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 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 radiotherapy 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**


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