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Prognostic significance of corticotroph staining in radiosurgery for non-functioning pituitary adenomas: a multicenter study

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Abstract

Silent corticotroph staining pituitary adenoma (SCA) represents an uncommon subset of Non-Functioning adenomas (NFAs), hypothesized to be more locally aggressive. In this retrospective multicenter study, we investigate the safety and effectiveness of Stereotactic Radiosurgery (SRS) in patients with SCA compared with other non-SCA NFA's. Eight centers participating in the International Gamma-Knife Research Foundation (IGKRF) contributed to this study. Outcomes of

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Compliance with ethical standards

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50 patients with confirmed SCAs and 307 patients with confirmed non-SCA NFA's treated with SRS were evaluated. Groups were matched. SCA was characterized by a lack of clinical evidence of Cushing disease, yet with positive immunostaining for corticotroph. Median age was 55.2 years (13.7–87). All patients underwent at least one *trans*-sphenoidal tumor resection prior to SRS. SRS parameters were comparable as well. Median follow-up 40 months (6–163). Overall tumor control rate (TCR) 91.2% (n = 280). In the SCA group, TCR were 82% (n = 41) versus 94.1% (n = 289) for the control-NFA (p = 0.0065). The SCA group showed a significantly higher incidence of new post-SRS visual deficit (p < 0.0001) assigned to tumor progression and growth, and post-SRS weakness and fatigue (p < 0.0001). In univariate and multivariate analysis, only the status of silent corticotroph staining (p = 0.005, p = 0.009 respectively) and margin dose (p < 0.0005, p = 0.0037 respectively) significantly influenced progression rate. A margin dose of 17 Gy was noted to influence the adenoma progression rate in the entire cohort (p = 0.003). Silent corticotroph staining represents an independent factor for adenoma progression and hypopituitarism after SRS. A higher margin dose may convey a greater chance of TCR.

Keywords

Radiosurgery; Gamma knife; Silent ACTH staining; Pituitary adenomas

Introduction

Pituitary adenomas are common, comprising as many as 10–20% of all intracranial tumors [1–3]. SRS was shown to provide an excellent solution for patients having residual tumor post-operatively, tumor progression or recurrence and invasion of the cavernous sinus or suprasellar compartment [4]. Silent corticotroph staining pituitary adenoma (SCA) represents an uncommon subset of NFAs. It was first reported in 1978 [5] and further defined in 1980 [6]. SCAs are characterized by a lack of clinical manifested serum hypercortisolemia, no clinical evidence of Cushing disease (CD), yet with positive immunostaining for adrenocorticotrophic hormone (ACTH). The exact incidence rate of SCAs is unknown, which is reported to vary from 9 to 32.7% [7, 8].

SCAs is hypothesized by some investigators as a more aggressive variant of NFA's, approaching the local recurrence and invasive nature of Cushing's disease causing FA [9–16]. Other researchers alternatively, claimed no prognostic significance for the silent ACTH staining feature [9, 17, 18]. Our knowledge of the natural history and clinical characteristics of SCAs is limited to a few small single-center studies of patients undergoing either surgical resection [9, 10, 12, 13, 16, 17, 19] or SRS [7]. We present a large retrospective cohort of patients with NFA's for which silent ACTH staining status is known, in an attempt to determine predictors of tumor control after SRS in a large multicenter cohort through the International Gamma Knife Research Foundation (IGKRF).

Materials and methods

Patient population

Eight medical centers participating through the IGKRF obtained individual institutional review board (IRB) approvals to participate in this study. A total of 357 NFA patients were treated with Gamma Knife radiosurgery (GKRS) from 1997 to 2015, for which histological diagnosis and ACTH staining data was available. At each center, a retrospective review of clinical and radiological patient outcome parameters was performed. The centers contributing data for this study were Taipei Veteran General Hospital, Taiwan (102 patients), Na Homolce Hospital Czech Republic (73 patients), University of Virginia (64 patients), Cleveland Clinic (43 patients), Beaumont Health System (39 patients), University of Sherbrooke, Centre de Recherche Clinique (16 patients), New York University (13 patients), and West-Virginia university (7 patients). A total of 50 histologically defined SCAs were noted and 307 histologically defined non-SCAs (control group) were noted. The records of NFA's patients who underwent Gamma Knife® (Elekta AB, Stockholm, Sweden) SRS during the period 1997–2015 were evaluated by the clinicians at each center for inclusion in the study. A database of pre-determined variables was created and sent to each of the participating center. Each center reviewed the medical records of their patients, entered their information. Pooled and de-identified data were screened by the IGKRF study coordinator for errors, and data were verified for compliance with patient privacy and the protection of patient information. Any uncertainties or ambiguities in the data were addressed by the contributing center.

By definition, the diagnosis of SCA required the lack of the clinical and biochemical manifestations of CD, positive immunoreactivity for ACTH according to the pathology report, and negative endocrine studies regarding CD before SRS. The control NFA group consisted of 307 patients with adequate histopathologic data to confirm the diagnosis of a non-ACTH staining NFA subtype, including gonadotroph adenomas (with immunoreactivity for the gonadotropin hormones β -follicle-stimulating hormone, β -luteinizing hormone, and/or α -subunit), silent growth hormone (GH) adenomas (with immunoreactivity for GH), or null-cell adenomas (with lack of any immunoreactivity for pituitary hormones). A minimum of 6 months of neuro-imaging and clinical follow-up after GKRS was defined as an inclusion criterion in the study.

Cohort overview

The specific patient and tumor attributes are detailed in Table 1. A Cohort of 357 patients harboring NFA's was analyzed. SCAs formed 14% ($n = 50$), and the control-NFA's group formed 86% ($n = 307$). Males formed 49.7% ($n = 156$), not significantly different between the groups ($p = 0.173$). The median age was 55.2 years (range 13.7–87), and the mean age was 50.9 ± 13 years, not significantly different between the groups ($p = 0.06$). Before SRS, all patients underwent at least one *trans*-sphenoidal tumor resection (TSR, range 1–3). Patients received a neuro-ophthalmologic evaluation and comprehensive endocrine studies, which included serum cortisol, ACTH, free thyroxine, thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1), GH, and testosterone (men) immediately before SRS. Pre-SRS visual deficit was comparable between the groups (44%, $n = 22$ in the SCAs versus

48.5%, $n = 149$ in the control NFA's respectively, $p = 0.658$), as were the weakness or fatigue ($p = 0.71$) and sexual dysfunction ($p = 0.796$). Pre-SRS headaches were reported significantly more in the SCA group (72.9% ($n = 35$)) in the SCAs versus 6.1% ($n = 14$) in the control NFA's respectively, $p < 0.0001$.

The different tumor features were also comparable between the groups, including the median and mean maximal tumor diameter (3 and 3.3 cm in the SCAs versus 2.9 and 3.1 cm in the control NFA's respectively, $p = 0.359$), median and mean tumor volume [4.3 cm^3 (0.2–27) and 5.6 cm^3 (± 6.9) in the SCAs versus 3.8 cm^3 (0.1–57.3) and 5.52 cm^3 (± 6) in the control NFA's respectively, $p = 0.951$], cavernous sinus invasion [77.3% ($n = 38$) in the SCAs versus 70.9% ($n = 210$) in the control NFA's respectively, $p = 0.434$], and suprasellar extension [75.5% ($n = 37$) in the SCAs versus 84.8% ($n = 251$) in the control NFA's respectively, $p = 0.157$].

Pre-SRS pituitary endocrine deficiency involving any axis was noted significantly more common in the control NFA's group [55.4% ($n = 170$)] than in the SCAs [34% ($n = 17$)] ($p = 0.008$). Specifically, hypogonadism was noted in 18% ($n = 9$) of SCAs and 30.6% ($n = 94$) of control-NFA's group ($p = 0.0973$), hypo-ACTH was noted in 16% ($n = 8$) of SCAs and 26.7% ($n = 82$) of control-NFA's group ($p = 0.0149$) and hypothyroidism was noted in 18% ($n = 9$) of SCAs and 37.1% ($n = 114$) of control-NFA's group ($p = 0.013$). Pan-hypopituitarism prior to SRS was noted in 12% ($n = 6$) of SCAs and 20.2% ($n = 62$) of control-NFA's group ($p = 0.024$).

Radiosurgical technique

Stereotactic radiosurgery for pituitary adenomas has been described previously [20]. Gamma Knife Models U, B, C, 4C, or Perfexion[®] were used during the study period, depending on the technology available at the time for each participating center. The Leksell Model G stereotactic frame[®] (Elekta AB, Stockholm, Sweden) was applied using local anesthetic supplemented with additional sedation as needed. A high resolution, volumetric T1-weighted MRI sequences were obtained with and without the administration of gadolinium. Thin-slice axial and/or coronal plane images were obtained after the intravenous contrast administration. The selection of dose to the pituitary adenoma was determined generally according to the status of the adjacent cranial nerve function, the size of the adenoma and the distance between the adenoma and adjacent critical structures, in particular the anterior optic pathways. Multidisciplinary radiosurgery dose planning was then performed by a neurosurgeon, a radiation oncologist, and a medical physicist.

In this series, the median margin dose delivered to the tumor margin were 14.5 (range 11–18) Gy in the SCAs group and 14 Gy (range 5–25) in the non-SCA group, and these were not significantly different between the groups ($p = 0.814$). Other radiosurgical parameters are detailed in Table 1.

Clinical and radiological assessment after SRS

Patients' follow-up evaluations included neurological examination, endocrinological evaluations and neuro-imaging at the respective treating center. Follow-up was conducted every 6 months for the first 2 years after SRS, and annually thereafter. Symptoms and signs

were followed and logged, imaging was reviewed, pituitary functions and hormone levels tested and appropriate additional medical or surgical treatment was instituted.

Tumor volume was determined either with a volume analysis approach (similar to that described by Snell et al. [21]) or using a common formula of $(X \times Y \times Z)/2$ where X, Y, and Z represent the adenoma diameters in the three cardinal planes. The follow-up images were compared with images obtained at the time of SRS. Tumor progression at last follow up was defined as an increase in tumor volume of $\geq 15\%$ relative to the baseline tumor volume. Tumor regression/decrease was defined as a decrease of the tumor volume by $\geq 15\%$ of the pretreatment volume. Tumor stability was defined as a tumor that had a volume change of $<15\%$ at the time of SRS. Tumor control was defined as a stable or regressing adenoma at last follow up.

Statistical analysis

Data were presented as median or mean and range for continuous variables, and as frequency and percentage for categorical variables. Calculations of normality were assessed graphically and statistically. Statistical analysis of categorical variables was carried out using Chi square and Fisher's exact test as appropriate. Statistics of means were carried out using unpaired Student *t* test, both with and without equal variance (Levene's test) as necessary and Wilcoxon rank sum tests when variables were not normally distributed. The adenoma progression rate was defined as a time interval between the date of initial SRS and the date of the tumor recurrence, or enlargement of the treated tumor. Data were considered censored if none of aforementioned conditions applied. The adenoma progression rate was plotted using Kaplan–Meier model. A log-rank test was used to compare the rate in two groups.

After verification of the proportional hazards assumption using a log-minus-log curve, the Cox proportional hazards regression model was used for calculating the impact of various clinical characteristics on the adenoma progression rate, including age at the time of initial SRS, pre-SRS pituitary dysfunction, tumor volume, silent ACTH staining status, and the SRS treatment parameters shown in Table 3. Any aforementioned factors that reached statistical significance ($p < 0.10$) in a univariate analysis were subjected to a multivariate analysis. Tumor margin radiation dose was further stratified into two groups (<15 and ≥ 15 Gy in the entire study). All statistical analyses were two-sided, with a *p* value of <0.05 being considered statistically significant. All studies were performed using the R project, R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

Results

Radiologic outcome

Outcome parameters are summarized in Table 2. Reviewing the entire cohort ($n = 357$), Tumor regression/volume decrease, was noted in 80.5% ($n = 247$) and tumor volume stability ($\pm 15\%$) was noted in an additional 10.7% ($n = 33$). Thus, this translated to an overall tumor control rate of 91.2% ($n = 280$). Tumor progression occurred in 27 patients (8.8%). Reviewing tumor control rates in each group separately, numbers differ.

In the SCA group, 18% (n = 9) of patients progressed, and tumor control rates were 82% (n = 41). In the control-NFA group, 5.9% (n = 18) of patients had tumor progression, and 94.1% (n = 289) exhibited tumor control. This difference between the groups is statistically significant (χ^2 test, $P = 0.0065$). Actuarial tumor progression rates at 1, 2, 3, 5 and 8 years were 2.3, 7.5, 10.7, 39.6 and 47.2% for the SCA group and 1.4, 5.8, 7.3, 11.3, and 14.4% for the non-SCA NFA's (Fig. 1).

Clinical outcomes

Outcome parameters are summarized in Table 2. The median follow-up time was 36.5 months (range 7–108) for the SCA groups and 40 months (range 6–163) for the control-NFA group. Five patients (10%) of the SCA cohort suffered a new or progressive post-SRS permanent visual deficit, assigned to tumor progression and growth. No such deficits reported in the control NFA cohort. This difference was deemed statistically significant ($p < 0.0001$). Weakness and fatigue post-SRS were noted significantly more in the SCAs group (18%, n = 8 in the SCAs group vs. 3.4%, n = 10 in the control NFA's group, $p < 0.0001$). Other post-SRS symptoms and signs were not statistically different between the groups (Table 2).

Hypopituitarism after SRS

New-onset pituitary axis endocrine deficiency was reported in 3 patients (6%) in the SCA group and in 12 patients (3.9%) in the control-NFA group on last follow-up. This difference was deemed non-significant ($p = 0.451$). A resolved endocrine deficiency post-SRS was reported in the control-NFA group in 19 patients (6.2%) and in none of the SCA group. This difference although noticeable did not reach statistical significance ($p = 0.088$). Outcome parameters are summarized in Table 2.

Additional treatments for progression

A total of nine patients who experienced tumor progression after SRS underwent further treatment (four patients from the SCAs group and five patients from the control NFA's group). This treatment consisted of either repeat SRS (five patients) or other forms of radiotherapy (four patients). Outcome parameters are summarized in Table 2. Post-SRS, 8% (n = 4) of the SCAs group required further treatment due to SRS failure compared to the control NFA's group, (1.6%, n = 5). This difference was deemed statistically significant ($p = 0.0252$).

Factors related to tumor progression

Univariate and multivariate analysis of prognostic factors related to adenoma progression rate after SRS is presented in Table 3. No statistical significance was identified with respect to age at the time of SRS, tumor volume, or any pre-SRS pituitary endocrine deficiency (hypogonadism, hypothyroidism, hypocortisolism or pan-hypopituitarism). In the entire study cohort, there was a favorable adenoma progression rate in patients who received a higher margin dose to the adenoma (Fig. 2; Table 3). Increasing margin and maximum dose were predictably noted as significantly influencing the adenoma progression rate (HR = 0.852, $p < 0.0001$ and 95% CI 0.781–0.93 for margin dose and HR = 0.953, $p = 0.011$ and

95% CI 0.918–0.989 for maximum dose). Silent ACTH staining feature of the tumor was found to significantly influence the adenoma progression rate (HR = 2.861, $p = 0.005$ and 95% CI 1.372–5.966).

In multivariate analysis, silent ACTH staining (HR = 2.656, $p = 0.009$ and 95% CI 1.274–5.532) and increasing margin dose (HR = 0.854, $p = 0.017$ and 95% CI 0.75–0.972) remained statistically significant in influencing the adenoma progression rate. Figure 1 presents the prognostic significance of silent ACTH staining as defined by a significant adenoma progression rate after SRS. Figure 2 presents the prognostic significance of SRS margin dose, grouped to patients treated with a margin dose ≥ 17 or <17 Gy for the entire cohort. The ≥ 17 and <17 Gy margin dose grouping was shown to be statistically significant for the entire cohort (Fig. 2).

Discussion

Trans-sphenoidal microscopic or endoscopic resection (TSR) remains the treatment of choice for a NFA. However, surgery alone is associated with an increased risk of tumor recurrence or regrowth in completely excised lesions, as compared with a combined approach using surgery followed by radiation [22]. Suprasellar extension and cavernous sinus invasion by a NFA are known risk factors for adenoma recurrence and progression after TSR [4]. SRS was shown to provide an excellent solution for patients having residual tumor post-operatively, tumor progression or recurrence and invasion of the cavernous sinus or suprasellar compartment [4, 20, 23, 24]. It has generally indicated to be safe and effective, with the main risk being radiation-induced hypopituitarism [25, 26].

Radiosurgery for non functioning adenomas

In a recent review of literature [2, 20, 27–31] the major SRS series since 2002 that detailed outcomes in NFA patients were reviewed. In single session SRS a median margin dose of 16 Gy (range 12–20 Gy) were used for most patients. The tumor volume control rate averaged at 95.2% (range 83–100%). Post-SRS hypopituitarism was observed in an average of 8.8% (range 0–40%). Starke et al. similarly reported a 90% tumor volume control rate and 30% patients exhibited new-onset of post-SRS hypopituitarism in a series of 140 patients with NFA's [31]. Sheehan et al. reported in 2013 a multicenter retrospective study evaluating the role of GKRS for 512 patients with NFA's. At a median follow up time of 36 months, an overall tumor volume control rate of 93% was noted. Hypopituitarism following GKRS was reported in 21% of patients [20]. Positive prognosticators included patient age older than 50 years, tumor volume less than 5 cc, and those without prior radiation to the pituitary region. These prognostic factors were integrated into a radiosurgical pituitary score (RPS) [20].

The prognostic role of silent ACTH staining

In the previously described RPS, histological subtypes of NFA were not considered a prognostic factor. SCAs is hypothesized by some investigators as a more aggressive variant of NFA's, approaching that of Cushing's disease causing FA [9–16]. Others claim no prognostic significance for the silent ACTH staining feature [9, 17, 18]. The current study strongly suggests that histologic subtype may impact outcome of NFA to SRS. In this

comparative study, the two groups were similar with respect to patient demographic parameters, tumor features (size, volume, cavernous sinus invasion and suprasellar invasion), and SRS treatment features (Table 1). Of note, a pre-SRS worse endocrine status were noted for the control NFA group, presenting with a higher incidence of pituitary axis dysfunction (55.4%, $n = 170$ for the control NFA group vs. 34%, $n = 17$ for the SCAs, $p = 0.008$). On the other hand, pre-SRS incidence of headaches was significantly more reported in the SCA group ($p < 0.0001$). The reason for these pre-SRS differences is not known for certain, although the more aggressive nature and growth pattern of the SCAs is one such explanation.

Despite these patient tumor and treatment similarities, reviewing the different outcome parameters (Table 2), significantly poorer tumor volume control rates were noted in SCA patients than in those patients harboring other NFA subtypes ($p = 0.0065$). In addition, a new visual deficit was noted significantly more in the SCA group ($p < 0.0001$). A significantly higher number of SCA patients required additional intervention post-SRS for tumor progression ($p = 0.0252$). In multivariate analysis of prognostic factors influencing the tumor progression. (Table 3), the silent ACTH staining feature and a higher margin dose employed were the influential prognostic parameters.

Our findings confirm the aggressiveness of the SCA subtype of NFA, which is consistent with previous reports [7, 10, 11, 19]. Cooper et al. [11] reported a significantly shorter time to recurrence after TSR for SCAs as compared to other NFA's in a series of 16 SCAs and 84 NFA's (3 years in the SCA group vs. 8 years in the non-SCA NFA group, $p < 0.0001$). A higher incidence of post-SRS pituitary deficiency was reported in the SCA group as well. Jahangiri et al. [12] reported a significantly higher incidence of cavernous sinus invasion in a cohort of 75 SCA compared to a cohort of 1726 NFA's (30 vs. 18%, $p = 0.03$). No such difference in cavernous sinus invasion was noted in this report, which may in part be a result of a selection bias for SRS. Namely, SRS is frequently employed in treating cavernous sinus invading NFA patients.

SCA adenomas seem to bear clinical aggressiveness somewhere in the middle between negatively staining NFA's and FA's (causing CD). The margin dose typically used to treat CD is between 18 and 25 Gy [26]. Considering the lower rate of tumor control after SRS, once SCA status is histologically and clinically verified, physicians should consider prescribing an elevated margin dose to achieve a better chance of adenoma control (Fig. 2). This of course should be attempted in the frame of multiple anatomical and clinical constraints.

Study limitations

This study represents the largest series of SCA SRS presented to date. Analysis however, remains limited by the retrospective nature of the data collected from each of the participating institutions. Corticotroph staining was not routinely performed on every NFA and not always properly documented, which resulted in a smaller cohort than expected, yet still the largest reported. In our series, the ratio of SCA (50 patients) to the total NFA (307 patients) is 14%, which seems higher than the 3–9% in prior surgical series, suggesting there may exist referral bias [6, 12]. Patients who suffered treatment failure, or post radiosurgery

complications were followed more closely and had frequent imaging and clinical evaluations, and thus might be over-represented in this cohort. Not all patients followed exactly regular followup time points making the event analysis imperfect. From a procedural standpoint, the radiosurgical technology, related imaging, software and treatment algorithms have been refined over the study period, which may have contributed to a bias.

Conclusion

Silent corticotroph adenomas (SCA) appear clinically aggressive and radio-resistant to SRS compared to other subtypes of NFAs (ACTH negative NFAs). This histological feature confers an independent negative prognosis, in terms of post-radiosurgical tumor volume control, preservation of normal pituitary functions, and lack of clinical complications.

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Fig. 1. Kaplan Meier plot. Cumulative tumor failure rates of nonfunctioning pituitary adenomas (NFA's), comparing Silent ACTH staining (SCA) versus non-SCA NFA's. Refer to text

Fig. 2.
Kaplan Meier plot. Cumulative tumor failure rates of nonfunctioning pituitary adenomas (NFA's) for the entire cohort (n = 357), segregated based on margin dose (≥ 15 vs. <15 Gy) (p = 0.012). Refer to text

Table 1

Patient and tumor related parameters, compared

	SCA (%)	Non-SCA NFA's (%)	P
n	50	307	
Gender (M:F)	19:29 (40:60)	137:129 (52:48)	0.173
Age (median, mean) years	51.6, 50.9	56, 55.1	0.06
Age at last TSR (median, mean) years	50.1, 49.3	53.2, 52.72	0.109
Pre-SRS Pituitary endocrine deficiency			
Deficiency of any axis	17 (34)	170 (55.4)	0.008
Hypogonadism	9 (18)	94 (30.6)	0.0973
Hypo-ACTH	8 (16)	82 (26.7)	0.149
Hypothyroid	9 (18)	114 (37.1)	0.013
Pan-hypopituitarism	6 (12)	62 (20.2)	0.2403
Pre-SRS symptoms/signs			
Visual deficit	22 (44)	149 (48.5)	0.658
Headache	35 (72.9)	14 (6.1)	<0.0001
Weakness/fatigue	11 (22.9)	44 (19.3)	0.71
Sexual dysfunction	6 (12.5)	35 (15.2)	0.796
Tumor features			
Maximal tumor diameter (mm) (median, mean)	3, 3.3	2.9, 3.1	0.359
TV (ml) (median and range, mean and standard deviation)	4.3 (0.2–27), 5.6 (±6.9)	3.8 (0.1–57.3), 5.52 (±6)	0.951
Cavernous sinus invasion	38 (77.6)	210 (70.9)	0.434
Supra-sellar extension	37 (75.5)	251 (84.8)	0.157
Treatment features			
Margin dose (Gy) (median and range, mean and standard deviation)	14.5 (range 11:18), 14.5 (±2)	14 (range 5–25), 14.4 (±2.8)	0.814
Maximal dose (Gy) (median and range, mean and standard deviation)	28.05 (range 19.4:40), 28.34 (±5.4)	28 (range 6.3–50), 28.19 (±6.3)	0.854
Clinical follow-up (months) (median, range)	36.5 (7–108)	40 (6–163)	

Statistically significant values are in bold

SCA silent ACTH staining pituitary adenoma, NFA's non-functioning pituitary adenomas, ACTH adrenocorticotrophic hormone, TSR trans-sphenoidal resection, SRS stereotactic radiosurgery, mm millimeter, Gy gray, TV tumor volume

Table 2

Outcome parameters

	SCA (n = 50) (%)	Non-SCA NFA's (n = 307) (%)	Pr
Tumor control			
Decrease (>15%)	34 (68)	213 (69.4)	289 (94.1)
Stable (±15%)	7 (14)	76 (24.7)	
Progression (>15%)	9 (18)	18 (5.9)	0.0065
New endocrine deficiency	3 (6)	12 (3.9)	0.451
Resolved endocrine deficiency	0	19 (6.2)	0.088
Post-SRS symptoms/signs			
New visual deficit	5 (10)	0	<0.0001
Headache	20 (40)	90 (30.2)	0.224
Weakness/fatigue	9 (18)	10 (3.4)	<0.0001
Sexual dysfunction	4 (8)	16 (5.4)	0.507
Post-SRS treatment after progression			
Repeat SRS	1 (2)	4 (1.3)	5 (1.6)
Radiotherapy	3 (6)	1 (0.3)	0.0252

Statistically significant values are in bold

SCA silent ACTH staining pituitary adenoma, NFA's non-functioning pituitary adenomas, ACTH adrenocorticotroph hormone, SRS stereotactic radiosurgery

Table 3

Prognostic factors related to PFS after SRS after SRS (Cox regression model)

Potential factors	Univariate analysis			Multivariate analysis		
	HR	P	95% CI	HR	P	95% CI
Age	1.004	0.651	0.987–1.022	–	–	–
Hypogonadism	1.371	0.206	0.841–2.236	–	–	–
Hypothyroidism	0.770	0.297	0.470–1.259	–	–	–
Hypocortisolism	0.709	0.218	0.410–1.226	–	–	–
Pan-hypopituitarism	0.680	0.239	0.358–1.292	–	–	–
Tumor volume	0.979	0.435	0.929–1.032	–	–	–
Silent ACTH staining	2.861	0.005	1.372–5.966	2.656	0.009	1.274–5.532
Margin dose	0.852	<0.0001	0.781–0.93	0.854	0.0167	0.75–0.972
Maximal dose	0.953	0.011	0.918–0.989	–	–	–

Statistically significant values are in bold

PFS progression free survival, SRS stereotactic radiosurgery, HR hazard ratio, CI confidence interval, ACTH adrenocorticotrophic hormone