

## Clinical Investigation

# Outcomes of Proton Therapy for Patients With Functional Pituitary Adenomas

Daniel A. Wattson, MD,\* Shyam K. Tanguturi, MD,\*  
Daphna Y. Spiegel, MD,<sup>†</sup> Andrzej Niemierko, PhD,<sup>‡</sup>  
Beverly M.K. Biller, MD,<sup>§</sup> Lisa B. Nachtigall, MD,<sup>§</sup> Marc R. Bussière, MSc,<sup>‡</sup>  
Brooke Swearingen, MD,<sup>||</sup> Paul H. Chapman, MD,<sup>||</sup> Jay S. Loeffler, MD,<sup>‡</sup>  
and Helen A. Shih, MD<sup>‡</sup>

\*Harvard Radiation Oncology Program, <sup>†</sup>Tufts University School of Medicine, <sup>‡</sup>Department of Radiation Oncology, <sup>§</sup>Neuroendocrine Unit, and <sup>||</sup>Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts

Received Jan 28, 2014, and in revised form Apr 8, 2014. Accepted for publication Jun 26, 2014.

## Summary

Proton therapy is increasingly being used to treat patients with benign central nervous system tumors in an attempt to minimize late effects of radiation. Herein we report the largest series of patients with functional pituitary adenomas treated with proton therapy using modern techniques, predominantly stereotactic radiosurgery. Biochemical effectiveness and local control were comparable with those in contemporary photon series, and the most

**Purpose/Objective(s):** This study evaluated the efficacy and toxicity of proton therapy for functional pituitary adenomas (FPAs).

**Methods and Materials:** We analyzed 165 patients with FPAs who were treated at a single institution with proton therapy between 1992 and 2012 and had at least 6 months of follow-up. All but 3 patients underwent prior resection, and 14 received prior photon irradiation. Proton stereotactic radiosurgery was used for 92% of patients, with a median dose of 20 Gy(RBE). The remainder received fractionated stereotactic proton therapy. Time to biochemical complete response (CR, defined as  $\geq 3$  months of normal laboratory values with no medical treatment), local control, and adverse effects are reported.

**Results:** With a median follow-up time of 4.3 years (range, 0.5-20.6 years) for 144 evaluable patients, the actuarial 3-year CR rate and the median time to CR were 54% and 32 months among 74 patients with Cushing disease (CD), 63% and 27 months among 8 patients with Nelson syndrome (NS), 26% and 62 months among 50 patients with acromegaly, and 22% and 60 months among 9 patients with prolactinomas, respectively. One of 3 patients with thyroid stimulating hormone—secreting tumors achieved CR. Actuarial time to CR was significantly shorter for corticotroph FPAs (CD/NS) compared with other subtypes ( $P = .001$ ). At a median imaging follow-up time of 43 months, tumor control was 98% among 140 patients. The actuarial 3-

Reprint requests to: Helen A. Shih, MD, Department of Radiation Oncology, Massachusetts General Hospital, 30 Fruit St, Boston, MA 02114. Tel: (617) 724-9627; E-mail: [hshih@partners.org](mailto:hshih@partners.org)

Presented in poster format at the 55th Annual Meeting of the American Society for Radiation Oncology (ASTRO), Atlanta, GA, September 22-25, 2013.

Conflict of interest: B.M.K.B. has served as the principal investigator of research grants to the Massachusetts General Hospital from Novartis and as a consultant for HRA Pharma, Novartis, and Pfizer. H.A.S. is an editor for this journal and is a writer for UpToDate. The authors report no other conflict of interest.

Supplementary material for this article can be found at [www.redjournal.org](http://www.redjournal.org).

common late effect was hypopituitarism.

year and 5-year rates of development of new hypopituitarism were 45% and 62%, and the median time to deficiency was 40 months. Larger radiosurgery target volume as a continuous variable was a significant predictor of hypopituitarism (adjusted hazard ratio 1.3,  $P = .004$ ). Four patients had new-onset postradiosurgery seizures suspected to be related to generously defined target volumes. There were no radiation-induced tumors.

**Conclusions:** Proton irradiation is an effective treatment for FPAs, and hypopituitarism remains the primary adverse effect. © 2014 Elsevier Inc.

## Introduction

Pituitary adenomas represent 10% to 20% of primary central nervous system tumors and are almost always benign. Approximately two-thirds are functioning pituitary adenomas (FPAs), which are often diagnosed as microadenomas that become symptomatic secondary to excesses of pituitary hormones. The majority of FPAs are prolactin secreting and cause galactorrhea, amenorrhea, infertility, and impotence. The next most common are growth hormone (GH)-secreting tumors, which lead to acromegaly. Adrenocorticotropic (ACTH)-secreting tumors cause the adrenal glands to produce elevated cortisol levels, resulting in Cushing disease (CD). In a small proportion of patients with ACTH-secreting tumors who undergo therapeutic bilateral adrenalectomy, Nelson syndrome (NS) develops, characterized by very high ACTH levels and rapid adenoma growth caused by withdrawal of negative feedback on the tumor. Fewer than 1% of FPAs secrete thyroid stimulating hormone (TSH), which causes hyperthyroidism, and are often more invasive than other adenoma types (1-3).

Treatment with medications is often the initial intervention for patients with prolactinoma, and symptom relief and decrease in tumor size are common after administration of dopamine receptor agonists (4). For other FPA types, transsphenoidal surgery (TSS) is the generally the first-line treatment. TSS by experienced surgeons results in a cure rate of 60% to 80% depending on tumor histology, size, degree of cavernous sinus or dural invasion, and surgical technique (5-9). However, the remainder of patients may have persistent disease after 1 or more surgical procedures, or the disease may recur after initial remission (10). For these patients, and for inoperable patients at the outset, irradiation is a treatment option.

Radiation therapy for FPAs is often accomplished with stereotactic radiosurgery (SRS), which is performed during a single session using high-dose, highly conformal radiation. An alternative schedule involves fractionated stereotactic radiation therapy (SRT) over several weeks. High-energy photon techniques are most prevalent, and treatment approaches have evolved in such a manner that convergent beam techniques and arc-based treatments minimize normal tissue dose deposition. Proton therapy offers another means of normal tissue sparing because the physical properties of protons allow maximal dose deposition within the target with

virtually no exit dose. The number of patients treated with proton therapy will likely increase because the number of proton centers has increased over the past decade (11). Here, we report our experience with proton therapy in managing FPAs.

## Methods and Materials

### Patient characteristics

This was a retrospective chart review approved by our institutional review board. All patients with FPAs treated with radiation between 1992 and 2012 were evaluated. Patients with less than 6 months of postradiation follow-up data were excluded.

### Radiation treatment details

All patients were treated with 3-dimensional conformal passive scattered proton therapy using 2 to 5 beams, most commonly 2 fields (laterals) through 1996, 4 fields (laterals, vertex, posteroanterior) through 2006, and 3 fields (laterals, posteroanterior) thereafter. A modified Gill-Thomas-Cosman stereotactic head frame with dental mold was used for external immobilization. Surgical grade stainless steel ball bearings 1/16 inch in diameter were placed in the outer table of the skull with the patient under local anesthetic and were used as fiducial markers for target localization (12). Computed tomography/magnetic resonance imaging (MRI) fusions facilitated target delineation (13). No dedicated gross tumor volume was defined. Instead, the clinical target volume most commonly encompassed the visible tumor and entire sella with the superior margin defined by radiation planning that would limit the single-fraction dose to the undersurface of the optic chiasm to 8 Gy(RBE). Volumes extended laterally to encompass the cavernous sinus(es) if tumor involved these regions. There was no uniform planning target volume expansion. Instead, a 3.5% density correction was added to the proximal and distal range of each beam plus 1 mm distally, and a 1-mm lateral margin was added for setup uncertainty (14). The doses to the brainstem (single-fraction limit 12 Gy[RBE]) and optic structures (single-fraction limit 8 Gy[RBE]) were minimized using lateral collimation rather than distal range adjustment, and they were thereby minimally affected by range uncertainties.

For the majority of patients, a dedicated proton stereotactic delivery system known as the stereotactic alignment radiation therapy system (STAR) was used for both SRS and fractionated treatments (15). Figure 1 shows a typical proton stereotactic radiosurgery (PSRS) plan.

## Endpoints

Patient charts were assessed for biochemical control, tumor local control, and potential adverse effects. Biochemical complete response (CR) was defined as at least 3 months of sustained normalized hormone levels after all medical therapy was withdrawn. Hormonal evaluation included 24-hour urinary free cortisol for patients with CD (supported in some cases by salivary cortisol) and plasma ACTH for patients with NS, with disease control defined as less than our institutional upper limit of 76 pg/mL. Age-appropriate and sex-appropriate insulin-like growth factor-1 was followed up for patients with acromegaly (supported in some cases by a normal oral glucose tolerance test result), prolactin for patients with prolactinoma, and TSH and free T4 for patients with TSH-secreting adenomas. Local control (LC) was defined as no tumor enlargement on follow-up imaging.

All patients who received primary neuroendocrine care at our center were routinely screened for radiation-associated hypopituitarism, including TSH, GH, sex hormone, and adrenocortical axes. Premenopausal women who experienced amenorrhea without elevated prolactin or FSH were considered to have a new pituitary deficit. Many patients were not consistently followed up at our institution, and hypopituitarism screening algorithms may have differed elsewhere. New hypopituitarism was therefore

more simply defined as the need to initiate replacement of any pituitary axis hormones after proton therapy. Pituitary axes known to be deficient before proton therapy (generally caused by prior TSS) were not scored for further deficit. Other potential adverse effects such as injury to vision or new-onset seizures were drawn from available clinical records.

## Statistical analyses

Actuarial rates of CR and new hypopituitarism were calculated by the Kaplan-Meier method. Variables evaluated for statistical association with these outcomes included FPA subtype, age at treatment, sex, target volume (as a continuous variable), PSRS versus fractionated stereotactic proton radiation therapy (PSRT), and history of prior irradiation. A 2-sided  $P < .05$  was considered statistically significant. Analyses were performed with Stata (StataCorp. 2011, Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

## Results

A total of 165 of 189 patients with FPAs treated with proton therapy had at least 6 months of follow-up data for at least 1 endpoint and formed the basis of the study. Figure 2 illustrates the numbers of patients with adequate follow-up information for each endpoint. Patients were excluded from 1 or more endpoints solely because we did not receive adequate information from remote caregivers.

Table 1 summarizes the characteristics of the evaluable patient cohort. All but 3 patients (2 with acromegaly, 1 with

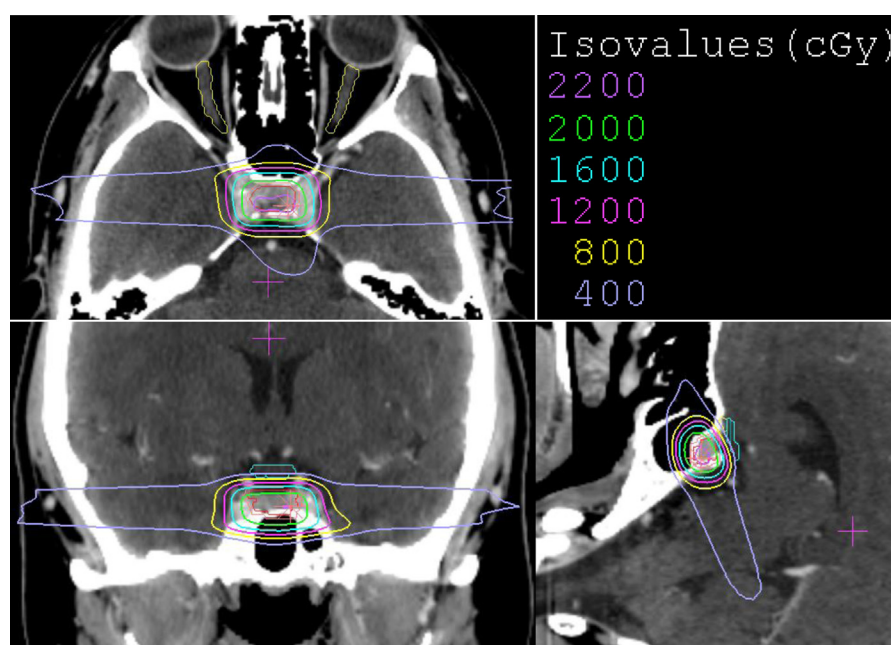
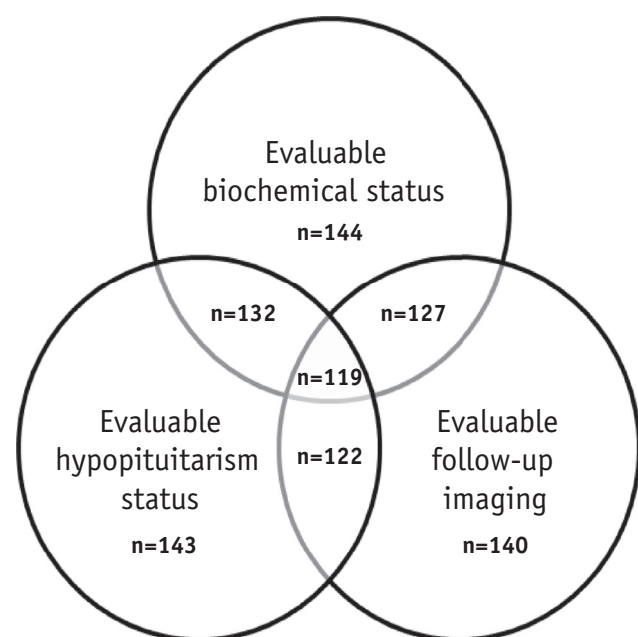


Fig. 1. Proton stereotactic radiosurgery plan for a pituitary adenoma.



**Fig. 2.** Numbers of patients with at least 6 months of follow-up information for each study endpoint.

prolactinoma) underwent at least 1 prior TSS without biochemical cure, and the median number of prior surgical procedures was 1. The median age at the time of proton therapy was 43 years, and the majority of patients (92%) were treated with PSRS to a median dose of 20 Gy(RBE) (range, 15-24 Gy[RBE]). Ten of these patients were treated with reduced-dose PSRS (15-18 Gy[RBE]) because they had previously received radiation. An additional 13 patients received PSRT (50.4-54 Gy[RBE] in 28-30 fractions) because of large tumor size, proximity to the optic chiasm, or both.

### Biochemical response

Of the 165 evaluable patients, 144 (87%) had adequate information to enable determination of CR status. The overall median follow-up time in this group was 52 months (range, 6-247 months), and the actuarial median time to CR was 47 months (95% confidence interval [CI], 36-59). [Table 2](#) summarizes the actuarial CR results for all FPA subtypes, with median time to CR ranging between 27 months for NS and 62 months for acromegaly. [Figure 3a](#) shows Kaplan-Meier estimates for CR for the adenoma subtypes. The time to CR for ACTH-producing adenomas (CD and NS) was significantly shorter than for the other FPA subtypes ([Fig. 3b](#)), with median time to CR of 31 months (95% CI, 22-44) versus 60 months (95% CI, 47-98), respectively. [Table E1](#) (available at [www.redjournal.org](http://www.redjournal.org)) shows the biochemical results grouped by indication of primary treatment versus reirradiation. No obvious difference in biochemical response was appreciated between the 2 groups, but only 10 patients received prior irradiation.

**Table 1** Characteristics of 165 evaluable patients treated with proton therapy for functional pituitary adenoma

Characteristic	No.
Total patients by adenoma type	165
CD	79 (48%)
NS	10 (6%)
GH	61 (37%)
PRL	12 (7%)
TSH	3 (2%)
Sex	
Female	109 (66%)
Male	56 (34%)
Median age at proton irradiation, y (range)	43 (12-84)
Median transsphenoidal surgical procedures (range)	1 (0-4)
Received prior irradiation	14 (8%)
Proton irradiation scheme	
PSRS, median 20 Gy(RBE)	152 (92%)
Fractionated PSRT, median 50.4 Gy(RBE)	13 (8%)
Mean PSRS target volume, cm <sup>3</sup> (range)	1.7 (0.2-8.6)

*Abbreviations:* CD = Cushing disease; NS = Nelson syndrome; GH = growth hormone-secreting adenoma; PRL = prolactin-secreting adenoma; TSH = thyroid stimulating hormone-secreting adenoma; PSRS = proton stereotactic radiosurgery; PSRT = proton stereotactic radiation therapy.

Univariate analyses (detailed in [Table E2](#), available at [www.redjournal.org](http://www.redjournal.org)) demonstrated that only the acromegaly subtype was significantly associated with longer time to CR (hazard ratio [HR], 0.53; 95% CI, 0.32-0.88;  $P = .01$ ). Sex, age at proton therapy, history of prior irradiation, PSRS versus PSRT, and PSRS target volume were not significant. On multivariate analysis, acromegaly subtype remained predictive for longer time to CR (adjusted hazard ratio [AHR], 0.45; 95% CI, 0.25-0.82;  $P = .009$ ). Among 127 patients with evaluable CR status and follow-up MRI, residual tumor on imaging was associated with longer time to CR, with HR of 0.62 (95% CI, 0.38-0.99;  $P = .05$ ).

Of the 61 patients not achieving CR at the last follow-up visit, 67% had biochemical control but required ongoing medical management, including 18 CD patients, 25 acromegalic patients, 1 prolactinoma patient, and 2 TSH patients. There was a single case of delayed biochemical recurrence after initial CR: a CD patient treated with PSRS to 20 Gy(RBE) who achieved CR 6 months thereafter, but then experienced biochemical recurrence approximately 7 years after PSRS and underwent bilateral adrenalectomy 2.5 years later. Six CD patients underwent bilateral adrenalectomies to achieve biochemical control a median of 21 months after proton therapy (range, 7-114 months). Two of these patients subsequently experienced NS, each after approximately 2 years, and neither has received additional radiation therapy. There were 3 CD patients, 2 NS patients, 1 acromegalic patient, and 3 prolactinoma patients who did not have biochemical control even with attempts at medical management.

**Table 2** Biochemical outcomes after proton therapy for functional pituitary adenoma

FPA type (n)	Median FU, mo (range)	3-year actuarial CR rate, % (95% CI)	5-year actuarial CR rate, % (95% CI)	Actuarial median months to CR (95% CI)
All (144)	52 (6-247)	42 (34-51)	59 (50-69)	47 (36-59)
CD (74)	47 (6-182)	54 (43-66)	67 (55-79)	32 (21-49)
NS (8)	57 (25-212)	63 (33-91)	75 (44-96)	27 (5-∞)
GH (50)	57 (10-247)	26 (16-42)	49 (34-67)	62 (44-111)
PRL (9)	71 (33-174)	22 (6-64)	38 (14-79)	60 (21-∞)
TSH (3)	118 (12-138)	-	50 (9-99)	51 (51-∞)

Abbreviations: CD = Cushing disease; CI = confidence interval; CR = complete response; FPA = functional pituitary adenoma; FU = follow-up; GH = growth hormone-secreting adenoma; NS = Nelson syndrome; PRL = prolactin-secreting adenoma; TSH = thyroid stimulating hormone-secreting adenoma.

## Radiographic response

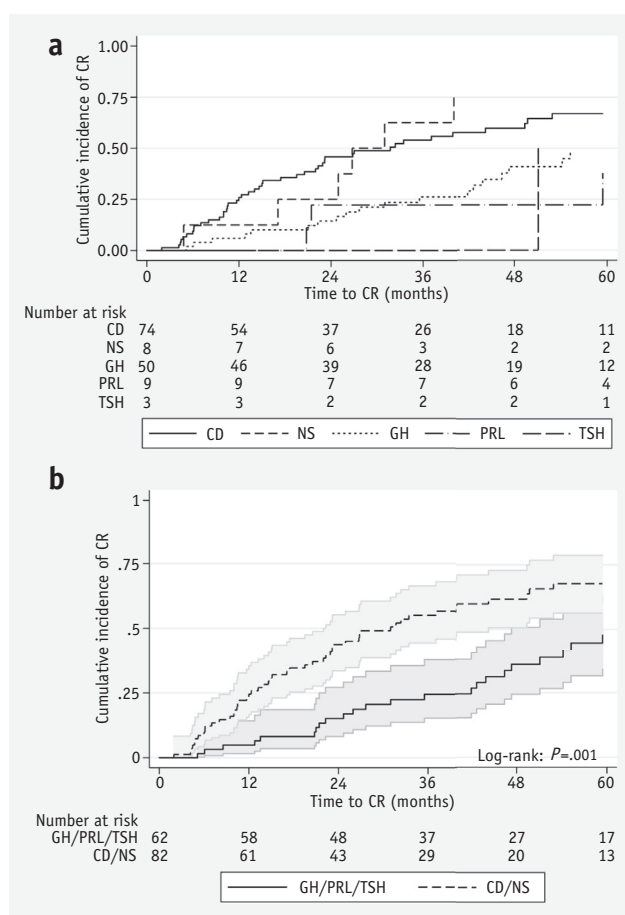
There were 140 patients (85%) with at least 1 available follow-up brain MRI, including 67 with CD, 6 with NS, 55 with acromegaly, 9 with prolactinoma, and 3 with TSH-secreting adenoma. The most recent images were available with a median of 43 months after proton therapy (range, 6-237 months). Local control was achieved in 98% of patients, with imaging demonstrating either absence of disease or stable residual disease. Of the 3 patients with progression, 1 had CD initially treated with PSRS to 20 Gy(RBE) and subsequently was treated with PSRT. The other 2 had prolactinomas initially treated with PSRS to 15 Gy(RBE) and PSRT to 52.2 Gy(RBE), and after local failure they were treated with PSRT and temozolomide, respectively.

## Adverse effects

The most common adverse effect after pituitary irradiation was hypopituitarism of single or multiple axes. In this series, 143 patients (87%) had evaluable data for determining whether new pituitary hormone deficiencies developed. Before receiving proton therapy, 66 of these patients (46%) had no hypopituitarism, 61 (43%) had partial hypopituitarism, and 16 (11%) had panhypopituitarism and were therefore not considered to be at risk. Among the 127 patients at risk for new hormone deficiencies, with a median follow-up time of 51 months after proton therapy, the actuarial 3-year and 5-year rates of new deficiency of at least 1 axis requiring replacement were 45% and 62%, respectively. The actuarial median time to hypopituitarism after treatment was 40 months (95% CI, 32-55). [Figure E1](#) (available at [www.redjournal.org](http://www.redjournal.org)) shows Kaplan-Meier estimates for time to hypopituitarism among the evaluable at-risk patients, and [Table E3](#) (available at [www.redjournal.org](http://www.redjournal.org)) details hypopituitarism outcomes separated by indication of primary versus reirradiation.

Risk of hypopituitarism was associated only with PSRS target volume on univariate analysis, with HR of 1.28 (95% CI, 1.08-1.51;  $P=.004$ ), as detailed in [Table E4](#) (available at [www.redjournal.org](http://www.redjournal.org)), and remained predictive on

multivariate analysis (AHR 1.28, 95% CI 1.08-1.52,  $P=.004$ ). Among patients with information on both CR status and hypopituitarism ( $n=132$ ), there was no



**Fig. 3.** (a) Kaplan-Meier estimates of rates of biochemical control after proton radiation therapy, by functional adenoma subtype. (b) Kaplan-Meier estimates of rates of biochemical control after proton radiation therapy, comparing corticotroph adenomas (Cushing/Nelson) versus other subtypes. CD = Cushing disease; CR = biochemical complete response; GH = growth hormone-secreting adenoma; NS = Nelson syndrome; PRL = prolactin-secreting adenoma; TSH = thyroid stimulating hormone-secreting adenoma.

correlation between those who achieved CR and loss of additional pituitary axes.

Additional adverse events are detailed in [Table E5](#) (available at [www.redjournal.org](http://www.redjournal.org)). There were 4 patients (3 with CD, 1 with acromegaly) who experienced temporal lobe seizures 1 month to 9 years after PSRS to 20 Gy(RBE), with temporal lobe changes seen on MRI (T2 hyperintensity) for 2 of these patients. One also experienced transient right CN6 palsy 5 years after PSRS with known tumor targeted in the right cavernous sinus, and symptoms resolved 4 months later and have not recurred in 8 years. At least 3 of the patients with seizures received documented 12 to 20 Gy(RBE) to the medial temporal lobes.

Other potential toxicities included 1 CD patient who underwent 3 prior TSS procedures and 45 Gy external beam radiation therapy 15 years previously, and experienced a transient left CN3 palsy 2 years after PSRS to 18 Gy(RBE), which resolved 9 months later without recurrence at 6 years. One acromegalic patient who received PSRS to 20 Gy(RBE) 19 years after external beam radiation therapy to 45 Gy experienced necrosis of the ethmoid sinus associated with a chronic fungal infection, although this was unlikely to be related to PSRS: the posterior ethmoids received 4 Gy(RBE), and the middle and anterior ethmoids received no dose. There were no documented cerebrovascular accidents after proton therapy, and no radiation-induced tumors.

## Discussion

The majority of patients with FPAs refractory to initial surgery experience a complete biochemical response to proton therapy. Adverse effects were predominantly limited to hypopituitarism; however, a few cases of seizures and cranial nerve palsies demonstrate that primary neurologic injury may also occur. This study expands on prior reports of ACTH-secreting and GH-secreting adenomas treated at our institution ([16](#), [17](#)) and also includes other FPA

subtypes treated with proton therapy. It is, to our knowledge, the largest report of pituitary adenomas treated with proton radiation.

The results of proton therapy appear comparable with those in patients treated with photon radiosurgery and fractionated radiation therapy ([18-24](#)). [Table 3](#) shows the results of the current study compared with those of the largest published single-institution series of pituitary adenoma patients treated with Gamma Knife ([18](#)), along with a review of studies (including the prior study and some patients from the current study) published to date ([19](#)). Of note, this table lists the crude CR results for the current study, rather than actuarial, to facilitate comparison with the crude results that were reported in other studies. Direct comparisons are complicated by potential selection bias, different follow-up times, and varying definitions of CR.

We do not expect superior efficacy with protons, given similar radiation doses delivered compared with photon series. However, the challenge in any radiation therapy lies in effectively treating the disease while optimally reducing the radiation dose to the normal surrounding tissue. The reduction of exit dose afforded by protons may result in fewer irreversible late sequelae, which is especially important in the setting of a benign condition such as pituitary adenoma, in which normal life expectancy is projected. Fractionated radiation therapy and radiosurgery series with long-term follow-up have documented late toxicities, including optic neuropathy and new-onset hypopituitarism arising after 10 years ([25](#)), and toxicity in more remote normal tissues such as radiation necrosis ([26](#)) and secondary tumors ([27](#)). Furthermore, several studies indicate an increased risk of cerebrovascular disease and mortality in patients treated with radiation therapy ([28-33](#)), although a causal link is not well established. However, many of the patients in these studies were treated with large conventional radiation therapy fields that were fluoroscopically planned, and modern computed tomographic planning and stereotactic techniques may reduce the risk.

In our patient series, there were 4 cases of new-onset seizures after PSRS, including 2 associated with temporal

**Table 3** Comparison of biochemical outcomes among different studies of radiation therapy for pituitary adenomas

Study	Cushing disease	Nelson syndrome	Acromegaly	Prolactinoma
<b>Current study</b>				
Number of patients	74	8	50	9
Crude proportion CR	64%	75%	48%	56%
Crude median months to CR	15	23	39	59
<b>Sheehan et al (<a href="#">18</a>)</b>				
Number of patients	82	22	130	32
Crude proportion CR	54%	20%	53%	26%
Crude median months to CR	13	50	30	25
<b>Review by Loeffler et al (<a href="#">19</a>)</b>				
Crude proportion CR	35%-80%	Not reported	45%-53%	15%-50%
Crude median months to CR	7.5-33	Not reported	36-120	24-96

Abbreviation: CR = complete response.

lobe changes on MRI. We hypothesize that these may be related to our historical practice of targeting the entire sella turcica, which may have unnecessarily delivered high doses to the medial temporal lobes. Our techniques have evolved, particularly with better imaging, in such a manner that target volumes are more judiciously limited to the adenoma and regions at risk of residual disease, and treatment fields are selected to limit temporal lobe and optic chiasm dose.

Longer follow-up of modern treatment practice is warranted to determine whether late radiation-related sequelae are reduced with proton therapy. Specifically, although there were no secondary tumors or cases of cerebrovascular disease and mortality in this series, both our patient numbers and the length of follow-up are inadequate to enable us to conclude whether the risk is definitively reduced with proton therapy. Given the general rarity of these adverse effects after pituitary irradiation, an advantage to proton therapy may be difficult to definitely show in a study.

Hypopituitarism, however, is common after pituitary irradiation, and patients require long-term neuroendocrine surveillance and medical management. Our series showed a 3-year actuarial rate of 45% among at-risk patients, with actuarial median time to hypopituitarism of 40 months. The crude hypopituitarism rate in our study was 57%, which is higher than the reported crude rate in the large single-institution Gamma Knife series of 24% (18), although the follow-up times in that study were shorter than in the current study (31 vs 51 months). The literature review by Loeffler et al (19) reported approximate hypopituitarism rates of 20% at 5 years and 80% at 10 to 15 years after radiation. The current series may demonstrate a higher incidence of postradiation hypopituitarism because our target volume commonly included the entire sella; thus, the pituitary itself intentionally received full target dose. At least 1 study suggests that reduction of radiation dose to the hypothalamus is associated with reduced hypopituitarism (34). Although this has not been supported by our data thus far, whether there may be a leveling of the rate of late hypopituitarism has yet to be seen.

Several limitations of this retrospective study deserve further consideration. First, given the long inclusion period, there may be heterogeneity in outcomes resulting from technologic advances in pituitary resection and microsurgery, neuroimaging, and endocrine testing and management. Our practice alone evolved several times during this 20-year span. Furthermore, because treatment was done at a single institution and patients were often referred from afar, there are likely patient selection biases. The results may also be biased by inconsistent follow-up of patients, with many not routinely followed up at our center.

In conclusion, for patients with FPAs refractory to initial surgery, pituitary irradiation can be a safe and potentially curative treatment option, and it may be especially effective among those with ACTH-secreting adenomas. Given the

few cases of late toxicity, we would consider defining target volumes no larger than the suspected adenoma to limit the dose to the temporal lobes. The findings in this study will be helpful in guiding clinical practice of proton radiosurgery for future FPA patients.

## References

1. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: A community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)* 2010;72:377-382.
2. Raappana A, Koivukangas J, Ebeling T, et al. Incidence of pituitary adenomas in Northern Finland in 1992-2007. *J Clin Endocrinol Metab* 2010;95:4268-4275.
3. Saeger W, Ludecke DK, Buchfelder M, et al. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol* 2007;156:203-216.
4. Klibanski A. Clinical practice. *Prolactinomas*. *N Engl J Med* 2010;362:1219-1226.
5. Beck-Peccoz P, Brucker-Davis F, Persani L, et al. Thyrotropin-secreting pituitary tumors. *Endocr Rev* 1996;17:610-638.
6. Kelly DF. Transsphenoidal surgery for Cushing's disease: A review of success rates, remission predictors, management of failed surgery, and Nelson's syndrome. *Neurosurg Focus* 2007;23:E5.
7. Kreutzer J, Vance ML, Lopes MB, et al. Surgical management of GH-secreting pituitary adenomas: An outcome study using modern remission criteria. *J Clin Endocrinol Metab* 2001;86:4072-4077.
8. Swearingen B, Barker FG 2nd, Katznelson L, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab* 1998;83:3419-3426.
9. Swearingen B, Biller BM, Barker FG 2nd, et al. Long-term mortality after transsphenoidal surgery for Cushing disease. *Ann Intern Med* 1999;130:821-824.
10. Patil CG, Prevedello DM, Lad SP, et al. Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. *J Clin Endocrinol Metab* 2008;93:358-362.
11. Paganetti H, Kooy H. Proton radiation in the management of localized cancer. *Expert Rev Med Devices* 2010;7:275-285.
12. Gall KP, Verhey LJ, Wagner M. Computer-assisted positioning of radiotherapy patients using implanted radiopaque fiducials. *Med Phys* 1993;20:1153-1159.
13. Kooy HM, van Herk M, Barnes PD, et al. Image fusion for stereotactic radiotherapy and radiosurgery treatment planning. *Int J Radiat Oncol Biol Phys* 1994;28:1229-1234.
14. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. *Phys Med Biol* 2012;57:R99-R117.
15. Chapman PH, Ogilvy CS, Butler WE. A new stereotactic alignment system for charged particle radiosurgery at the Harvard Cyclotron Laboratory, Boston. In: Alexander E, Loeffler JS, Lunsford LE, editors. *Stereotactic Radiosurgery*. New York: McGraw-Hill; 1993. p. 105-108.
16. Petit JH, Biller BM, Yock TI, et al. Proton stereotactic radiotherapy for persistent adrenocorticotropin-producing adenomas. *J Clin Endocrinol Metab* 2008;93:393-399.
17. Petit JH, Biller BM, Coen JJ, et al. Proton stereotactic radiosurgery in management of persistent acromegaly. *Endocr Pract* 2007;13:726-734.
18. Sheehan JP, Pouratian N, Steiner L, et al. Gamma Knife surgery for pituitary adenomas: Factors related to radiological and endocrine outcomes. *J Neurosurg* 2011;114:303-309.
19. Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. *J Clin Endocrinol Metab* 2011;96:1992-2003.
20. Castinetti F, Nagai M, Morange I, et al. Long-term results of stereotactic radiosurgery in secretory pituitary adenomas. *J Clin Endocrinol Metab* 2009;94:3400-3407.

21. Minniti G, Osti M, Jaffrain-Rea ML, et al. Long-term follow-up results of postoperative radiation therapy for Cushing's disease. *J Neurooncol* 2007;84:79-84.
22. Jezkova J, Marek J, Hana V, et al. Gamma Knife radiosurgery for acromegaly—long-term experience. *Clin Endocrinol (Oxf)* 2006;64:588-595.
23. Losa M, Gioia L, Picozzi P, et al. The role of stereotactic radiotherapy in patients with growth hormone-secreting pituitary adenoma. *J Clin Endocrinol Metab* 2008;93:2546-2552.
24. Pan L, Zhang N, Wang EM, et al. Gamma knife radiosurgery as a primary treatment for prolactinomas. *J Neurosurg* 2000;93(Suppl 3.):10-13.
25. Hoybye C, Grenback E, Rahn T, et al. Adrenocorticotrophic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. *Neurosurgery* 2001;49:284-291. discussion 291–282.
26. Mitsumori M, Shrieve DC, Alexander E 3rd, et al. Initial clinical results of LINAC-based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. *Int J Radiat Oncol Biol Phys* 1998;42:573-580.
27. Brada M, Ford D, Ashley S, et al. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *BMJ* 1992;304:1343-1346.
28. Ayuk J. Does pituitary radiotherapy increase the risk of stroke and, if so, what preventative actions should be taken? *Clin Endocrinol (Oxf)* 2012;76:328-331.
29. Erridge SC, Conkey DS, Stockton D, et al. Radiotherapy for pituitary adenomas: Long-term efficacy and toxicity. *Radiother Oncol* 2009;93:597-601.
30. Brada M, Ashley S, Ford D, et al. Cerebrovascular mortality in patients with pituitary adenoma. *Clin Endocrinol (Oxf)* 2002;57:713-717.
31. Ayuk J, Clayton RN, Holder G, et al. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. *J Clin Endocrinol Metab* 2004;89:1613-1617.
32. Kauppinen-Makelin R, Sane T, Reunanen A, et al. A nationwide survey of mortality in acromegaly. *J Clin Endocrinol Metab* 2005;90:4081-4086.
33. Flickinger JC, Nelson PB, Taylor FH, et al. Incidence of cerebral infarction after radiotherapy for pituitary adenoma. *Cancer* 1989;63:2404-2408.
34. Pai HH, Thornton A, Katznelson L, et al. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: Demonstration of a dose-effect relationship using dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys* 2001;49:1079-1092.