Unresolved issues: radiosurgery versus radiation therapy; medical suppression of growth hormone production during radiosurgery; and endoscopic surgery versus microscopic surgery

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This issue of Neurosurgical Focus contains important reviews of several aspects of acromegaly. Three themes are emphasized in at least 3 contributions: the attributes of radiosurgery compared with conventional fractionated radiation therapy for patients with residual tumor after surgery; the use of medical therapy to suppress tumor production of growth hormone (GH) during radiosurgery; and the “pure” endoscopic approach for surgery. The authors of these reports already emphasize much of what I have to say here. However, certain arguments, arguments that have been recently proposed and widely avowed, albeit without solid validation by scientific or clinical studies, justify further discussion here.

Radiosurgery Versus Fractionated Radiation Therapy

The most compelling arguments for the selection of radiosurgery over fractionated radiation therapy are that the former is more convenient because of its single-session treatment than a course of radiation treatments over 4–5 weeks and because it reduces GH earlier. In addition, many authors propose that the risk of loss of pituitary function is smaller with radiosurgery than with fractionated therapy. There is, however, no compelling evidence to support this. Loss of pituitary function after either therapy is usually limited to 1 or 2 pituitary functions, rather than panhypopituitarism, and it occurs over several years, accumulating for 10–15 years after treatment, as summarized in the current issue in reports by Stapleton et al.8 and Yang et al.9 Because with radiosurgery we have access to very few studies with follow-up durations beyond 5 years (see the tables in the reports by Rowland et al.,7 Stapleton et al.,8 and Yang et al.), the true incidence of adverse effects on pituitary function over time cannot be known until the data to measure it are available. For instance, in the only radiosurgery series with a minimum median follow-up of 10 years,6 46% of patients with acromegaly who underwent radiosurgery had endocrine remission at 10 years and 50% developed new anterior pituitary insufficiencies, the majority of which appeared more than 5 years after treatment. This incidence of hypopituitarism is similar to that reported in many studies of radiation therapy with follow-up of similar duration.

Other factors that influence a perception of radiosurgery’s increased utility of and lower risk of loss of pituitary function include comparison of the results of the 2 modalities in different eras. The summary of radiation therapy experience is almost always from period before the general use of radiosurgery. The imaging modalities used to detect the tumor and define its anatomy in the pre-radiosurgery era were less sensitive (before MR imaging), and modern surgery is more effective at removing tumor. Considering the 2 treatment eras and the smaller tumor size and more minimally damaged pituitary before delivery of radiosurgery, differences in tumor size at diagnosis or after surgery could affect the success of treatment and influence the incidence of impaired pituitary function that cannot be accurately compared between 2 groups. For instance, in the frequently cited study comparing radiosurgery and conventional radiation therapy by Landolt et al.,2 radiation therapy was administered between March 1973 and January 1992, whereas the radiosurgery was performed from 1994 to 1996. Furthermore, the total dose of fractionated therapy was only 4000 cGy, a dose below the generally recommended minimum dose of 4500 cGy. Moreover, the average pretreatment GH level, the main predictor of response to radiosurgery or radiation therapy, was 67% higher in the radiation therapy group, perhaps explaining some of the difference in the percentage of patients in whom endocrine remission was achieved as well as the mean time to response in the 2 groups, as patients with higher levels are less likely to reach normal levels, and if the levels do normalize, they do so over a longer interval. In the absence of a prospective randomized trial the same selection biases would also contaminate contemporary case series because tumors selected for fractionated therapy today are likely to be lesions that are either too large for radiosurgery or are immediately contiguous to the optic system (fractionated therapy is selected since it is necessary to include the optic nerves or chiasm in the treatment field and the risk of normal tissue toxicity is reduced by fractionation).

Also, discussion of the side effects associated with conventional fractionated therapy almost always includes studies that used delivery techniques that did not incorporate modern radiation techniques. In the last decade it has
become routine to precisely target pituitary tumors while simultaneously avoiding normal brain through the use of conformal techniques such as intensity modulated radiation therapy (IMRT). IMRT is based on multileaf collimation in which leaves move in and out of the radiation beam to modulate the intensity of the beam, thereby allowing the radiation dose to target the sella and avoid normal brain. In contrast, prior to conformal techniques two opposing temporal fields were often used, resulting in the temporal lobes receiving a similar radiation dose as the pituitary tumor.

A limitation of radiosurgery is that the field of treatment is often the region of visible tumor on MR imaging. Yet MR imaging is very insensitive for detecting microscopic tumor infiltration of the cavernous sinus or other structures adjacent to the pituitary. Because of the limited knowledge of what will occur 3–5 years after radiosurgery, the recurrence rate after what appears initially to be successful treatment, because of clones of resistant tumor, or due to progression of microscopic tumor outside the field of treatment, cannot now be known.

These arguments should not be perceived as refutations against the routine use of radiosurgery in most patients who need additional therapy after surgery (either because of incomplete endocrine control with medical therapy or because of the extraordinary expense that currently accompanies a lifetime of medical therapy with somatostatin analogues or GH receptor blockade). The convenience of having a single-session therapy and the potential of an early hormonal response are reasons enough for radiosurgery to be the first choice in most patients. However, there is no reason to add superfluous arguments, such as a reduced incidence of hypopituitarism compared with modern radiation therapy, when the data do not yet exist for us to reach those conclusions. There are also circumstances in which the use of modern techniques to deliver conformal fractionated radiation is the best choice, such as when, after surgery, residual or recurrent tumor abuts (within 2 mm) the optic nerves or chiasm or when the field that requires treatment is larger than what can be safely treated with radiosurgery.

Influence of Medication on Response to Radiosurgery

Many of the aforementioned issues also apply to the concept that medical therapy to suppress GH secretion during treatment reduces the efficacy of radiosurgery. There are only a handful of studies that address this issue. Some investigators suggest that the somatostatin analogs, if used during radiosurgery, reduce tumor response, whereas others find no correlation between the use of medical therapy during radiosurgery and the likelihood, degree, or pace of the endocrine response.

It is possible that considerable patient selection bias in the use of medication during the irradiation has been present. For instance, Landolt et al. reported that in patients treated with octreotide during radiosurgery, normal levels of GH and insulin-like growth factor–I took longer to develop than in patients without medical therapy. However, compared with patients receiving medical treatment, the group of patients without medical therapy during radiosurgery had lower average levels of GH (see Fig. 1, Landolt et al.), which is the only consistent predictor of response to radiosurgery. The authors of other studies have reported no difference in response related to medical therapy during radiosurgery, as discussed by Rowland and Aghi and Stapleton et al. in this issue of Focus. Whether or not medical therapy during radiation exposure influences tumor response—one benefit of briefly withdrawing medical suppression of GH-producing tumors, as summarized by Rowland and Aghi—it also provides a beginning baseline of GH and insulin-like growth factor–I without the confounding influences of hormonal suppression, for later comparisons; furthermore, unlike prolactin-producing tumors, brief withdrawal of medical therapy is unlikely to result in a rapid rebound of tumor size.

Endoscopic Surgery Versus Conventional Approaches Using the Operating Microscope

The potential advantages of using the surgical endoscope for pituitary surgery have been detailed for the past 20 years. In the past 15 years the advantages of the “pure” endoscopic technique compared to surgery with the operating microscope have been championed by its enthusiasts. Despite this claim, none of the 3 surgical series reported in the current issue, nor those reported elsewhere, demonstrates superior outcomes to conventional techniques by experienced surgeons. In fact, one group (Hofstetter et al.) experienced with endoscopy describes a 46% remission rate, a 50% incidence of intraoperative CSF leakage, and 2 (8%) of 24 patients were left with panhypopituitarism after endoscopic surgery. Although several of the reports describe commendable results, there is no evidence that they are superior to other approaches. As stated by Gondim et al. who use the pure endoscopic approach, “Although presenting better illumination and visualization of the lesions, no report has definitively proved the superiority of endoscopy over microsurgery in pituitary surgery…” and by Campbell et al.: “While endoscopic approaches provide many theoretical benefits over standard microscopic techniques, recent publications have not consistently shown improvement in resection and complication rates in the endoscopic group.”

Let us examine the advantages and disadvantages of the endoscopic and microscopic approaches. The principal advantage of the endoscope is that it can be used to provide a view lateral to the direct line-of-sight view of the operating microscope. This is particularly valuable for removing large tumors that extend laterally, beyond the direct view of the operating microscope, including large suprasellar tumors with lateral extension.

The disadvantages of the endoscope are as follows: 1) it provides monocular vision, whereas one has true binocular 3D vision with the microscope, permitting more precise microscopic dissection; 2) despite that endoscopic pituitary surgery was initially advertised as being less invasive, as practiced now it is the most invasive. The pure endoscopic procedures remove the posterior one-third of the midline structures of the nose (some surgeons include removal of a turbinate), whereas the microscopic approaches leave the midline, including the nasal mucosa, intact (there appear to
be no side effects from resection of the posterior segment of the midline nasal structures, but this cannot be accurately described as being “less invasive”).

Finally, what is the basis of the emphasis on the “pure” endoscopic approach? If the surgeon needs to see laterally beyond where he can directly see with the operating microscope, he can do so with an endoscope-assisted approach, either by simply using the corridor of the nasal speculum, or, if more room is required, by removing the nasal speculum, replacing the nasal mucosa to the midline, and using a binasal endoscopic approach. In fact, the endoscope-assisted approach permits combining the advantages of the operating microscope and the endoscope in many patients. To take advantage of some of the features of the operating microscope, one of our coeditors, Dr. Laws, recently reported reverting to the microscope in 18% of 148 consecutive “pure” endoscopic cases, including 5 patients with acromegaly, and patients with Cushing’s disease, repeated pituitary surgery, or those with an extended transsphenoidal approach.10

As neurosurgeons we are still exploring the ideal circumstances for using the endoscope compared with the microscope. At our institution we use both; Dr. John Jane Jr. uses the endoscope primarily, I use the operating microscope primarily, and in some circumstances we combine the two. It is clear from our experience that larger suprasellar tumors and tumors extending laterally beyond the direct view of the operating microscope are often best addressed with the endoscope, whether endoscopic surgery alone or endoscope assisted, whereas the very small tumors, those occurring with some frequency in Cushing’s disease, may be best addressed with the operating microscope. Tumors between these extremes—most pituitary tumors requiring surgery—can be addressed via either approach with the expectation of success in most patients. In fact, the absence of improved outcomes when comparing series that uniquely used the endoscopic approach or the operating microscope may simply reflect the fact that the optimal approach was not selected for individual patients, but one approach or the other was used for all patients. Selection of patients for surgery with the endoscope whose circumstances are best managed by that approach, using the microscope for situations that are best suited for it, and either approach that the surgeon is most experienced with, and most adept at, for the tumors that fall between these extremes, may yield optimal overall outcomes. Of course, before that strategy can be implemented we must define which tumors are better managed with which approach.

We are still learning how to best use various new tools recently brought by advances in technology, including the most advanced techniques of radiosurgery and fractionated irradiation, surgery with the endoscope and the microscope, intraoperative MRI, etc. It is premature for claims of superiority to be made for one approach over another until the facts are in. (DOI: 10.3171/2010.8.FOCUS10215)

References