

Management of Recurrent and Refractory Cushing's Disease with Reoperation and/or Proton Beam Radiosurgery

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Cushing's disease is an endocrine disorder defined by hypercortisolemia resulting from overproduction of adrenocorticotropic hormone by a pituitary adenoma. Cushing's disease has many potentially devastating systemic sequelae and increased mortality, which are reversible with control of the cortisol excess.¹⁴ Once the diagnosis of Cushing's disease has been made by appropriate endocrine testing and localized by magnetic resonance imaging (MRI) or inferior petrosal sinus sampling, the initial treatment is usually microsurgical resection of the pituitary adenoma by a transsphenoidal approach. Although this approach is often successful in patients with micro-adenomas,¹³ surgical cure can be challenging in several situations. For example, up to one-third of patients with Cushing's disease have normal MRIs,¹⁵ which makes locating the adenoma by surgical exploration more difficult, whereas other patients have macro-adenomas with cavernous sinus invasion, leading to incomplete resection.

Surgical removal remains the first line of treatment with reported success rates ranging from 77 to 85%.^{9,10,12} However, the optimal management of residual disease after unsuccessful surgery, or recurrent disease after initial remission, remains unclear. Reoperation has been recommended with some success, including a 38% cure rate in one small series.² Alternatively, radiation treatment, both conventional fractionated and stereotactic radiosurgery, has been used as well. Fractionated radiation therapy was the first radiation treatment modality explored for recurrent or refractory Cushing's disease. Although remission rates of 56 to 83% are reported,^{3,5} fractionated radiation therapy is associated with a high rate of hypopituitarism, ranging from 50 to 100%,^{1,16} along with other complications, including radiation necrosis with damage to surrounding sellar and parasellar structures.^{4,11} Over time, stereotactic radiosurgery has been used with increasing frequency for recurrent or refractory Cushing's disease, both for patient convenience as a result of the single

day of treatment compared with 6 weeks of fractionated treatment and the theoretical possibility of increased efficacy. From 1991 to 2007, there were more than 20 published studies describing the efficacy of the gamma knife for patients with recurrent or refractory Cushing's disease. The largest series studied 90 patients who underwent gamma knife treatment for Cushing's disease between 1990 and 2005 and reported a 54% cure rate with a mean time to remission of 13 months, with a 22% rate of hypopituitarism, and a 5% rate of cranial nerve neuropathies.⁶ Recently, there has been increased interest in the use of proton radiosurgery for these cases. Many proton beam centers are opening across the United States and may begin treating patients with pituitary adenomas. Protons offer improved dose distributions as compared with photon beams and thus enable dose escalation within the tumor while sparing normal tissues.

We report our experience with an algorithm of repeat transsphenoidal surgery for recurrent or refractory Cushing's disease, so long as there was no disease in the cavernous sinus with stereotactic proton radiosurgery (SPRS) for recurrent or refractory adenomas in the cavernous sinus and persistent disease after reoperation.

METHODS

Patient Selection

The records of 171 patients undergoing their initial transsphenoidal surgery for Cushing's disease between 1998 and 2006 at Massachusetts General Hospital were retrospectively reviewed for preoperative MRIs, pathology, and endocrine data. Remission rates for 63 of the 171 patients in this series were reported in a previous publication from our group.¹³ Cushing's disease remission was defined by 24-hour urine cortisol subnormalization (below 20 $\mu\text{g}/24$ hour) and early morning fasting serum cortisol subnormalization (below 5 $\mu\text{g}/\text{dL}$ on nonsuppressive doses of dexamethasone). This study was approved by our Institutional Review Board.

Cushing's Disease Management

Cure after radiosurgery was defined as normalization of 24-hour urine-free cortisol off all medical therapy for at least 3 months. Patients with recurrent or refractory Cushing's disease underwent repeat transsphenoidal surgery unless there was clearcut adenoma in the cavernous sinus. In cases in which there was no adenoma seen on initial MRI, the gland was explored bilaterally with hemihypophysectomy performed when no tumor was found using inferior petrosal sinus sampling data to predict lateralization. Patients who were not cured or recurred after two transsphenoidal operations underwent SPRS with a median dose of 20 cobalt-gray equivalents at the 90th percentile line. SPRS targeted the entire pituitary gland and the medial wall of the cavernous sinus, regardless of whether tumor was visible on the MRI. Of the 31 patients treated with SPRS in this series, 24 were reported in a previous publication from our group.⁸

Statistical Analysis

Actuarial recurrence rates after curative transsphenoidal surgery and remission rates in response to SPRS were calculated using Kaplan-Meier estimates.

RESULTS

We retrospectively reviewed the records of 171 patients undergoing their initial transsphenoidal surgery for Cushing's disease at our institution. The mean duration of biochemical follow-up was 43 months (range, 2 to 118 months). Biochemical remission rate for newly diagnosed patients with microadenomas after an initial transsphenoidal operation was 87 of 97 (90%), which increased to 94 of 97 (97%) after a second operation within 6 weeks of the first operation for the 10 patients who were not cured. Biochemical remission rate for patients with normal preoperative MRIs after an initial procedure was 46 of 58 (79%), increasing to 52 of 58 (90%) after a second operation within 6 weeks of the first operation. Remission rate for macroadenomas after an initial procedure was 11 of 16 (69%) with patients who had known residual tumor after surgery and/or biochemical evidence of persistent Cushing's disease postoperatively referred for proton beam radiosurgery after a single procedure given the high likelihood of dural and cavernous sinus invasion (*Fig. 18.1*).

Of the 157 patients who were cured after their initial or immediate second procedure, 16 of 157 (10%) recurred an average of 39 months (range, 13 to 62 months) postprocedure (*Fig. 18.2A*). Kaplan-Meier analysis yielded actuarial recurrence rates of 3% (95% confidence interval, 0–5%) at 2 years and 13% (95% confidence interval, 5–20%) at 5 years (*Fig. 18.2A*). The recurrence rate for patients with macroadenomas was two of 11 (18%), with microadenomas eight of 94 (9%), and with normal MRIs six of 52 (12%). Patients with macroadenomas experienced recurrence more frequently and more quickly than patients with microadenomas or normal

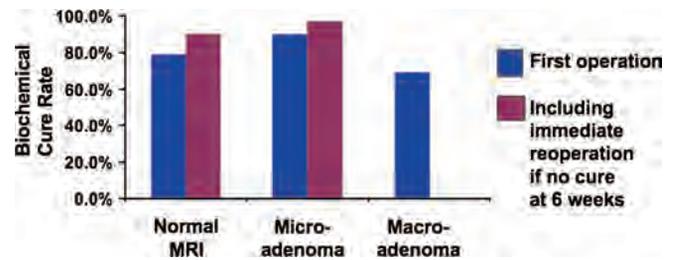


FIGURE 18.1. Biochemical remission rate for patients with normal MRI, microadenoma, and macroadenoma. Cure rates shown are after first transsphenoidal operation (blue) and after including patients who underwent an immediate re-operation whenever there was failure to cure 6 weeks after surgery (maroon).

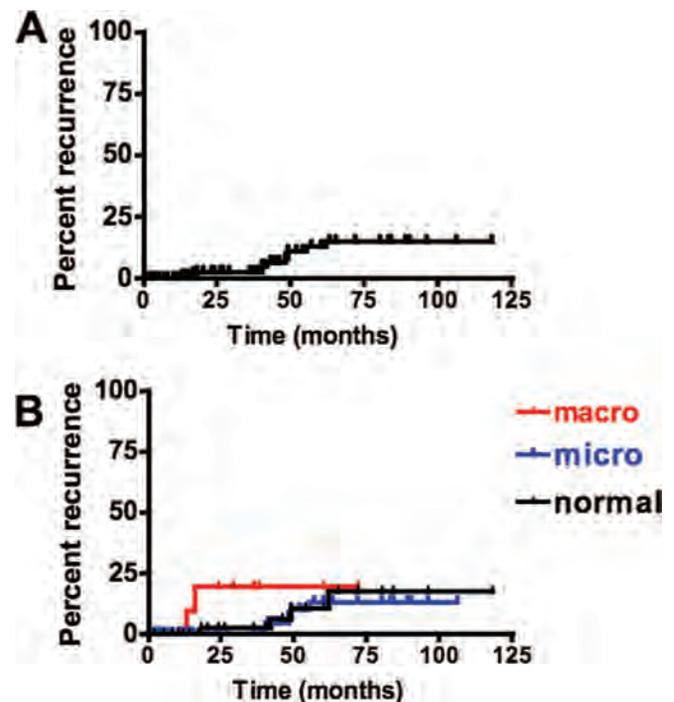


FIGURE 18.2. Biochemical recurrence rate versus time after cure from transsphenoidal surgery. *A*, Recurrence rate for all patients. *B*, Recurrence rate for patients with macroadenomas on initial MRI (red) was slightly higher with earlier recurrence as compared with patients with microadenomas (blue) or normal MRIs (black).

MRIs (*Fig. 18.2B*). Of the 16 initial recurrences, three patients with recurrent tumor in the cavernous sinus (two macroadenomas and one microadenoma) received SPRS and 13 underwent repeat transsphenoidal surgery with 10 of 13 (77%) cured after reoperation. There was a 15% incidence of hypopituitarism in those patients who underwent a second surgical procedure.

Thirty-one patients underwent SPRS: 17 patients who were never cured after 1 or 2 transsphenoidal surgeries; eight

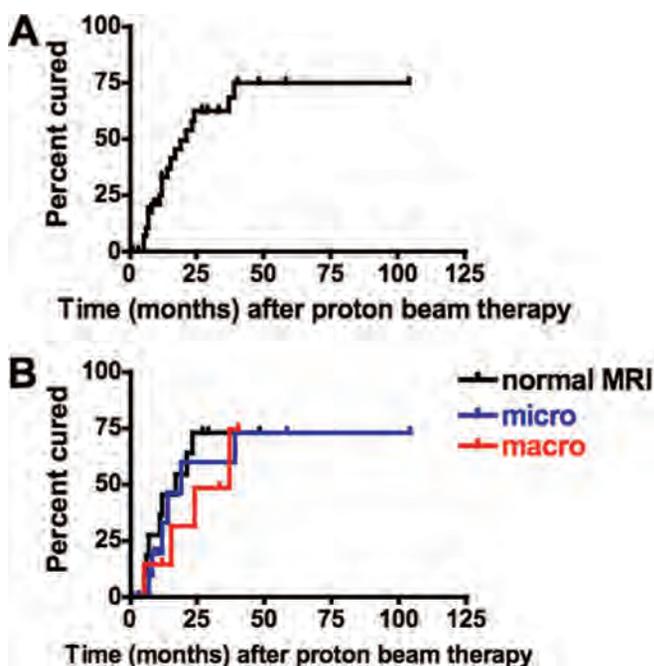


FIGURE 18.3. Biochemical cure rate versus time for SPRS used to treat recurrent or refractory Cushing's disease. *A*, Cure rate for all 31 patients who received SPRS. *B*, Cure rate versus time was the same for patients whose imaging before transsphenoidal surgery was normal (black), showed microadenoma (blue), or showed macroadenoma (red).

patients who were initially cured after transsphenoidal surgery, then had noncurative reoperation for recurrence; three patients who were initially cured then had recurrence in the cavernous sinus; and three patients who had recurrence after an initial curative transsphenoidal surgery and a curative reoperation for recurrence. Eighteen of 31 patients (58%) were cured after SPRS, and the median time to cure by Kaplan-Meier analysis was 21 months (range, 5 to 31 months) (Fig. 18.3A). The efficacy of SPRS did not depend on treatment volume. That is, SPRS was equally effective for patients whose imaging before transsphenoidal was normal ($n = 11$), showed microadenoma ($n = 13$), or showed macroadenoma ($n = 7$) ($P = 0.5$; Fig. 18.3B). Of the 31 patients who underwent SPRS, none developed cranial nerve neuropathies. Thirteen of 31 patients undergoing SPRS (42%) developed proton beam-induced endocrine dysfunction, with eight of the 31 patients undergoing SPRS (26%) developing multiple pituitary axis dysfunction. Of the cases with SPRS-induced endocrine dysfunction, 10 were hypothyroid, seven were growth hormone-deficient, two were deficient in gonadal steroids, and two were adrenally insufficient. The rate of endocrine dysfunction was 50% (nine of 18) in patients cured by SPRS and 31% (four of 13) in patients not cured by SPRS. Two of 18 patients cured by SPRS were adrenally insufficient and required steroid supplementation,

whereas none of the 13 patients not cured by SPRS were adrenally insufficient. One of 18 patients cured by SPRS developed recurrent Cushing's disease 1 year after SPRS.

DISCUSSION

Although microsurgical resection of a pituitary adenoma is the initial treatment of choice for patients with Cushing's disease, the optimal treatment of patients with recurrent or refractory disease after surgery remains unclear. In this series of 171 patients, 95% were cured using an algorithm of repeat surgery for recurrent or refractory disease with proton beam radiosurgery used for cases with adenoma in the cavernous sinus or cases that failed surgical re-exploration.

Our definition of Cushing's disease remission as 24-hour urine cortisol subnormalization (below $20 \mu\text{g}/24 \text{ hour}$) and early morning fasting serum cortisol subnormalization (below $5 \mu\text{g}/\text{dL}$ on nonsuppressive doses of dexamethasone) was more stringent than that used in other series, and this may have created a lower recurrence rate by minimizing the number of false-positives in our remission group. For example, a recent series defining Cushing's disease remission as normal postoperative 24-hour urine cortisol reported a 26% recurrence rate at 5 years,⁷ double the 13% recurrence rate we found at 5 years. Longer follow-up will determine whether the apparently lower recurrence rate in this series will be sustained.

Although this series did not prospectively compare repeat transsphenoidal surgery to SPRS for recurrent or refractory Cushing's disease and instead offered repeat transsphenoidal surgery before SPRS for these cases, it should still be noted that the rates of remission were better with repeat surgery compared with SPRS at 2 years, and the incidence of hypopituitarism was lower with repeat transsphenoidal (15%) than with SPRS (42%). This lends support to the idea of using SPRS primarily for patients who are not cured after repeat transsphenoidal surgery.

Although there have been more than 20 published case series in which the effectiveness of photon-based treatments such as the gamma knife has been explored for recurrent or refractory Cushing's disease, this series and another from our institution⁸ are the only two in which SPRS was investigated. In comparison to published results with the gamma knife,⁶ SPRS appears to cause reduced toxicity to adjacent structures such as cranial nerves, a comparable time to cure and cure rate, a reduced recurrence rate, and an increased incidence of hypopituitarism. However, the numbers of subjects and time of follow-up are too small to draw firm conclusions. These possible differences support the hypothesis that SPRS may have more targeted dosimetry to the pituitary gland than photon-based treatments and warrant further investigation in larger case series.

Disclosure

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