Editorial

Radiosurgery for pituitary adenomas

MARTIN H. WEISS, M.D.

University of Southern California, Los Angeles, California

This work by Sheehan et al. represents an incremental contribution to our understanding of the utility of Gamma Knife surgery in the treatment of persistent pituitary adenomas. The large cohort of patients enables an appropriate statistical analysis where possible. The topic addresses an issue that is important to all neurosurgeons and endocrinologists dealing with the complexities of pituitary adenomas.

The manuscript does not define the basis for selection of patients with prolactin (PRL)–secreting tumors for radiosurgery. I assume that this selection was based on an inadequate response of these patients to dopaminergic therapy, because in most of them the disease can be controlled very well with such therapy. The small number of such cases in this series suggests that this is the basis of their selection. It seems unfortunate that only 26% of these patients achieved remission. It would be interesting to see if one could break this down into patients who had residual tumor approximating the optic apparatus that therefore limited the marginal dosage, although the relatively small number of such patients makes such an analysis difficult. It would also be interesting to know if the patients in whom radiosurgery failed were able to attain subsequent control with dopaminergic agents.

The remission rate for patients with acromegaly (53%) is encouraging for this complex group of patients. The high incidence of infiltration at the time of initial surgery requires adjuvant postoperative therapy in a significant population of these patients. In the Methods section, the authors note that patients with acromegaly were selected for treatment on the basis of a postoperative glucose tolerance test (GTT), looking for appropriate suppression of growth hormone (GH) to a glucose load. This is an excellent, if perhaps not the best, index of normal GH dynamics. However, in the Results section, the authors refer to a normalized insulin-like growth factor–I (IGF-I) as the general index of response to radiosurgery, noting that “many” patients also underwent a posttherapy GTT. All of us with significant experience in this area have seen patients whose IGF-I falls within the norm for age and sex, yet fail to suppress appropriately to a glucose load. It is this group that seems particularly vulnerable to late failure in our experience. Because the authors seem to have “many” patients who had posttherapy GTTs, it might be interesting to see if that group had a different outcome. In addition, as with the PRL secretors, it would be of interest to learn if the group that failed to achieve remission became more responsive to the medical modes of therapy that are available.

The response rate for patients with Cushing disease (CD) is also promising. Along with the patients with acromegaly, these are the most complicated and demanding patients to treat. Resolution of hypercortisolemia is critical in these patients, whatever technique is used. Because there are no good long-term medical agents available for treatment of CD, the value of adjuvant radiosurgery is particularly critical in this group.

The authors describe 38 patients with persistent excess hormone secretion but without visible tumor who received radiosurgery to the entire sellar contents as well as both cavernous sinuses. It seems to me that this group would be particularly vulnerable to posttherapeutic hypopituitarism, and that such information would be important to know in the decision-making algorithm prior to initiation of therapy. Can the authors tell us if this group fared differently from those who underwent more “selective” radiotherapy, as to remission and complications?

As to the small but disconcerting group of patients who sustained visual loss as a consequence of therapy, it would be interesting to note whether the authors think that there is a specific subgroup that ought not to be exposed to single-fraction radiosurgery (consider the reference to the fact that 75% of patients who experienced visual loss had prior radiation therapy). Is there a group in which one should consider fractionated radiosurgery with an alternative system that might reduce the potential for visual compromise?

Lumping of the various groups together to assess the issue of tumor growth suppression as opposed to recurrent tumor growth seems appropriate. This obviously provides the power necessary for appropriate statistical analysis. The relationship to tumor margin dosage is not surprising. Do the authors have data to compare tumor growth rates, as measured by such parameters as Ki 67, in the 90% of tumors that appear to be controlled versus the 10% in which therapy failed? Such information might be helpful, once again, in analyzing patients for therapy.

Finally, it is interesting to speculate on the discord between the remission rates as measured by endocrine analysis in functional tumors versus the data evidenced in tumor growth control, both functional and nonfunctional. To me, because the ability to measure persistent elevated hormone secretion is probably the best index of tumor viability, we need to work to explain the different observed results. It certainly may be that the follow-up
time for patients with functional tumors is too short for definitive analysis and that more time will reveal better endocrine control of these tumors. This is certainly suggested in Table 3 of the manuscript. The alternative is that time will diminish the excellent tumor growth suppression herein reported.

This patient population will undoubtedly lend itself to a classic analysis for pituitary management strategies. I look forward with great enthusiasm to a subsequent analysis with a minimum 10-year follow-up for all patients. I encourage the authors to continue to follow this significant population to provide such data. In its present form, this must be considered a significant contribution that will undoubtedly warrant further long-term analysis.

Reference

Response

JASON P. SHEEHAN, M.D., PH.D.,1 EDWARD R. LAWS, M.D.,2 AND MARY LEE VANCE, M.D.1

1University of Virginia Health System, Charlottesville, Virginia; 2Brigham and Women’s Hospital, Harvard University, Boston, Massachusetts

We thank Dr. Weiss for his thoughtful analysis of the accompanying paper on Gamma Knife surgery for patients with pituitary adenoma. The limitations of the study are many, and yet it remains one of the largest and most detailed studies published to date. Patient selection, insufficient follow-up, and changes in endocrine assessment and management options represent factors that may have affected the study findings. Strengths of the study include the cohesive treatment approach of practitioners at the University of Virginia, the detailed endocrine and ophthalmological follow-up, and the size of the patient population.

Further work remains to be done to improve endocrine remission rates following stereotactic radiosurgery, and to achieve an endocrine success on par with the tumor control rates seen in this and other series. Pituitary adenoma tumors usually behave as late-responding tissue. This late-responding behavior encompasses radiological and also endocrine responses to radiosurgery. Overcoming the hormone overproduction of adenoma cells requires a substantially higher dose than is required simply to achieve growth control. A higher dose to the adenoma inevitably exposes surrounding structures such as the normal pituitary gland and cranial nerves to a greater amount of radiation. With regard to the most common postradiosurgical risk of delayed hypopituitarism, endocrinologists can typically identify and replace deficient hormone as required. Given the reasonable but far from perfect rate of endocrine remission achieved with radiosurgery, dose reduction to the planned treatment volume so as to preserve pituitary function does not seem warranted because it will probably reduce endocrine remission rates further. As Dr. Weiss astutely noted, a radiosurgically induced endocrine improvement but not a remission may still translate into a profound clinical benefit for patients, and make medical management with pituitary suppressive medications more successful.

When deciding on treatment for a particular patient with pituitary adenoma, a multidisciplinary approach is optimal. At the University of Virginia and at Harvard, many pituitary adenoma patients are referred from other institutions. Some of these patients may require just one treatment. However, in many cases the most effective treatment strategy requires medical, open surgical, and radiosurgical approaches. These approaches may be delivered in a staged fashion by design or used in a sequential fashion after signs of failure following the prior treatment.

With regard to radiosurgery, the tumor location, tumor volume, histological subtype, prior treatments, endocrine function, ophthalmological state, and overall health of the patient must be carefully considered. In particular, those patients undergoing radiosurgery after prior radiation therapy appear to be at greater risk of cranial nerve injury. Even with a steep gradient index, dose falloff is generally 10–20% per millimeter. Optimizing the biologically equivalent dose delivered to the tumor will depend on the technological constraints of the radiosurgical devices available, the attributes of the tumor, and the patient’s neurological function status. In some instances, a single session of radiosurgery may be ideal. In others, multisession radiosurgery or stereotactic radiotherapy may prove more advantageous. A multidisciplinary follow-up for patients with pituitary adenoma is critical in characterizing the risk-to-benefit profile of stereotactic radiosurgery and improving patient outcomes in the future.

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