J Neurosurg 119:446–456, 2013

Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study

Clinical article

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Object. Pituitary adenomas are fairly common intracranial neoplasms, and nonfunctioning ones constitute a large subgroup of these adenomas. Complete resection is often difficult and may pose undue risk to neurological and endocrine function. Stereotactic radiosurgery has come to play an important role in the management of patients with nonfunctioning pituitary adenomas. This study examines the outcomes after radiosurgery in a large, multicenter patient population.

Methods. Under the auspices of the North American Gamma Knife Consortium, 9 Gamma Knife surgery (GKS) centers retrospectively combined their outcome data obtained in 512 patients with nonfunctional pituitary adenomas. Prior resection was performed in 479 patients (93.6%) and prior fractionated external-beam radiotherapy was performed in 34 patients (6.6%). The median age at the time of radiosurgery was 53 years. Fifty-eight percent of patients had some degree of hypopituitarism prior to radiosurgery. Patients received a median dose of 16 Gy to the tumor margin. The median follow-up was 36 months (range 1–223 months).

Results. Overall tumor control was achieved in 93.4% of patients at last follow-up; actuarial tumor control was 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years postradiosurgery, respectively. Smaller adenoma volume (OR 1.08 [95% CI 1.02–1.13], p = 0.006) and absence of suprasellar extension (OR 2.10 [95% CI 0.96–4.61], p = 0.064) were associated with progression-free tumor survival. New or worsened hypopituitarism after radiosurgery was noted in 21% of patients, with thyroid and cortisol deficiencies reported as the most common postradiosurgery endocrinopathies. History of prior radiation therapy and greater tumor margin doses were predictive of new or worsening endocrinopathy after GKS. New or progressive cranial nerve deficits were noted in 9% of patients; 6.6% had worsening or new onset optic nerve dysfunction. In multivariate analysis, decreasing age, increasing volume, history of prior radiation therapy, and history of prior pituitary axis deficiency were predictive of new or worsening cranial nerve dysfunction. No patient died as a result of tumor progression. Favorable outcomes of tumor control and neurological preservation were reflected in a 4-point radiosurgical pituitary score.

Conclusions. Gamma Knife surgery is an effective and well-tolerated management strategy for the vast majority of patients with recurrent or residual nonfunctional pituitary adenomas. Delayed hypopituitarism is the most common complication after radiosurgery. Neurological and cranial nerve function were preserved in more than 90% of patients after radiosurgery. The radiosurgical pituitary score may predict outcomes for future patients who undergo GKS for a nonfunctioning adenoma.
(http://thejns.org/doi/abs/10.3171/2013.3.JNS12766)

Key Words • stereotactic radiosurgery • Gamma Knife • pituitary adenoma • pituitary surgery • oncology

Abbreviations used in this paper: CN = cranial nerve; EBRT = external-beam radiation therapy; GKS = Gamma Knife surgery; NAGKC = North American Gamma Knife Consortium; RPS = radiosurgical pituitary score; SRS = stereotactic radiosurgery.

Pituitary adenomas account for approximately 10%–20% of all intracranial tumors.[24,25] Adenomas are broadly classified into functioning and nonfunctioning ones. Nonfunctioning adenomas are composed of cells

that do not secrete a known, biologically active pituitary hormone. They are also called nonsecretory or null-cell pituitary adenomas. These nonfunctioning adenomas constitute approximately 15%–30% of all pituitary tumors.[10,13] Growing macroadenomas can compress the optic apparatus and result in visual field or acuity loss. Nonfunctioning adenomas can also result in hypopituitarism by compressing the normal pituitary gland.

Patients with symptomatic or enlarging nonfunctioning pituitary adenomas usually undergo resection. Complete resection may not always be feasible. Even in the best of hands and in those patients in whom a complete resection appears to have been achieved, recurrences develop in 24%–80% of pituitary adenoma patients.[6,9,24,25,38] Patients who experience a recurrence often have evidence of cavernous sinus or dural invasion or have high proliferation indices on neuropathological analysis.[6,33,37]

Stereotactic radiosurgery provides an important management option in patients with recurrent nonfunctioning pituitary adenomas, and less commonly as the initial management of patients with high surgical comorbidities.[48] The current study details the pooled results of GKS performed at multiple centers that participate in the NAGKC.

TABLE 1: Attributes for the nonfunctioning pituitary adenoma series

Parameter	Value*
no. of patients	512
male	286 (55.9)
female	226 (44.1)
age in yrs	
mean	53.1
median (range)	53 (16–88)
prior resection (%)	479 (93.6)
no. of patients w/ >1 surgery	212 of 511 (41.5)
prior radiation therapy (%)	34 (6.6)
any prior hypopituitarism (%)	296 of 510 (58.0)
cortisol (%)	158 of 508 (31.1)
thyroid (%)	207 of 509 (40.7)
gonadotropin (%)	166 of 507 (32.7)
growth hormone (%)	77 of 485 (15.9)
diabetes insipidus (%)	32 of 509 (6.3)

* Values are presented as the number of patients (%) unless specified otherwise.

Methods

Patient Selection

Nine medical centers affiliated with the NAGKC received individual internal review board approvals to submit their retrospective clinical outcome analysis of patients with nonfunctioning pituitary adenomas. The following centers contributed data: the University of Pittsburgh (125 patients), University of Kentucky (49 patients), Cleveland Clinic (37 patients), University of Sherbrooke (38 patients), University of Pennsylvania (21 patients), Yale University (39 patients), University of California, San Francisco (47 patients), New York University (16 patients), and the University of Virginia (140 patients).

The records of patients with pituitary adenomas who underwent GKS between 1988 and 2011 were assessed by each center for inclusion (Table 1). An Excel spreadsheet database with selected variables was created and sent to all participating centers. Participating centers reviewed the medical records of their patients, entered the data in the spreadsheet, and removed all patient identifiers from the data. Under institutional review board approval, pooled and de-identified data were screened by an independent third party and were then transmitted to the first author, who drafted this report on behalf of the NAGKC.

Clinical and imaging outcomes were assessed at a median follow-up period of 36 months (range 1–223 months) after SRS (Table 2).

Clinical Material

The clinical series included 512 patients (226 [44%] females and 286 [56%] males) (Table 1). The median age of the patients at the time of GKS was 53 years (range 16–88 years). Most patients (93.6%) underwent at least 1 prior resection and therefore had histological confirmation of the tumor. Of interest, 41.5% had a history of more than 1 previous resection. Those without histological diagnosis were classified as having a nonfunctioning pituitary adenoma on the basis of clinical presentation, neuroendocrine assessment, and imaging features (for example, location, MRI and/or CT characteristics, and growth behavior). Prior fractionated radiation therapy was performed in 34 patients (6.6%); all 34 had documented tumor progression despite radiation therapy. All patients were assessed serially by clinical, CN, and neuroendocrine evaluations. Cranial nerve function was rated as improved, stable, or worse.

The Radiosurgical Procedure

The models U, B, C, 4C, or Perfexion Gamma Knife units (Elekta AB) were used depending on the technology available and time of treatment at the various participating centers. The radiosurgical procedure began with the application of the Leksell Model G stereotactic frame (Elekta AB) using a local anesthetic supplemented by additional intravenous conscious sedation as needed. After frame placement, high-resolution stereotactic MRI was performed. In rare cases in which MRI was not feasible, CT scanning was used as an alternative. Thin-slice axial and/or coronal plane images were obtained after intravenous contrast administration. Stereotactic radiosurgery dose planning was then performed in consultation with a neurosurgeon, radiation oncologist, and medical physicist.

The median tumor volume was 3.3 cm^3 (range 0.08–35.2 cm^3). A median of 8 isocenters (range 1–28) was used for dose planning. The median prescription dose delivered to the tumor margin was 16 Gy (range 5–35 Gy). The maximum dose varied from 10 to 70 Gy (median 32 Gy) (Table 2). At each center, dose selection was based on a complex iteration of tumor volume, contiguity to the op-

TABLE 2: Gamma Knife surgery parameters, tumor extension, and length of follow-up

Characteristic	Mean ± SD	Median (range)	No. of Patients (%)
margin dose (Gy)	16.4 ± 4.1	16 (5–35)	
max dose (Gy)	35.0 ± 9.9	32 (10–70)	
no. of isocenters	9.1 ± 5.4	8 (1–28)	
max dose to optic apparatus (Gy)	6.6 ± 2.7	7.4 (0–21.4)	
treatment vol (cm^3)	4.6 ± 4.9	3.3 (0.08–35.2)	
length of follow-up	47.1 ± 41.3	36 (1–223)	
no. w/ cavernous sinus involvement (%)			366 of 512 (71.5)
no. w/ suprasellar extension (%)			162 of 493 (32.9)

tic apparatus, and history of prior fractionated radiation therapy exposure.

Evaluation Criteria

Clinical and imaging evaluations were typically performed at follow-up intervals of 6 months in the 1st or 2nd year after radiosurgery. In patients demonstrating evidence of tumor growth control and absence of new neurological findings, follow-up intervals then increased to every 1–2 years. Whenever possible, patients underwent follow-up examination, endocrine testing, and neuroimaging at the respective treating center. However, since all institutions were referral centers for a broad geographic area, some patients underwent follow-up evaluations by their referring physicians. In those cases, clinical notes, laboratory tests, and neuroimaging studies were sent and reviewed by the treating neurosurgeons who performed the GKS. The follow-up images were compared with the images obtained at the time of GKS. Tumor dimensions were measured in the axial, sagittal, and coronal planes. A volume was then roughly calculated by multiplying the left-right (x), anterior-posterior (y), and superior-inferior (z) dimensions and dividing this number by 2. Tumor growth within the prescribed isodose volume or adjacent to it was considered tumor progression.

Statistical Analysis

Data are presented as the median or mean and range for continuous variables, and as frequency and percentages for categorical variables. Statistical analyses of categorical variables were carried out using the chi-square test, Fisher exact test, and Mantel-Haenszel test for linear association as appropriate. Statistics of means were carried out using the unpaired Student t-test, both with and without equal variance (Levene test) as necessary, and Wilcoxon rank sum tests when variables were not normally distributed. Kaplan-Meier curves were plotted for survival and progression-free survival using the dates of first SRS, follow-up MRI session, and death or last follow-up. Progression-free survival and overall survival times were calculated from the day of the first SRS using the Kaplan-Meier method.

Univariate analysis was performed on the Kaplan-Meier curves using log rank statistics. Factors predictive of tumor progression ($p < 0.15$) were entered into Cox regression analysis to assess hazard ratios.[2] Additionally, clinical covariates predicting new or worsening neurological dysfunction or new endocrinopathy with a univariate p value < 0.15 were included in multivariable logistic regression analysis. Continuous variables were also assessed as dichotomized transformations based on quartile and median percentiles as well as breakpoints with the most statistically significant predictive value. Clinically significant variables and interaction expansion covariates were further assessed in both Cox and logistic multivariable analyses as deemed relevant. Logistic regression analysis was also used to assess predictors of unfavorable outcome (tumor progression and/or new or worsening CN deficit). Covariates predicting unfavorable outcome with a univariate p value < 0.15 were included in multivariable logistic regression analysis. Covariates with $p < 0.05$ in multivariate analysis were weighted according to their odds ratios to compute the nonfunctioning pituitary adenoma prognostic score for each patient. Probability values ≤ 0.05 were considered statistically significant. For statistical analysis, we used Stat software (version 12, StataCorp LP 2012).

Results

Tumor Response

The median follow-up after GKS was 36 months (mean 47.1, range 1–223 months). The percentages of patients having 3 or more, 5 or more, and 7 or more years of follow-up were 49.3%, 37.3%, and 16.4%, respectively. At last follow-up, 31 (6.6%) of 469 patients with available follow-up and imaging had tumor progression (Table 3). Thus, the overall tumor control after radiosurgery was 93.4%. Actuarial progression-free survivals were 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years postradiosurgery, respectively (Fig. 1). There was no significant difference in the progression-free survival in patients with upfront radiosurgery versus those who had a prior resection ($p > 0.05$, log-rank test; Fig. 2). Further surgery or radiation therapy as either a planned combination approach (for example, GKS plus surgery), shunting of hydrocephalus, or treatment due to tumor progression was carried out in 7.7% of patients.

Factors predictive of tumor progression in univariate analysis are listed in Table 4. Volume was a significant predictor of tumor progression when broken down between patients with lesions 5 cm^3 or smaller versus those

TABLE 3: Complications after SRS

Complication	No. of Patients (%)
patients w/ new CN dysfunction*	41 of 442 (9.3)
CN II	29 (6.6)
CN III	6 (1.36)
CN IV	1 (0.23)
CN V	4 (0.90)
CN VI	2 (0.45)
CN VII	1 (0.23)
any new or worsened hypopituitarism	92 of 435 (21.1)
cortisol	29 of 293 (9.9)
thyroid	40 of 246 (16.3)
gonadotropin	24 of 288 (8.3)
growth hormone	31 of 369 (8.4)
diabetes insipidus	6 of 422 (1.4)
further tumor growth	31 of 469 (6.6)
further surgery or radiation therapy	34 of 444 (7.7)

* Forty-one patients had 43 deficits.

with lesions larger than 5 cm^3 (Fig. 3). Patients having suprasellar extension (32.9%) also had an increased risk of tumor progression (Fig. 4). The median dose used in this series was 16 Gy. Those treated with 16 Gy or greater were less likely to demonstrate tumor progression (Fig. 5). Nine (26.5%) of 34 patients receiving a marginal dose of less than 12 Gy had tumor progression versus 17 (4.5%) of 355 12–20 Gy, versus 5 (8%) of 60 receiving greater than 20 Gy ($p < 0.001$) (Fig. 6).

In multivariate analysis, volume was such a strong predictor of tumor progression that it removed all other covariates (OR 1.08 [95% CI 1.02–1.13], p = 0.006). After controlling for volume, there was a trend for patients with

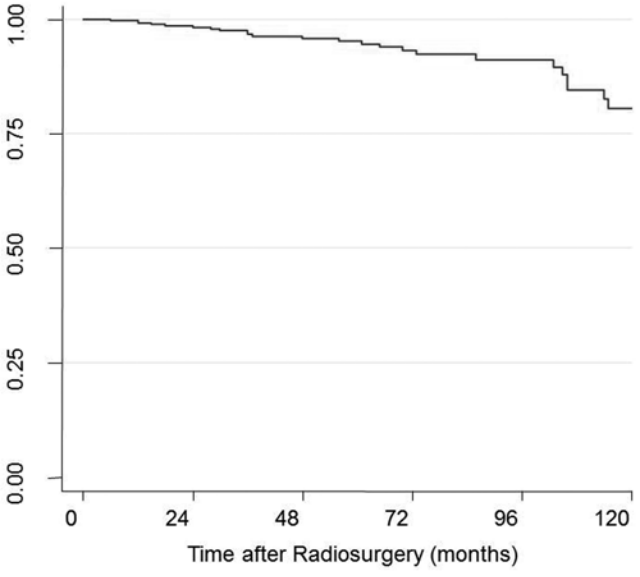

Fig. 1. Progression-free survival after GKS for a cohort of 512 patients with nonfunctioning pituitary adenomas.

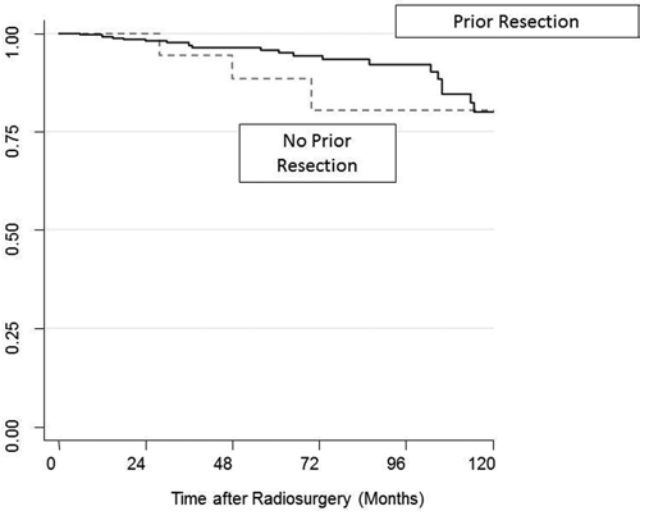

Fig. 2. Progression-free survival after GKS for those undergoing upfront compared with salvage radiosurgery.

suprasellar extension (OR 2.10 [95% CI 0.96–4.61], p = 0.064) to have tumor progression (Table 4).

Clinical Response

At last follow-up, 41 (9.3%) of 442 patients had some worsening of a preexisting CN deficit or developed a new CN deficit (Table 3). Patients with tumor progression despite radiosurgery were more likely to have new or worsened CN deficits (p = 0.038, chi-square test). Twenty-nine (6.6%) of 442 patients had worsening or new-onset optic nerve dysfunction. Further deficits by individual CN are detailed in Table 3.

Factors predictive of new or worsening CN dysfunction are demonstrated in Table 5. In multivariate analysis patients with larger tumor volumes (OR 1.09 [95% CI 1.02–1.15], p = 0.004), history of any prior hypopituitarism (OR 3.44 [95% CI 1.39–8.54], p = 0.008), history of prior radiation therapy (OR 4.90 [95% CI 1.67–13.40], p = 0.004), and younger age (OR 1.03 [95% CI 1.00–1.05], p = 0.048) were more likely to have CN deficits after SRS. Four (12.1%) of 33 patients receiving less than 12 Gy, 31 (8.9%) of 347 receiving 12–20 Gy, and 5 (8.8%) of 57 receiving more than 20 Gy had new or worsening CN dysfunction (p = 0.827).

Endocrine Response

In this report, 435 patients had detailed endocrine follow-up. Preexisting pituitary hormone deficits were present in 21.1% of those patients, including 8 patients with panhypopituitarism. Ninety-two patients developed new or worsening pituitary dysfunction. Specific new or worsening pituitary dysfunction after GKS is demonstrated in Table 3. New or worsened endocrine deficits in order of increasing frequency were as follows: diabetes insipidus, gonadotropin, growth hormone, cortisol, and thyroid hormone. Comparing patients with and without preoperative endocrine deficits, those with preoperative endocrine deficits were not more likely to develop additional post-GKS deficits (p = 0.92, chi-square test).

TABLE 4: Factors predictive of tumor progression

Covariate	HR (95% CI)	p Value
univariate analysis*		
male sex	1.67 (0.79–3.52)	0.177
history of radiation	2.29 (0.97–5.40)	0.058
history of hypothyroidism	0.57 (0.27–1.23)	0.154
suprasellar extension	2.50 (1.20–5.20)	0.014
decreasing margin dose	0.93 (0.84–1.01)	0.078
increasing no. of isocenters	1.07 (0.99–1.16)	0.070
new post-GKS visual deficit	2.15 (0.81–5.67)	0.123
any new post-GKS CN deficit	2.15 (0.87–5.32)	0.096
increasing vol	1.11 (1.05–1.16)	<0.001
multivariate analysis†		
vol	1.08 (1.02–1.13)	0.006
suprasellar extension	2.10 (0.96–4.61)	0.064

* Factors predictive of tumor recurrence in univariate analysis ($p < 0.20$).

† Factors predictive of tumor recurrence in multivariate analysis.

Univariate predictors of new or worsening pituitary dysfunction are demonstrated in Table 6. In multivariate analysis, increasing margin dose (OR 1.07 [95% CI 1.01–1.12], $p = 0.018$) and history of prior radiotherapy (OR 2.44 [95% CI 1.04–5.77], $p = 0.041$) were predictive of either new or worsening pituitary dysfunction. Patients with new or worsening CN dysfunction were also more likely to have new or worsening pituitary dysfunction after treatment (OR 2.39 [95% CI 1.19–4.83], $p = 0.015$).

Other Serious Complications

No center reported additional complications such as carotid occlusion, stroke, or radiation-induced neoplasia.

A Proposed Pituitary Adenoma Radiosurgical Grading System

We defined a favorable radiosurgical outcome as no tumor growth and preservation of neurological function (no new or worsened CN deficits). Of the 512 patients included in the series, 451 (88%) achieved a favorable radiosurgical outcome at last follow-up. Factors that were statistically ($p < 0.05$) related to this favorable outcome were age older than 50 years, tumor volume less than 5 cm^3, and no prior radiotherapy.

An RPS was developed based on multivariate modeling. The score was as follows: age: 1 point for > 50 years old, 0 points for ≤ 50 years old; tumor volume: 1 point for tumor volume < 5 cm^3, 0 points for tumor volume ≥ 5 cm^3; and prior radiation: 2 points for no previous radiation, 0 points for prior radiation. Favorable outcomes for the RPS were as follows: RPS of 4 had a favorable outcome of 95%; RPS of 3 had a favorable outcome of 88%; RPS of 2 had a favorable outcome of 67%; RPS of 1 had a favorable outcome of 50%; and RPS of 0 had a favorable outcome of 20% (Fig. 7).

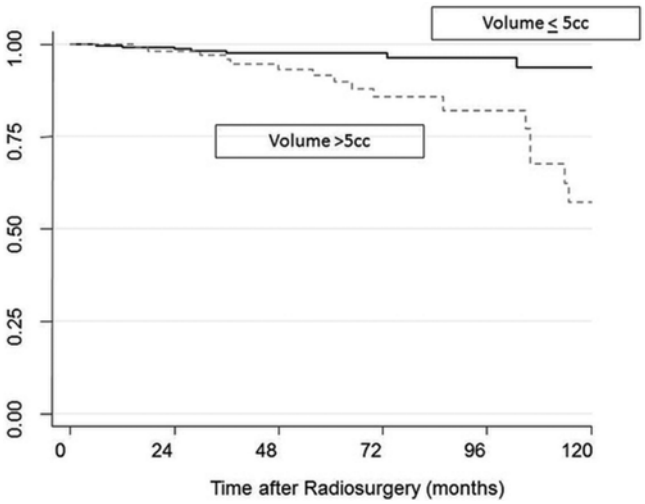

Fig. 3. Progression-free survival after GKS as a function of adenoma volume.

Discussion

Pituitary adenomas are fairly common intracranial tumors, and nonfunctioning adenomas constitute a significant subset of all pituitary adenomas. Although they are generally considered benign tumors, the difficulties of accomplishing a complete resection as well as the tendency for adenomas to recur can make some tumors challenging to treat. Recurrent or residual invasive tumors are associated with significant morbidity over the lifetime of patients.

Historically, radiation therapy had been used to treat patients with recurrent or growing invasive or residual pituitary adenomas.[5] Standard approaches used a total dose of 45–55 Gy administered over 25–30 fractions at 1.8 Gy per fraction. This approach enhanced radiological control after resection.[31] Collateral morbidity increased with time. After EBRT, the risk of hypopituitarism was

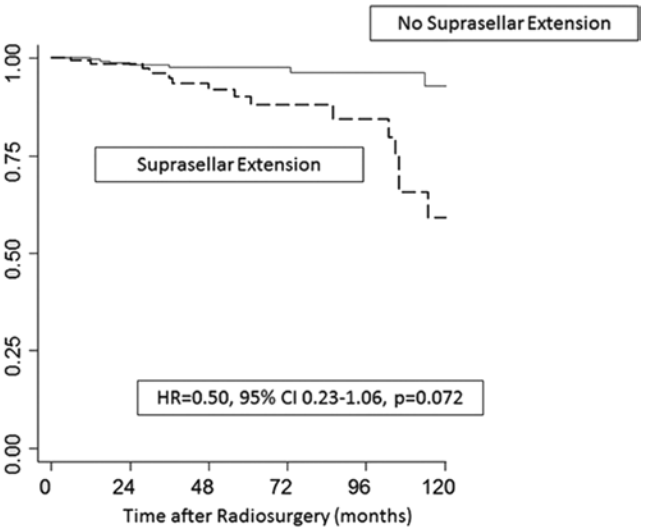

Fig. 4. Progression-free survival after GKS as a function of presence or absence of suprasellar extension of the pituitary adenoma. HR = hazard ratio.

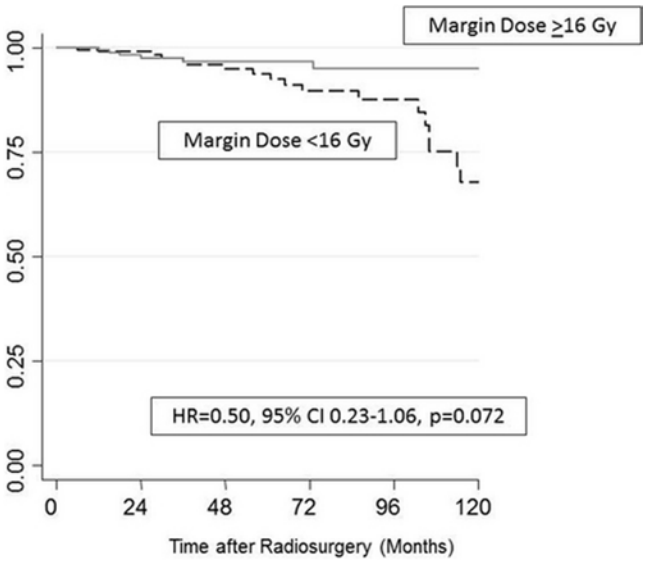

Fig. 5. Progression-free survival after radiosurgery as a function of margin dose ≥ 16 Gy or < 16 Gy.

20%–40% at 10 years posttreatment, and the risk of optic neuropathy was 1.5%.[4] The risk of development of radiation-induced neoplasia was 2% at 10 and 2.4% at 20 years.[35] The approach was also associated with a significantly increased risk of cerebrovascular deaths (relative risk of death 1.58).[4]

Stereotactic radiosurgery has become a widely used alternative to repeat resection and fractionated radiation therapy for patients with recurrent or growing residual nonfunctioning pituitary adenomas. Between 1968 and 1982, Leksell[27] reported performing radiosurgery to treat 37 patients with nonfunctioning pituitary adenomas. Stereotactic radiosurgery offered a focal, minimally invasive treatment for nonfunctioning pituitary adenomas. Since then, the results of SRS have largely been detailed in single center, retrospective studies.[8,16,20,49,52] While such studies are of value in demonstrating a place for radiosurgery in the treatment paradigm of patients with nonfunctioning adenomas, the scientific implications of these studies have been limited by low statistical power, limited follow-up, and selection biases that are inherent to any single center. The current report represents the first multicenter study on this subject to date.

TABLE 5: Factors predictive of new or worsening CN dysfunction after GKS

GKS Covariate	OR (95% CI)	p Value
univariate analysis*		
younger age	1.40 (1.00–1.58)	0.0164
male sex	1.68 (0.84–3.367)	0.014
increasing no. of surgeries	1.44 (1.08–1.90)	0.013
history of prior radiation	5.01 (2.04–12.35)	<0.001
history of any hypopituitarism	3.14 (1.41–6.99)	0.005
history of hypothyroidism	1.97 (1.02–3.78)	<0.043
history of growth hormone insufficiency	0.37 (0.11–1.23)	<0.107
history of diabetes insipidus	2.14 (0.77–5.93)	0.145
increasing vol	1.11 (1.05–1.17)	<0.001
increasing follow-up	1.01 (1.00–1.01)	0.174
growth after GKS	3.07 (1.16–8.07)	0.023
multivariate analysis†		
pre-GKS variables		
younger age	1.03 (1.00–1.05)	0.048
history of prior radiation	4.90 (1.67–13.40)	0.004
history of any hypopituitarism	3.44 (1.39–8.54)	0.008
increasing vol	1.09 (1.02–1.15)	0.004

* Factors predictive of tumor recurrence (p < 0.20).
† Factors predictive of tumor recurrence in multivariate analysis.

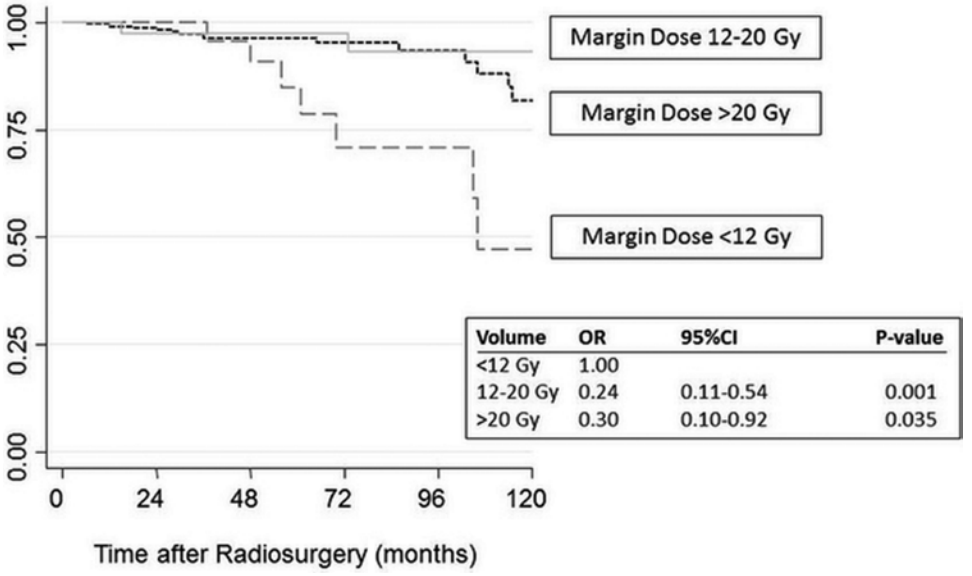

Fig. 6. Progression-free survival after radiosurgery as a function of margin dose < 12 Gy, 12 to 20 Gy, and > 20 Gy.

TABLE 6: Predictors of new or worsening pituitary dysfunction

GKS Covariate	OR (95% CI)	p Value
univariate analysis*		
male sex	1.40 (0.87–2.23)	0.165
history of prior radiation	2.21 (1.01–1.11)	<0.080
increasing margin dose	1.06 (0.91–4.93)	<0.030
increasing max dose	1.01 (1.00–1.04)	<0.087
increasing optic dose	0.92 (0.83–1.01)	0.069
increasing follow-up	1.01 (1.01–1.02)	0.001
growth after GKS	1.89 (0.86–4.15)	0.116
new visual deficit	1.93 (0.84–4.43)	0.120
CN deficit other than CN II	4.05 (1.27–12.87)	0.018
any nerve deficit	2.39 (1.19–4.83)	0.015
multivariate analysis†		
pre-GKS covariate		
history of prior radiation	2.44 (1.04–5.77)	0.041
increasing margin dose	1.07 (1.01–1.12)	0.018
post-GKS covariate		
any nerve deficit	2.39 (1.19–4.83)	0.015

* Factors predictive of tumor recurrence in univariate analysis ($p < 0.20$).

† Factors predictive of tumor recurrence in multivariate analysis.

Radiosurgical Outcomes

Tumor Control. Stereotactic radiosurgery is associated with a high rate of tumor control for most patients with nonfunctioning pituitary adenomas. Most large radiosurgical series demonstrate a tumor control rate approaching 90%.[39,48] The current series demonstrates an overall tumor control rate of 93.4% and an actuarial 5-year progression-free survival of 95%. Mingione and colleagues[34] demonstrated that with longer follow-up, patients tended to demonstrate tumor shrinkage or tumor growth.

Certain factors portend a greater chance of tumor control. In the current series, smaller tumor volume and no suprasellar extension of the tumor were related to improved progression-free survival. Given the importance of volume and suprasellar extension on tumor control rates with GKS, transcranial or transsphenoidal cytoreductive surgery should be undertaken when reasonable to reduce the tumor volume and, in particular, the suprasellar component prior to GKS. Progression-free survival has been previously reported to be superior for patients with adenomas smaller than 5 cm^3.[16,39] Worse tumor control was observed in patients who received less than 16 Gy to the adenoma margin. Even worse tumor control was observed when the adenoma was treated with less than 12 Gy (Figs. 5 and 6). Such doses are more commonly used when the tumor has a larger volume adjacent to the optic apparatus or when the patient has already received radiation therapy. These findings mirror those in prior reports and underscore the need for appropriate dose delivery to achieve satisfactory tumor control.[34,39] When constraints such as critical structures or tumor volume preclude delivery of a dose greater than 12 Gy or preferably greater than 15 Gy, other approaches such as repeat microsurgery should be considered.

With contemporary radiosurgical dose selection, adenoma shrinkage typically occurs slowly. The median time to tumor volume reduction was 33 months after GKS.[16] Such a time period exceeds the mean follow-up reported in many published series. Thus, although radiosurgery controlled the vast majority of nonfunctioning pituitary tumors treated in this series, we continue to recommend long-term radiological, endocrine, and neurological follow-up to assess results at 20 or more years. Such long-term studies are increasingly desirable in the field of neurooncology.

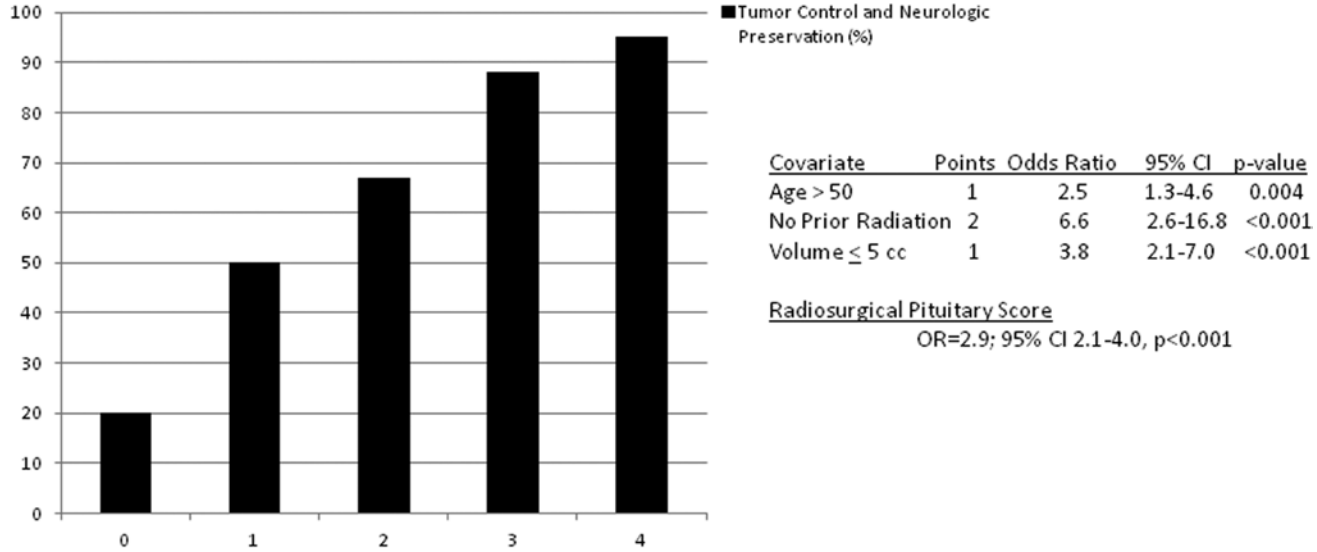

Fig. 7. Radiosurgical pituitary score. The score is as follows: age: 1 point for > 50 years old, 0 points for ≤ 50 years old; tumor volume: 1 point for tumor volume < 5 cm^3, 0 points for tumor volume ≥ 5 cm^3; and prior radiation: 2 points for no previous radiation, 0 points for prior radiation. A higher score represents a more favorable outcome, and numbers on the y axis refer to percentage of favorable outcomes.

Neurological Outcome. Outcome studies indicate that patients who undergo radiosurgery have a relatively low risk of neurological morbidity after radiosurgery.[19,21,22,28,29,36,39,40,42,43,47,48,50] This likely has to do with the highly conformal nature of the treatment, the rapid dose falloff, low to moderate doses required for most nonfunctioning adenomas, and the small treatment volume. Nevertheless, radiosurgery does involve some risk of neurological decline, and, in the setting of patients with pituitary adenomas, the neurological decline is usually CN deterioration. The optic apparatus is generally considered to be the most radiosensitive of the CNs in the sellar region. Single-session radiosurgery tolerance for CN II has been reported to range from 8 to 12 Gy.[32,53] Others have noted a higher tolerable dose of up to 18 Gy in some patients.[18] Substantially less is written about the tolerance of CNs traversing the cavernous sinus. Leber and colleagues[26] noted no neuropathies in patients receiving radiosurgery with doses ranging from 5 to 30 Gy to the cavernous sinus. Tishler and colleagues[53] reported that 8 of 62 radiosurgery patients with cavernous sinus pathology developed some type of CN III to VI deficit. However, the authors could not determine a clear maximum tolerable dose to the cavernous sinus CNs within the range of 10–40 Gy delivered in this study. In a large series of patients undergoing GKS for nonfunctioning adenomas, radiation-induced visual decline and CN palsies were observed in 0.8% and 1.6% of patients, respectively.[39]

In the current study, radiosurgery afforded preservation of neurological function in 90.7% of patients. However, 9.3% of patients had some degree of neurological decline after GKS and of those, 15% had evidence of tumor progression on follow-up neuroimaging. Neurological improvement has been previously reported in some patients with pituitary adenomas after radiosurgery. For example, Kuo et al.[22] reported CN improvement in 36.5% of patients after GKS for benign sellar and parasellar tumors. Similarly, in a group of patients with meningiomas of the cavernous sinus, improvements were noted in 29% of affected trigeminal nerves, 22% of CN III, and 13% of CNs IV and VI.[51]

In the current study, CNs appeared to demonstrate a differential rate of impairment after GKS. Cranial nerve impairment in order of increasing frequency was as follows: CNs VII and IV; CN VI; CN V; CN III; and CN II (Table 3). The risk of new or worsened optic neuropathy either from tumor growth or radiation injury was 6.6%. Although the current study did not specifically evaluate time to neurological decline, CN impairment after GKS usually occurs in a gradual fashion and does so typically within the first 48 months after radiosurgery.[22]

Endocrine Outcome. Delayed hypopituitarism is believed to be the greatest risk for an adverse event after radiosurgery.[55] Nevertheless, it appears to happen in a minority of patients and rarely leads to panhypopituitarism. Reported rates of hypopituitarism after radiosurgery range from 0% to as high as 72%.[19,21,28,42,46,47] The current series demonstrated an overall rate of hypopituitarism of 21.1%. Thyroid and cortisol were the 2 most common hormonal deficiencies to be detected after radiosurgery. Once detected, such patients require appropriate endocrine replacement.[56]

Hypopituitarism may be related to the dose received by the pituitary stalk and may differentially affect the various pituitary hormonal axes.[14,56] The risk of developing hypopituitarism after radiosurgery continues even 10 years after radiosurgery and, as such, is likely underestimated in this and other published series.[15] There may be no dose that is absolutely safe for preservation of normal gland function. Limiting the dose to the normal gland through pituitary transposition has been proposed to reduce the risk of delayed hypopituitarism, but the transposition may pose risks to the patient too.[52] Tumor progression rather than delayed hypopituitarism represents a more serious problem for patients and, as such, an optimal dose to the adenoma should be delivered whenever possible.[16,56]

Serious Complications After Radiosurgery

An often voiced concern after radiosurgery is the risk of delayed neoplasia and stroke.[30,36,43,45,48] To date, a case meeting Cahan's criteria[7] has not been reported after GKS for a pituitary adenoma. There have been 4 cases of carotid artery narrowing after radiosurgery; 2 patients were symptomatic.[29,36,43] Shin et al.[50] recommended restricting the dose to the cavernous portion of the carotid artery to less than 30 Gy with the notion that this might avoid postradiosurgery stenosis. However, given the low incidence of this adverse event, it seems unlikely that the recommendation will be able to be rigorously validated. In addition, the likely slow development of carotid stenosis facilitates collateral vascular supply.

In the current series, no evidence of a severe complication such as neoplasia or stroke was noted. This provides additional evidence that serious complications after radiosurgery are rare. Selection of radiosurgery as a treatment option involves assessment of the risks of alternative management strategies. For example, in the modern era, the reported risk of perioperative anesthetic mortality ranges from 1 in 53 (1.9%) to 1 in 5417 (0.018%) procedures.[3,23] For resection via a transsphenoidal approach, the rates of neurological complications, postoperative hemorrhage, and in-hospital mortality were reported to be 5.6%, 2.6%, and 0.7%, respectively, in a review of 3525 cases.[41] The serious complications associated with EBRT include a 2.4% risk of radiation-induced neoplasia at 20 years and a relative risk factor of 1.58 for a stroke.[4,35] This report provides additional support for the use of GKS as a low risk and effective option for patients with recurrent nonfunctioning adenomas.

The Role of SRS

In this study, we found that GKS provided a strong benefit-to-risk profile for patients with recurrent or residual growing of nonfunctioning pituitary adenomas. In a recent meta-analysis of the natural history of nonfunctioning pituitary adenomas, the incidence of growth in macroadenomas was determined to be 12.53 per 100 person-years and for microadenomas it was 3.32 per 100 person-years.[15] In another study, O'Sullivan and colleagues[38] analyzed 159 patients with nonfunctioning adenomas who underwent resection but no postoperative radiation therapy or radiosurgery. Of these, 33.5% of patients had

evidence of recurrence or growth at a median follow-up of 4.1 years (range 1–20.7 months). The 5- and 10-year actuarial rates of recurrence or growth of a residual adenoma were 24.4% and 51.5%, respectively.[38] The 10-year rate of recurrence of a nonfunctioning adenoma after resection ranges from 19% to 78%.[11,12,38,40,54] Given the high rate of progression in a 10-year period, radiosurgery in younger patients with recurrent or residual tumors in particular may be especially valuable. Patients with aggressive neuropathological attributes warrant strong consideration for early SRS.

For those in whom incomplete resection is followed by surveillance rather than radiosurgery, close interval follow-up with yearly MRI and neuroophthalmological and endocrine follow-up are recommended at least for the first 3–5 years after surgery and then at slightly longer but defined intervals.[12,17] Postponing radiosurgery may be particularly appealing to patients who have good remaining function of their normal pituitary gland. However, the ease of hormonal replacement and the risk of hypopituitarism from tumor progression must be weighed against the risk of radiosurgical-induced hypopituitarism.

In the past, most centers have avoided radiosurgery for patients with nonfunctioning pituitary adenomas when the rostral extent of the adenoma was in proximity to the optic apparatus. The concern was that the dose gradient between the adenoma and the optic apparatus would prove insufficient to allow for both safe and effective treatment. That separation distance was generally noted to be 5 mm.[48] However, with modern radiosurgical technologies such as the Gamma Knife Perfexion, single or multisession approaches (using technologies under evaluation such as EXTEND) facilitate tumor radiosurgery even when the tumor is immediately adjacent to the optic apparatus.[1,20,44]

In this report, we introduce a proposed RPS. We found that patients older than 50 years, those with a nonfunctioning pituitary adenoma smaller than 5 cm^3, and those who had not undergone prior radiation therapy (an RPS of 4) are most likely to achieve a favorable outcome after radiosurgery. Of note, we chose not to include hypopituitarism in the RPS. Although delayed hypopituitarism is a risk after GKS, it is one that can be corrected with medical management provided that it is detected. Thus, it would seem to be a manageable complication after GKS compared with tumor growth or neurological decline.

Study Limitations

Although the current study represents the largest series of patients with nonfunctioning pituitary adenomas treated by GKS to date, we acknowledge the following selection bias issues. 1) The selection criteria and dose planning techniques used at the various centers were not uniform. 2) The Gamma Knife technology evolved over the time period of the study. 3) Image integration and dose planning that maximized conformality and selectivity evolved. 4) Some patients had relatively short follow-up intervals that do not allow long-term determination of the risks of hypopituitarism, radiation-induced neoplasia, or carotid stenosis. 5) The existence of patient and clinician biases typical of any retrospective study. Such a retrospective study should not be considered a substitute for a prospective one. Also, some patients had less than 6 months of follow-up. However, such patients had experienced a complication in the first few months after GKS. They were included in the analysis so as not to bias the outcomes of the series in a more favorable fashion.

Conclusions

In this largest study to date, GKS provided a high rate of local tumor control and a low risk of collateral neurological, CN, or endocrine axis injury for patients with nonfunctioning pituitary adenomas.

Disclosure

Drs. Lunsford and Kondziolka are consultants with Elekta AB. Dr. Lunsford is a stockholder in Elekta AB.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sheehan, Chiang, Kondziolka, Barnett, Rush, Golfinos, Lunsford. Acquisition of data: Mathieu, Young, Sneed, Chiang, Lee, Kano, Park, Niranjan, Barnett, Rush, Lunsford. Analysis and interpretation of data: Starke, Lunsford. Drafting the article: Sheehan. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sheehan.

Acknowledgments

For this research of the North American Gamma Knife Consortium (NAGKC) outcome data were provided by the University of Pittsburgh Medical Center, Cleveland Clinic, University of Kentucky, University of Virginia, the University of Sherbrooke, Yale University, University of Pennsylvania, University of California, San Francisco, and New York University. Sharon DeCesare served as a study coordinator for the NAGKC and helped to ensure patient confidentiality.

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Manuscript submitted April 14, 2012.
Accepted March 29, 2013.
Please include this information when citing this paper: published online April 26, 2013; DOI: 10.3171/2013.3.JNS12766.

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