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Cavernous Sinus Invasion by Pituitary Adenomas

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One hundred ninety-eight surgically explored pituitary adenomas were evaluated preoperatively by high-resolution computed tomography (CT). At surgery, evidence of direct cavernous sinus invasion was demonstrated in 19. CT findings in these cases included cavernous sinus expansion (17 patients) and visible encasement of the internal carotid artery (14 patients). The invasive tumor often enhanced to a lesser degree than the cavernous sinuses and ipsilateral internal carotid artery. Intracavernous cranial nerve compression, obliteration, or displacement (14 patients), invasion of the lateral wall of the cavernous sinus (seven patients), and diffuse bone destruction (seven cases) were other findings. Magnetic resonance imaging in three patients provided excellent demonstration of intracavernous internal carotid artery encasement, but displacement and obliteration of intracavernous cranial nerves was not shown as well as it was with CT. Histologically, only three patients showed anaplastic features and only one of them had distant metastases. There was no correlation between histologic features, hormone assays, and invasiveness. This experience indicates any type of pituitary adenoma, regardless of its endocrinologic activity, can invade the cavernous sinus. Cavernous sinus involvement makes complete surgical removal difficult. Preoperative recognition of invasive behavior of these tumors has prognostic value and aids in designing appropriate management. CT is the most useful technique generally available for evaluation and follow-up.

Although invasive pituitary adenomas are known to exist, only rarely has the diagnosis of cavernous sinus invasion been made preoperatively [1–4]. Generally adenomas that penetrate into the cavernous sinus are difficult to resect completely, and they are associated with a greater risk of morbidity and mortality [4, 5]. Therefore, preoperative demonstration of cavernous sinus invasion may aid the neurosurgeon and endocrinologist in planning appropriate medical and surgical management. The purpose of this study was to determine the computed tomographic (CT) (and, more recently, magnetic resonance [MR] imaging) signs of cavernous sinus invasion. Such invasion was further correlated with tumor histopathology and hormone assays. We performed a retrospective review of high-resolution CT studies in 19 surgically documented cases of cavernous sinus invasion by pituitary tumor. Patients having bone invasion without cavernous sinus involvement were not included in this study.

Materials and Methods

Of 198 surgically explored pituitary adenomas evaluated by high-resolution CT, direct cavernous sinus involvement was demonstrated in 19. Six of these patients had had previous pituitary surgery. There were 14 men and five women (age range, 16–85 years). The CT studies were performed at three separate institutions affiliated with the University of Southern California School of Medicine and, hence, techniques differed. Fifteen patients were evaluated with a General Electric CT/T 8800 scanner using overlapping 5 mm collimation and 3 mm spacing. Two patients were scanned with a Picker 1200 SX scanner using 3 mm slice
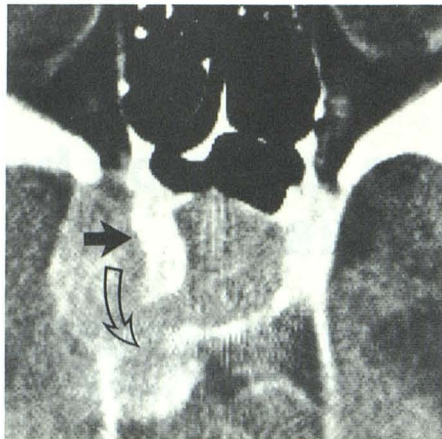
Fig. 1.—Pituitary adenocarcinoma extending into right cavernous sinus in 84-year-old patient. The Intracavernous part of partly calcified internal carotid artery is engulfed and slightly displaced medially (*solid arrow*). Tumor had penetrated dural barrier a second time and extended into posterior fossa (*open arrow*).
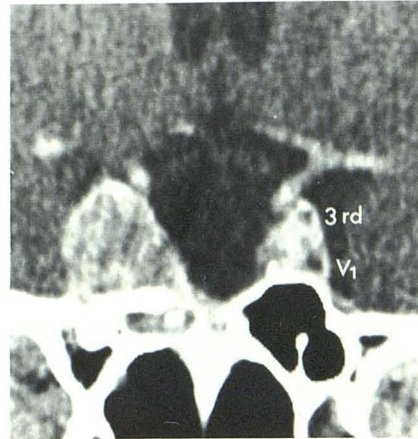
Fig. 2.—Null-cell adenoma. Intra- and suprasellar part of tumor was resected 2 months earlier. Obvious compression and partial obliteration of right gasserian ganglion (*black arrow*) and nerves V₁ and III (cf. normal appearances of these nerves on opposite side). Engulfment of intracavernous right internal carotid artery is also seen as it exits from carotid canal (*open arrow*). *White arrows* show where enhancing dura mater, which forms lateral margins of cavernous sinus, is interrupted with tumor bulging locally through and beyond this area. G = gasserian ganglion.
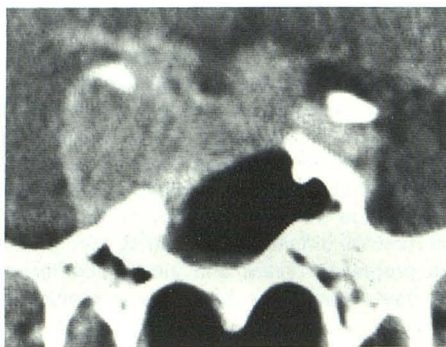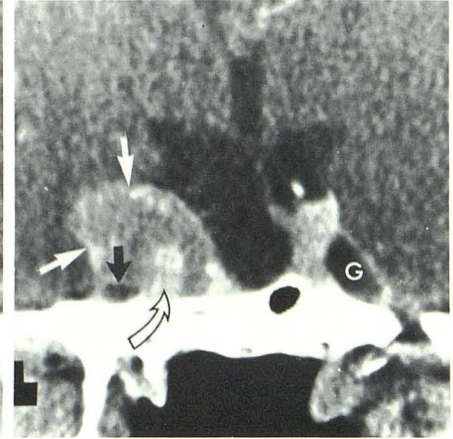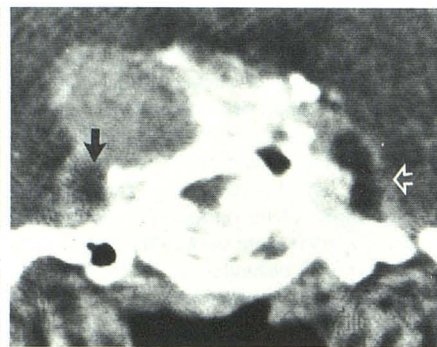
Fig. 3.—Prolactin-cell adenoma. Displacement and compression of right gasserian ganglion/V₁–V₂ complex (*solid arrows*) on both coronal (**A** and **B**) and axial (**C**) views. (Cf. opposite side [*open arrows*].)

thickness and 2 mm spacing. The other two patients were examined with a Philips Tomoscan 310 scanner using 3 mm collimation and 1.5 mm spacing. Nine patients were scanned in the axial plane only (with coronal and sagittal reformation), three in the direct coronal plane only, and the other seven in both coronal and axial planes. Most CT scans were obtained after rapid drip infusion of iodinated contrast material (Reno-M-DIP, 42.3 g I/300 ml solution). Four patients had an intravenous bolus plus a drip infusion of contrast material (71.3 g I). Three patients also had MR scanning. Medical records, including operative notes, of all these patients were reviewed. The results of pituitary hormone assays, histologic features of the surgical specimens, and CT were correlated. Surgical specimens in nine patients were also examined by immunohistologic staining techniques and electron microscopy.

Results

CT revealed unilateral involvement of the cavernous sinus in 14 patients, with bilateral invasion in the other five cases.

Tumor size was variable. There was a suprasellar component (ranging from 1 to 6 cm above the diaphragma sellae) in 16 patients; three patients had no suprasellar extension. In 17 patients, invasion of the cavernous sinus through the lateral dural envelope of the sella resulted in varying degrees of cavernous sinus expansion with bulging of the lateral margin of the sinus. In seven of these patients, the tumors had grown outside of the cavernous sinus (having penetrated the dural barrier a second time) into the middle or posterior cranial fossa (figs. 1 and 2). Invasive tumor often enhanced to a lesser degree than did the cavernous sinuses and internal carotid artery. The intracavernous internal carotid artery was clearly demonstrated in 14 patients because it enhanced to a greater degree than did the surrounding tumor. In the other five patients, however, carotid artery engulfment was difficult to distinguish from adjacent tumor because of an almost equal degree of enhancement. A larger bolus of contrast material or dynamic scanning might have enabled demonstra-
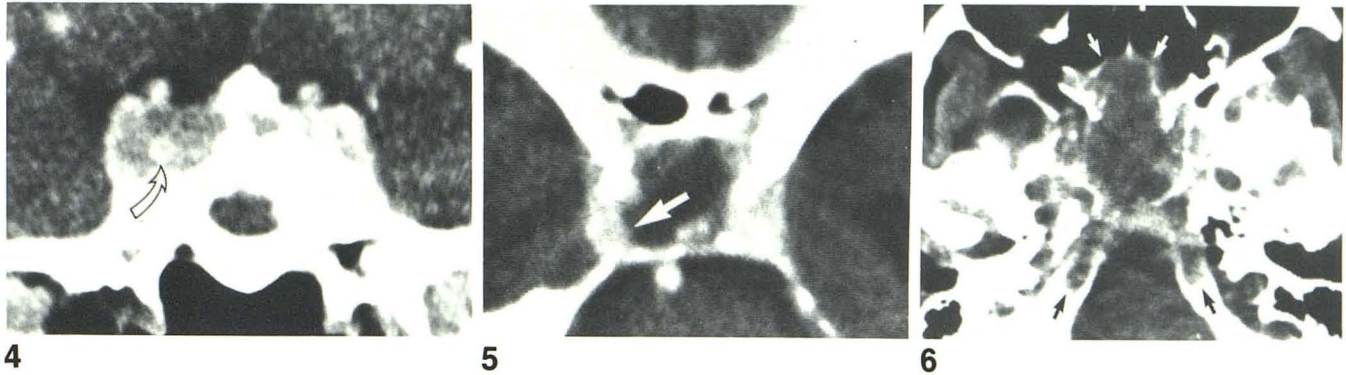
4　　　　　　**5**　　　　　　**6**

Fig. 4.—Corticotrophic cell adenoma. Rapid invasion of right cavernous sinus developed after bilateral adrenalectomy for control of hypercortisolism (Nelson syndrome). Displacement and engulfment of intracavernous right internal carotid artery (*arrow*) is readily visible because it enhances to a greater degree than surrounding tumor.

Fig. 5.—Corticotrophic cell microadenoma with recent pituitary apoplexy and infarction. Minimal extension into right cavernous sinus (*arrow*) without clearly evident increase in width of cavernous sinus. At this stage, it would be

somewhat difficult to distinguish invasion from focal displacement of cavernous sinus.

Fig. 6.—Null-cell adenoma. Axial CT scan of base of skull reveals extensive destruction of sphenoid body, greater sphenoid wings, pterygoid plates, vomer, petrous apices, clivus, and basiocciput (*black arrows*). Tumor extends into sphenoid and posterior ethmoid sinuses (*white arrows*). Histologically, it had benign microscopic appearance.

Fig. 7.—Null-cell adenoma. MR images. Coronal (**A**) and axial (**B**) spin-echo scans, 2 sec TR, 40 msec TE. Bilateral extension of pituitary tumor into cavernous sinuses, left greater than right (*solid arrows*), and engulfment of intracavernous internal carotid arteries (*open arrows*).

A　　　　　　**B**
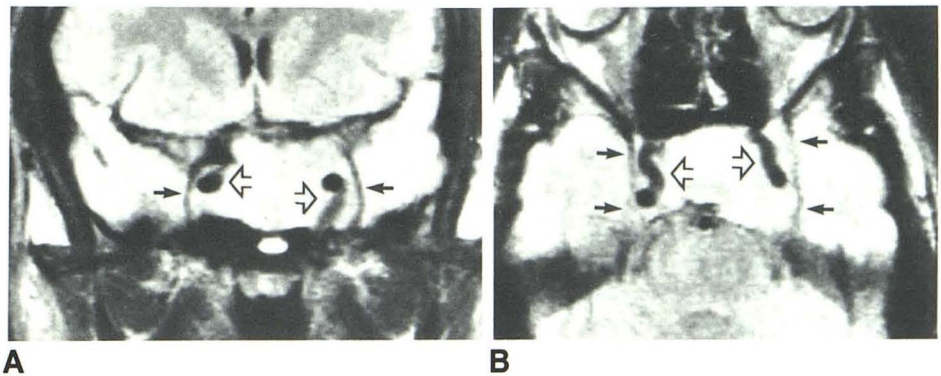
tion of the internal carotid artery in more of these cases had the study been performed prospectively.

Extension of the tumor into the cavernous sinus resulted in displacement, compression, or obliteration of the intracavernous cranial nerves in 14 patients (figs. 2 and 3). In 10 patients, both carotid artery engulfment and cranial nerve compression were present (fig. 2). In four patients, carotid artery engulfment could not be seen. However, compression of the intracavernous cranial nerves was present (fig. 3). In four patients, the carotid artery was visibly engulfed, but we were unable to detect compression of the cranial nerves (fig. 4). In only one patient was there neither expansion of the cavernous sinus nor engulfment or compression. In this case, invasion was exhibited by very subtle bulging into the cavernous sinus (fig. 5). This case presented the greatest difficulty in distinguishing extrinsic compression from invasion of the cavernous sinus. Direct coronal scans might have been more helpful in demonstrating subtle invasion. Nevertheless, invasion into the cavernous sinus was proven at surgery.

In six patients, the significance of osseous abnormalities could not be assessed easily because of previous transsphenoidal surgery. In seven of the other 13 patients, there were

varying degrees of destruction of the sella and adjacent bones (fig. 6). The CT findings in these 19 patients were cavernous sinus expansion (17 patients), compression of the gasserian ganglion V_1 complex (14), visibly engulfed internal carotid artery (14), invasion of the lateral wall of the cavernous sinus (seven), and diffuse bone destruction (seven). (Diffuse bone destruction was evaluated in only 13 of the 19 patients because of difficulties involved in differentiating surgical changes from tumor invasion.) MR imaging in three patients clearly showed engulfment of the internal carotid artery by an invasive pituitary tumor. The low signal intensity of flowing blood in the carotid artery provided excellent contrast to the high signal intensity of the surrounding tumor (fig. 7).

The serum prolactin level was substantially elevated (ranging from 105 to 50,000 ng/ml) in only eight patients (table 1). Hypopituitarism was present before surgery in four patients. Histologic examination of surgical specimens showed benign pituitary adenoma in 16 patients. Histologically, marked cellular pleomorphism, multinuclear cells, and mitotic features were present in three patients, and only one of them had distant metastases (positive cerebrospinal fluid cytology and liver lesions).

TABLE 1: **Functional Classification of Invasive Pituitary Tumors**

Cell Types	No. of Cases (n = 19)	Level of Prolactin in ng/ml (Other Hormones)
Prolactin-cell adenoma	7	195–50,000
Corticotropic (ACTH) cell adenoma	2	11, 16 (ACTH: 4325, 342)
Growth-hormone- (GH) cell adenoma	1	12 (GH: 0.7)*
Mixed prolactin- and GH-cell adenoma . . .	1	105 (GH: 45)
Null-cell adenoma	7	14–47
Adenocarcinoma	1	19

Note.—Normal values: prolactin, <20 ng/ml; ACTH, 10–100 ng/ml; GH, <1 ng/ml.
* In this patient, serum GH hormone was normal. However, GH granules were identified in the tumor by electron microscopy and immunocytologic staining. Similar cases have been well documented [6].

These patients have been followed for periods of 2 months to 5 years. Two patients with a small amount of cavernous sinus invasion had a total resection of their tumors with no recurrence (they have been followed 1½ and 3 years, respectively). Five patients were treated with bromocriptine and partial resection (the size of the residual tumor was reduced in three patients and remained unchanged in two other patients). Nine patients had partial resection followed by radiation therapy. There was a dramatic response to radiation therapy in two of the nine patients. Both of these patients had anaplastic features histopathologically. There was a minimal response to radiation therapy in another two. The residual tumor was unchanged in three patients and was actually larger in the other two. Two patients had partial resection and bromocriptine and radiation therapy. One of these had a mild response and the other had no response. One patient with cerebrospinal fluid and liver metastases died 2 months after the diagnosis of pituitary adenocarcinoma was documented.

Discussion

On the basis of their biologic behavior, tumors that originate in the adenohypophysis may be divided into expanding adenomas, invasive adenomas, and carcinomas [1–5, 7]. Most pituitary adenomas are slow-growing and tend to grow in an upward direction into the suprasellar cistern. Intrasellar expansion of these adenomas may erode the sella turcica and compress the cavernous sinuses laterally. The dura matter forming the medial walls of the cavernous sinus remains intact but is displaced somewhat because of pressure from the expanding pituitary adenoma. Most pituitary adenomas demonstrate a globular configuration regardless of their size. The diaphragma sellae, however, may impose a waistline indentation between the intrasellar and suprasellar components of large adenomas [5]. Occasionally, more rapid growth of one part of an adenoma results in an asymmetric configuration. Nodular outgrowths may burst (focally) through the thin mesodermal envelope (pituitary adenomas do not have a capsule) encasing the adenoma. This has been likened to a bud perforating the skin of a potato [5]. In some cases this nodular outgrowth may destroy adjacent structures by invading them.

Those tumors that invade directly into adjacent soft tissue and osseous structures are often referred to as "invasive pituitary adenomas" [1–5, 7]. Most of the invasive pituitary tumors in our series had a benign microscopic appearance, which demonstrates the poor correlation between biologically aggressive behavior and histopathologic features. A review of the literature revealed a diversity of opinion with regard to nomenclature in connection with pituitary adenomas. Several authors have indicated that features such as increased cellularity, cellular pleomorphism, and the presence of mitotic features are not necessarily proof of malignancy [2, 7–12]. They believe that the diagnosis of pituitary carcinoma can be considered conclusively only when distant metastases occur. Others consider anaplastic histopathologic features to be sufficient for the diagnosis of carcinoma [13–15].

Hardy [16] proposed a classification of pituitary tumors based on biologic behavior. Grade I is localized to the sella, grade II extends into the suprasellar cisterns, grade III refers to localized invasion of the floor of the sella, and grade IV indicates diffuse invasion. Grade V was added to indicate distant metastases [5]. Using this grading system our report basically consists of grade IV tumors, although one patient had progressed to grade V. Invasion of the sella turcica and adjacent bones may result in extensive destruction of the base of the skull. The tumor may extend into the nasopharynx or sphenoid and/or ethmoid sinuses. Posterior extension may lead to destruction of the clivus and petrous apices (fig. 6); occasionally it may be difficult to distinguish an invasive pituitary adenoma having such a destructive pattern from other neoplasms, such as metastases, chordomas, and nasopharyngeal carcinomas [17, 18]. Furthermore we have also seen meningiomas, as well as one glomangioma and one dysgerminoma, that invaded the cavernous sinus.

Although the abnormal serum levels of hormones produced by functional pituitary tumors generally correlate with the size of the tumor, there are occasions when a small tumor may be related to marked elevations of serum prolactin. Very high serum prolactin values (over 1000 ng/ml) have been implicated as strong evidence of invasion of pituitary adenomas into the cavernous sinuses [3, 19]. Nonetheless, a normal serum prolactin level may be seen with invasive pituitary tumors. In 11 of 19 cases of invasive pituitary tumors in our report, there was no significant elevation of serum prolactin values (table 1).

There is no rule that facilitates predicting when invasion of the surrounding structures will begin. In three of our patients as well as in a few other reports [16, 19], invasion of the cavernous sinus began when the tumor was small and was limited to the sellar region. Furthermore, one of our patients had cavernous sinus invasion only a few months after clinical onset of galactorrhea and amenorrhea. On the other hand, another patient had a 27 year history of pituitary adenoma before a diagnosis of cavernous sinus invasion was made. In our series and in others [2–4, 19] males predominated; more men than women appeared to have larger and more aggressive tumors. Symptoms such as decreased libido, impotence, and perhaps sterility tended to be either ignored by patients or undiagnosed. Therefore, in men the diagnosis of pituitary tumor is more likely to be made later, and consequently, the
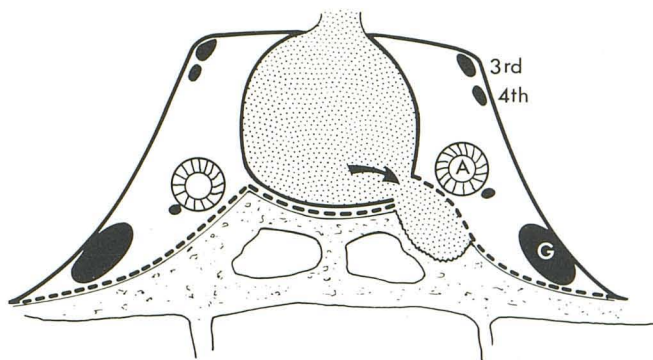
Fig. 8.—Coronal cross section of sellar region. Extradural subcavernous extension of pituitary tumor without invasion into cavernous sinus (*arrow*). Dura mater forming medial and lateral walls of cavernous sinus (*thick, solid line*); periosteal layer of dura (*broken line*). A = intracavernous internal carotid artery; G = gasserian ganglion.
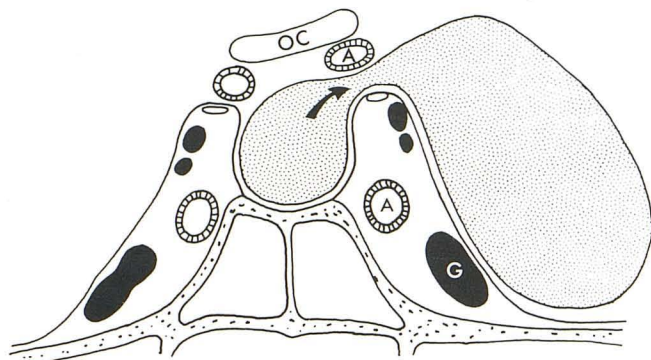

Fig. 9.—Intradural parasellar extension of pituitary tumor without invasion into cavernous sinus. Intracavernous cranial nerves and carotid artery (A) are not involved. OC = optic chiasm; G = gasserian ganglion.

tumor is usually considerably larger at presentation.

In evaluating pituitary tumors, careful attention should be paid to certain intracavernous structures. Appreciation of involvement of the intracavernous cranial nerves and/or carotid artery by tumor enabled a CT diagnosis of cavernous sinus invasion in 18 of the 19 cases in this series. Normally, the gasserian ganglion/V_1–V_2 complex is consistently demonstrated on CT as a relatively symmetric, oblong, intracavernous structure [20, 21]. Although in 14 of our patients there was partial obliteration or compression of the cranial nerves traversing the cavernous sinus, only six of our patients exhibited opthalmoplegia, trigeminal anesthesia, or pain.

The infrequency of cranial nerve signs and symptoms suggests that these tumors do not invade but rather displace or encircle the nerves. In addition, CT demonstration of visible engulfment of the intracavernous carotid artery, obliteration of the gasserian/V_1–V_2 complex, and direct penetration of the dura of the cavernous sinus aids in differentiating tumor invasion of the cavernous sinus from two other types of extension. On occasion, pituitary adenomas may displace the

cavernous sinus laterally after perforating the dura at the junction of the floor of the sella and the cavernous sinus. Subcavernous extension of tumor, growing in an extradural location between the cavernous sinus and sphenoid bone, may develop without invasion into the cavernous sinus [4, 5] (fig. 8). Another possibility is upward expansion of a pituitary adenoma into the suprasellar cistern. The tumor may then extend laterally above the cavernous sinus. It may pass between either the supraclinoid carotid artery and the upper margin of the cavernous sinus or between the carotid artery and the optic chiasm. The adenoma then can extend into the middle cranial fossa intradurally and between the cavernous sinus on its medial aspect and the temporal lobe on its lateral aspect [7] (fig. 9). In either situation, intracavernous structures such as the carotid artery and the gasserian ganglion are neither engulfed nor compressed by tumor. This will help to differentiate cavernous sinus invasion from these two possible routes of tumor growth.

Cavernous sinus invasion by a pituitary tumor has been related to a relatively low surgical cure rate because of the complexities of surgical exploration when carried into the cavernous sinus [1–5, 7]. With preoperative recognition of cavernous sinus invasion by a pituitary tumor, particularly the commonly occurring prolactin-secreting tumor, one would attempt to reduce the size of the tumor by medical means in an effort to make surgical excision less difficult [22, 23]. When a good CT study has been obtained documenting a small amount of cavernous sinus invasion, an experienced neurosurgeon may be able to resect the tumor completely. Thus, CT is very helpful in surgical planning. In the case of larger tumors, where total resection has not been possible, CT enables recognition of persistent tumor and will be helpful in judging the response resulting from chemical manipulation or radiation therapy. CT is particularly valuable in the case of secretory-inactive adenomas where hormone markers are not present to enable evaluation for persistence of tumor in the cavernous sinus.

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