Management of invasion by pituitary adenomas

EDWARD H. OLDFIELD, M.D.

Department of Neurosurgery, University of Virginia Health Sciences Center, University of Virginia, Charlottesville, Virginia

Nishioka and colleagues describe excellent immediate results in the outcome of patients with acromegaly in whom surgery included excision of the medial wall of the cavernous sinus and removal of free tumor from within the cavernous sinus when invasion occurred.13 Their results suggest that more aggressive surgery than is commonly practiced will increase the fraction of patients with acromegaly who are in remission after surgery.

Cavernous Sinus Invasion

It has been clear for many years that invasion is the most frequent basis for noncurative surgery for pituitary adenomas of all types, and the cavernous sinus is the most common site of invasion. In the first systematic analysis of invasion, in 1948, Goeffrey Jefferson emphasized that when invasion “spills over” into the cavernous sinus it invades the medial wall of the cavernous sinus, but also invades other sites of the dural enclosure of the cavernous sinus and infiltrates the adventitia of the intracavernous portion of the internal carotid artery (ICA) and the cranial nerves.9 He suggested that it is unlikely that surgery alone can be curative in the presence of tumor filling the cavernous sinus.

Excision of the Medial Wall to Achieve Remission

One of the advantages of the smaller tumors that commonly cause Cushing’s disease, compared to the frequently larger tumors that cause acromegaly and the other types of pituitary tumors, is that the high incidence of smaller tumors in Cushing’s disease permits assessment of the various stages in the evolution of cavernous sinus invasion. With Cushing’s disease, which then can be used as a model of the early stages of invasion of pituitary adenomas in general, it is apparent that at the very earliest stage of invasion the tumor penetrates the capsule of the pituitary gland to reach and invade the inside edge of the medial wall of the cavernous sinus, invasion that is, at least initially, only partial thickness in the medial wall and thus is still contained by the lateral edge of the medial wall and is susceptible to complete excision and cure by surgical removal of the tumor and the involved portion of the medial wall.5,12 It is that limited degree of involvement of the medial wall that is responsible for most recurrences of Cushing’s disease and that often goes unnoticed if the lateral margin of the gland and the medial wall of the cavernous sinus are not carefully inspected at surgery and the involved patch of the medial wall is not removed, if invaded.5 Excision of the medial wall, then, when invasion is limited to the medial wall, potentially provides not only curative surgery,12 but also provides histological verification of invasion by the tumor, as occurred in 42 of 42 samples of the medial cavernous sinus wall in patients with persistent or recurrent Cushing’s disease after prior surgery, histologically verified invasion that was not detected with MRI in any of the 42 patients.5

The key to knowing that the medial cavernous sinus wall is invaded is to surgically define and follow the lateral edge of the anterior lobe of the pituitary by dissecting the tissue plane between the lateral edge of the anterior lobe and the medial wall of the cavernous sinus; if no tumor passes through the capsule of the lateral margin of the gland, the surgeon can be confident that there is no cavernous sinus invasion and does not have to unnecessarily remove the medial wall. On the other hand, if the medial wall is invaded the tumor will be seen passing through the lateral margin of the pituitary and into the medial edge of the cavernous sinus wall. The surgeon then knows to enter the cavernous sinus and examine if the invasion is limited to the medial wall or if there is free tumor passing completely through the medial wall and filling the interstices of the cavernous sinus. This strategy produces immediate remission in most tumors with invasion that is limited to a portion of the medial wall, whether it is with Cushing’s disease13 or a growth hormone (GH)–secreting adenoma.13

Free Tumor in the Cavernous Sinus

In contrast to the aforementioned circumstance, when invasive tumor “spills over” into the cavernous sinus, the histological findings suggest that surgical removal of the tumor filling the cavernous sinus may aid in obtaining endocrine remission but that it is unlikely to be curative.
because of the infiltration of the adventitia of the ICA, cranial nerves, and other regions of the dura that cannot be safely removed. It must be acknowledged that in many instances in which the early endocrine results after pituitary surgery suggest curative surgery, the patient is not cured, since many tumor recurrences in Cushing’s disease and acromegaly occur later in patients who clearly meet the most stringent endocrine criteria for cure and have a negative pituitary MRI after surgery (see below). I have many patients with Cushing’s disease and acromegaly in whom I have left deposits of tumor embedded in the dura inside the cavernous sinus, microscopic deposits visible under the magnification of surgery, and in whom postoperative endocrine testing met the most stringent endocrine criteria for remission, patients with known residual tumor that is destined to recur in the absence of postoperative irradiation. Moreover, others have described such patients with acromegaly. Many years ago Wrightson et al. reported a patient whose postoperative insulin-like growth factor–I (IGF-I) levels were normal in a series of evaluations every 6 months, but whose autopsy, after he died of a heart attack, showed a 5-mm GH-positive residual tumor in the sella.6

How Do We Know if a Patient With Acromegaly is Cured After Surgery Versus in Remission With the Risk of Occurring Later?

In recent years, with the development of more sensitive and more precise hormonal assays, it has become apparent that prior standards used to define remission were unreliable, as patients had disease recurrence despite having normal IGF-I levels and having glucose-suppressed postoperative GH levels of < 1 ng/ml.7 Thus, a consensus has been reached by a group of esteemed endocrinologists that a normal IGF-I level for age and sex and a glucose-suppressed GH of < 0.4 ng/ml should be the criteria for remission after surgery for acromegaly, the current “stringent” criteria.6 However, whether even this lower level of glucose-suppressed GH will successfully screen patients with microscopic residual tumor compared to those who are truly cured remains to be shown. In fact, studies using the most sensitive and reliable techniques for measuring GH, using an immunoradiometric assay (IRMA) or an enzyme-linked immunosorbent assay (ELISA), have demonstrated that normal subjects have much lower dex-

Role of “Aggressive” Surgery for Tumor Invading the Cavernous Sinus

It has been shown in many clinical series of acromegaly that adjuvant therapy, whether it is with fractionated irradiation, radiosurgery, or medical therapy, has the greatest likelihood of achieving remission when the levels of GH and tumor mass are lowest.1,3,10,12 Thus, it is reasonable to attempt to remove surgically as much of the tumor as can be safely removed, providing remission in some patients and enhancing the chances of remission using adjuvant therapy in the others. Some of these patients, those with invasion limited to a portion of the medial wall of the cavernous sinus, are probably cured by excision of that wall. However, it seems doubtful that most patients with removal of free tumor from the cavernous sinus will have curative surgery, despite endocrine testing indicating remission and a negative pituitary MRI after surgery. Is excision of the medial wall of the cavernous sinus indicated in patients whose tumor fills the cavernous sinus? Over the past 3 decades several authors have described techniques for removal of tumor from the cavernous sinus region.2,4,11–13,16 Almost all patients with acromegaly today, even those with a postoperative GH level of < 15–20 ng/ml, are in remission after treatment, either as a result of surgery alone or as a result of adding other therapies after the surgery. It is worth noting that 22 of the 23 patients who were not in remission after surgery in the series of Nishioka et al. were in remission after introduction of adjuvant therapies.13 Thus, even in the absence of “curative” surgery, adjuvant therapy produced remission of acromegaly and eliminated the adverse effects of the exposure to excess GH and IGF-I in these patients. In patients with extensive invasion and tumor filling the cavernous sinus, patients who clearly will have at least microscopic residual tumor even with the most aggressive surgery, what is the value of surgical removal of the medial wall of the cavernous sinus? One approach, and the one that I have followed, is to limit the step of excising the medial wall of the cavernous sinus to patients in whom it is reasonably likely that a cure can be achieved and in patients whose tumor fills the cavernous sinus to remove the intracavernous tumor that can be safely and easily removed and not attempt to excise the medial wall.

In many patients, removal of all accessible tumor from the cavernous sinus, even if it does not eliminate every microscopic tumor deposit, will provide endocrine remission, and adjuvant therapy can then be delivered while the patient is still in remission, avoiding the need for medical therapy to suppress hormone levels while awaiting the delayed results of irradiation, or the patient can be followed closely and adjuvant therapy can be introduced at the earliest sign of recurrence. Although it may take many years, it seems inevitable that in the absence of adjunctive therapy recurrence ultimately will occur in most, if not all, of these patients; the follow-up of less than 22 months in half of the patients and the maximum follow-up of 34 months in the series by Nishioka et al.
for GH-secreting tumors, tumors that are extremely slow growing (signs of acromegaly are present on average for 9 years before diagnosis in patients with acromegaly), is of limited use for predicting the incidence of long-term remission in these patients.

(http://www.thejns.org/doi/full/10.3171/2014.5.JNS132817)

Disclosure

The author reports no conflict of interest.

References


Response

HROSHI NISHIOKA, M.D., PH.D., AND SHOZO YAMADA, M.D., PH.D.

Department of Hypothalamic and Pituitary Surgery, Toranomon Hospital; and Okinana Memorial Institute for Medical Research, Tokyo, Japan

We are very grateful to Dr. Edward H. Oldfield for his thoughtful and insightful comments regarding our recent study of the surgical approach to tumors with cavernous sinus invasion (CSI) in acromegaly. Indeed, it is still controversial whether adenomas with CSI are biologically more active or aggressive than those without CSI, but CSI is the most important and independent unfavorable factor affecting surgical outcome. Therefore, we believe that improving the surgical results associated with tumors with CSI will increase the overall surgical cure rates of all types of pituitary adenoma. To accomplish this, we must first definitively determine whether the tumor is invading the cavernous sinus (CS). However, except for Knosp Grade 4 tumors, this may not always be possible on the basis of preoperative MRI alone. It is also extremely difficult to correctly identify invasion of the CS intraoperatively if the extended lateral part of the tumor is removed blindly with the use of suction and a ring curette, during either microscopic or endoscopic surgery.

We completely agree with Dr. Oldfield that ascertaining the relationship between the lateral edge of the anterior lobe of the pituitary or the tumor itself and the medial wall of the CS is essential to determine whether the medial wall of the CS is invaded or whether the tumor is additionally passing completely through the medial wall and filling the CS interstices. We believe that this can be accomplished only by meticulous dissection under direct vision of the lateral edge of the anterior lobe of the tumor, although an angled endoscope is often required to judge the relationship if the tumor extends laterally underneath the genu of the ICA. When tumor invasion is partial (involving the medial wall with or without protrusion into the CS), we dissect and finally excise the CS medial wall sharply with the use of suction and a ring curette, during either microscopic or endoscopic surgery.

Dr. Oldfield indicated that when invasive tumor “spills over” into the CS, surgery is unlikely to be curative because of tumor infiltration of the ICA adventitia, cranial nerves, and other regions of the dura that cannot be safely removed. This is especially likely to occur with Knosp Grade 4 tumors. Nevertheless, although total re-
moval of Knosp Grade 4 tumors is generally impossible, we advocate that they be excised as much as possible to enhance the possibility of tumor remission with postoperative adjuvant therapy (involving either medications or irradiation). This is particularly applicable for tumors associated with drug-resistant acromegaly.

For adenomas with complete CSI, wide exposure of the CS floor is the key to attaching both sides of the ICA, and the endoscopic approach is superior for this purpose. The quantity of tumor around the ICA that can be removed surgically depends on the degree of fibrosis and consistency of the tumor. In our experience, tumors with complete CSI are usually soft and easily removed by suction during primary surgery, but they are often too firm to be removed during repeat surgery for remaining or recurrent GH-cell adenomas, especially if there was a history of medication or radiation treatment. We also emphasize that intraoperative monitoring devices are indispensable tools to improve the safety of aggressive surgical approaches to tumors invading the CS. These devices include surgical navigation systems to facilitate orientation, micro-Doppler devices to confirm the location of the ICA, and eye ocular movement devices to help prevent postoperative eye movement impairment.

Dr. Oldfield stated that the follow-up period of less than 22 months in one-half of our patients and our maximum follow-up of 34 months are of limited use for predicting the incidence of long-term remission in patients with GH-secreting tumors. We acknowledge that long-term follow-up for at least 5 years would be necessary to draw more definitive conclusions. Dr. Oldfield also noted that in many instances in which the early endocrine results after pituitary surgery suggest curative surgery, the patient is indeed not cured, since many tumors later recur in patients with Cushing’s disease and acromegaly who clearly meet the most stringent endocrine criteria for cure and have a negative pituitary MRI after surgery. We agree with this statement for patients with Cushing’s disease but note that it is not necessarily applicable to those with acromegaly. For example, in their series of 668 patients, Nomikos et al. identified only 2 patients (0.4%) with recurrent acromegaly during a mean follow-up period of more than 10 years after the current endocrine criteria for remission were met. Our surgical experience of no less than 1000 patients with acromegaly is consistent with this finding. The recurrence of acromegaly is extremely rare compared to the recurrence of other functioning adenomas, such as prolactinomas or those producing Cushing’s disease, if patients fulfill the current endocrine criteria for cure at 1 year after surgery (that is, a nadir serum GH level < 0.4 ng/ml after a 75-g glucose load and normal age- and sex-adjusted IGF-I level) and have no apparent residual tumor on the postoperative MRI. However, it is important to note, as Dr. Oldfield also indicated, that some acromegalic patients with macroadenoma meet the current endocrine criteria for remission yet have residual tumor in the CS that is clearly visible on MRI. This may be attributed to low GH secretion by these tumors, which are usually sparsely granulated GH-cell adenomas.

References

Please include this information when citing this paper: published online July 11, 2014; DOI: 10.3171/2014.5.JNS132817.