More than 30 years ago, Olaf Pearson coined the term “malignant endocrinopathy” to describe the severe effects of persistent acromegaly and Cushing disease (personal communication, 1988). Although the tumors responsible for the genesis of these clinical syndromes are rarely malignant with respect to their histological and biological behavior, the systemic consequences of these endocrinopathies include profound morbidity and premature death for patients whose abnormal endocrine status is not resolved. For this reason, the challenge facing the endocrinologists and neurosurgeons charged with treating these patients is the normalization of pathological levels of adrenocorticotropic hormone (ACTH) and thus serum cortisol levels. Minimal residual tumor, which is often invisible on even the most high-resolution magnetic resonance (MR) imaging studies, will express itself as persistent disease; the measure of success in treatment resides in the endocrine evaluation rather than the neuroimaging study.

In their paper in this issue of the Journal of Neurosurgery, Jagannathan et al. analyze the utility of stereotactic Gamma Knife surgery (GKS) as salvage therapy for patients in whom resection has failed or who harbor lesions that are not amenable to conventional surgery. We agree with the authors’ assertion that the first line of treatment for patients with biochemical evidence of Cushing disease should be an attempt at resection of a defined pituitary tumor. In the absence of an identifiable lesion on MR images (but with results of appropriate petrosal or cavernous sinus venous sampling indicating a pituitary source of ACTH hypersecretion), surgical exploration of the pituitary should be undertaken. Surgical therapy offers the best option for rapid cure of the endocrinopathy, with excellent long-term results. Nevertheless, it is known that in approximately 25% of patients with biochemical evidence of Cushing disease, MR images will reveal negative findings, and surgery will fail to demonstrate a pituitary tumor in almost half of those cases. In addition, a significant percentage of such tumors will infiltrate the dura mater and surrounding structures either macro- or microscopically, markedly reducing the opportunity for successful surgical extirpation of the lesion.

In such circumstances, it becomes necessary to institute adjuvant therapeutic ventures to treat the underlying endocrine disorder. Unfortunately, in the case of Cushing disease, no pharmacological agent that offers a long-term therapeutic option has been defined. Bilateral adrenalectomy can be considered at this juncture; alternatively, the preferred treatment in such circumstances has been administration of some form of radiation, as described by the authors. Because of the limited options for these patients, it would be valuable to understand the benefits and potential for such adjuvant therapy in addition to the risks attendant on these treatments. This paper is a noteworthy effort to address these issues, yet we must raise the following points for consideration.

In the paper’s introduction, the authors state that their objective was to report on their experience treating “patients with ACTH-secreting pituitary adenomas.” In 23 of the 90 patients treated in this series, however, no tumor was seen on MR images; in 14 of these 23, total hypophysectomy failed to resolve the endocrinopathy. We are not told whether tumor was found in the specimens resected at the time of hypophysectomy, but if the experience of these authors parallels our own, these specimens would most often yield no evidence of pituitary tumor. To our minds, this is evidence that we do not fully understand the genesis of biochemical Cushing disease in all patients who manifest such findings, and that ACTH-secreting tumors may not be the sole cause. This group should be considered a subset of those treated and should be analyzed independently. Given the large number of patients in this series, a separate subgroup analysis might help us to understand the variation observed in such cases. In addition, to assume that such cases represent invasion of the cavernous sinus requiring its inclusion in the treatment plan is unwarranted.

In summary, Gamma Knife surgery offers a promising option for patients with biochemical evidence of Cushing disease who have failed conventional surgical or medical therapy. Further study is needed to define the role of GKS in the treatment of Cushing disease, and to determine its efficacy and safety in a subset of patients who have large, invasive pituitary tumors that are not amenable to conventional surgical approach.
the radiation field may unjustifiably expose the patient to undue risk to the cranial nerves traversing the cavernous sinus. If, after analysis of this subset of patients, one can demonstrate a reasonable result from the radiation therapy, this would warrant a trial of exclusively sellar radiation to determine whether inclusion of the cavernous sinuses is desirable. We must first have evidence, however, that radiation had a positive effect on this group.

Jagannathan et al. note normalization of 24-hour urinary free cortisol (UFC) levels in 54% of patients after a mean follow-up duration of 45 months. It is important to note that 30% of the patients described in the paper were followed for less than 24 months. We do not know how many of the individuals whose disease was considered to be in remission were in this group; however, six of the 10 recurrences in patients considered to have achieved remission occurred after 24 months of follow-up monitoring. Therefore, for any patient whose disease was in remission for less than 24 months we have to consider the data to be preliminary, because long-term follow-up evaluation is essential to understand the true rates of recurrence. In this regard, the recent study published by the Federation of Endocrinology in Marseille, France, indicated a 40% remission rate seen in 40 patients with a median follow-up duration of 54.7 months (less than the 54% noted in the present paper), suggesting that with longer follow-up periods the remission rate may decrease. The rates of recurrence in patients treated using surgery, with or without the need for postoperative radiotherapy, are higher than in those in whom an initial endocrine normalization occurs in cases of acromegaly or prolactin-secreting tumors. Our experience is similar to that reported here, and this raises an issue regarding the assessment that is used to evaluate outcome.

The authors used the 24-hour UFC levels as the measure of remission or treatment failure. That test is certainly the gold standard in assessing cortisol secretion; however, the measure may be a reflection of temporary suppression of corticotroph function but may not be indicative of total elimination of tumor cells. It may be desirable for all of us to use dynamic testing of cortisol function in addition to the 24-hour UFC testing to get a more accurate measure of response to therapy. We have certainly seen patients with acromegaly who have normal insulin-like growth factor–I values postoperatively yet who fail to show adequate suppression of growth hormone to a glucose load, as should be seen in healthy patients. These patients with acromegaly may be more prone to recurrence of their disease, and the same may be true for the patient with Cushing disease whose postoperative dynamic testing shows treatment failure. Measurement of 24-hour UFC levels, along with a.m./p.m. serum cortisol and response to a dexamethasone suppression test may provide the best way to identify patients who are likely to suffer recurrence. It may be that a partial disruption of tumor activity by some intervention such as surgery or radiosurgery may allow a temporary reduction in the UFC level until the tumor recovers from the insult sufficiently to generate elevated levels once again. It would be interesting to stratify the levels of posttherapy UFC to see whether the values for patients with recurrences are higher than the values for patients who have long-term remission.

The incidence of neurological complications arising as a consequence of this procedure is reported as 5%, representing the five patients in the group in whom cranial nerve palsies developed. However, in four of these same patients visual loss occurred in addition to the cranial nerve palsies. Therefore 5% of patients experienced neurological complications, but there were nine neurological complications (10%) in the group as a whole. We have seen some cranial nerve palsies after GKS that have resolved over time, although certainly not all of them have done so. It would be interesting to know whether the authors have had the same experience. In addition, our experience with GKS in patients who have intact pituitary axes shows that multiple axes tend to be affected when one encounters postradiation endocrinopathies. It would be helpful to know how many normal pituitary axes were disrupted by this therapy in the 22 patients who experienced pituitary insufficiency afterward. In addition, as the authors follow up with these patients for longer periods, it is likely that the incidence of postradiation endocrinopathy will increase. It would be interesting to know whether Nelson syndrome developed in any of the patients who underwent adrenalectomy after radiotherapy failed.

Finally, the authors chose not to evaluate the efficacy of GKS in patients with Nelson syndrome. In this group of patients with rapidly growing symptomatic tumors after adrenalectomy, some may have harbored previously defined pituitary tumors whose response to stereotactic radiosurgery would be important to understand, particularly in cases of localized lesions in the sellar and parasellar region. It would even have been interesting to know whether there was a difference in response to radiation to the sella turcica and cavernous sinus in these patients compared with those with no history of adrenalectomy in whom radiosurgery was directed to the same structures. This would certainly help us to understand further any variation from the usual outcome within this particular subset of patients.

Jagannathan et al. are to be congratulated for undertaking this analysis of an extremely complicated problem that frequently eludes successful therapy. It is clear that radiosurgery is not the final answer to this problem, but the authors have demonstrated that it is a significant addition to our armamentarium in the fight against this deadly disease.

References


RESPONSE: We thank Drs. Weiss and Couldwell for their comments on our report. At the University of Virginia, mi
crosurgery remains the initial treatment option for patients with Cushing’s disease. Gamma Knife surgery represents the preferred treatment for patients with recurrent or residual Cushing’s disease; during the period following GKS, ketoconazole is given until the anticipated remission occurs. Laparoscopic adrenalectomy is reserved for patients who fail to achieve a remission or who experience a recurrence after initial remission from GKS.

Our study represents the single largest published series to date of patients with Cushing’s disease treated with stereotactic radiosurgery. Subgroup analysis in a study in which the total population consists of 90 patients is generally inappropriate from a statistical point of view and may yield dubious findings. As is true with virtually every neurosurgical study published on pituitary adenomas, a longer follow-up period and a greater sample size would be preferable to assess long-term rates of recurrence, remission, and complications. Notably, our use of the term “remission” rather than “cure” for patients with Cushing’s disease speaks to our belief that long-term neurosurgical, endocrine, radiological, and ophthalmological follow-up care is needed for these patients, and we emphasize this to our patients and to our neurosurgical and medical colleagues.

With regard to other published radiosurgical series for Cushing’s disease, differences in patient populations, treatment algorithms, sample size, length of follow up, and the endocrine criteria used to define success make it quite difficult to perform a detailed comparison between this study and others.\(^\text{2,3,5,6,8}\) For instance, Drs. Weiss and Couldwell cite a longer follow-up duration as a potential explanation for the difference in endocrine remission rates between our study and the recent work published by the Federation of Endocrinology in Marseille, France.\(^\text{2}\) However, other differences between the studies include the following: 1) 27.5% of patients in the French study underwent GKS as the primary treatment, whereas in our study GKS was administered predominantly after failed resection (GKS was the primary treatment in only 1.1% of patients in our study); 2) the median dose to the margin differed; and 3) the treatment volumes in the studies differed substantially. These differences could just as easily explain our higher rate of endocrine remission. We do advocate that radiosurgical series for patients with secretory pituitary adenoma follow accepted endocrine testing as outlined in consensus statements, and that they include only patients who have had at least 12 months of follow up.\(^\text{1,4}\)

Drs. Weiss and Couldwell note that measurement of the 24-hour UFC concentration “is certainly the gold standard in assessing cortisol secretion . . .” but that “the measure may be a reflection of temporary suppression of corticotroph function but may not be indicative of total elimination of tumor cells.” This is correct. They suggest that dynamic testing in addition to the 24-hour UFC would be a more accurate measure of response to therapy. There are two reasons why dynamic testing was not performed in our patients. The first was the cortisol response to dexamethasone: this test has limitations that include precise timing of dexamethasone ingestion (11 p.m.); precise timing of the blood test on the following morning (8 a.m.; a sample that is drawn at 10 a.m. is not valid); and most importantly, intrinsic variability in patients’ metabolism of dexamethasone and the influence of medications on this process. The second reason was that the majority of patients in this series did not reside in the area and could not return to our institution for supervised dynamic testing. Thus, we had to rely on the “gold standard” measure of integrated cortisol production: 24-hour UFC. Additionally, in three large studies the reliability of 24-hour UFC levels has been shown; the serum cortisol response to 1 mg overnight dexamethasone and 11 p.m. or midnight salivary cortisol levels are equally reliable in identifying Cushing’s disease. Thus, we think that the use of 24-hour UFC measurements is an accurate and reliable method of assessing the response to GKS treatment and in identifying recurrence of Cushing’s disease.

Our experience is that cavernous sinus and dural invasion are frequent indicators of initial failure or recurrence following microsurgery. Drs. Weiss and Couldwell note that “inclusion [of the cavernous sinus] in the radiation field may unjustifiably expose the patient to undue risk” to the cranial nerves within the paraseellar region. However, even the Gamma Knife with its steep falloff cannot spare the structures in the paraseellar region from radiation while still targeting sellar contents with a peripheral dose of 25 Gy or more. We used to expose the nerves in the paraseellar region to no more than 20 to 25 Gy, and we never observed permanent damage to the nerves at these doses. However, in cases that required a residual tumor to be treated again after radiation therapy or radiosurgery, we adhered to the contention that the cumulative tolerable dose to the paraseellar cranial nerves was 40 Gy.\(^\text{9}\) This dogma has long since been abandoned at our center. Compared with the generally well-accepted tolerable radiosurgical dose to the optic apparatus, the tolerance of the cranial nerves in the paraseellar region is not at all well defined.\(^\text{2}\) Moreover, the tolerance of the paraseellar cranial nerves in patients with adenoma compression and preexisting palsies may be very different than in those without such neuropathological conditions. The proposal to compute a complication rate wherein some patients are counted as having two events is not a practice adopted in the neurosurgical literature, and statistically it would necessitate an increase in both the numerator and the denominator if one considered every cranial nerve to be at risk of injury from the Gamma Knife.

Finally, we did exclude from the analysis those patients with Nelson’s syndrome who underwent GKS at our institution. The radiosurgical techniques and goals of GKS for patients with Nelson’s syndrome differ from those for patients with Cushing’s disease, and accordingly, we believe that patients with Nelson’s syndrome remain outside the scope of the current report. A companion article detailing our experience with GKS in patients with Nelson’s syndrome will be published in this issue of the *Journal of Neurosurgery* (Mauermann et al., see pages 988–993).

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