Effect of Distance from Target on Hypopituitarism After Stereotactic Radiosurgery for Pituitary Adenomas

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Abstract

Introduction

Delayed hypopituitarism is the most common complication after stereotactic radiosurgery (SRS) for pituitary adenomas. The aim of this study was to investigate the relationship between the distance from the hypothalamic-pituitary axis to the treatment target and anterior pituitary function preservation after SRS.

Methods

Between 2007 and 2020, consecutive adult patients who underwent single-session SRS for pituitary adenomas with ³6 months of follow-up were included. Distance measurements between hypothalamic-pituitary axis structures and the SRS target volume were quantified on MRI. The primary outcome was anterior pituitary function preservation. Outcomes were compared using multivariable regression and area under the receiver operator characteristic curve (AUROC) analyses.

Results

The study cohort comprised 224 patients, who were categorized by preservation (n=168) and no preservation (n=56) of anterior pituitary function after SRS. Independent predictors of anterior pituitary function preservation were a greater distance between the center of the pituitary gland and center of the SRS target (OR=1.101 [1.000–1.213], p=0.050), and a shorter clinical follow-up duration (OR=0.985 [0.977–0.993], p<0.0001). The adjusted AUROC for the distance from the center of the pituitary gland and center of the SRS target in predicting anterior pituitary function preservation was 0.595. The sensitivity, specificity, positive predictive value and negative predictive value in predicting anterior pituitary function preservation at the optimal cut-off distance of 15mm were 30.0%, 88.0%, 89.9% and 26.2%, respectively.

Conclusions

Greater distance between the normal pituitary gland and the SRS target is associated with anterior pituitary function preservation and increasing this distance should be a goal of adenoma resection. Larger prospective, multi-center studies are necessary to corroborate this finding and establish the effects of distance on hypopituitarism after SRS for pituitary adenomas.

Introduction

Pituitary adenomas comprise 10-20% of all primary intracranial tumors, and they are classified into functioning and nonfunctioning adenomas based upon the presence and absence of endocrine secretory activity, respectively.[1] Resection is often the first-line treatment for functioning adenomas (FA) and larger nonfunctioning adenomas (NFA) with optic nerve compression.[2] Recurrence or progression occurs in 10-50% of pituitary adenomas after surgical resection.[2, 3] Stereotactic radiosurgery (SRS) is an important adjuvant and salvage treatment for patients with subtotal resection or recurrence.[4, 5] It has also been used as an upfront treatment for select patients with high surgical risk.[4]

SRS leverages its ability to administer focused, high-dose radiation in a single session while sparing nearby critical neurovascular structures of unwanted radiation.[5] However, anterior pituitary insufficiency still occurs in

approximately 18-50% of patients after SRS for pituitary adenomas.[6–8] It is the most common intermediate to late complication, with a time-to-onset ranging from 2 months to 14 years after treatment.[7, 8] Hypopituitarism is associated with increased mortality and significant health-related costs.[9, 10] Higher treatment dose and differences in SRS dose intensities along the hypothalamic-pituitary (HP) axis have been identified as risk factors for post-SRS hypopituitarism.[6, 11] We hypothesize that the distance between the radiosurgical target and the HP axis may be associated with SRS-induced endocrine complications. The aim of this retrospective cohort study was to determine the effects of distance between HP axis neuroanatomical structures and the SRS target volume on anterior pituitary function preservation after SRS for pituitary adenomas.

Methods

Study design

Between October 2007 and October 2020, consecutive adult patients who underwent single-session SRS at the University of Virginia Health System for treatment of pituitary adenomas were reviewed. The study was approved by the Institutional Review Board (IRB) committee at our institution and follows the guidelines set forth by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[12] Data were obtained retrospectively according to a standardized collection protocol, which included a medical chart abstraction and review of SRS planning MRI data.

Patient identification and selection

The inclusion criteria for this study were: (1) age ≥ 18 years, (2) available SRS planning MRI data, and (3) ≥ 6 months of clinical neuroendocrine follow-up. Patients were excluded for the following criteria: (1) whole-sellar SRS, (2) absence of a discrete adenoma, normal pituitary gland or stalk on the SRS planning MRI and (3) history of cranial fractionated radiation therapy before the first SRS treatment. Patients underwent treatment consistent with our institutional standard, which included a comprehensive neuroendocrine assessment comprising clinical evaluation and laboratory testing of adrenocorticotropic hormone (ACTH), cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), insulin-like growth factor–1 (IGF-1), prolactin, thyroid-stimulating hormone (TSH), free thyroxine (T4), 24-hour urinary free cortisol (patients with Cushing's disease), growth hormone (patients with acromegaly), testosterone (males) and estradiol (females < 50 years) prior to the initial SRS. Patients with subjective visual disturbance or signs of optic apparatus compression were also referred for a formal neuroophthalmological assessment. Routine imaging and neuroendocrine assessments were performed at 6-month intervals for the first year, and then yearly until 5 years after SRS. After 5 years, follow-up was performed at 1 to 3-year intervals.

SRS technique

The SRS technique for treatment of patients with pituitary adenomas at our institution has been previously described.[11] In brief, a high-resolution MRI was obtained before and after contrast administration, combined with fat suppression, at 1mm slice thickness. A Leksell stereotactic Gamma Knife frame was placed under monitored anesthesia care. Following frame placement, a CT was obtained and merged with the high-resolution MRI. Dose planning was performed using the GammaPlan software (Elekta AB, Sweden) by a multidisciplinary team comprising a neurosurgeon, radiation oncologist, and medical physicist. SRS was performed using the Leksell Gamma Knife Unit (Elekta AB, Sweden); the model varied depending upon the time of treatment.

Clinical data

Baseline demographic data included age and sex. Medical history data included history of pituitary adenoma resection, history of hypopituitarism, history of central diabetes insipidus, history of visual deficit, presence of a functioning adenoma and duration of clinical neuroendocrine follow-up. SRS planning data included margin dose, treatment volume, and isodose. Hypopituitarism was defined as anterior pituitary hormone deficiency, or requirement of hormone replacement therapy due to pituitary insufficiency. Visual deficit was defined as subjective visual disturbance, evidence of visual field loss, or ocular motility disturbance on formal neuroophthalmological evaluation.

Neuroimaging review

From the post-contrast fat suppressed dose planning MRI, a single two-dimensional coronal slice with a clearly identifiable pituitary adenoma, pituitary gland and pituitary stalk was selected. The treatment plan was outlined, and distance measurements were made by connecting points between the following structures: (1) edge of the pituitary gland to the prescription isodose line, (2) center of the pituitary gland to the center target within the prescription isodose line, (3) edge of the pituitary gland to the center target within the prescription isodose line, (4) center of the pituitary gland to the prescription isodose line, (5) edge of the pituitary stalk to the prescription isodose line, (6) center of the pituitary stalk to the center target within the prescription isodose line, (7) edge of the pituitary stalk to the center target within the prescription isodose line and (8) center of the pituitary stalk to the prescription isodose line. The MRI was further reviewed for a two-dimensional coronal slice where the adenoma and the hypothalamus were clearly identifiable. Additional distance measurements were made by connecting points between the following structures: (9) edge of the hypothalamus to the prescription isodose line, (10) center of the hypothalamus to the center target within the prescription isodose line, (11) edge of the hypothalamus to the center target within the prescription isodose line and (12) center of the hypothalamus to the prescription isodose line (Figure 1). All measurements were performed by individuals blinded to clinical information.

Outcomes

The primary outcome was the preservation of pre-SRS anterior pituitary function. No preservation of pre-SRS anterior pituitary function was defined as a new anterior pituitary hormone deficiency below the expected age and gender specific reference range and a formal diagnosis by the treating endocrinologist, or requirement of a new hormone replacement therapy after the initial SRS. The exception to this was growth hormone deficiency, which was defined as a positive result from provocative testing, or a formal diagnosis by the treating endocrinologist. Patients who underwent repeat resection, SRS or adjuvant cranial fractionated radiation therapy were censored at the time of additional treatment.

Statistical analysis

Statistical analyses were performed using Stata (version 15.0, College Station, TX). Univariable logistic regression analyses, dichotomized by the primary outcome, compared baseline demographic, medical history, treatment and imaging data. A multivariable logistic regression analysis, initially including all potential predictor variables, with stepwise backward elimination of non-contributory variables ($p>0.10$), was performed to identify independent predictors of the primary outcome. Statistical models were assessed for goodness-of-fit using the Hosmer-Lemeshow test. Covariates were tested for multicollinearity using tolerance and variance inflation factor, and collinear variables were removed from the final model. An area under the receiver operator characteristic curve

(AUROC) analysis was performed to assess the discrimination of independent variables included in the multivariable logistic regression model. Cut-off points for distance measurements between HP axis neuroanatomical structures and the SRS target volume were calculated using the Youden's Index (YI).[13] Accuracy was assessed using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Statistical significance was defined as $p<0.05$, and all tests were two-tailed. Missing data were not imputed.

Results

Study cohort

Of the 466 eligible patients, 242 were excluded from the present study (153 patients for whole-sellar SRS, 4 patients for the absence of a discrete pituitary adenoma, pituitary gland or pituitary stalk on the dose planning MRI, 73 patients for < 6 months of clinical neuroendocrine follow-up, 4 patients for the lack of accessible medical history data, and 8 patients for a history of cranial fractionated radiation therapy, Figure 2). The remaining 224 patients (mean age 50.1±15.2 years; 52.2% female) were categorized by the primary outcome of preservation (n=168) and no preservation (n=56) of pre-SRS anterior pituitary function. 54.5% (n=122) of the patients had a history of hypopituitarism prior to SRS. The rate of new or worsening hypopituitarism after SRS was 25.0% (n=56) at a mean and median time to onset of 30.5 (30.0) and 18.0 (6.5–38.5) months, respectively. The affected axis was adrenal in 12 patients (21.4%), thyroid in 44 patients (78.6%), gonadal in 25 patients (44.6%) and somatic in 16 patients (28.6%). More than one axis was affected in 16 patients (28.6%). Of the patients who experienced post-SRS gonadotropin deficiency, 11 (44.0%) were female, 5 of whom (20.0%) were under the age of 50. The mean and median clinical follow-up durations were 53.7 (38.0) and 46.0 (17.0–75.0) months, respectively.

Determinants of endocrine outcomes

Table 1 compares the baseline characteristics between the preservation and no preservation of pre-SRS anterior pituitary function cohorts. Univariable predictors of anterior pituitary function preservation were a greater distance between the center of the pituitary gland and center of the target volume (mean 13.5 vs. 12.4mm; OR=1.097 [1.000–1.203], p=0.048), a greater distance between the edge of the pituitary gland and the center of the target volume (mean 8.7 vs. 7.5mm; OR=1.120 [1.012–1.240], p=0.028), and a shorter clinical follow-up duration (mean 48.0 vs. 70.6 months; OR=0.985 [0.977 – 0.993], p<0.0001). In the multivariable model, independent predictors of anterior pituitary function preservation were a greater distance between the center of the pituitary gland and center of the target volume (OR=1.101 [1.000–1.213], p=0.050), and a shorter clinical follow-up duration (OR=0.985 [0.977–0.993], p<0.0001) (Table 2).

Table 1

Univariable comparisons of patients with and without anterior pituitary function preservation after SRS. Abbreviations: SRS = stereotactic radiosurgery, DI = central diabetes insipidus, SD = standard deviation, % = per cent, Gy = Gray, n = number, cm^3 = cubic centimeters, NE = not estimable.

Baseline Characteristics	Overall cohort (n=224)	Preservation (n=168)	No Preservation (n=56)	Odds ratio [95% C.I.]	p-value
Age, mean years (SD)	50.1 (15.2)	51.1 (15.3)	47.1 (14.6)	1.017 [0.993 – 1.038]	0.093
Female, n (%)	117/224 (52.2)	89/168 (53.0)	28/56 (50.0)	1.127 [0.615 – 2.063]	0.699
Pre-treatment history					
Functioning adenoma, n (%)	199/224 (44.2)	71/168 (42.3)	28/56 (50.0)	0.731 [0.399 – 1.343]	0.313
Pre-GKRS visual deficit, n (%)	47/224 (21.0)	34/168 (20.2)	13/56 (23.2)	0.839 [0.406 – 1.734]	0.636
Pre-GKRS hypopituitarism, n (%)	122/224 (54.5)	90/168 (53.6)	32/56 (57.1)	0.865 [0.470 – 1.593]	0.642
Pre-GKRS DI, n (%)	13/224 (5.8)	11/168 (6.6)	2/56 (3.6)	1.892 [0.406 – 8.808]	0.417
Prior surgical resection, n (%)	218/224 (97.3)	162/168 (96.4)	56/56 (100.0)	NE	0.152
SRS parameters					
Margin dose, mean Gy (SD)	19.7 (4.1)	19.5 (4.0)	20.4 (4.3)	0.946 [0.879 – 1.019]	0.146
Treatment volume, mean cm^3 (SD)	3.2 (2.0)	3.2 (2.1)	3.3 (1.8)	0.981 [0.837 – 1.149]	0.810
Isodose, mean % (SD)	50.0 (1.1)	50.1 (1.2)	50.0 (0.0)	1.057 [0.750 – 1.489]	0.751

Baseline Characteristics	Overall cohort (n=224)	Preservation (n=168)	No Preservation (n=56)	Odds ratio [95% C.I.]	p-value
SRS dose distance					
Edge gland - Edge dose, mean mm (SD)	1.1 (2.6)	1.2 (2.8)	0.8 (2.0)	1.074 [0.933 – 1.236]	0.322
Center gland – Center dose, mean mm (SD)	13.2 (3.6)	13.5 (3.6)	12.4 (3.2)	1.097 [1.000 – 1.203]	**0.048**
Edge gland – Center dose, mean mm (SD)	8.4 (3.3)	8.7 (3.5)	7.5 (2.7)	1.120 [1.012 – 1.240]	**0.028**
Center gland – Edge dose, mean mm (SD)	5.1 (3.2)	5.2 (3.4)	4.8 (2.7)	1.047 [0.947 – 1.158]	0.367
Edge stalk – Edge dose, mean mm (SD)	4.2 (2.2)	4.2 (2.3)	3.9 (2.0)	1.080 [0.934 – 1.250]	0.299
Center stalk – Center dose, mean mm (SD)	12.4 (3.1)	12.6 (3.1)	11.9 (3.2)	1.066 [0.967 – 1.175]	0.197
Edge stalk – Center dose, mean mm (SD)	11.1 (2.8)	11.2 (2.8)	10.7 (2.7)	1.064 [0.954 0 1.186]	0.266
Center stalk – Edge dose, mean mm (SD)	5.4 (2.4)	5.5 (2.5)	5.0 (2.3)	1.102 [0.962 – 1.262]	0.161
Edge hypothalamus – Edge dose, mean mm (SD)	8.7 (2.9)	8.8 (2.8)	8.3 (2.9)	1.078 [0.965 – 1.203]	0.184
Center hypothalamus – Center dose, mean mm (SD)	16.5 (3.2)	16.5 (3.2)	16.6 (3.1)	0.995 [0.904 – 1.095]	0.922
Edge hypothalamus – Center dose, mean mm (SD)	14.8 (3.1)	14.8 (3.1)	14.7 (3.0)	1.019 [0.922 – 1.127]	0.707

Baseline Characteristics	Overall cohort (n=224)	Preservation (n=168)	No Preservation (n=56)	Odds ratio [95% C.I.]	p-value
Center hypothalamus – Edge dose, mean mm (SD)	10.6 (3.2)	10.7 (3.2)	10.2 (3.2)	1.054 [0.955 – 1.164]	0.295
Follow-up					
Clinical, mean months (SD)	53.7 (38.0)	48.0 (36.0)	70.6 (39.0)	0.985 [0.977 – 0.993]	**<0.0001**

Table 2
Multivariable model of the independent predictors of anterior pituitary function preservation after SRS.

Preservation	Odds ratio	95% C.I.	p-value
Center gland – Center dose	1.101	1.000 – 1.213	**0.050**
Clinical follow-up	0.985	0.977 – 0.993	**<0.0001**
Abbreviations: SRS = stereotactic radiosurgery, C.I. = confidence interval, % = per cent.			

Effects of distance on endocrine outcomes

The adjusted AUROC for the distance between the center of the pituitary gland and center of the target volume in predicting anterior pituitary function preservation was 0.595 (0.506–0.684) (Table 3, and Figure 3). The optimal cut-off distance between these structures in predicting anterior pituitary function preservation was 15.0mm (YI=0.173). The sensitivity, specificity, PPV and NPV in predicting anterior pituitary function preservation at distance of 15mm between the center of the pituitary gland and the center of the target volume were 30.0%, 88.0%, 89.9%, and 26.2%, respectively. Preservation of anterior pituitary function was observed at a distance of 0-5mm in 0 of 1 patient (0.0%), 5-10mm in 24 of 37 patients (64.9%), 10-15mm in 92 of 126 patients (73.0%), 15-20mm in 42 of 49 patients (85.7%), 20-25mm in 9 of 10 patients (90.0%), and 25-30mm in 1 of 1 patient (100.0%) (Figure 4).

Table 3
AUROC analysis identifying the optimal cutoff distance predictive of anterior pituitary function preservation after SRS. Abbreviations: SRS = stereotactic radiosurgery, AUROC = Area under the receiver operator characteristic curve, YI = Youden Index, PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval, SD = standard deviation, % = per cent.

Preservation (n=174) Mean distance ± SD (mm)	No preservation (n=56) Mean distance ± SD (mm)	AUROC	95% CI	Optimal cut-off, (mm)	YI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
13.5 ± 3.6	12.4 ± 3.2	0.595	0.506 – 0.684	**15.0**	0.173	30.0	88.0	89.9	26.2

Illustrative case demonstrating dose fall off as a function of distance between structures

A 60-year-old female was found to have a non-functioning pituitary adenoma after presenting with pituitary apoplexy in 2009. She underwent three transsphenoidal resections, first in January 2010, second in July 2011 for tumor recurrence, and third in April 2016 for tumor recurrence. Prior to her third resection, her visual and endocrine functions were intact. She underwent adjuvant SRS in September 2016 for residual tumor in the cavernous sinus. In December 2017, she developed cortisol insufficiency and was placed on hydrocortisone replacement. To date, she has experienced no further side effects from treatment and no evidence of tumor recurrence. Figure 5A depicts the dose plan utilized at the time of her treatment. The distance between the center of the gland and the center of the SRS target was 9.2mm. Figure 5B depicts an alternative plan utilizing a steeper fall off in dose towards the pituitary gland and stalk, thereby better shielding these structures from unwanted radiation dose. This may be considered in patients undergoing SRS dose planning with less than 15mm between the center of the pituitary gland and the center of the SRS target volume.

Discussion

Resection is frequently the first-line treatment for symptomatic pituitary adenomas.[14] The prevalence of pre-operative hypopituitarism in patients undergoing surgical resection ranges from 70-85%, and the incidence of new or worsening post-operative hypopituitarism ranges from 5-15%.[15–17] SRS offers adjuvant or salvage treatment for those with subtotal resection or recurrence, and an alternative to surgical resection for patients with high surgical risks.[4, 14] The incidence of hypopituitarism after SRS, reported to range from 18-50%, is lower than the reported rates of 30-100% after fractionated radiotherapy.[6–8, 11, 18–22] However, pituitary insufficiency remains the most common adverse effect after SRS for pituitary adenomas.[6, 8] Hypopituitarism is associated with significant morbidity, increased mortality, poorer quality of life, and greater health related costs.[9, 10, 23–25] Given the frequent utilization of SRS as an adjuvant post-surgical treatment, identification of solutions to minimize the risk of new or worsening hypopituitarism after SRS for pituitary adenomas is critical.

In this study, we sought to identify relationships between HP axis to SRS target volume distances and anterior pituitary function preservation after SRS. We identified that a greater distance between the center of the pituitary gland and the center of the SRS target volume was an independent predictor of anterior pituitary function preservation. Based upon these findings, we performed an AUROC analysis to generate a predictive tool for anterior pituitary function preservation. A distance of 15mm between the center of the gland and the center of the SRS target volume was associated with a specificity of 88% and PPV of 90% for anterior pituitary function preservation. Taken together, our observations suggest that distances of 15mm or greater between the center of the gland and the center of the SRS target are associated with anterior pituitary function preservation, whereas distances of less than 15mm may be associated with new or worsening hypopituitarism after SRS. Thus, a minimum 15mm distance between the pituitary gland and any residual adenoma should be a goal of resections undertaken prior to SRS.

We also found an independent association between shorter clinical follow-up duration and anterior pituitary function preservation after SRS. This finding likely reflects a delay in the onset of SRS treatment-related hormonal adverse effects.[6, 8] In our patient cohort, the median time to onset of new or worsening hypopituitarism was 18 months (IQR 6.5 – 36.5 months) after SRS. This was consistent with previous reports, which ranged between 21

and 120 months after SRS.[8, 11, 22, 26–28] The time to development of new endocrinopathy may also depend upon the affected hormone. In a cohort of 48 non-functioning adenoma patients treated with SRS, Gopalan et al. reported early onset of cortisol deficiency at a mean of 27 months, compared to gonadotropin deficiency, which occurred a mean of 120 months after SRS.[22] Thyroid hormone and growth hormone deficiency occurred at a mean of 40 and 71 months after SRS, respectively. While the majority new endocrinopathies develop within 5 years after SRS, late-onset hypopituitarism can occur in approximately 15% of cases.[8] In the context of the present study, these observations underscore the need for continued longitudinal endocrine follow-up in SRS-treated pituitary adenoma patients.

Treatment dose is a previously described risk factor for new hypopituitarism after SRS for pituitary adenomas.[8, 11, 21, 28, 29] Furthermore, higher doses to the pituitary gland or the pituitary stalk have been found to independently predict development of pituitary insufficiency after SRS.[11, 21, 29] Therefore, to mitigate these adverse radiation effects, Taussky et al. proposed the placement of a fat graft between the residual tumor and the normal gland at the time of surgery among patients expected to undergo adjuvant SRS or fractionated radiation therapy.[14] In their patient cohort, there were no new cases of pituitary insufficiency observed over a median follow-up period of 4 years, substantiating their hypothesis that a greater distance between the two anatomical structures can preserve anterior pituitary function after SRS. Our observation of an association between the distance from the center of the pituitary gland to the center of the SRS treatment target and new hypopituitarism may be related to the effects of radiation dose delivery to surrounding structures. Given that radiation falls off via an inverse square law, the dose fall off is proportional to the inverse of the square of the distance. Knowledge of this relationship between dose and distance should be utilized during pituitary adenoma resection to safely maximize the distance between the two structures among patients expected to undergo adjuvant SRS. In patients with smaller distances between SRS target and normal pituitary gland, a steeper dose fall off towards the gland through the use of advanced radiosurgical planning techniques should be emphasized to preserve anterior pituitary function.

Limitations

There are a number of limitations to this study which must be acknowledged. Most importantly, our retrospective study design is subject to confirmation bias, in that variables were chosen based upon data availability and hypothesis generation. Our results are contingent upon the accuracy of reported data, which was largely based upon medical chart abstraction. Furthermore, the power of our analysis was limited by the relatively small number of patients who developed new or worsening hypopituitarism. Measurements between the SRS treatment target and HP axis structures may be subject to restricted generalizability and measurement bias. Loss to follow-up may have contributed to selection bias, resulting in outcome differences. While this was adjusted for in our analyses, it is not possible to entirely account for the possibility of late-onset hypopituitarism in patients with insufficient follow-up. Additional limitations include reporting, recall and missing data biases, due to the sourcing of the study data from a single center. Finally, our AUROC analysis found the distance between the gland and the SRS target to be a weak predictor of anterior pituitary function preservation.

Conclusions

Greater distance between the center of the pituitary gland and the center of the SRS target volume appears to be associated with anterior pituitary function preservation after SRS for pituitary adenomas. A distance of 15mm or more between the center of the pituitary gland and the center of the SRS target volume predicts anterior pituitary

function preservation. This finding underscores the importance of dose and distance in SRS radiosurgical planning and the relevance of maximizing the distance between the pituitary gland and the residual adenoma during resection. Larger prospective, multi-center studies are necessary and underway to corroborate this finding and determine the effects of distance on hypopituitarism after SRS for pituitary adenomas.

Declarations

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All authors contributed to the study conception and design. Material preparation, data collection and analysis was performed by Natasha Ironside. Statistical guidance was provided by Zhiyuan Xu and Ching-Jen Chen. The first draft of the manuscript was written by Natasha Ironside and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

This study data is available from the corresponding author upon reasonable request.

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Ethical approval: This article utilizes retrospective data and does not contain any studies with human participants performed by any of the authors.

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Figures

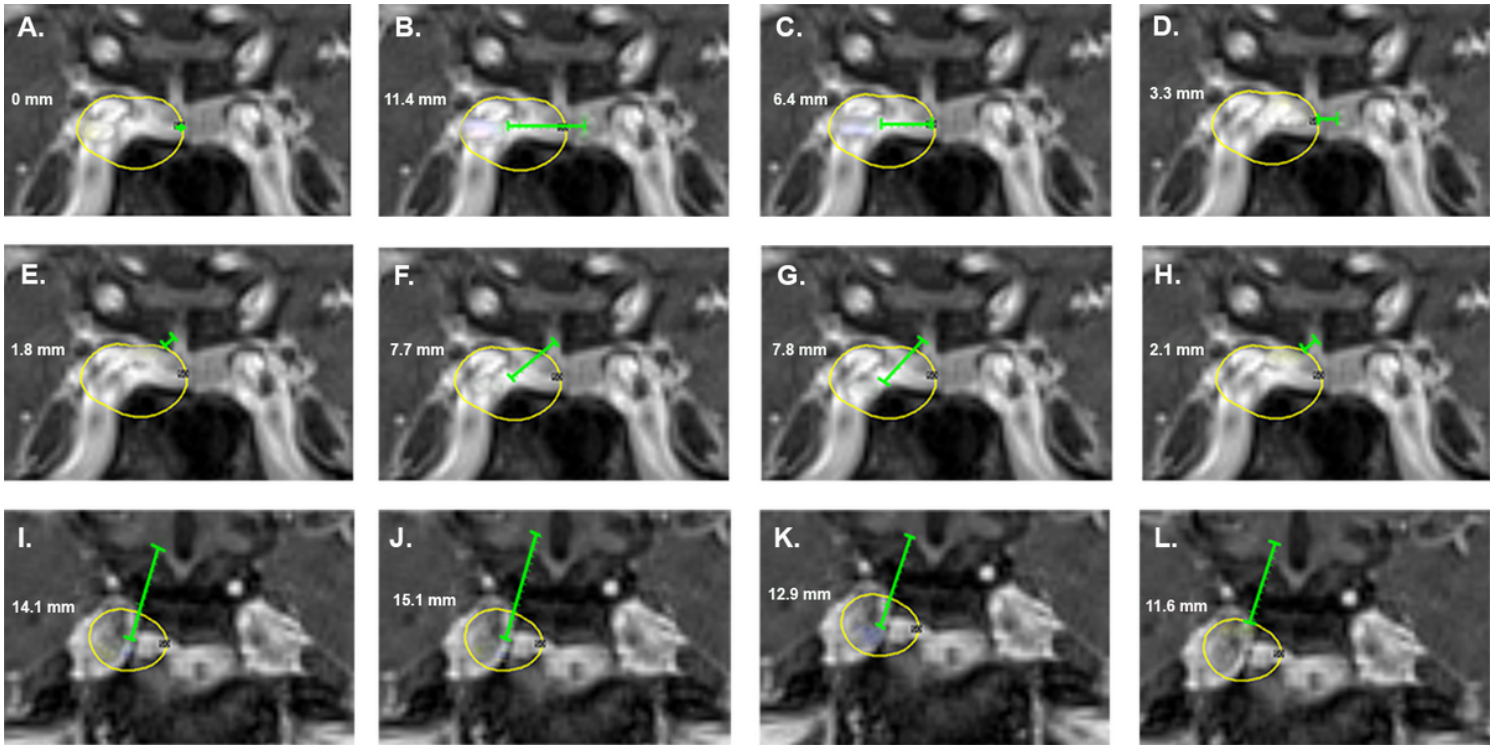

Figure 1

Representative images of the SRS dose to HP axis distance measurements. (A) edge of the pituitary gland to the prescription isodose line, (B) center of the pituitary gland to the center target, (C) edge of the pituitary gland to the center target, (D) center of the pituitary gland to the prescription isodose line, (E) edge of the pituitary stalk to the prescription isodose line, (F) center of the pituitary stalk to the center target, (G) edge of the pituitary stalk to the center target, (H) center of the pituitary stalk to the prescription isodose line, (I) edge of the hypothalamus to the prescription isodose line, (J) center of the hypothalamus to the center target, (K) edge of the hypothalamus to the center target, (L) center of the hypothalamus to the prescription isodose line. Contouring: Yellow = prescription isodose line. Abbreviations: SRS = stereotactic radiosurgery, HP = hypothalamic pituitary.

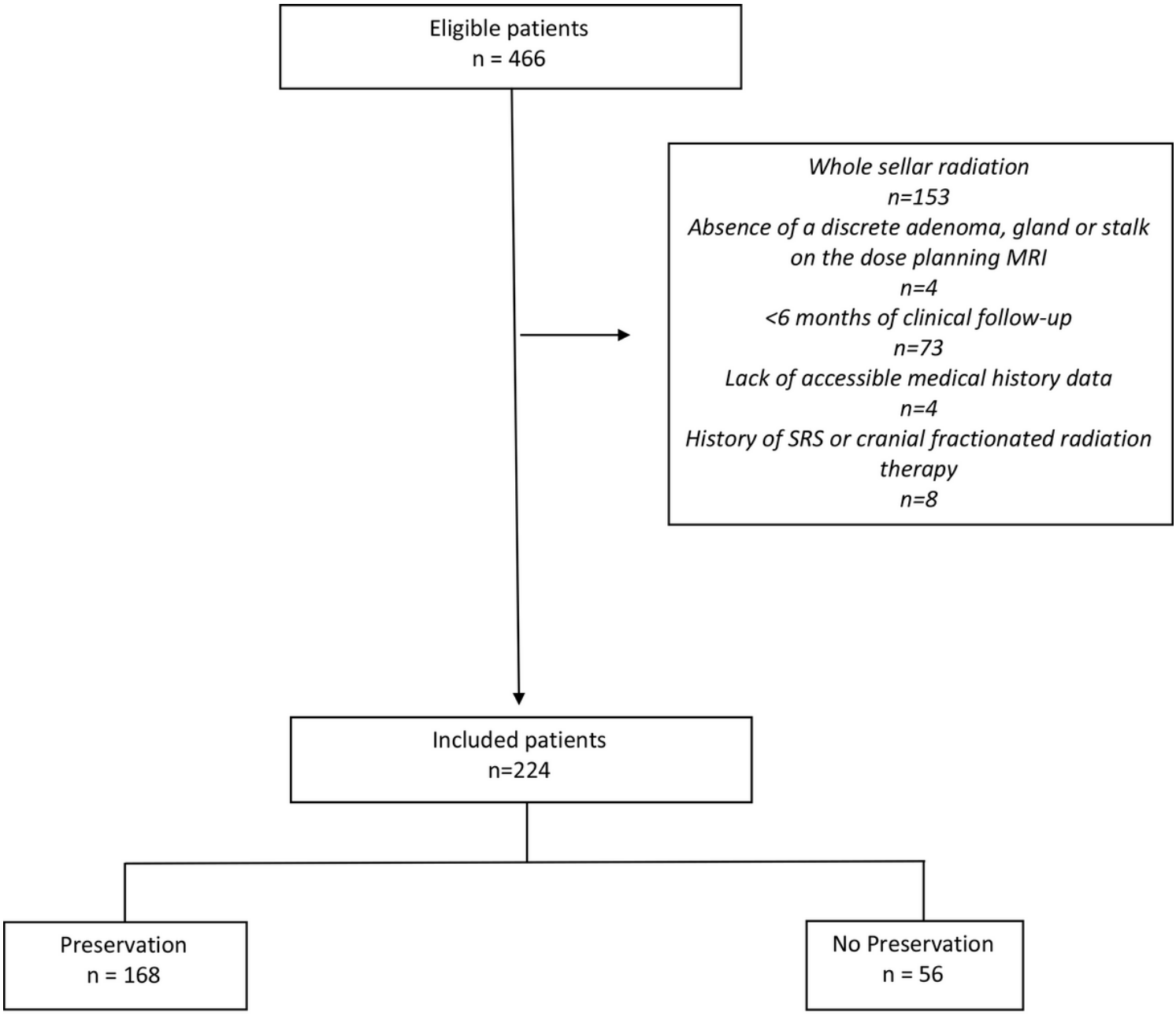

Figure 2

Flow chart of the patient selection process. Abbreviations: SRS = stereotactic radiosurgery, MRI = magnetic resonance imaging.

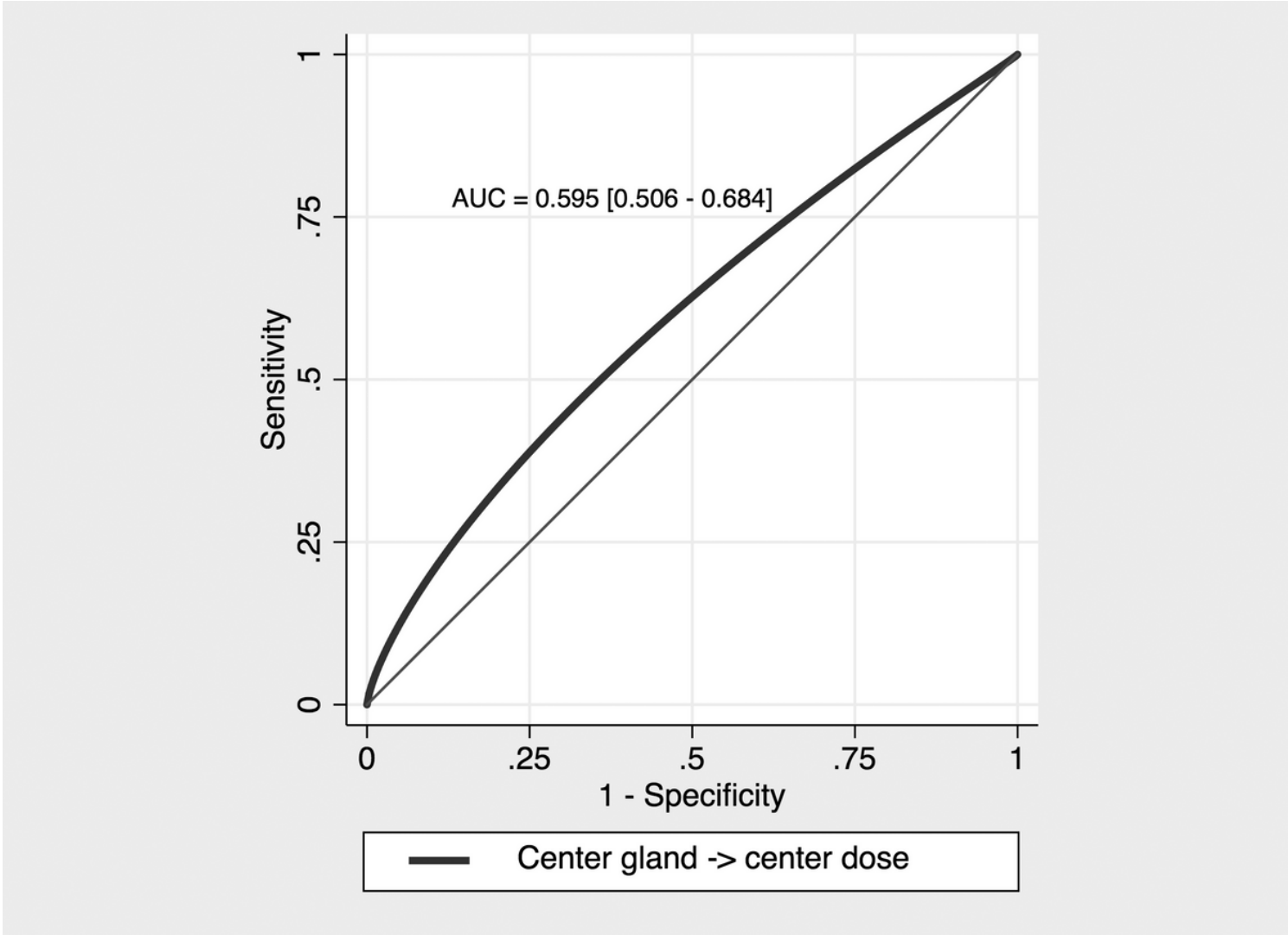

Figure 3

Adjusted AUROC of the distance between the center of the pituitary gland and the center of the SRS target in predicting anterior pituitary function preservation. Abbreviations: AUROC/AUC = area under the receiver operator curve, SRS = stereotactic radiosurgery.

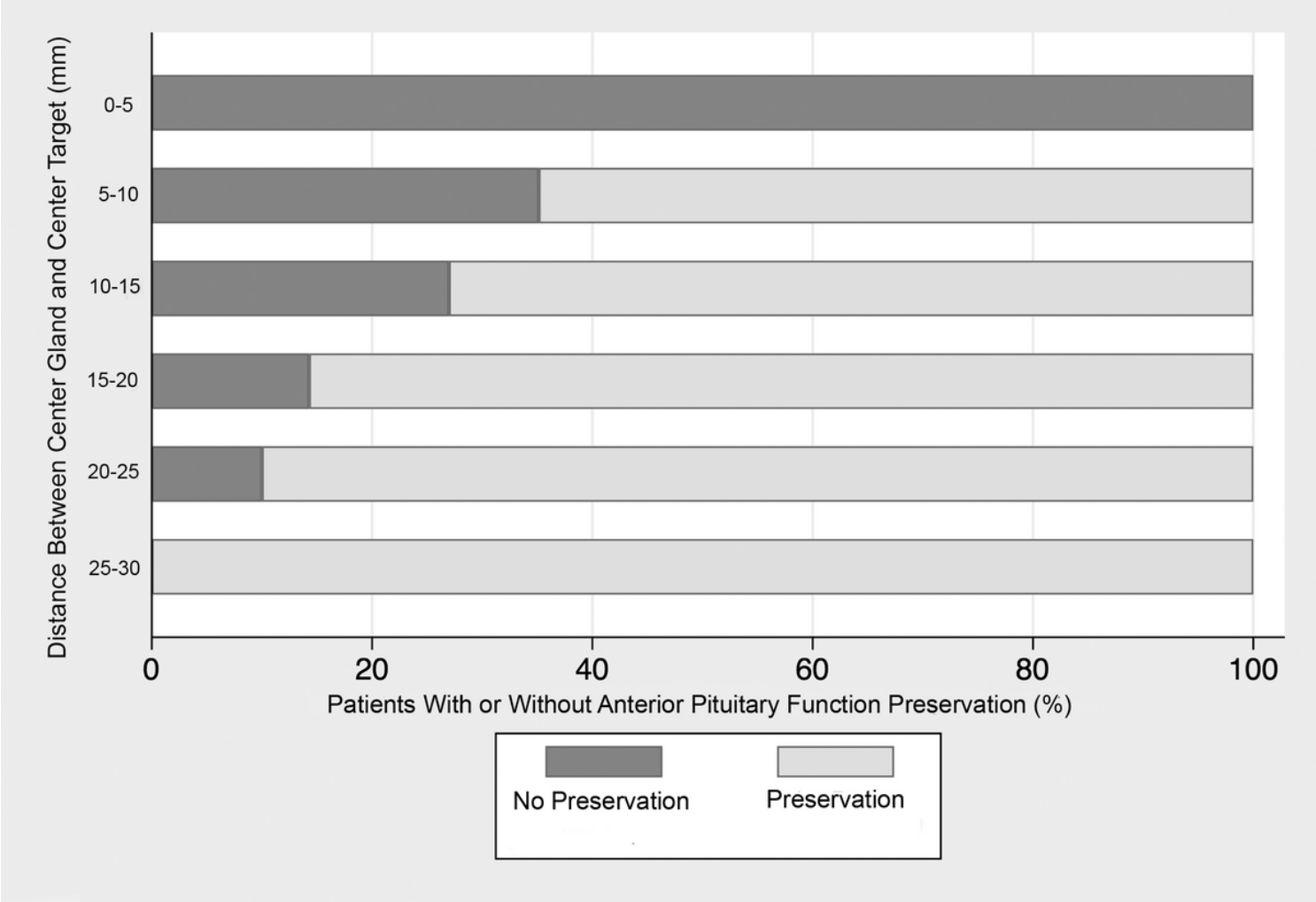

Figure 4

Relationship between distance from the center of the pituitary gland and the center of the SRS target and anterior pitutary function preservation.

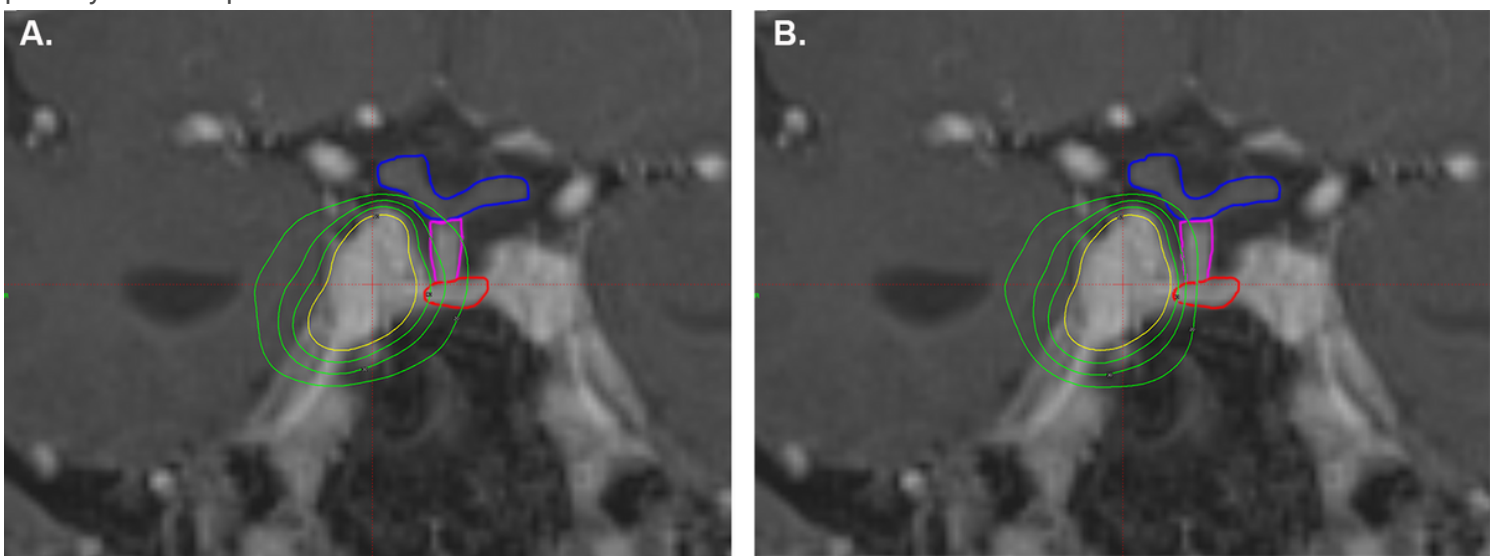

Figure 5

(A) Representative SRS dose plan for the treatment of residual pituitary adenoma in the cavernous sinus. The distance between the center of the pituitary gland and the center of the SRS target is 9.2mm. (B) Alternative dose plan demonstrating a steeper dose fall off in the direction of the pituitary gland and stalk. Contouring: Yellow = prescription and in this case 50% isodose line, green = 20% isodose line, red = pituitary gland, pink = pituitary stalk, blue = optic apparatus.