Bilateral adrenalectomy is the definitive treatment for patients with Cushing’s disease (CD) that is unresponsive to therapy directed at the pituitary.21 A significant proportion of these patients develop NS, or enlargement of residual pituitary tumor due to removal of the negative feedback effect of cortisol.17,18 Rapid, unchecked tumor growth may cause local mass effect and significant morbidity. Large case series have defined the incidence of NS as 8%–29%, occurring up to 24 years after bilateral adrenalectomy.17,21,22 Historically, the diagnosis of NS has been made using clinical criteria. A recent study in which modern MRI techniques were used has demonstrated that the rate of tumor growth is probably underappreciated and occurs in 47% of patients by 7 years.1

In our clinical experience at a tertiary referral center for CD, we have observed a lower incidence of NS than has been reported previously. Our management protocol differs from other institutions in that patients who do not achieve remission after pituitary surgery undergo sellar irradiation with GK SRS prior to bilateral adrenalectomy. Conventional radiation has been suggested to have an effect on the rate of NS after adrenalectomy; however, not all studies have confirmed this association.7,11,15,16,19,23 We postulated that preoperative SRS could explain our observed reduced rate of NS. Two patients developed new pituitary dysfunction and no patient developed cranial neuropathy or visual deficit after GK SRS.

Methods

Patient Population

Patients with confirmed CD who had persistently elevated cortisol despite transphenoidal pituitary surgery and subsequent pituitary GK SRS, and who later underwent bilateral adrenalectomy for significant persistent disease at the University of Virginia were included. Patients
with less than 6 months of neuroimaging follow-up were excluded. Institutional review board approval was obtained before initiation of the study.

Radiosurgery Details

Sellar irradiation was performed using a cobalt-60 Elekta Gamma Knife unit as previously described. Treatment plans were based on thin-slice MRI studies obtained before and after contrast administration after placement of the Leksell model G stereotactic frame (Elekta, Inc.). Dose plans were generated by a multidisciplinary team consisting of a neurosurgeon, a radiation oncologist, and a medical physicist. The number of isocenters, maximum radiation dose, prescribed dose to the tumor margins, and treatment isodose were recorded.

Imaging Studies

Pretreatment and posttreatment T1-weighted MRI studies of the pituitary were obtained at regular intervals. A neuroradiologist independently interpreted all studies. The MRI impressions were then categorized as consistent with tumor growth when the tumor exceeded 10% of its original volume; no change when the tumor was within ± 10% of its original volume; tumor regression when the tumor decreased by more than 10% of its original volume but was still visible; or no tumor visible. We routinely obtained MRI studies at 6-month intervals for the first 2 years after GK SRS and then yearly thereafter.

Clinical Evaluation

Patients were evaluated clinically at 6-month intervals for the first 2 years after GK SRS and then yearly thereafter to confirm remission, to evaluate for NS, and to manage hormone replacement. As part of this endocrine evaluation, serum ACTH, cortisol, thyroid-stimulating hormone, free thyroxine, and insulin-like growth factor–I levels were routinely obtained. Serum testosterone levels were followed in men and menstrual function was monitored in premenopausal women. Specific to NS, patients were clinically evaluated for hyperpigmentation, visual changes, and cranial neuropathy.

Statistical Analysis

Given the recent findings by Assié and colleagues, corticotroph tumor growth was considered the most sensitive measure of treatment failure and therefore was the primary end point. The Fisher exact test was used to assess the relationship between categorical variables and corticotroph tumor growth during the follow-up after bilateral adrenalectomy. For continuous predictors, univariate analysis, clinical factors were evaluated for significance was determined by a 2-sided p value < 0.05.

Results

Patient Characteristics

Twenty patients (17 women and 3 men) met the inclusion criteria for the study (Table 1). Four patients with neuroimaging follow-up of less than 6 months were not included. All patients received a diagnosis of CD and underwent one or more transphenoidal operations to remove an ACTH-secreting tumor from the pituitary gland. Four patients (20%) underwent a total hypophysectomy. Patients either had unresectable residual tumor (11 patients, 55%) or persistently elevated cortisol despite no clear microadenoma on pituitary MRI studies (9 patients, 45%).

Treatment Characteristics

All patients underwent GK SRS at the University of Virginia. The sellar target was treated with a mean margin dose of 24 Gy (range 18–30 Gy). A mean of 6 isocenters (range 2–17) were used. All patients had persistence of hypercortisolism. Four cases (20%) initially improved, but later developed recurrent hypercortisolism and underwent repeat GK SRS with a mean margin dose of 23 Gy (range 20–25 Gy). The time between initial and repeat GK SRS varied from 2.6 to 10 years. All 4 patients developed recurrent hypercortisolism after this second treatment.

After failure of surgical and radiosurgical treatment directed at the pituitary, patients with significant persistent disease underwent bilateral adrenalectomy at the University of Virginia. Adrenalectomy was performed a median of 1.5 years (range 2 days–9.7 years) after the most recent GK SRS procedure. Although GK SRS may take several years to result in endocrine remission in CD, the majority of these patients had uncontrolled CD with significant morbidity, and therefore could no longer wait for the latency of GK SRS.

Radiological Outcomes

Patient outcomes were determined using MRI studies obtained at regular intervals, with a median neuroimaging follow-up of 5.4 years (range 0.6–12 years). In 15 cases (75%) no tumor was visible on any of the serial scans. In 4 cases (20%), visible residual tumor at the time of bilateral adrenalectomy was stable throughout follow-up. One patient (5%) demonstrated new tumor growth on follow-up imaging 9 months after bilateral adrenalectomy and was considered to have developed NS (Fig. 1). This patient was treated with GK SRS focused on the new growth and was started on cabergoline pharmacotherapy. At last follow-up, the tumor was no longer visible on neuroimaging studies throughout an additional 8.5 years of evaluation.

By Kaplan-Meier analysis, progression-free survival rates at 1, 3, and 7 years were each 94.7% (number of patients at risk: 18, 12, and 5, respectively) (Fig. 2). Using univariate analysis, clinical factors were evaluated for their effect on tumor growth. Age, sex, time from radiosurgery to adrenalectomy, length of follow-up, treatment of residual tumor, prior total hypophysectomy, margin
TABLE 1: Demographic and treatment characteristics in 20 patients with CD who underwent bilateral adrenalectomy

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>20</td>
</tr>
<tr>
<td>mean age in yrs at adrenalectomy (range)</td>
<td>42 (22–63)</td>
</tr>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>M (%)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>F (%)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>median MRI follow-up in yrs (range)</td>
<td>5.4 (0.6–12)</td>
</tr>
</tbody>
</table>

GK SRS

| mean margin dose in Gy (range) | 23.9 (18–30) |
| mean no. of isocenters (range) | 6.2 (2–17) |
| mean % isodose (range)         | 47.1 (30–50) |
| median time from GK SRS to adrenalectomy (range) | 1.5 yrs (2 days–9.7 yrs) |
| mean maximum ACTH in pg/ml after adrenalectomy (range)* | 314 (11–1598) |

* Two patients without data.

dose, or a second GK SRS did not significantly predict tumor progression (Table 2).

Clinical and Endocrinological Outcomes

Clinical and endocrine follow-up was available for 18 patients. Patients had a median clinical follow-up of 5.2 years (range 1.5–12 years). No patient demonstrated evidence of hypercortisolemia. Eleven (61%) of these 18 patients developed ACTH levels greater than 200 pg/ml and 4 patients (22%) developed levels greater than 1000 pg/ml during follow-up (mean maximum ACTH: 314 pg/ml, range 11–1598 pg/ml) (Fig. 3). The patient with MRI-confirmed tumor growth developed a maximum ACTH of 1285 pg/ml. After repeat GK SRS, ACTH levels in this patient fell to less than 100 pg/ml, but have recently increased to levels greater than 1000 pg/ml despite negative MRI findings. Six patients (33%) developed hyperpigmentation, which was significantly more likely in patients with higher plasma ACTH levels during follow-up (p = 0.04). There were no clinical signs of tumor growth noted, including new cranial neuropathy or visual deficits.

Complications of Radiosurgery

No patient developed new cranial neuropathy or visual deficit after GK SRS. Ten patients (50%) had residual pituitary function prior to GK SRS. Of these patients, 2 (20%) developed new hypothyroidism in the follow-up period after GK SRS. No other new endocrinopathy was noted. No evidence of postradiosurgery carotid ischemia, carotid stenosis, or radiation-induced neoplasia was seen on follow-up MRI studies.

Discussion

Cushing’s disease is among the most challenging endocrine disorders to manage. First-line therapy is pituitary surgery, which can be curative in a large number of patients. Cases not cured by surgery often require multi-modality management consisting of radiation and medical therapies, including steroidogenesis inhibitors such as ketoconazole and metyrapone. If these measures fail to achieve remission, then bilateral adrenalectomy can be used for definitive elimination of cortisol secretion. Although the morbidity of this procedure has diminished with improving techniques, postoperative patients still require lifetime mineralocorticoid and glucocorticoid replacement and are at risk for developing NS.

Nelson’s Syndrome

In 1958, Don Nelson and colleagues reported on a patient with Cushing’s syndrome who underwent bilateral adrenalectomy in 1954, and developed cutaneous hyperpigmentation, amenorrhea, bitemporal visual loss, and rising plasma ACTH values over the following 3 years. She was found to have an expanded sella turcica on skull films.
and a large pituitary adenoma at subsequent surgery. In 1960, Nelson and coworkers\textsuperscript{18} reported similar findings in 9 additional patients. The eponymous Nelson’s syndrome is now a well-recognized risk of bilateral adrenalectomy.\textsuperscript{2,7,8,11,12,15,16,19,21,22} NS can cause significant morbidity due to rapid, unchecked tumor growth and local mass effect, and occurs after 8%–29% of cases of bilateral adrenalectomy. Long-term surveillance is critical, because clinical symptoms have been reported as many as 24 years after adrenalectomy.\textsuperscript{16}

A recent study demonstrated that tumor growth after bilateral adrenalectomy is an underreported phenomenon.\textsuperscript{1} Although NS has long been defined by clinical presentation, Assié and colleagues used modern pituitary MRI techniques to identify the incidence of tumor growth after adrenalectomy, the underlying cause of NS. With a median follow-up of 4.6 years, the incidence of tumor growth in this cohort was 39% at 3 years and 47% at 7 years.

Prior studies have attempted to identify factors that predict development of NS. Young age at adrenalectomy and a documented pituitary adenoma at surgery have been identified as predisposing factors in some studies.\textsuperscript{8,11,12,23} Conventional pituitary irradiation before bilateral adrenalectomy has also been associated with a reduced incidence of NS by some authors.\textsuperscript{7,11,16} The definition of NS varied among these studies, with some authors determining outcome on the basis of elevated ACTH levels and hyperpigmentation alone.\textsuperscript{11} Other studies that have assessed the effect of pituitary irradiation on the development of NS have found no influence.\textsuperscript{15,19,23}

**Gamma Knife SRS for CD**

Radiation therapy is an important treatment modality in the management of CD. A recent consensus statement by the Endocrine Society on the management of CD defined pituitary radiotherapy as second-line therapy after transsphenoidal surgery, with control of hypercortisolism achieved in 50%–60% of patients.\textsuperscript{2} Although different from fractionated radiation therapy, GK SRS does use ionizing radiation in a fashion that limits radiation exposure to the surrounding critical neurovascular structures. Modern, long-term series have shown that GK SRS is effective in achieving remission in 42%–87% of patients in whom transsphenoidal surgery failed.\textsuperscript{3,9,20} Radiosurgery also appears to induce a faster endocrine remission compared with radiation therapy.\textsuperscript{13} Potential risks of GK SRS have been defined by these and other large series and include hypopituitarism (20%–23%) and cranial neuropathy (4%).\textsuperscript{3,4,9}

**Gamma Knife SRS and NS**

In addition to having a biological effect on primary lesions in CD, GK SRS can also control the lesions that develop with NS. Several recent studies have found that GK SRS controls tumor growth in 82%–100% of patients who develop NS lesions.\textsuperscript{14,20,24} No study, however, has assessed the effect of GK SRS performed before bilateral adrenalectomy on the incidence of NS. Additionally, although conventional pituitary radiation before adrenalectomy has, in some cases, been shown to decrease the rate of NS, this relationship has not been analyzed using sensitive MRI techniques to detect subclinical tumor development.\textsuperscript{7,11,16}

Our study demonstrates that the use of GK SRS before bilateral adrenalectomy reduces the rate of NS (5.3% at 3 and 7 years by Kaplan-Meier analysis) when using MRI sequences to detect tumor growth, compared with historical controls. Assié and colleagues\textsuperscript{1} found the rate of tumor growth after bilateral adrenalectomy to be 39% and 47% at 3 and 7 years, respectively, and did not include patients who received pituitary radiotherapy. Our series includes longer follow-up (median 5.4 years compared with 4.7 years) but fewer patients (20 patients compared with 47 patients).

In our study, no specific preoperative factors predict which patients will benefit from GK SRS. This univariate analysis may be limited by the observation that only 1 patient had tumor growth. Additionally, multivariate analysis is not appropriate given the paucity of instances of tumor growth.\textsuperscript{3} Because NS is a rare clinical entity and the rate of events in patients treated with GK SRS is relatively low (5.3%), adequate analysis of predisposing factors would require a multicenter study. Additionally, because this is

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
Variable & Parameter & p Value (test) \\
\hline
age at adrenalectomy & higher & 0.28 (L) \\
sex & male & 0.99 (F) \\
total hypophysectomy & yes & 0.99 (F) \\
residual tumor treated by GK SRS & yes & 0.45 (F) \\
2nd GK SRS treatment & yes & 0.25 (F) \\
margin dose & higher & 0.99 (L) \\
time from GK SRS to adrenalectomy & longer & 0.31 (L) \\
length of follow-up & longer & 0.29 (L) \\
\hline
\end{tabular}
\caption{Univariate analysis of factors influencing tumor growth in 20 patients with CD who underwent bilateral adrenalectomy*}
\footnote{F = Fisher exact test; L = logistic regression.}
\end{table}
a retrospective study it is subject to inherent biases, and this population may be studied prospectively in the future.

Overall, GK SRS was well tolerated in this cohort, with the rate of new endocrinopathy in patients with residual pituitary function (20%) similar to previously published results for CD. Additionally, no cranial neuropathy was noted, reinforcing the previously described neurovascular safety profile of this technique. Therefore, particularly in patients with panhypopituitarism who have undergone total or subtotal hypophysectomy, GK SRS may be used with minimal risk of complications.

Conclusions

Nelson’s syndrome is a potentially devastating complication of bilateral adrenalectomy for CD. The present study demonstrates that GK SRS appears to have the benefit of reducing the incidence of NS after bilateral adrenalectomy in the cases in which it fails to achieve remission. These results suggest that in addition to being a safe and effective second-line approach for CD, GK SRS also serves as durable prophylaxis for NS. Therefore, GK SRS should be considered before bilateral adrenalectomy in the management of CD.

Disclosure

This research was supported by the Intramural Research Program of the NINDS at the NIH. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Vance, Sheehan. Acquisition of data: Mehta. Analysis and interpretation of data: all authors. Drafting the article: Mehta. 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: Vance. Statistical analysis: Mehta. Study supervision: Vance, Sheehan.

References


Manuscript submitted March 5, 2013. Accepted July 8, 2013. Please include this information when citing this paper: published online August 16, 2013; DOI: 10.3171/2013.7.JNS13389.

Address correspondence to: Mary Lee Vance, M.D., Department of Medicine, University of Virginia Health System, Charlottesville, VA 22908. email: mlv@virginia.edu.

J Neurosurg / Volume 119 / December 2013