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Stereotactic radiosurgery for nonfunctioning pituitary tumor: A multicenter study of new pituitary hormone deficiency

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Abstract

Background. Stereotactic radiosurgery (SRS) is used to treat recurrent or residual nonfunctioning pituitary neuroendocrine tumors (NFPA). The objective of the study was to assess imaging and development of new pituitary hormone deficiency.

Methods. Patients treated with single-session SRS for a NFPA were included in this retrospective, multicenter study. Tumor control and new pituitary dysfunction were evaluated using Cox analysis and Kaplan–Meier curves.

Results. A total of 869 patients (male 476 [54.8%], median age at SRS 52.5 years [Interquartile range (IQR): 18.9]) were treated using a median margin dose of 14Gy (IQR: 4) for a median tumor volume of 3.4 cc (IQR: 4.3). With a median radiological follow-up of 3.7 years (IQR: 4.8), volumetric tumor reduction occurred in 451 patients (51.9%), stability in 364 (41.9%) and 54 patients (6.2%) showed tumor progression.

The probability of tumor control was 95.5% (95% Confidence Interval [CI]: 93.8–97.3) and 88.8% (95%CI: 85.2–92.5) at 5 and 10 years, respectively. A margin dose >14 Gy was associated with tumor control (Hazard Ratio [HR]:0.33, 95% CI: 0.18–0.60, $P < 0.001$). The probability of new hypopituitarism was 9.9% (95% CI: 7.3–12.5) and 15.3% (95% CI: 11–19.4) at 5 and 10 years, respectively. A maximum point dose >10 Gy in the pituitary stalk was associated with new pituitary hormone deficiency (HR: 3.47, 95% CI: 1.95–6.19). The cumulative probability of new cortisol, thyroid, gonadotroph, and growth hormone deficiency was 8% (95% CI: 3.9–11.9), 8.3% (95% CI: 3.9–12.5), 3.5% (95% CI: 1.7–5.2), and 4.7% (95% CI: 1.9–7.4), respectively at 10 years.

Conclusions. SRS provides long-term tumor control with a 15.3% risk of hypopituitarism at 10 years.

Key Points

- Tumor control for NFPA was 95.5% at 5 years and 88.8% at 10 years.
- The probability of new hypopituitarism was 9.9% at 5 years and 15.3% and 10 years.
- Dose >14Gy leads to better local control. Maximum dose <10Gy to the pituitary stalk reduces the risk of new hypopituitarism.

Importance of the Study

Recurrent or residual nonfunctioning pituitary neuroendocrine tumors are a difficult entity to manage. Stereotactic radiosurgery seems a reasonable alternative to new open surgery. However, long-term outcomes evaluation and refinement in techniques are required to improve the quality of care. This study presented, to the best of our knowledge, is the largest multicentric cohort (869 patients) evaluating outcomes after radiosurgery for nonfunctioning pituitary neuroendocrine tumors. Our finding demonstrates a good probability of tumor control at 10 years with a reasonable risk of new pituitary hormone deficiency. It is the first time that new cortisol, thyroid, gonadotroph, and growth hormone deficiencies were individually described to provide specific advice to patients. Risk factors of tumor control and new hormonal deficiency were studied. Treatment with a dose of more than 14Gy to the tumor and a dose to the stalk of less than 10 Gy demonstrated improved outcomes.

Pituitary neuroendocrine tumors, also known as pituitary adenomas, occur with an incidence between 3.9 and 7.4 cases per 100 000 per year,[1] nonfunctioning pituitary adenomas (NFPA) represent 15% to 30% of them.[1] Stereotactic radiosurgery (SRS) is used to treat residual and recurrent tumors or as primary treatment in carefully selected patients.[2,3]

Hypopituitarism is the most common complication of SRS, ranging between 23% and 50%[4–10] and with increasing rates over time: 7.8%, 16.2%, 22.4%, 27.5%, and 31.3% at 1, 3, 5, 7, and 10 years, respectively.[4] Probability rates of individual pituitary axis deficiencies are either not reported or their predicted rates are limited by the small number of patients included in the studies.[11–13] To our knowledge, this is the largest series of NFPA treated with radiosurgery.[3]

The aim of this study is to evaluate both tumor control and complications of new pituitary hormone deficiency after radiosurgery for NFPA.

Material and Methods

Twelve centers participated in this retrospective study and contributed clinical and radiological data on 869 patients treated with SRS, between 1992 and 2022, for a residual NFPA. Each participating center was responsible for data collection and IRB approval. Patient consent was not required because this is a retrospective study. A deidentified database was shared and checked for inconsistencies. Each center was asked to re-evaluate and correct its database if missing or inconsistent values were found. This study follows the STROBE (Strengthening the reporting of observational studies in epidemiology) criteria.

Study Inclusion Criteria

Each institutional radiosurgical database was queried for patients treated for a pituitary adenoma. Patients were included in the study if they fulfilled all of the following criteria: (1) had histologic confirmation of a pituitary adenoma, (2) had no evidence of a secreting tumor, (3) were treated in a single session, (4) had no prior irradiation to the sellar region, and (5) had at least 1 clinical and radiographic follow-up study.

Radiosurgical Technique

Radiosurgery was performed with the technology available at each center as described previously.[14] SRS was performed in all centers using the Gamma Knife (Elekta AB). The stereotactic frame was placed under local anesthesia, with or without intravenous conscious sedation, and a high-resolution, stereotactic magnetic resonance imaging, or computed tomography scan was acquired. The local multidisciplinary team approved the treatment plan.

Clinical and Radiological Follow-up

Radiological and clinical follow-up was performed according to the local policy.

Tumor size was documented on serial neuroimaging at each treatment center. Tumor progression was defined as a volumetric increase of ≥20% from baseline, and regression as a volumetric decrease of ≥20%. Lesions with volumetric changes of less than <20% were considered stable.[9,15] Tumor volumetric analysis was performed and reviewed at each participating center.

Pre- and post-SRS clinical endocrine evaluation was performed at each center to confirm the nonsecreting nature of the tumor and to assess pituitary function. Endocrine assessment included measurement of adrenocorticotropic hormone (ACTH) and serum cortisol, thyroid-stimulating hormone (TSH) and free thyroxine (T4), follicle-stimulating hormone (FSH) and testosterone or estradiol, insulin-like growth factor–1 (IGF-1), growth hormone (GH), prolactin. Clinical evaluation included assessment of symptoms of adrenal insufficiency, hypothyroidism, diabetes insipidus (DI), and hypogonadism.[4,14]

New-onset hypopituitarism was defined as dysfunction of at least 1 pituitary axis, documented either with a decrease in a hormone level below the limit of normal or a new requirement for hormone replacement by the endocrinologist. The occurrence of a new visual field or cranial nerve deficit was also recorded.

Statistical Analysis

Data were analyzed using R language (R foundation of Statistical computing).[16] Missing data were not imputed. Continuous variables are presented as the median and

Table 1. Description of the Cohort in Before SRS

Parameters	Number (%)
Median (IQR) age at SRS, y	52.5 (18.9)
Gender	
Male	476 (54.8%)
Female	393 (45.2%)
Number of surgical resections pre-SRS, median	
One surgical resection	558 (64.2%)
Two surgical resections	226 (26.0%)
Three or more surgical resections	85 (9.7%)
Median (IQR) time between resection and SRS, y	1.2 (3.2)
Pre-SRS visual field deficit	381 (44.0%)
Pre-SRS cranial nerve deficit (III–IV–VI)	34 (3.9%)
Pre-SRS cranial nerve deficit (V)	5 (0.6%)
Pre-SRS hormone deficiency (unknown 6)	
None	464 (53.8%)
One hormone	180 (20.9%)
Two hormones	97 (11.2%)
Three hormones	75 (8.7%)
Four hormones	21 (2.4%)
Five hormones	26 (3.0%)
ACTH deficiency	226 (26.2%)
TSH deficiency	270 (31.3%)
Gonadotropin deficiency	205 (23.8%)
IGF-1 deficiency	56 (6.5%)
Diabetes insipidus	56 (6.5%)
Histology[a]	
ACTH	55/566 (9.7%)
GH	20/565 (3.5%)
TSH	13/555 (2.3%)
LH	79/552 (14.3%)
FSH	104/555 (18.7%)
Prolactin	31/567 (5.5%)
PIT 1	6/75 (8%)
TPIT	1/69 (1.4%)
SF1	18/84 (21.4%)

Notes: ACTH = Adrenocorticotropic Hormone; FSH = follicle-stimulating hormone; GH = Growth hormone; IQR = Interquartile range; LH = Luteinizing hormone; PIT1 = Pituitary-specific positive transcription factor 1; SF-1 = Steroidogenic factor 1; SRS = Stereotactic radiosurgery; TPIT = T-box transcription factor; TSH = Thyroid-stimulating hormone.
[a]The histological analysis was not fully standardized among centers and have evolved over the study period. Additionally, in some cases the precise histological report was not available, as patients were referred to tertiary centres for radiosurgery. We provide in the table the number of patients with positive result among the total number for which data were available and the corresponding percentages for more clarity.

interquartile range (IQR); normality was assessed by graphical representation and the Shapiro test.

A *P* value <0.05 was considered statistically significant. Cox regression was used to assess predictive factors for tumor control (no growth) and new pituitary hormone deficiency. Continuous variables were dichotomized using the Youden Index. Significant and relevant factors with a *P* value <0.20 were included in the multivariable analysis. The Cox model assumptions were verified using Schoenfeld residuals for the proportional hazard assumption and Martingale residuals for the linearity assumption.

Kaplan–Meier curves were plotted for the probability of tumor control and new onset hypopituitarism.

Results

Demographics and SRS Characteristics

The study included 869 patients (men: 476 [54.8%]). The median age at SRS was 52.5 years (IQR: 18.9). The median time interval between the last surgical resection and SRS was 1.2 years (IQR: 3.2). Indication for SRS was residual growth in 403 patients (46.5%), adjuvant treatment in 307 patients (35.4%), tumor recurrence in 139 patients (16.0%), and patient preference in 18 (2.1%). In 2 cases, the reason was unknown (Table 1).

The residual treated involved the sella in 547 (62.9%) patients, the cavernous sinus in 560 (64.4%), the suprasellar region in 206 (23.7%), the clivus in 9 (1.0%), the sphenoid sinus in 4 (0.5%), and the middle cranial fossa in 1 (0.1%) patient. The median tumor volume was 3.4 cm^3 (IQR: 4.3) administering a median margin dose of 14Gy (IQR: 4, Table 2).

Table 2. SRS procedure Characteristics

Parameters	Number (%)
Location of treated lesion	
Sella	547 (62.9%)
Cavernous sinus	560 (64.4%)
Suprasellar	201 (23.1%)
Other	26 (3.0%)
Median (IQR) margin dose, Gy	14.0 (4.0)
Median (IQR) number of isocenters	11.0 (8.0)
Median (IQR) prescription isodose line, %	50.0 (0.0)
Median (IQR) tumor volume, cm^3	3.4 (4.3)
Median (IQR) optic apparatus maximum point dose, Gy	7.5 (2.7)
Median (IQR) pituitary stalk maximum point dose, Gy	9.0 (6.5)

Note: IQR = Interquartile range; SRS = Stereotactic radiosurgery.

Tumor Control

At the last median radiological follow-up of 3.7 years (IQR: 4.8), the tumor decreased in size in 451 patients (51.9%), was stable in 364 (41.9%), and increased in size in 54 (6.2%, Table 3).

The probability of tumor control was 97.7% (95% Confidence Interval [CI]: 96.6–98.9), 95.5% (95% CI: 93.8–97.3), and 88.8% (95% CI: 85.2–92.5) at 3, 5, and 10 years, respectively (Figure 1A).

Forty-seven patients required a new treatment after SRS. Twenty-nine underwent repeat SRS, 21 repeat surgical resection, 5 conventional or proton beam radiotherapy, and 2 medical therapy. The median time from SRS to a new treatment was 6 years (IQR: 6).

Using Cox analysis, a margin dose >14Gy was associated with a reduction in the risk of tumor progression (Hazard Ratio [HR]: 0.33, 95% CI: 0.18–0.60, $P < 0.001$; Supplementary Table 1, Figure 1B).

Table 3. Post-SRS Characteristics

Parameters	Number (%)
Median (IQR) clinical follow-up, y	3.6 (5.0)
Median (IQR) radiological follow-up, y	3.7 (4.8)
Median (IQR) time from SRS to first hormone deficiency, y	2.2 (3.5)
New hormone deficiency post-SRS	73 (8.7%)
At 5 y	9.9% (95% CI: 7.3–12.5)
At 10 y	15.3% (95% CI: 11–19.4)
ACTH deficiency	
At 5 y	5.5% (95% CI: 3.3–7.7)
At 10 y	8% (95% CI:3.9–11.9)
TSH deficiency	
At 5 y	4.6% (95% CI: 2.5–6.7)
At 10 y	8.3% (95% CI: 3.9–12.5)
Gonadotropin deficiency	
At 5 y	2.9% (95% CI: 1.5–4.4)
At 10 y	3.5% (95% CI: 1.7–5.2)
Growth hormone (IGF-1) deficiency	
At 5 y	2.8% (95% CI: 1.2–4.4)
At 10 y	4.7% (95% CI: 1.9–7.4)
New visual field defect	12 (1.4%)
Other cranial nerve deficit	6 (0.7%)
Tumor response post-SRS	
Stable	364 (41.9%)
Decreased	451 (51.9%)
Increased	54 (6.2%)

Note: ACTH = Adrenocorticotropic hormone; IGF-1 = Insulin growth factor 1; SRS = Stereotactic radiosurgery; TSH = Thyroid stimulating hormone.

Hypopituitarism

The pre-SRS hormone function was available for 863 patients. The pituitary function was unaffected in 53.8% (464/863) pre-SRS. The most common hormone deficits were: thyroid deficiency in 31.3% (270/863) patients, cortisol deficiency in 26.2% (226/863), gonadotrophin deficiency in 23.8% (205/863), growth hormone deficiency in 6.5% (56/863), and diabetes insipidus in 6.5% (56/863).

After excluding patients with panhypopituitarism (n = 26), the post-SRS pituitary function was evaluated in 837 patients with at least 1 pituitary hormone still at risk (Supplementary Figure 1). At a median follow-up of 3.5 years (IQR: 5.1), 73 patients (8.7%) developed a new hormone deficiency with a median latency from SRS of 2.2 years (IQR: 3.5). Most of the patients developed a deficit of a single pituitary hormone (53/837 [6.3%]), followed by 2 (16/837 [1.9%]), and 3 hormones (4/837 [0.5%]).

The cumulative probability of new hypopituitarism was 6.5% (95% CI: 4.6–8.4), 9.9% (95%CI: 7.3–12.5), and 15.3% (95% CI: 11–19.4) at 3, 5, and 10 years, respectively (Figure 2).

A maximum point dose >10Gy in the pituitary stalk was associated with the occurrence of a new hormone deficiency in multivariate Cox analysis (HR: 3.53, 95% CI: 1.98–6.29, $P < 0.001$; Supplementary Table 2, Figure 3).

Among patients without dysfunction of the hypothalamic–pituitary–adrenal axis prior to SRS (n = 643), a new deficit was reported in 29 (4.5%) with a median time of 1.5 years (IQR:1.5) after SRS. The cumulative probability was 4.3% (95% CI: 2.6–6.1), 5.5% (95% CI: 3.3–7.7), and 8% (95% CI: 3.9–11.9) at 3, 5, and 10 years, respectively (Supplementary Figure 1).

Of the 599 patients without hypothalamic–pituitary–thyroid dysfunction prior to SRS, 25 (4.2%) patients demonstrated a new hormone deficiency; the median time to new-onset dysfunction was 1.6 years (IQR: 3.0). The cumulative probability of a new deficit was 3.1% (95% CI: 1.6–4.6), 4.6% (95% CI: 2.5–6.7), and 8.3% (95% CI: 3.9–12.5) at 3, 5, and 10 years, respectively.

Among patients without gonadotroph dysfunction prior to SRS (n = 664), a new deficit was reported in 20 (3.0%) with a median delay of 1.5 years (IQR: 2.0). The cumulative probability was 2.9% (95% CI: 1.5–4.4) at 3 and 5 years and 3.5% (95% CI: 1.7–5.2) at 10 years.

At SRS, 813 patients were at risk for new growth hormone deficiency; new post-SRS deficiency was reported in 17 patients (2.1%) with a delay of 3.7 years (IQR: 2.9). The cumulative probability was 1.1% (95% CI: 0.3–1.9), 2.8% (95% CI: 1.2–4.4), and 4.7% (95% CI: 1.9–7.4) at 3, 5, and 10 years, respectively (Figure 2).

Among patients with intact vasopressin production prior to SRS (n = 813), new diabetes insipidus developed in 5 (0.6%) of the patients with a delay of 3.2 years (IQR: 1.0) from SRS.

Clinical Outcomes

Prior to SRS, 381 (44.0%) patients had a visual field defect, 16 (1.8%) patients had an oculomotor nerve palsy, 2 (0.2%)

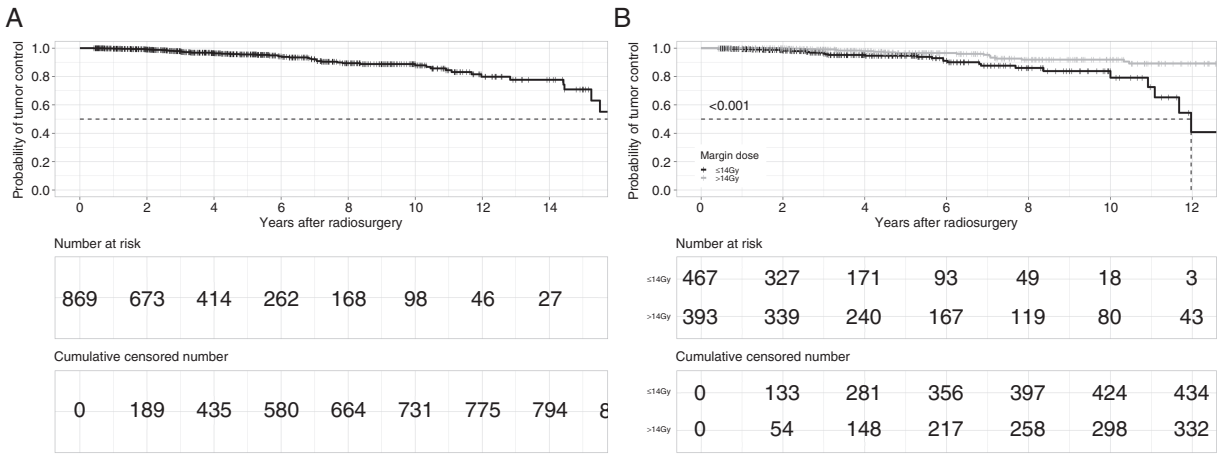

Figure 1. Kaplan–Meier curves demonstrating tumor control following SRS treatment in the entire cohort (**A**) and in function of margin dose (**B**). The probability of tumor control was 95.5% and 88.8% at 5 and 10 y, respectively. Tumors treated with prescription doses >14Gy exhibited higher long-term tumor control ($P < 0.001$).

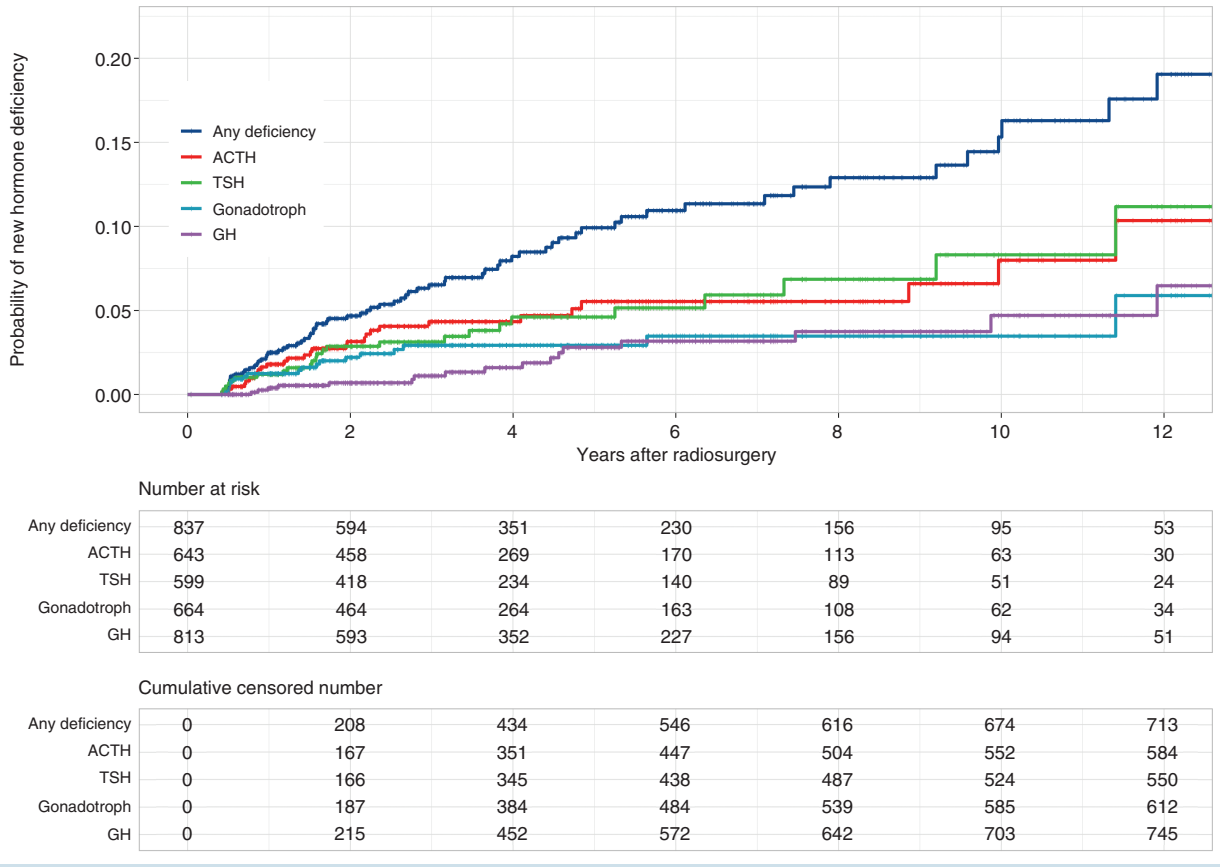

Figure 2. Probability of new hormonal deficit by hormonal subtype. The cumulative probability of gonadotroph (3.5%) and growth hormone (4.7%) deficiency at 10-y was lower than that of ACTH (8%) and TSH (8.3%).

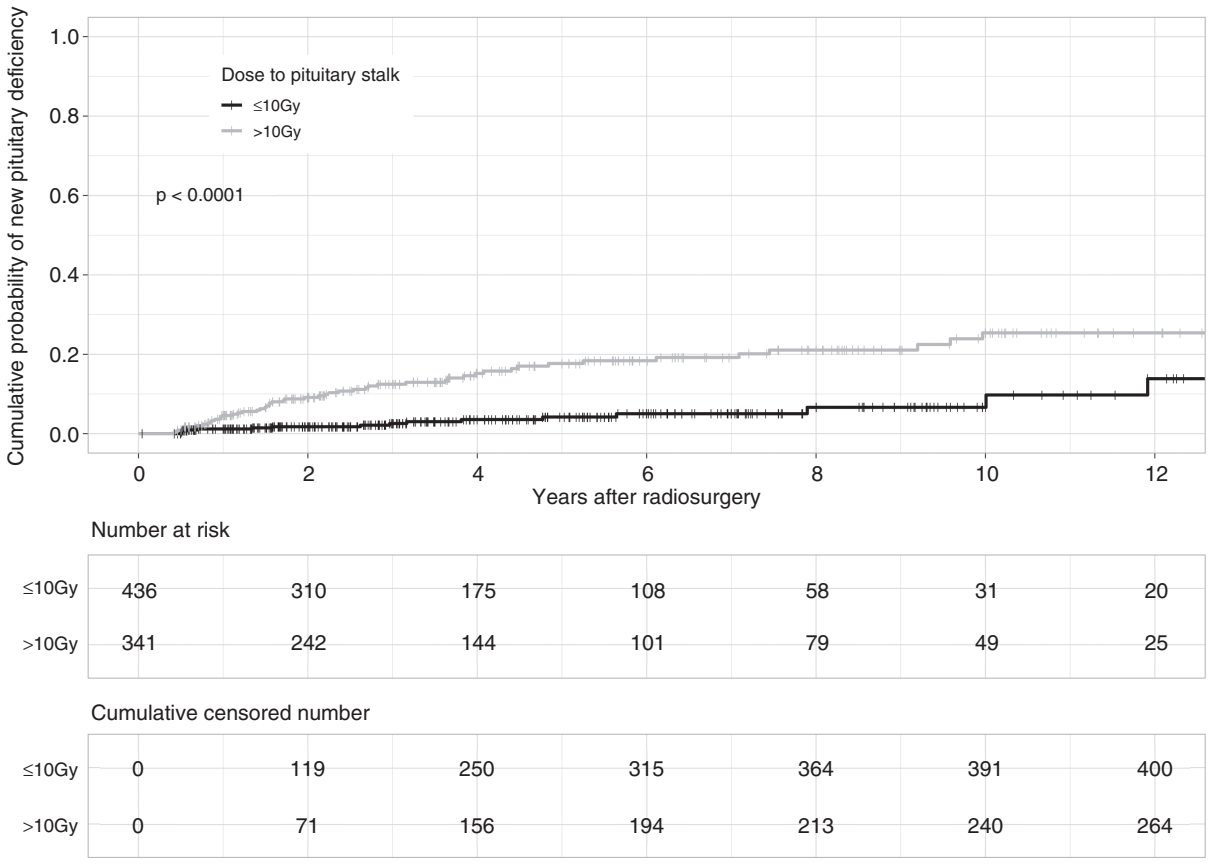

Figure 3. Cumulative probability of new hypopituitarism in function of the median point dose to the stalk. Maximum point doses ≥10Gy on the pituitary stalk correlated with higher probability of new pituitary dysfunction ($P < 0.001$)

patients had a trochlear nerve palsy, and 12 (1.4%) abducens nerve palsy alone. One (0.1%) patient had a palsy of the third and fourth cranial nerve, 1 (0.1%) of the third and sixth cranial nerve, and 1 (0.1%) of the third, fourth, and sixth cranial nerves. One (0.1%) patient had diplopia, but the cranial nerves affected were unknown. In 5(0.6%) patients, the fifth cranial nerve was affected.

After SRS, 2 (0.2%) patients developed a third, 2 (0.2%) a sixth, 1 (0.1%) a third and a sixth, and 1 (0.1%) a fifth cranial nerve palsy. In 3 of the cases, the new deficit was associated with tumor progression. A new or worsening of a visual field defect occurred in 12 (1.4%).

Fourteen (1.6%) patients died during follow-up. The reason was unrelated to the NFPA in 8 cases and unknown in the remaining 6.

Discussion

Tumor Control

In this study, 869 patients were treated with single-session SRS for residual or recurrent NFPA. At a median radiological follow-up of 3.7 years, progression occurred in 54 (6.2%) cases. The probability of tumor control was 97.7%, 95.5%, and 88.8% at 3, 5, and 10 years, respectively. Owing to the large number of patients and the long-term follow-up (334 patients with a follow-up of more than 5 years and 97 of more than 10 years), these results are notable for evaluation of the long-term efficacy of SRS. These long-term tumor control rates are in accordance with previous reports.[12,13,17–19] However, bias might have been introduced, as the analysis of tumor volume was performed locally and not centrally using a blind evaluation method. Using multivariable analysis, the only factor found to reduce the risk of tumor progression is a higher margin dose (HR: 0.33, 95% CI: 0.18–0.60, $P < 0.001$). Tumor volume and parasellar invasion were not significantly associated with tumor progression, contrary to prior studies.[13,19] The inclusion of pituitary adenomas with a relatively limited volume range (3.4 cm^3 [IQR: 4.3]) may be an explanation for these differences.

Hypopituitarism

The probability of developing a new pituitary hormone deficiency was 6.5%, 9.9%, and 15.3% at 3, 5, and 10 years, respectively. This rate is lower than described in the literature ranged between 25.3% and 30% at 5 years for NFPA.[13,18,20] In 2 recent meta-analyses by Kotecha et al. and Albano et al., the pooled estimate of post-SRS hypopituitarism was 21% and 18%, respectively.[3,21]

The 10-year cumulative probability of new specific hormone deficiency was 8% for cortisol, 8.3% for thyroid, 3.5% for gonadotroph, and 4.7% for growth hormone. This is the first time that the risk of new deficiency was evaluated by hormone subtype, providing a better prospect for each patient of the risk for developing another specific deficit. Animal model studies and radiosurgical series of functioning pituitary adenomas have suggested a higher sensitivity to radiation for growth hormone secretion compared with ACTH.[10,22] The lower rate of pituitary deficiency found in our study could be due to the higher number of patients and the inclusion of solely nonfunctioning pituitary adenoma patients compared to more heterogenous and smaller series; this should provide a better estimate of long-term hypopituitarism rates. However, it is possible that the new hormonal deficit underreporting could have influenced our results. The lower rate of gonadotroph and growth hormone deficiency observed in the current study could be explained by a lack of systematic testing and replacement for these hormones in the clinical setting, rather than a true difference in radiosensitivity. This is part of the limitations of multicentric studies with local endocrinology evaluation using different laboratory assays with variable reference ranges over time. In the same way, we did not ask for a specific hormone follow-up as the endocrine testing is relatively consensual on which hormone should be tested. So instead of having a specific hormone follow-up, we have a global hormone follow-up which was used for the statistical analysis. This could lead to uncertainty in the rate of new endocrinopathies estimation.

The multicentric design allows a more generalizable study but outcomes (endocrine and tumoral follow-up) can be affected by differences in local habits, patients' selection, and length of follow-up. The direction of these differences in the results cannot be defined. A maximum point dose >10 Gy in the pituitary stalk was associated with the occurrence of new hormone deficiency (HR: 3.53, 95% CI: 1.98–6.29, $P < 0.001$). Some factors that show association with the development of hypopituitarism in other studies such as the total dose to the gland[7,23] or distance from the center of the tumor[6] were not evaluated in the current study.

Histology

NFPAs encompass a wide spectrum of immunohistological subtypes.[24] Specific subtypes, such as silent corticotroph adenomas, exhibit more aggressive natural history[25,26] and recur more frequently after SRS.[27] ACTH staining was only available in 566 patients in this study, precluding its inclusion as a potential factor in the Cox analysis. In the same way, Ki-67 was only available in 116 patients with a clear bias between centers. As such, this factor could not be included in the multivariable analysis and its impact on prognosis in radiosurgical outcomes could not be evaluated.

The 2021 World Health Organization classification introduced cell transcription factors, such as the pituitary-specific positive transcription factor 1 (PIT1), the T-box transcription factor (TPIT), and the steroidogenic factor 1 (SF-1), to better characterize pituitary adenomas. As our study involved patients treated from 1999 to 2021, these factors were only available for a small number of patients (75 for PIT1, 69 for TPIT, and 84 for SF-1). Silent PIT-1 lineage tumors have been suggested to exhibit more aggressive behavior.[28] The exact implication of this tumor subtype in radiosurgery outcomes needs further evaluation.

Conclusions

SRS for NFPA affords long-term tumor control, with the probability exceeding 88% at 10 years. The cumulative probability of new pituitary dysfunction was 15.3% at 10 years. Treatment with a dose of more than 14Gy to the tumor and a dose to the stalk of less than 10 Gy demonstrated improved outcomes.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

hypopituitarism | nonfunctioning | pituitary adenoma | pituitary neuroendocrine tumors | stereotactic radiosurgery

Conflict of Interest

D.L.L. is a stockholder in AB Elekta, Stockholm, Sweden. J.D.P. is part of Novocure advisory board and receives Varian speaking fees, Kroger trial funding, NIH R01CA269948, NIH R702 award, Biocept clinical trial funding, and Genentech clinical trial funding. The other authors report no conflicts of interest.

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Data Availability

Data are available upon reasonable request to the corresponding author.

Author Contributors

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