocorticism (MS 245 d), while 16 had non-functional masses (MS 626 d). Clinical improvement was reported in 37/45 cases. Presumptive signs of acute adverse effects within four months of SRT were noted in 10/45, and most had improvement spontaneously or with steroids. Late effects versus tumor progression were not discernable, but post-treatment blindness (2), hypernatremia (2), and progressive neurological signs (31) were reported. There was no statistical difference in MS for different protocols. Patients with non-functional masses had longer MS than those with hyperadrenocorticism ($p = 0.0003$). This study provides preliminary evidence that pituitary tumor SRT provides a clinical benefit. When compared to historical studies using definitive radiation, the survival outcomes for SRT appears shorter, especially in cases with hyperadrenocorticism.

Introduction:

Clinically, dogs with pituitary masses may present with endocrine disease and/or intracranial neurological signs. The most common neurological signs are behavior changes, obtundation, aggressiveness, anisocoria, loss of vision, and seizures.[10] Both definitive and palliative radiation therapy have been used in dogs with pituitary masses, with a reported 2-year survival rate of 87% with definitive radiation.[6-14] These brain radiation therapy protocols involve either weeks of treatments and/or large regions of normal brain receiving high radiation dose, total doses of 45-54 Gray (Gy) with 2.5-3 Gy given in multiple fractions, or palliative protocols with weekly doses of 5-9 Gy.[1-5] Although chemotherapy has been used with some intracranial tumors, a survival benefit has not clearly been demonstrated, including for pituitary masses.[15, 16] The potential benefits of SRT for a variety of intracranial tumor types in dogs have previously been described, but pituitary tumors have accounted for very few SRT patients in the literature.[16, 19-21, 23-25]

Stereotactic radiotherapy (SRT) utilizes high radiation doses in 1-5 fractions, and normal tissues are typically spared by avoidance rather than fractionation.[17, 18] SRT delivers an ablative dose, and this type of administration is achievable by use of combined immobilization, image-guidance, and advanced computer radiation planning systems that create the highly conformal dose. [17, 18] Intracranial tumors are ideal candidates for SRT because they are often small and well-defined malignancies on imaging, and steep dose gradients can be achieved to minimize the irradiated brain volume and allow for higher dose per fraction.[19] SRT can be delivered with a linear accelerator via a multi-leaf collimator (MLC) system, either with IMRT or 3D-conformal fields, or with a cone-based system for beam collimation.[20-22] There is one study of 51 dogs with various intracranial tumors that received SRT treatment. In this SRT study, four dogs had pituitary masses and received a median dose of 16.25 Gy (range 15 – 25 Gy), with a median

survival of 118 days.[23] SRT was also used in another study that included three dogs with pituitary masses; they received 24 Gy in three fractions of 8 Gy every other day, and they had survival times ranging from 255-342 days.[24]

The goal of this study was to assess survival in a larger group of dogs receiving SRT for suspected pituitary tumors with two different SRT protocols on two different radiotherapy platforms. A secondary goal was to assess what clinical and radiation variables correlate with survival in this study group.

Methods:

This study was a retrospective observational study of medical records for dogs treated at the UC Davis William R. Pritchard Veterinary Medical Teaching Hospital between December 2009 and December 2015. Animals were cared for in accordance with hospital policies, and because this was a retrospective study, informed consent for patients in the study was not obtained. Dogs were included that underwent a single course of SRT therapy for a suspected pituitary mass diagnosed on magnetic resonance imaging (MRI) or computed tomography (CT) using standardized CT acquisition techniques, and that also had follow-up information for survival analysis. For this study, patients were included that had pituitary masses 1 cm or longer in height, or that had clinical signs attributed to a prominent pituitary gland that was < 1 cm in height. Patient data were recorded for patient follow-up by the radiation clinicians on clinical duty, and included patients were identified by two clinical radiation oncologists (KH and MK). Because of the retrospective nature of this study, there was not a control for bias in the clinical information available.

Descriptive information, including age, weight, sex, and breed were recorded. Information regarding routine bloodwork, thoracic radiographs, abdominal ultrasound, cerebrospinal fluid analysis, endocrine testing, MRI and CT imaging, and clinical signs were collected for all patients. Patients were separated into three categories: 1) non-functional tumors (those having no clinical signs nor testing consistent with Cushing's disease), 2) functional tumors having Cushing's disease (having classic signs of Cushing's that included polyuria and polydipsia) or 3) functional tumors having atypical Cushing's disease (having an LDDS test consistent with Cushing's, but without classic signs of the disease). For cases with classic Cushing's signs, diagnostic testing and/or previous medical management was not an inclusion criterion. Radiation treatment parameters, follow-up visit information, and survival times were also recorded.

Initial diagnostic images were obtained from referring facilities using CT or MR imaging without standardized protocols. All cases had a simulation CT scan prior to SRT at UC Davis, which was acquired with a helical CT scanner (Prospeed General Electric Co., Milwaukee, WI or Lightspeed 16 General Electric Co., Milwaukee, WI). Patients were positioned as previously described with either a stereotactic target positioner box for the BrainLab (BrainLab AG, Feldkirchen, Germany) system or with three crosshairs drawn directly onto the positioning mask for the Eclipse system (Varian, Palo Alto, CA).[21, 26]

A non-contrast CT with 120 kV and 150 mA with 0.625-1 mm collimation was performed. Contrast-enhanced images with 1 mm collimation were acquired with iodinated contrast medium (Iopamidol, 370 mg I/ml, Bracco Diagnostics Inc., Princeton, NJ) at a dose of 740 mg I/kg. The scans encompassed the entire skull, and the field of view included the positioning frame for non-contrast images.

All CT images were imported into one of two treatment planning systems (cone-based planning = Iplan version 4.1, BrainLab, Munich, Germany; and 3D-conformal or IMRT planning = Eclipse v. 11, Palo Alto, CA) as previously described, and fused with MR images if available.[21, 26, 27] Relevant target volumes were contoured, including the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) by the attending radiation oncologist recommendations. The relevant organs at risk (OAR) were contoured, including the brain, brain minus PTV (region of brain not included in the PTV), brainstem, eyes, optic chiasm, and inner ears based on clinician preferences for plan optimization. Radiation plans were derived with a definitive intent for treatment. Treatment plans were evaluated based on dose-volume histogram (DVH) coverage of the PTV and dose to the normal organs at risk (OAR) based on radiation oncologist decisions. When possible, radiation oncologists attempted to have 90-95% of the PTV covered by the prescription dose while keeping dose to the adjacent OARs as low as reasonably achievable, but standardized OAR constraints were not in place. All plans were assessed by either film (FilmQA, Ashland, Covington, KY) and chamber dose measurement (A16 microchamber, Standard Imaging, Middleton, WI) as previously described, or with a QA system (Mapcheck, Sun Nuclear Corporation, Melbourne, FL) using standard quality assurance techniques, with acceptable gamma error analysis of 3% dose difference and 3 mm distance to agreement with at least 95% of measured points passing.[21]

For treatment setup with cone-based planning cases, two orthogonal-view digitally reconstructed radiographs (DRR) were created for each planned isocenter such that a double exposure digital port film (4 X 4 cm double exposed region overlying the open port film) around the treatment isocenter at 0^{o} (dorsal port) and 90^{o} (patient lateral port) could be utilized for image comparison on treatment days, and the target positioning box was used as previously described.[21] For 3D-

conformal/IMRT cases using the TrueBeam linear accelerator, cone beam CT (CBCT) scans were acquired on treatment days and matched digitally to the diagnostic CT images used for treatment planning to match the isocenters. The couch adjustments were automatically registered through the TrueBeam software, and couch shifts were made after clinical approval of the imaging match by the attending radiation oncologist. Once in the correct position, the dog was treated. All dogs were treated with 6 MV photons delivered by a linear accelerator (Clinac or Truebeam).

All dogs were placed on approximately 0.5 mg/kg per os daily prednisone prior to or on the first treatment day. The dogs had recheck visits two weeks after radiation, then phone calls or recheck visits were performed every two weeks thereafter, with 20-50% reductions in prednisone dose at each contact until the dogs were no longer on prednisone, as long as the dogs were doing well at home. The dogs were followed either with phone calls or recheck visits until death or until last contact prior to publication submission. Information including side effects seen within 16 weeks after radiation, which were considered acute side effects, and also long-term clinical signs, possible long-term adverse events, and survival were noted.

Tumor height and brain height were measured on the post-contrast CT image slice on which the tumor was the largest using the measuring tool.[10] The various volumes used in the study for tumor and brain were measured using the volume measuring tool in the planning systems.[28] The GTV: brain volume and PTV: brain volume were then calculated.

All graphs and statistical analyses were made by use of commercially available statistics programs (STATA 10.0, Stata Corporation, College Station, TX; Microsoft Excel 2008 for Mac, Version 12.1, Microsoft Corporation, Redmond, WA) by MK who obtained an MAS in Clinical Research with training in statistical analysis. Descriptive statistics were done and are reported as

medians with ranges or means with standard deviations. For continuous variables, normality was checked using a Shapiro Wilks W test. To evaluate if there were differences in age, weight, GTV, PTV, brain volume, GTV: brain volume, and the PTV: brain volume between the two treatment protocols, a t-test was used for normally distributed variables, and a Wilcoxin rank-sum test was used for non-normally distributed variables. To evaluate if there were differences between the treatment protocol groups for categorical variables, a chi-squared test or Fisher's exact test was used. To see if the contoured GTV (tumor volume) was correlated with either the diagnosis of Cushing's disease or with the presence of neurological signs at diagnosis, logistic regression was used.

The Kaplan-Meier method was used to estimate survival times. Survival time was defined as the difference between the first day of treatment and the date of death or date of last contact for those lost to follow-up or those dogs still alive at the time of analysis. For censoring, all deaths were considered events, with only those dogs lost to follow-up or alive at the time of analysis being censored. Analysis was done on an intent to treat basis, meaning if treatment was not completed, dogs were grouped into the protocol that they were intended to receive.

Categorical values evaluated for effect on survival included: radiation protocol used, whether or not dogs were diagnosed with Cushing's disease (including atypical cases), and whether or not they had any neurological signs. The single dog that received an every other day treatment was not included the survival analysis examining differences in treatment protocols. Continuous variables evaluated for effect on survival included: tumor baseline height, tumor: brain height ratio, tumor baseline height for each fractionation scheme, tumor: brain volume ratio per fractionation scheme, GTV volume treated, GTV volume treated per fractionation scheme, GTV: brain volume ratio, PTV volume treated, PTV volume per fractionation scheme, PTV: brain

volume ratio and number of clinical neurological signs present at diagnosis. The following nine clinical signs were considered neurological signs, collected from the record at the time of treatment, and counted: pacing (or circling or head-pressing); “spacing out” (or staring at walls); behavior change; apparent weakness; blindness; obtundation; seizures; ataxia; and tremors. The following signs were also collected from the record at the time of treatment: Cushing’s disease, central diabetes insipidus, lethargy, weight loss, and poor appetite. To look for estimated differences in survival between categorical variables, a log rank test was used. To look for differences in survival times for continuous variables, a Cox regression with a Breslow method for ties was done. A p value <0.05 was considered statistically significant.

Results:

Forty-five dogs undergoing SRT therapy for suspected pituitary tumors met the inclusion criteria. No patients received a definitive, standardly-fractionated course of radiation for suspected pituitary tumors during the same time period at this institution. Thirty-three dogs were purebred, including Australian shepherd (3), Labrador retriever (3), golden retriever (3), boxer (3), pitbull terrier (3), English bulldog (2), French bulldog (2), Pomeranian (2), Boston terrier (2), and one each of the following: Brittany spaniel, silky terrier, poodle, toy poodle, Shetland sheepdog, shih tzu, rough coated collie, American foxhound, miniature pinscher, and papillon. Twelve dogs were of mixed breed. A total of 18 dogs were female spayed ((Cushing’s (15), non-functional (3); 3-fraction protocol (4), 1-fraction protocol (14); 3D-conformal/IMRT plan (4), cone-based plan (14)). There was one female intact dog that was Cushingoid and treated with a single fraction using cone-based planning. A total of 22 dogs were male neutered ((Cushing’s (12), non-functional (10); 3 fraction (8), 1 fraction (14); conformal/IMRT plan (8), cone-based plan (14)).

There were four male intact dogs ((Cushing's (1), non-functional (3); 3 fraction (2), 1 fraction (2); 3D-conformal/IMRT plan (2), cone-based plan (2)). The other patient population description details are shown in Table 1. There was no statistical difference in age or weight based on fractionation scheme (two sample t-test, $p = 0.16$ for age; two-sample Wilcoxon rank-sum, $p = 0.94$ for weight), and there was one dog without a recorded weight and one without a recorded age. No tumor biopsies were performed.

Cerebrospinal fluid analyses were available for four dogs, with two normal CSF readings and two with mild increase in protein and increased inflammatory cells on CSF analyses. Abdominal ultrasound was performed within six months of radiation in 32/45 dogs with the following pertinent results: bilateral adrenomegaly (17, all Cushingoid), hyperechoic liver (10), hepatomegaly (9), and single enlarged adrenal gland (1). Thoracic radiographs were available in 27/45 and did not reveal abnormalities significant for case management except for one case with cardiomegaly. Routine bloodwork was reported in 41/45 cases, with abnormalities consistent with Cushing's in those cases and otherwise unremarkable changes.

A total of 27 cases were diagnosed with classic Cushing's and two cases were diagnosed with atypical Cushing's. LDDS or ACTH stimulation were positive in 26/29 cases where Cushing's was suspected, including 24 classic Cushing's cases and both atypical cases. The remaining three were presumptively diagnosed based on a combination endogenous ACTH values, urine cortisol creatinine ratio, ultrasound, and clinical signs. One atypical Cushing's cases had thin skin, muscular atrophy, and an LDDS test consistent with Cushing's, while the other was dull with an LDDS test consistent with Cushing's, but no other classic signs of the disease were present. Of the dogs with Cushing's disease, eight did not receive any medical therapy prior to radiation, and

21 did receive medical therapy with Trilostane or Lysodren prior to radiation (good medical control (4), poor medical control (4), unreported medical control (13)).

Twenty-four dogs had previously been diagnosed with other disease, with relevant other diagnoses including central diabetes insipidus (4 dogs, all also diagnosed with Cushing's), Addison's disease related to treatment for Cushing's, and cerebral microhemorrhages in a Cushingoid case.

Twelve dogs had no neurological abnormalities at presentation (10 Cushingoid, one worked up for poor appetite and energy, and one incidental pituitary mass on imaging; 2 non-functional tumors), and 33 dogs had neurological signs related to their tumors (19 Cushingoid, 14 non-functional tumors), including behavior change, pacing, circling or head pressing, tremors, obtundation, ataxia, apparent weakness, spacing out/staring at walls, seizures, and blindness. The presence of lethargy, poor appetite, and weight loss were also common in this study population, and the frequency of these signs was not different between treatment groups. Of the Cushing's cases, one atypical Cushing's patient had neurological signs and 18 typical Cushing's cases had neurological signs. Of the cases with non-functioning tumors, only two did not have neurological signs. The size of the tumor (GTV) at presentation was not correlated with a dog being diagnosed with Cushing's disease (OR 0.89, 95% CI 0.58 – 1.34, p= 0.57), but it was correlated with a dog presenting with a neurological sign (OR 2.52, 95% CI 1.21 – 5.28, p= 0.003).

All dogs had a CT scan prior to treatment with some dogs also receiving an MRI at the time of diagnosis. All dogs began treatment within 14 days of the radiation-planning CT scan (range 1-14 days) and cases that were treated more than one week after CT imaging were delayed so based on owner schedule limitations. Forty-three dogs began treatment within five weeks of diagnosis by MRI or CT imaging. Two dogs began treatment within 6 months and 1 year of

imaging diagnosis, respectively, after repeat imaging showing progression of the suspected pituitary mass. One dog with a delay from imaging to treatment had an incidentally found pituitary mass with subsequent neurological signs and tumor progression, while the other had Cushing's disease without neurological signs, but was poorly controlled on medications with progression.

The GTV included all visible tumor or suspect tumor-related contrast enhancement on CT and MRI, and the CTV was defined as the GTV without any additional margin. The PTV was created by adding a 1-2 mm margin around the CTV for cone-based cases and 0 mm margin for 3D-conformal/IMRT cases, primarily due to differences in portal imaging on the linear accelerator used for the cone-based cases vs. CBCT imaging used on 3D-conformal/IMRT cases (Figure 1A-B). [26, 29, 30] Peritumoral edema was not included in the target volume for any case.

Patients were treated with the cone-based system until October 2013 and were treated with the 3D-conformal/IMRT system after that time. Additionally, patients were treated with a single 15 Gy fraction on the cone-based system with a Clinac 2100C, and with 8 Gy X 3 fractions with the 3D-conformal/IMRT and Truebeam system (Clinac 2100C or TrueBeam, Varian Medical Systems, Palo Alto, CA). For cone-based treatment plans, a radiation plan was created using one or more isocenters with varying numbers and lengths of arcs using a cone-based system. When more than one isocenter or more than one arc were used, the isocenters and arcs were differently weighted to optimize the radiation dose distribution in the target volume and minimize radiation exposure to OARs. For 3D-conformal/IMRT treatment plans, a radiation plan was created using 11-12 fields with a single isocenter. Either intensity modulated radiotherapy (IMRT) or multiple, static, 3D-conformal fields were used. 3D-conformal/IMRT calculations were performed with the anisotropic analytical algorithm (0.25 cm calculation grid), and cone-based calculations were

performed using the software's pencil beam calculation (dose resolution 0.2 cm, arc calculation step 10°). Tissue heterogeneity correction was used for both types of planning, and bolus was not used in any case (Figure 2A-B).

In total, 31 dogs were treated with a Clinac 2100C (Varian, Palo Alto, CA) with a tertiary small field collimator cone set (StereoPlan, Mill Creek, WA) and 14 dogs were treated with a TrueBeam Linac (Varian, Palo Alto, CA) with high-definition MLC (1 fraction: Cushing's n = 20, non-functional masses n = 11; 3 fraction: Cushing's n = 9, non-functional masses n = 3). The treatment and brain volumes are described in Table 2. Those cases receiving one fraction had a mean GTV = 2.3 cm^3 (standard deviation (SD) 1.26 cm^3) and mean PTV = 4.8 cm^3 (SD 2.07 cm^3). Cases receiving three fractions had a mean GTV = 3.2 cm^3 (standard deviation (SD) 1.99 cm^3) and mean PTV = 3.2 cm^3 (SD 1.99 cm^3).

Those cases receiving one fraction had a mean brain volume = 79.7 cm^3 (SD 16.05 cm^3), GTV/Brain volume ratio = 0.03 (SD 0.02), and PTV/Brain volume ratio = 0.06 (SD 0.03). Cases receiving three fraction had a mean brain volume = 84.4 cm^3 (SD 21.6 cm^3), GTV/Brain volume ratio = 0.04 (SD 0.02), and PTV/Brain volume ratio = 0.04 (SD 0.03).

Treatment plans used 1-2 isocenters and 2-4 arcs of radiation with the cone diameter ranging from 15-35 mm for cone-based cases. Two cases had noncoplanar arcs, the remainder used coplanar arcs, and all arcs had equal weighting except in five cases. For 3D-conformal/IMRT cases, 10 cases were treated with 11-12 field IMRT (sliding window technique), and five cases were treated with static, 3D-conformal fields.

The doses to the PTV are described in Table 3, with cone-based plans having a wider range for PTV doses (32-175% of prescription) compared to 3D-conformal/IMRT cases (77-144% of prescription). The following values were also available only for 3D-conformal/IMRT plans:

median D2 = 26.02 Gy (range 24.77-27.19 Gy), and median D98 = 23.51 Gy (range 22.99-23.78 Gy). The mean PTV dose was over 100% of prescription for all cases. PTV median and mode dose reporting is available through Eclipse, and those cases had a median dose ranging from 102.0%-108.4% and modal dose ranging from 102.1%-111.7%, which has been previously recommended for reporting in veterinary radiation manuscripts.[31] Plan normalization was based on limiting the dose to normal OARs, and most plans had at least 90-95% of the target volume receiving prescription dose.

Conformity (CI), gradient (GI), and heterogeneity (HI) indices are commonly used to describe SRT treatment plans. CI describes how the volume of an SRT plan conforms to the size and shape of the PTV, with values < 2 being recommended, and values closer to 1 being ideal.[32] GI describes how steep the dose gradient is outside of the PTV, with smaller values having steeper gradients.[33] HI describes the dose heterogeneity existing within the PTV, and can be calculated with the simple Radiation Therapy Oncology Group (RTOG) calculation, or with a more complex calculation based on the D98 and D2 (available for 3D-conformal/IMRT cases).[34] Table 4 outlines these values for the plans, and reveals that CI values for all plans were within guidelines, but 3D-conformal/IMRT plans had smaller mean and median CI values consistent with IMRT and 3D-conformal planning. RTOG HI values were also smaller for 3D-conformal/IMRT plans. In contrast, the median and mean GI values were smaller for cone-based plans, consistent with the sharp dose fall-off seen with cone-based planning. Tables 5a-d report the dose characteristics for the brain, inner ears, chiasm, and brainstem, which were contoured for a subset of cases.

Thirty-two dogs were treated with 15 Gy in one fraction, while twelve dogs received three fractions of 8 Gy on consecutive days, and one dog received 8 Gy X 3 on an every other day

basis. There were two treatment interruptions or deviations from protocol due to two patient deaths (one suspected anesthetic death and one suspected death due to pulmonary thromboembolism), and no other immediate adverse effects were noted.

All images acquired before and after treatment were reviewed by a single radiologist. The CT imaging characteristics were as follows: all masses were isoattenuating to hyperattenuating on noncontrast images and hyperattenuating on contrast-enhanced images. A total of 18 cases showed cystic structures, and nine cases showed mineralization. One case had imaging characteristics consistent with perilesional edema and one was suggestive of intratumoral hemorrhage.

Ten dogs had follow-up imaging approximately three months and six months after SRT treatment as part of another, previously published study.[35] All re-imaged dogs were treated with the single fraction protocol because the imaging grant was funded during the same time period as the single fraction cases. All dogs experienced a partial response based on RECIST criteria for tumor size reduction. Of the eight dogs that received a final CT 6 months after treatment; 7/8 had a further reduction in tumor size again consistent with a persistent partial response, and 1/8 had a marginal increase in tumor size still defined as a partial response compared to the pre-treatment images, or stable disease when compared to the 3 month CT. All dogs that were re-imaged also were reported to have clinical improvement with radiation (9/10 had neurological signs at diagnosis, the remaining case was Cushingoid). More detail on the imaging follow-up for this subset of cases has been previously published.[35]

A total of 41 dogs were deceased (follow-up period range 1-2134 days) and four were alive at the time of analysis at 819, 1423, 1859 & 2134 days. No dogs were lost to follow up, and only the four living dogs were censored from overall survival analysis. Of those still alive, three had no

neurological signs after treatment, and one had recrudescence of the same neurological signs seen prior to treatment that were being managed with prednisone. The median overall survival time was 311 days (95% CI 226-410 days; range 1-2134 days, Figure 3A-B). Thirty-two dogs received a single 15 Gy dose (MS 311 days; 95% CI 221-427 days), and 12 received 24 Gy divided on three consecutive days (MS 245 days, 95% CI 2-626 days). One dog received 24 Gy every other day and was not included in the protocol-specific survival analysis. Twenty-nine dogs had evidence of hyperadrenocorticism (median survival 245 days, 95% CI 194-336 days), while 16 had non-functional tumors (median survival 626 days, 95% CI 296 – upper limit not reached). Possible acute adverse effects within 12-16 weeks of SRT could not be completely ruled out for 10/45 cases, and most had improvement spontaneously or with steroids. Potential acute side effects included: acute worsening of neurological signs within three weeks of radiation (4), increased tremors (1), hypernatremia (1), blindness (1), increase in prednisone noted in record without reference to clinical signs (1), labored breathing without pneumonia (1), death during the radiation course (2). Subjective clinical improvement was reported by owners or clinicians after radiation in 37/45 cases (18 cases had owner-perceived and/or clinician-reported improvement by the 2-week recheck visit, the remainder took one month or more for a clinical benefit to be noted). Improvement in Cushing's signs or management was reported in nine cases after radiation, while 12 cases reported no improvement in Cushing's signs during the post-radiation period, and the remaining records did not have data reported on Cushing's control. In many cases with reported improvement in Cushing's signs, a timeline for improvement was not clearly defined in the record. Improvement in neurological signs were noted in the record at some point after radiation treatment for the 27/33 cases with pre-treatment neurological signs. However, details on concurrent prednisone administration and tapering were variable.

Five dogs were euthanized in part due to worsening hyperadrenocorticism signs despite medical and radiation treatment 124-582 days after treatment. Four of these dogs were treated with a single fraction using cone-based software, while one was treated with three fractions using 3D-conformal/IMRT. Twenty-three dogs were euthanized 104-1028 days after treatment, in part due to worsening neurological signs. Seventeen of these dogs were treated with a single fraction using cone-based software, while six were treated with three fractions using 3D-conformal/IMRT. Nine dogs were euthanized for unknown reasons, but were included as dead of disease in analysis. Two dogs were euthanized due to hypernatremia that occurred 109 days and 148 days after treatment, one treated with the single fraction protocol using cone-based planning, and one treated with three fractions of 8 Gy using 3D-conformal/IMRT. Both patients were euthanized within one month of developing hypernatremia that could not be medically controlled. The following dogs were euthanized due to other causes than intracranial symptoms: suspected thromboembolic event 39 days after treatment (1), nasal tumor with progressive epistaxis 108 days after treatment (1), death secondary to pulmonary metastatic disease secondary to osteosarcoma 1021 days after treatment (1), and pancreatitis 427 days after treatment (1).

Regarding potential late radiation side effects or tumor progression, two dogs developed blindness after radiation that did not have blindness prior to radiation. Additionally, 31 patients had progressive neurological signs reported at the time of death, while eight patients did not have enough information in the record to confirm neurological signs at death.

There were no statistically significant differences in survival for dogs with the following features: presenting with neurological signs (MS without neurological signs (n = 12) 227 days (95% CI 183 – 410 days), MS with neurological signs (n = 33) 336 days (95% CI 226-511

days), p = 0.16); 3 fraction (n = 14) vs. 1 fraction (n = 31) radiation protocol (p = 0.42) which also directly correlates with the radiotherapy unit utilized and treatment planning system used; tumor baseline height (HR = 0.58, p = 0.19); tumor/brain height ratio (HR = 0.08, p = 0.15); tumor baseline height per fractionation scheme (1 fraction: HR = 0.09, p = 0.26; 3 fraction: HR = 0.03, p = 0.35); tumor/brain volume ratio per fractionation scheme (1 fraction: HR = 1.6×10^{-12}, p = 0.05; 3 fraction: HR = 4.0 X 10-11, p = 0.14); GTV volume treated (p = 0.11); GTV volume treated per fractionation scheme (1 fraction: HR = 0.74, p = 0.09; 3 fraction: HR = 0.75, p = 0.10); PTV volume treated (HR = 0.91, p = 0.20); PTV volume treated per fractionation scheme (1 fraction: HR = 0.93, p = 0.52; 3 fraction: HR = 0.75, p = 0.10). There were three cases with what may be categorized as microtumors (tumors less then 1 cm in height), ranging from 0.5-0.9 cm tall. These cases were all Cushingoid and had survivals of 183 d, 189 d, and 431 d. There were statistically significant differences in survival for the following features as negative prognostic factors: increasing GTV : brain volume ratio (HR = 3.7×10^{-9}, p = 0.03), increasing PTV : brain volume ratio (HR = 2.4×10^{-6}, p = 0.04), Cushing's disease (Cushing's n = 29, non-functional tumor n = 16, p = 0.0003), and increasing number of clinical signs present at diagnosis (HR = 0.74, p = 0.005).

Discussion:

This study demonstrates that cone-based and MLC-based (either IMRT or 3D-conformal field) SRT are treatment options for suspected pituitary tumors in dogs with a median overall survival of 311 days. There were few potential acute adverse effects that were generally transient and/or responsive to steroid adjustment, and long-term or late effects may occur but are not well defined in this cohort.

Lesion characteristics in this study were consistent with the previously reported information on suspected pituitary tumors. However, it is not possible to conclude whether the dogs in this study had a particular subgroup of pituitary tumors such as adenomas vs. carcinomas, and necropsy was not available for most dogs. Given that biopsy access is difficult in this location, owners often decline biopsy.

Historically, 2-4 conformal fields were used for canine brain tumors treated with radiation with some cases receiving whole brain radiation and others receiving a 4 X 4 cm field for treatment.[3, 5] Larger PTV volumes are often employed when using limited field numbers and imaging capabilities. SRT limits normal tissue dose, in part by use of advanced on-board imaging and reliable positioning for patients, and also by use of advanced planning systems. [26, 27, 36-40] To the authors' knowledge, there are only two peer-reviewed veterinary studies that describe SRT for very few canine pituitary cases.[23, 24] In one study, four dogs received a median dose of 16.25 Gy and had a median survival of 118 days.[23] This small group of dogs had a shorter survival than is reported in the literature for definitive radiation of pituitary masses, which is similar to our findings. In the other study, three dogs received 24 Gy in three fractions and had survivals ranging from 255-342 days; however, only one of the three patients was reported to die of tumor-related causes, and that dog had clinical progression after 189 days.[23] In our study, there was no difference in outcome based on the 1-fraction vs. 3-fraction protocol. Although the use of Biological Equivalent Dose calculations for stereotactic radiation is controversial, the tumor BED for 24 Gy in three fractions (BED_{10} 43.2, BED_3 88) is higher than the BED for 15 Gy in a single fraction (BED_{10} 37.5, BED_3 90).[41] One might expect the more fractionated protocol to result in higher tumor cell kill, but we did not see a difference in our treatment groups strictly based on protocol. There was also a transition to the Eclipse planning system and the Truebeam

system with CBCT at the time of the protocol transition, which also may make any difference that was strictly due to treatment protocol less clear.

In the current study dog population, SRT appeared to offer an initial clinical benefit in most dogs (37/45 dogs); although, as seen in the small number of previously published cases, the SRT survivals may in fact be shorter than those seen with definitive radiation studies. Additionally, all dogs with demonstrated tumor reduction on repeat imaging had clinical improvement consistent with reduction in their tumor size (9/10 had neurological signs at diagnosis, the remaining case was Cushingoid).

Of the cases with neurological signs at the time of treatment, 27/33 reported neurological improvement by the owner or clinician at some point after starting radiation. However, because prednisone was administered at the same time, it is very difficult to assess how much radiation versus prednisone contributed to the clinical improvement. The records were not always clear as to when prednisone was stopped, making it further unclear which cases were more likely benefiting from radiation neurologically. A prospective, randomized study comparing SRT and definitive radiation would help elucidate the difference in outcomes.

There may be several reasons for the difference in outcomes between historical definitively treated cases and our current SRT cases. First, the method of calculating survival varies between publications; for example, a 2007 publication regarding definitive radiation in comparison to control patients calculated survival from imaging diagnosis until death.[10] Our study calculates from the first radiation treatment day until death, which may be a more conservative estimate of survival depending on the delay between imaging and treatment (up to 14 days in our study; not reported in the 2007 study). It is also possible that there is a case selection bias with SRT, and sicker patients may now be pursuing SRT than would otherwise pursue a radiation intervention

due to the shorter treatment course. One might expect to see this bias across all brain tumor types if it is the main cause of the difference; it is notable that excellent outcomes were seen with meningioma cases in a recent SRT study that compared favorably to past definitive radiation studies.[20] It is also possible that pituitary tumor cells may be more responsive to fractionated treatment or the higher total dose or BED achieved with fractionation. The PTV margin may not have been adequate for some cases, or the regions of lower dose in some cases may have resulted in inadequate dose to the tumor when compared to the large PTVs and more homogenous doses that may be achieved with larger fields and definitively fractionated treatment plans. It is also possible that there were differences in risks for the normal tissues and cell kill for the tumor with stereotactic protocols compared to definitive protocols that may have an effect on clinical signs and survival.

Additionally, given the apparent better outcomes with nonfunctional tumors, it is possible that the cells of functional tumors may be more sensitive to fractionation, which may be supported by the longer survivals seen in the non-functional tumors in our study (MS 626 days). Still, the survival for the non-functional tumors are shorter than those reported historically for more fractionated radiation.[2, 10] The non-functional tumors and Cushing's tumors did not have significantly different GTV values, which suggests that the difference is not simply due to Cushing's cases having larger tumors. In fact, cases without neurological signs had smaller tumors (mean GTV for non-neurological 1.6 cm^3 vs. neurological 2.8 cm^3, median GTV for non-neurological 1.5 cm^3 vs. neurological 2.7 cm^3) and the Cushing's tumors were statistically more often smaller, which is consistent with Cushing's tumors being detected earlier due to the clinical signs associated with hyperadrenocorticism. Ultimately, a prospective trial would be needed to

478determine if pituitary masses without Cushing's disease have superior outcomes, as retrospective
479studies can carry biases and control groups are needed to fully elucidate this question.
480Similar to a previous study, patients with smaller tumor: brain ratios, using the treated GTV and
481PTV as surrogates for tumor size, had better outcomes.[10] We used the tumor: brain ratio rather
482than strictly the tumor volume to better reflect the size of the tumor compared to the dog's total
483intracranial volume. However, it is important to note that the shape of the tumor, and whether it
484impacts regions of the brain dorsally or laterally, may also affect the degree of neurological signs
485(e.g., affecting the chiasm ventrally) even if the tumor is not particularly large. Owners might be
486advised that those cases with larger tumors may have shorter survival times with stereotactic
487treatment options. It will also be important to investigate at what size tumors might be poorer
488candidates for hypofractionated stereotactic treatment as opposed to definitive treatment in future
489studies.
490Additionally, our study suggests that a larger number of clinical neurological signs may be
491associated with a worse outcome. Previous studies have not consistently shown this finding, and
492it is possible that our population of owners and dogs that agreed to SRT treatment may be
493different from previous studies. Finally the impact of a cystic component may affect tumor
494biology and affect clinical signs beyond a simple mass effect as well.
495We noted that there was a difference in target dose variability between the IMRT or 3D-
496conformal plans versus the cone-based plans. This finding is expected because target dose
497variability is generally larger for cone-based planning.[42, 43] D2 and D98 values may better
498represent dose heterogeneity than point doses, but these values were only available for 3D-
499conformal/IMRT plans. As noted, the D2 and D98 values showed relatively low dose variability.
5003D-conformal/IMRT plans had smaller mean and median CI values consistent with IMRT

and 3D-conformal planning, while median and mean GI values were smaller for cone-based plans, consistent with the sharp dose fall-off seen with cone-based planning.

As noted there was not a statistical difference between cases treated with a particular linear accelerator, planning method or fractionation method.

Stereotactic methods have become a good alternative for human patients who are poor surgical candidates due to high control rates and relatively high rates of remission for Cushing's cases compared to definitive radiation, and with similar stereotactic fractionation schemes as in veterinary medicine.[44-46] It is interesting that the canine cases in our study appeared to have shorter survivals than with conventional fractionated radiation in the dog. It is important to note that direct comparisons to historical studies is challenging due to the small overall numbers of dogs receiving different treatments with different imaging and delivery equipment, and sometimes with different survival calculation methods. Additionally, when comparing human and veterinary literature, it is not clear whether a difference in biology between the two species, difference in sensitivity of tumor cells, or potentially the difference in delivery may partially contribute as some previous studies in humans have used gamma knife while IMRT is more commonly being implemented in veterinary cases. Additionally the response seen in humans may occur over a decade, which is a very different timeline when compared to the assessed time period for most veterinary studies. It is notable that previous human studies have shown benefits for both functional and non-functional pituitary tumors in terms of neurological improvement, yet the PDH control is still variable.[10] In our study, several cases did not have data reported on whether the Cushing's signs improved, while nine reported improvement after radiation and 12 did not have improvement. The exact timeline for improvement was not well documented in the records. Given that at least some of the cases were referred for radiation prior to attempting

medical treatment (8) or due to poor control (4), it is important to note at least 12/29 Cushing's cases did not report improvement in their signs, so potentially there were even more cases without improvement in Cushing's signs. Overall it is possible that some cases experienced improvement in their Cushing's management strictly from radiation, but the degree that radiation and medications contributed is not easily clarified in this population. Therefore, radiation may not be a reliably effective way to control clinical signs of Cushing's disease in functional tumors.[6, 13]

Interestingly, a small number of patients developed hypernatremia after treatment. These patients developed restlessness and decreased mentation related to the hypernatremia. It is possible that these patients develop hypernatremia related to lack of water intake, for example as with adipsic central diabetes insipidus.[47] These patients may also have damage to their hypothalamus from the tumor or radiation itself, resulting in damage to osmoreceptors.[48] It is possible that the radiation damage to the tumor, the tumor itself, or radiation damage to the normal tissue resulted in an altered osmostat, or set-point, in these cases resulting in elevated sodium values and consequential neurological deterioration. In contrast, hyponatremia is a noted complication of radiation in humans, but it is possible that the dogs in our study did not live long enough in many cases to experience this side effect.[44] There are only a small number of cases here, and thus broad conclusions cannot be made.

It is important to note that the expedient SRT protocols remain an attractive option for owners despite potential differences in pituitary case outcomes with definitive vs. SRT techniques. Additionally, a risk-benefit analysis also must be considered for the anesthetic risk of multiple fractions vs. only 1-3 fractions of treatment. There are an increasing number of veterinary centers for stereotactic radiation, but there are still very limited total locations for these treatments in the

United States, Canada, and Europe.[49] It is important to note that there are many 3D-conformal-capable machines available in veterinary medicine, and depending on imaging capabilities, positioning devices, physicist availability and machine tolerances, 3D-conformal planning can be a useful technique for SRT.[22]

Because SRT delivers high doses of radiation to the tumor, it is imperative to minimize the PTV required for treatment to reduce unnecessary dose to neighboring tissues. With the Clinac 2100C and MV imaging, we chose a PTV of 2 mm due to the minimal expected intrafraction motion of the cranial and intracranial structures with the BrainLab positioning system.[26] Target location is known with greater certainty using on-board CBCT imaging, so no PTV target expansion was used for the TrueBeam system given the well-delineated characteristics of pituitary masses on imaging.[50] Advanced imaging, along with positioning devices and advanced planning systems, are a critical part of reducing the PTV for SRT cases and minimizing errors in treatment.[27, 37, 51, 52] However, even with image guidance, narrow or no PTV expansion may lead to higher risk for geographic misses, especially for treatments with high dose gradients such as SRT.

The doses delivered to the normal tissues appeared to be acceptable in this population, albeit with limited follow-up information, with mean doses to the brain under 6 Gy and the brainstem under 2 Gy. The maximum point doses to these regions include regions of the PTV (brain minus PTV was only contoured in a few cases), and these regions could be at higher risk for necrosis, although necropsies were not available for patients to assess any pathological changes due to radiation.

Interestingly, the doses to the chiasm, which were reported for 13 cases, were notably high with a mean dose of 12.43 Gy in mostly single-fraction cases. Only one case that was blind prior to radiation had their chiasm contoured: a mean chiasm dose of 15.61 Gy and a maximum dose of

57016.32 Gy was delivered for this patient. Presumably the chiasm doses were similarly high in the
571cases without chiasm data available, because of the location of pituitary masses in relation to the
572chiasm. Only two patients were noted to be blind 4 months or more after SRT treatment that did
573not originally have any visual aberrations prior to radiation, and the chiasm was not contoured in
574these cases so no radiation dose information was reported. It is not clear whether tumor
575progression vs. radiation ultimately contributed to their vision loss. In humans, single fraction
576doses greater than 12 Gy result in vision loss risks, but we did not detect a high rate of vision
577loss in our patients.[53] Bilateral vision loss may be expected with high-dose chiasm irradiation as
578used here; however, partial vision field loss can instead occur[53] and was not assessed for in the
579present study. Limited follow-up, and the fact that the chiasm was contoured in only a subset of
580cases, also limits our conclusions on chiasm dose. Finally, it is difficult to fully define late
581radiation effects in this population; however new blindness (2), hypernatremia (2), and
582progressive neurological signs (31) could be attributed either to tumor progression or to late
583radiation effects.
584There are limitations to this study. There was no control group to indicate the course of disease in
585untreated dogs with pituitary tumors and similar neurological statuses. Additionally, lack of
586necropsy information on the dogs makes it difficult to fully assess whether tumor regrowth or
587late radiation side effects occurred, or a histological diagnosis as to which tumor type was being
588treated. It is possible that some tumors were carcinomas, meningiomas, or round cell tumors.
589Further, MR or CT imaging of all dogs at multiple time-points after receiving radiation would be
590ideal to fully assess the course of tumor response. Including dogs with both endocrine and non-
591endocrine disease also limits the study, as summarizing data from both groups may not reveal the
592true expected survival for either group. Additionally, endocrine disease is historically less

impacted by radiation than neurological disease.[10, 12] The severity of clinical signs was also not assessed in this study, and the severity of Cushing's signs or neurological signs may impact referral for treatment, owner desire to pursue treatment, and ultimately survival. Moreover, the use of different protocols, treatment planning approaches and delivery techniques limits the study as well. Finally, lack of statistical differences between some groups could be due to low power with this relatively small number of cases.

In conclusion, cone-based, IMRT-based, and 3D-conformal SRT planning appear to be treatment options for suspected pituitary tumor cases that result in clinical improvement, although short-term and late-term side effects cannot be ruled out in those that had acute signs and/or progressive neurological signs at the time of death. Further assessment of SRT techniques for intracranial tumors is warranted, and fractionation may need to be altered in order to achieve survival times seen with traditional fractionated radiotherapy techniques. The outcomes seen with non-functional tumors are superior to those seen with functional tumors in this study, although both groups have shorter survival times than those reported with traditional fractionated radiation.

List of Author Contributions:

Category 1

(a) Conception and Design: Katherine S. Hansen, Michael S. Kent

(b) Acquisition of Data: Katherine S. Hansen, Allison L. Zwingenberger, Alain P. Théon, Michael S. Kent

(c) Analysis and Interpretation of Data: Katherine S. Hansen, Allison L. Zwingenberger, Alain P. Théon, Michael S. Kent

Category 2

(a) Drafting the Article: Katherine S. Hansen, Allison L. Zwingenberger, Michael S. Kent

(b) Revising Article for Intellectual Content: Katherine S. Hansen, Allison L. Zwingenberger, Alain P. Théon, Michael S. Kent

Category 3

(a) Final Approval of the Completed Article: Katherine S. Hansen, Allison L. Zwingenberger, Alain P. Théon, Michael S. Kent

Acknowledgments:

The authors acknowledge Randall Holt, Earl A. Trestrail, Paul Primas, Brooke Jones, Randolph Gordon, Paul Magee, and Isabella Pfeiffer for their assistance in patient care and data acquisition.

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Table 1: Patient population description

		All dogs	Median age (years) Range [3.6-15.5]	Median weight (kg) Range [2.5-41]	Neurological signs at time of imaging[b]	
					Yes	No
All dogs		45	9.7	23.6	33	12
Tumor status	**Cushing's**	29	9.6	25.7	19	10
	Non-functional mass	16	10.4	21.6	14	2
Treatment scheme	**3 fraction**	14[a]	9.6	22.3	12	2
	1 fraction	31	9.7	24.1	21	10
Planning method	**3D Conformal/ IMRT**	14	9.6	22.3	12	2
	Cone Based	31	9.7	24.1	21	10

[a] One patient received 8 Gy X 3 doses every other day and was not included in protocol-specific survival analysis

[b] Neurological signs included behavior change (n= 13), pacing, circling or head pressing (n= 12), tremors (n= 9), obtundation (n= 7), ataxia (n= 7), apparent weakness (n= 4), spacing out/staring at walls (n= 4), seizures (n= 3), and blindness (n= 2)

822Table 2: Mean, median, and range volumes for brain and radiation targets.
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	3D ConformaI IMRT n =14 cm^3		Cone Based n = 31 cm^3		All Cases n = 45 cm^3		Cushing's[a] cm^3		Neurological Pre-SRT cm^3		
							Yes n= 29	No n = 16	Yes n= 33	No[a] n = 12	
	GTV[b]	PTV[c]	GTV	PTV	GTV	PTV	GTV	GTV	GTV	GTV	All Cases Brains
Mean	3.2	3.2	2.1	4.9	2.5	4.4	2.4	2.7	2.8	1.6	80.98
Median	3.1	3.1	2.1	4.7	2.3	4.2	2.0	2.7	2.7	1.5	81.64
Range	0.6-8.1	0.6-8.1	0.2-4.6	1.0-9.7	0.2-8.1	0.6-9.8	0.2-8.1	0.7-4.6	0.6-8.1	0.2-3.4	47.4-123.3

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68a Only two cases without neurological signs did not have Cushing's disease
69[b] Gross Target Volume (GTV)
70[c] Planning Target Volume (PTV)
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Table 3: Dose characteristics for all planning target volumes relative to prescribed dose.

	3D Conformal or IMRT					Cone Based			All Cases		
	Min[a]	Max[b]	Mean[c]	Median[d]	D98[f]	Min	Max	Mean	Min	Max	Mean
Overall Mean	0.83	1.09	1.05	1.05	1.08	0.98	0.68	1.21	1.12	0.75	1.17	1.10
Overall Median	0.90	1.09	1.05	1.05	1.08	0.98	0.72	1.16	1.10	0.77	1.13	1.06
Overall Range	0.77-0.95	1.04-1.14	1.02-1.08	1.02-1.08	1.03-1.13	0.96-0.99	0.32-0.88	1.06-1.76	1.03-1.35	0.31-0.95	1.04-1.76	1.02-1.35

[a] Minimum dose to the planning target volume (PTV) relative to prescribed dose
[b] Maximum dose to PTV relative to prescribed dose
[c] Mean dose to PTV relative to prescribed dose
[d] Median dose to PTV relative to prescribed dose, 3D Conformal/IMRT only
[e] D2 = dose to 2% of PTV (i.e., highest dose to PTV) relative to prescribed dose, 3D Conformal/IMRT only
[f] D98 = dose to 98% of PTV (i.e., lowest dose to PTV) relative to prescribed dose, 3D Conformal/IMRT only

Table 4: Conformity Index, Gradient Index, and Heterogeneity Index data for different planning systems.

	CI[a]			GI[b]			HI_{RTOG}[c]			HI[d]
	3D/ IMRT	**Cone Based**	**All Cases**	**3D/ IMRT**	**Cone Based**	**All Cases**	**3D/ IMRT**	**Cone Based**	**All Cases**	**3D/ IMRT**
Overall Mean	1.09	1.35	1.26	5.31	3.96	4.40	1.09	1.21	1.17	10.70
Overall Median	1.07	1.30	1.19	5.22	3.82	4.04	1.09	1.15	1.13	10.10
Overall Range	0.96-1.21	0.77-2.22	0.77-2.22	3.66-8.50	3.30-5.49	3.30-8.50	1.04-1.14	1.06-1.76	1.04-1.76	4.10-15.90

[a] Conformity Index
[b] Gradient Index
[c] RTOG Heterogeneity Index
[d] D2-D98 Heterogeneity Index – available for 3D Conformal/IMRT cases only

Table 5a: Dose characteristics for patient brain volumes: mean, median and range values for the minimum, maximum, mean and median organ doses.

	Brain									
	3D Conformal/IMRT n = 14 (Gy)				Cone Based n = 28 (Gy)			All Cases n = 42 (Gy)		
	Min[a]	Max[b]	Mean[c]	Median[d]	Min	Max	Mean	Min	Max	Mean
Overall Mean	0.11	26.13	5.52	3.16	0.13	18.31	4.16	0	20.91	4.61
Overall Median	0.12	26.09	5.59	2.75	0.15	17.45	3.86	0.14	19.01	4.15
Overall Range	0.05-0.17	24.91-27.34	3.26-8.62	0.62-7.32	0-0.27	15.85-26.26	1.55-7.3	0-0.27	15.85-27.34	1.55-8.62

a Minimum dose in Gy
b Maximum dose in Gy
c Mean dose in Gy
d Median dose in Gy (3D Conformal/IMRT cases only)

Table 5b: Dose characteristics for patient inner ear volumes: mean, median and range values for the minimum, maximum, mean and median organ doses.

	Inner Ears									
	3D Conformal/IMRT n = 14 (Gy)				Cone Based n = 26 (Gy)			All Cases n = 40 (Gy)		
	Min[a]	Max[b]	Mean[c]	Median[d]	Min	Max	Mean	Min	Max	Mean
Overall Mean	0.31	4.04	1.09	0.91	0.21	4.15	0.78	0.25	4.11	0.89
Overall Median	0.23	3.11	0.53	0.38	0.18	3.40	0.37	0.18	3.22	0.40
Overall Range	0.08-1.56	0.42-11.50	0.16-6.44	0.14-6.38	0.09-0.61	0.41-12.73	0.2-4.39	0.08-1.56	0.31-12.73	0.16-6.44

a Minimum dose in Gy
b Maximum dose in Gy
c Mean dose in Gy
d Median dose in Gy (3D Conformal/IMRT cases only)

Table 5c: Dose characteristics for patient chiasm volumes: mean, median and range values for the minimum, maximum, mean and median organ doses.

	Chiasm									
	3D Conformal/IMRT n = 1 (Gy)				Cone Based n = 12 (Gy)			All Cases n = 13 (Gy)		
	Min[a]	Max[b]	Mean[c]	Median[d]	Min	Max	Mean	Min	Max	Mean
Overall Mean	--	--	--	--	8.09	16.31	12.22	7.87	16.71	12.43
Overall Median	--	--	--	--	8.42	16.29	13.08	8.23	16.32	13.65
Overall Range	5.28	21.5	21.50	15.0	1.59-16.68	12.1-22.82	5.9-16.89	1.59-16.68	12.1-22.82	5.9-16.89

a Minimum dose in Gy
b Maximum dose in Gy
c Mean dose in Gy
d Median dose in Gy (3D Conformal/IMRT cases only)

Table 5d: Dose characteristics for patient brainstem volumes: mean, median and range values for the minimum, maximum, mean and median organ doses.

	Brainstem									
	3D Conformal/IMRT n = 4 (Gy)				Cone-Based n = 3 (Gy)			All Cases n = 7(Gy)		
	Min[a]	Max[b]	Mean[c]	Median[d]	Min	Max	Mean	Min	Max	Mean
Overall Mean	0.09	10.97	0.97	0.26	0.85	9.09	2.08	0.42	10.17	1.45
Overall Median	0.10	9.40	0.77	0.27	1.19	8.8	1.8	0.12	8.8	0.82
Overall Range	0.05-0.12	0.65-24.46	0.17-2.18	0.14-0.34	0.15-1.21	1.3-17.17	0.32-4.12	0.05-1.21	0.65-24.46	0.17-4.12

a Minimum dose in Gy
b Maximum dose in Gy
c Mean dose in Gy
d Median dose in Gy (3D Conformal/IMRT cases only)

Figures Legends:

Figure 1: Example of contouring for A, Cone-based vs. B, 3D conformal/IMRT plans. Gross Tumor Volume (solid arrow), Planning Target Volume (dashed arrow, expansion used only for cone-based cases).

Figure 2: Isodose distribution for the radiation plans. Isodose lines represent percentage of prescribed dose: 1: 30%, 2: 40%, 3: 80%, 4: 90%, 5: 95%, 6: 100%, 7: 107%. A, Cone-based plan, B, IMRT plan.

Figure 3: Kaplan Meier survival curves. A, overall survival for all cases, and B, survival for functional (n = 28, dashed line) vs. non-functional pituitary tumors (n = 12, solid line), Forty-five were treated with stereotactic radiotherapy, resulting in an overall median survival of 311 days. The survival was longer for non-functional tumors (245 vs. 626 days) and was statistically significant (p = 0.0003). Four cases were censored from analysis, all were non-functional tumor cases and still alive at the time of analysis.