Basis of persistent and recurrent Cushing disease: an analysis of findings at repeated pituitary surgery

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Object. The goal of this study was to establish the clinical importance of occult dural invasion—invasion of the dura mater or cavernous sinus that is not evident on imaging studies and is not obvious to the surgeon—as the basis of recurrent or persistent tumor and endocrinopathy.

Methods. The authors retrospectively reviewed the case files of patients who underwent repeated transsphenoidal surgery for resection of an adrenocorticotropic hormone (ACTH)—producing pituitary adenoma. Patient selection required the availability of operative and pathology reports from the initial and repeated transsphenoidal surgeries. Because no determination of the cause of persistent or recurrent disease could be made if the tumor could not be localized during the repeated surgery, a pathology report confirming the presence of tumor from the second surgery was also required.

Sixty-eight patients met these criteria. In 43 patients (63%) an ACTH-producing tumor was identified at the initial surgery, in 25 patients (37%) no tumor was found, and in three patients (4%) dural invasion was noted at surgery. In 49 (72%) of the 68 patients there was initial resolution of hypercortisolism and recurrent Cushing disease (CD), whereas in 19 patients (28%) there was persistent CD after the initial surgery. At repeated surgery (44 ± 35 months after the initial surgery) in all 43 patients in whom tumor had been identified at the initial surgery, the tumor was found at the same site or contiguous to the same site. Dural invasion was noted by the surgeon in only three patients at the original surgery, whereas dural invasion by an ACTH-producing tumor was identified during repeated surgery in 42 (62%) of the 68 patients. In addition, 39 (93%) of the 42 invasive adenomas were located laterally and involved the cavernous sinus. Adenomatous invasion of the dura mater was found in 31 (54%) of the 57 microadenomas and in all 11 macroadenomas at repeated surgery. The presence of tumor was not detected in 28 of the 59 patients studied with magnetic resonance (MR) imaging and in none of these 59 patients was dural invasion evident on MR images.

Conclusions. Recurrent and persistent CD consistently result from residual tumor. At repeated surgery the residual tumor can be found at or immediately contiguous to the site at which the tumor was found originally. Unappreciated dural invasion with growth of residual tumor within the cavernous sinus dura, which frequently occurs without residual tumor or dural invasion being evident on MR images or to the surgeon during surgery, is the basis of surgical failure in many patients with CD. Occult lateral dural invasion by tumor may also underlie recurrences of other types of pituitary adenomas.

KEY WORDS • adrenocorticotropic hormone • dural invasion • pituitary adenoma • sella turcica • cavernous sinus • Cushing disease

Transsphenoidal pituitary surgery is the primary treatment for most types of pituitary adenomas. Despite advanced pituitary imaging and enhanced techniques for tumor localization and removal, however, many pituitary tumors are not cured by surgery. Surgical failure rates range from 20 to 80% and recurrence rates for pituitary adenomas range from 7 to 35%, depending on the length of follow up, tumor size, adenoma subtype, and the particular surgeon. Pituitary adenomas that do so usually recur within the first 5 years after surgery, although recurrences have been documented up to 28 years postoperatively. The cause of this failure of transsphenoidal surgery remains to be fully elucidated, especially in patients with small tumors. The three primary causes of recurrent or persistent pituitary tumor and associated endocrinopathy after transsphenoidal surgery can be categorized as follows: 1) residual tumor that lies within the pituitary gland or the intrasellar or intracranial space; 2) residual tumor that lies within the dura mater of the sella turcica or within the cavernous sinus by extension from the dura of the lateral sella; or 3) de novo tumor formation in a patient with a predisposition to tumor occurrence. Grossly evident extrasellar extension and dural invasion by macroadenomas, which is recognized on neuroimages and/or at surgery, is a major cause of failure of transsphenoidal surgery. Although microscopic dural invasion has been reported to occur frequently in the anterior dura mater in patients with microadenomas and macroadenomas, there is scant information available on the clinical importance of occult dural invasion—invasion of the dura mater or cavernous sinus that is not evident on imaging studies and is...
not obvious to the surgeon—as the basis of recurrent or persistent tumor and endocrinopathy.

Clinical Material and Methods

The medical records of 144 patients with CD who underwent a second transsphenoidal surgery for recurrent or persistent disease at the NIH between 1983 and 1999 were reviewed retrospectively to determine the reason that the initial surgery had failed. All patients were hypercortisolemic with clinically evident Cushing syndrome at repeated surgery. Patient selection for the current report required the availability of surgical operative reports and pathology reports from both the initial and repeated transsphenoidal surgeries. In addition, because no determination of the basis of persistent or recurrent disease could be made if the tumor could not be localized at the repeated surgery to allow elucidation of the cause of the initial surgical failure, a pathology report from the second surgery confirming the presence of tumor was also required. At the repeated surgery if dural involvement by tumor was noted, the involved dura mater was excised.

Chart Review and Data Collection

Sixty-eight patients met the criteria for inclusion in the study. The remaining 76 patients failed to qualify for the following reasons: in 39 patients either no operative report or no pathology report was available from the initial surgery.
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surgery; in 22 patients no tumor could be identified at the repeated surgery; and in 15 patients the site of the tumor at the original surgery could not be determined from the operative summary. To determine the cause of the adenoma recurrence, we compared findings at the initial and repeated operations (adenoma size, location, and documentation of dural invasion) and the surgical pathology reports (presence of an adenoma that stained positively for ACTH and the presence of dural invasion by the ACTH-producing tumor). Patients were grouped into the categories of persistent CD or recurrent CD based on their clinical responses to the initial surgery. With persistent CD the patient's hypercortisolism endured after the initial transsphenoidal surgery, whereas with recurrent CD eucortisolism or hypocortisolism and clinical remission were evident after the initial transsphenoidal surgery but were later followed by clinical and laboratory evidence of recurrent hypercortisolism. Three possible causes of the initial surgical failure were defined: 1) incomplete extirpation of a tumor identified at surgery (the presence of an identified adenoma found at repeated surgery that was located within or contiguous to the site of the tumor found at the initial surgery); 2) an initial non-diagnostic surgical exploration (an exploration in which no tumor was found); and 3) de novo tumor formation (diagnostic pathology reports of a tumor identified at the initial surgery and an adenoma discovered at a separate location during repeated surgery). All mean values of data in this report are listed as the mean ± standard deviation.

Results

Patient Population

The 68 patients consisted of 52 female and 16 male patients, ranging in age from 9 to 68 years (mean 33 ± 13 years). The patients underwent repeated transsphenoidal surgery between 5 and 144 months after the initial transsphenoidal surgery (mean 44 ± 35 months; median 32 months). Fifty-three of the patients underwent the initial surgery between 5 and 144 months after the initial transsphenoidal surgery at the NIH by the same surgeon (E.H.O.).

Initial Transsphenoidal Surgery

At the initial surgery in 43 (63%) of the 68 patients the resected tissue was identified as tumor at surgery, producing a positive pathology report; in 25 patients (37%) no tumor was detected in the tissue submitted. Only three (4%) of the 68 adenomas were reported by the initial surgeon to be invading the dura mater: two in the lateral sella turcica and one in the midline. In both adenomas in the lateral sella there was histological documentation of dural invasion. In only 16 reports was the adenoma size documented at the initial surgery; the maximum tumor diameter ranged from 1.5 to 14 mm (mean 5.7 ± 3.6 mm). Eleven (69%) of these 16 reported adenomas were smaller than 5 mm at their greatest diameter. There was no difference in size among the adenomas noted to be invasive or noninvasive at the initial surgery, perhaps because of the small number of patients in whom invasion was noted at that time. Most of the tumors were described as being in a lateral location (28 [65%] of 43 lesions). There was no difference in the frequency of right- compared with left-sided location among the adenomas.

Repeated Transsphenoidal Surgery

Of the 68 patients, 49 (72%) suffered from recurrent CD and 19 (28%) from persistent hypercortisolism after the initial transsphenoidal surgery. Because the patient inclusion criteria required a pathology report that verified the presence of tumor at the repeated surgery, all 68 repeated transsphenoidal surgeries were associated with histologically confirmed ACTH-producing tumor. The sizes of the tumors identified at the repeated surgery ranged from 1 to 14 mm (mean 5.8 ± 2.9 mm). Thirty-six (52%) of the adenomas resected during repeated surgery were smaller than 5 mm at their greatest diameter. Overall, 63 (93%) of 68 tumors were located in the lateral aspect of the sella turcica. There was no difference in the frequency of lateral location (right side compared with left side) among the adenomas.

Despite the fact that there were only three patients in whom dural invasion had been noted by the surgeon during the original surgery, dural involvement by tumor was detected by the surgeon during the second surgery in 42 (62%) of 68 patients. The presence of tumor invading the dura mater was verified histologically in all 42 patients (Fig. 1). Of these 42 invasive adenomas 39 (93%) were reported to be lateral and three to be located at the midline. Adenomatous invasion of the dura mater was found in 31 (54%) of the 57 microadenomas and in 11 (100%) of 11 macroadenomas at the repeated surgery. The mean size of invasive adenomas, 6.7 ± 3.2 mm, was larger than that of noninvasive adenomas, 4.3 ± 1.8 mm (p = 0.002, unpaired t-test). Because the dura was only resected if the surgeon suspected dural involvement by tumor, the incidence of histological evidence of dural invasion in patients in whom it was not detected during surgery cannot be determined.

Magnetic resonance imaging was diagnostic in 31 (53%) of the 59 patients who were studied, eight (73%) of the 11 patients harboring macroadenomas and 23 (48%) of 48 harboring microadenomas. In none of these 59 patients was there evidence of dural invasion by tumor on the MR images.

Relationship Between Site of Tumor at the Second Surgery and Findings at the Initial Surgery

In all 43 patients in whom tumor had been identified at the initial surgery, the tumor was found to be at the same site or contiguous to the same site at the repeated surgery. Among adenomas resected at the second surgery, the size of the tumor was significantly larger (mean 6.3 ± 2.8 mm) in patients in whom a tumor had been identified at the initial surgery (cases with histological evidence of tumor from the initial surgery, that is, incomplete removal) compared with that measured in patients in whom the pathology report at the initial surgery was nondiagnostic (mean 4.9 ± 3 mm) (p = 0.03, unpaired t-test).

In all 25 patients in whom no lesion had been found at the initial surgery, the tumor identified at repeated surgery was found in the lateral aspect of the sella turcica. These 25 tumors comprised 22 microadenomas and three macroadenomas. Lateral dural invasion (invasion of the dura mater of the medial wall of the cavernous sinus) was observed.
in 15 (60%) of 25 cases at the second operation: three (100%) of three macroadenomas and 12 (54%) of 22 microadenomas.

Among the 68 patients there was no significant difference between the mean age of patients with invasive adenomas (34 ± 14 years) and the mean age of patients with noninvasive adenomas (31 ± 11 years). In addition, there was no difference in the mean tumor size between female (5.8 ± 3.1 mm) and male (5.5 ± 2.3 mm) patients.

Patients Who Underwent Both Initial and Repeated Surgery at the NIH

Because more complete information was available on the initial surgery in patients in whom both the initial and repeated operations were performed at the NIH, we analyzed the results separately for these 15 patients (14 female patients and one male patient) to ensure that the overall series was comparable with patients who had undergone both operations by the same surgeon. All 15 patients had recurrent CD.

Eleven patients underwent MR imaging before the initial surgery. In seven patients MR images of the pituitary did not reveal a tumor (in one of these patients an ectopic tumor was later recognized in the sphenoid sinus [previously described])

In another patient a macroadenoma was visible on the MR image, and in three patients microadenomas were detected contiguous to the cavernous sinus, but there was no evidence of cavernous sinus invasion on the MR images.

At repeated surgery there were 13 patients with microadenomas and two with macroadenomas. Thirteen of these 15 patients underwent MR imaging before the second surgery and in five (38%) of these no tumor was revealed. In eight patients the site of tumor was evident on the MR images, but neither dural invasion nor cavernous sinus involvement was evident on any of these images. At repeated surgery in 14 patients with sellar tumors dural invasion was identified (12 tumors laterally involving the dura of the medial wall of the cavernous sinus and two lesions invading the inferior dura). In the three patients in whom no tumor had been identified during the initial surgical exploration, cavernous sinus invasion (two patients) or inferior dural invasion (one patient) was evident during repeated surgery and was demonstrated histologically. In all 12 patients in whom tumor was identified at both the initial and repeated operations, the lesion was located at or contiguous to the same site in both operations; in two patients cavernous sinus invasion was observed at the same site during both operations and the ectopic parasellar (sphenoidal) tumor was found at the same site at both operations. In eight patients the margin of the tumor was observed to reach the pituitary surface laterally at the original surgery, but no transgression of the pituitary capsule or dural invasion was recognized; at the second surgery dural invasion involving the medial wall of the cavernous sinus next to the site of the original tumor was observed in all eight of these patients. In one patient tumor was found adherent to the inferior dura at the initial surgery and was found to be invading the dura at that site at repeated surgery.

The reason the initial surgery failed to be curative in these 15 patients can be explained by an unrecognized ectopic parasellar microadenoma in one case, visible invasion of the cavernous sinus in two cases, and occult dural involvement not recognized at the initial surgery in 12 cases (10 cases in which the medial wall of the cavernous sinus was involved and two cases in which the inferior dura was involved). Thus, the circumstances in these 15 cases were similar to those of the overall group of 68 patients, as described earlier.

Discussion

Our findings indicate that recurrent and persistent cases of CD after transsphenoidal surgery are caused by residual tumor and that, at repeated surgery, the residual tumor can be found at or immediately contiguous to the site at which it had been found at the original surgery. These observations support similar previous observations of others in small numbers of patients with recurrent tumors. Nakane, et al., reported that at repeated surgery in eight patients with recurrent CD, the tumor was found at the same site at which it had been identified at the initial surgery (including seven patients with microadenomas at the initial surgery); these authors concluded that regrowth of adenoma from cells left behind is responsible for late recurrences. At repeated surgery Friedman and colleagues reached similar conclusions after finding 11 of 12 tumors at the same site as in the initial surgery. Finally, Lüdecke, et al., described finding tumor at or near the same site during first and second surgeries in 10 of 11 patients.

Our observations further indicate that unappreciated dural invasion with growth of residual tumor within the dura of the cavernous sinus, in which case frequently neither the residual tumor nor the dural invasion is evident on MR images, is the cause of surgical failure in most patients with CD who have persistent or recurrent Cushing syndrome. They also suggest that microscopic rests of tumor that are left behind at surgery are responsible for most otherwise unexplained surgical failures and recurrent endocrinopathy. These rests may comprise only a few tumor cells, constituting focal sites of lateral dural invasion that are not obvious to the surgeon, despite the aid of the operating microscope. Furthermore, the results indicate that this is not only the case for large tumors, but also applies to microadenomas.

Incidence of Dural Invasion by Pituitary Tumors

Researchers who previously examined dural invasion by pituitary tumors have concluded that invasion is dependent on tumor size because it has been most commonly recognized with macroadenomas and tumors large enough to produce visible suprasellar extension. Estimation of the incidence of dural invasion, however, is related to the criteria used to define it and the sensitivity and specificity of the technique used to detect it. For instance, the surgeon may be more likely to obtain a dural biopsy if the tumor is visibly invading the dura mater at surgery, and may be less likely to obtain a biopsy in the absence of suspicion of dural invasion. The results of this sampling bias would misleadingly suggest a higher incidence of histological dural invasion than is present. On the other hand, it also assumes that the surgeon is a reliable observer of the absence of dural invasion. In this regard it should be noted that even the surgeon’s interpretation of the degree of gross pituitary tumor removal is often not accurate. This is so even...
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for the most experienced pituitary surgeon. For example, Ross and Wilson\textsuperscript{23} achieved gross-total tumor removal in 202 (90%) of 224 patients with acromegaly and felt confident that surgery was curative in 158 (71%) of the 224 patients. Nevertheless, fasting early-morning GH levels were 5 ng/ml or lower (levels that are no longer considered sufficient to define remission) in 57% of the patients. Davis, et al.\textsuperscript{16} concluded at surgery that total tumor removal occurred in 162 (93%) of 173 patients with acromegaly, although in only 65 (38%) of these 173 patients was basal or glucose-suppressed GH 2.5 ng/ml or lower at the early postoperative assessment. Similarly, at surgery Freda, et al.\textsuperscript{28} considered that complete tumor removal had been achieved in 100% of 25 GH-secreting microadenomas and 82% of 90 GH-secreting macroadenomas, whereas biochemical remission (basal or glucose-suppressed GH $\leq$ 2.5 ng/ml) occurred in 88% of the microadenomas and 53% of the macroadenomas. Thus even the experienced pituitary surgeon's appraisal of the distribution of tumor and the degree of tumor removal of macroadenomas frequently is unreliable.

It is reasonable to assume that the presence of subtle evidence of dural invasion may be just as difficult, or more difficult, to appreciate at surgery. Selman, et al.\textsuperscript{28} reported that dural invasion, as determined on routine biopsies of the dura of the anterior sella turcica, occurred in 85% of 60 pituitary adenomas (94% of 31 macroadenomas with suprasellar extension, 88% of 17 intrasellar macroadenomas, and 69% of 12 microadenomas). In that same series, however, the surgeon identified visible dural invasion at surgery in only 24 (40%) of the 60 patients. In the more recent study conducted by Meij and associates\textsuperscript{16} there was histological confirmation of dural invasion in 26% of 192 patients in whom no evidence of invasion was present during surgery. These studies by Laws and colleagues are the only studies, as far as we can determine, in which the authors assessed systematically and prospectively the microscopic features of the sella dura in patients with pituitary tumors. Nevertheless, certain features of these studies, as the authors themselves acknowledge, are difficult to reconcile with clinical observations and, because of this, the clinical relevance of certain findings remains unclear. For instance, only approximately a 2- to 3-mm$^2$ specimen of dura mater from the central anterior portion of the sella turcica was examined, regardless of the location of the adenoma, and no attempt was made to correlate the site of histological evidence of dural invasion with the site of tumor recurrence.\textsuperscript{16,28} Furthermore, the high incidence of dural invasion in the studies of Selman, et al., and Meij and associates (85% and 45% of all tumors and 66% and 24% of microadenomas, respectively), derived from examination of this 2- to 3-mm$^2$ region of dura mater, predicts an incidence of dural involvement approaching 100%, even in microadenomas, if all the dura of the sella turcica could be examined. This incidence is inconsistent with the high likelihood of long-term remission, which commonly occurs after selective adenomectomy alone (without excision of any dura). Moreover, detectable recurrences rarely arise at that specific dural site (invagination of the medial wall of the cavernous sinus).\textsuperscript{8,24} Thus, although extreme degrees of invasion with encasement of the CA or extension into the inferior portion of the cavernous sinus can be reliably defined on MR imaging, this modality is often unreliable for defining the absence of dural invasion in larger tumors and is generally unreliable for detecting dural invasion in smaller tumors.\textsuperscript{11,27} Although the presence and location of 53% of adenomas in the current series were detected on MR imaging before the second surgery, no adenomas were interpreted on preoperative MR images as having dural invasion by pituitary tumors can only be determined by complete sampling of the dura mater in the region of the tumor. It is unlikely, however, that this can be accomplished with large or small tumors. An extensive resection of sella dura would be required for the very large tumors, whereas for small, lateral tumors in which no evidence of dural involvement was recognized by the surgeon, this would be difficult to justify the risks associated with routine resection of the lateral sella dura or the nuisance of the venous bleeding associated with routine entry into the cavernous sinus.

The findings of the current study, which almost certainly are influenced significantly by the passage of sufficient time for microscopic rests of tumor to grow to a size that was visible at the repeated surgery—on average almost 4 years after the initial surgery—indicate that the presence of dural invasion contiguous to an adenoma often goes unnoticed by the surgeon.

Detection of Dural Invasion on MR Imaging. Although MR imaging has greatly enhanced the sensitivity for detection and localization of large and small pituitary adenomas, preoperative imaging in patients who harbor a small endocrine-active tumor, such as an ACTH-secreting microadenoma, is often nondiagnostic. In recent studies diagnostic MR imaging findings have been reported in as few as 36% of patients in whom adenomas are identified at surgery.\textsuperscript{24} Moreover, almost all patients with endocrine-active pituitary tumors in whom surgery is not curative and in whom MR imaging does not detect residual tumor respond to irradiation of the sella turcica, which supports the low sensitivity of MR imaging for detection of clinically relevant volumes of endocrine-active tumor. Thus, MR imaging is not a sensitive technique for detection of small but clinically important volumes of pituitary tumor, either before or after surgery. Furthermore, although MR imaging can be used to confirm cavernous sinus invasion, if the tumor is large and extends into the cavernous sinus beyond the lateral border of the intracavernous portion of the internal CA or encases the CA, these events occur only with large tumors.\textsuperscript{5} Moreover, what appears to be intracavernous extension of pituitary adenomas on preoperative MR images may be invagination, rather than invasion, of the medial wall of the cavernous sinus.\textsuperscript{8,24} Studies of cadavers have demonstrated that invagination of the medial wall of the cavernous sinus by displacement, rather than infiltration, occurs in 33% of normal pituitary glands.\textsuperscript{11} Thus, although extreme degrees of invasion with encasement of the CA or extension into the inferior portion of the cavernous sinus can be reliably defined on MR imaging, this modality is often unreliable for defining the absence of dural invasion in larger tumors and is generally unreliable for detecting dural invasion in smaller tumors.\textsuperscript{11,27} Although the presence and location of 53% of adenomas in the current series were detected on MR imaging before the second surgery, no adenomas were interpreted on preoperative MR images as having dural invasion, despite the fact that dural invasion was directly observed at surgery and was confirmed histologically in 42 (62%) of the 68 patients.

Detection of Lateral Dural Invasion at Surgery

In our study, in only 4% of the patients was dural invasion detected by the surgeon at the initial surgery, whereas...
invasion of the dura was evident during repeated surgery in 62% of the 68 adenomas, including all 11 macroadenomas.

Although corticotrophs comprising adenomas were originally thought to occur within the central one third of the anterior lobe, most studies have found the distribution of these adenomas, and of most other types of secretory pituitary tumors, to be predominantly in the lateral aspects of the pituitary gland.\(^{(3,5,10,22)}\) If most tumors are in the lateral portion of the gland, the lateral dura mater should be a common site for invasion; however, there is little information on the incidence of laterally located dural invasion with small, lateral tumors. Moreover, because of concerns for injury to the CA or excessive venous bleeding, there usually is no histological confirmation of dural invasion when it occurs laterally. In the patients presented here this high percentage of adenomas located far laterally within the sella turcica seems to have contributed frequently to the initial nondiagnostic findings of the surgical explorations. The inability of MR imaging to detect invasion of the dura of the lateral sella, with or without MR imaging evidence of a pituitary adenoma, may lead the surgeon away from a direct inspection of the most lateral dura, including the medial wall of the cavernous sinus, and thus contributes to the low incidence of detection of cavernous sinus invasion. Yet this was by far the most likely site for dural invasion to be detected and confirmed histologically in the current experience.

A wide transsphenoidal approach, similar to one used previously to identify corticotrophs comprising recurrent adenomas,\(^{(21)}\) and extratipital, parasellar tumors,\(^{(20)}\) was used in all patients in this series. This approach, which routinely includes a wide bone exposure of the anterior surface of the sella turcica to expose the medial portion of the anterior face of each cavernous sinus, allows direct visualization of tumors in the far-lateral aspect of the sella (93% of the adenomas in the current series of 68 patients were found laterally). The large discrepancy in documented dural invasion in the initial (4%) and repeated (62%) surgical procedures may be due to closer inspection of the far-lateral sella and to the direct inspection of the medial wall of the cavernous sinus, which was routinely performed during the second surgery. In addition, because the interval between the first and repeated surgeries averaged 44 months (median 39 months), there was sufficient time for microscopic tumor in the dura to grow larger and become evident at repeated surgery, contributing to the increased incidence of detection of lateral invasion at the repeated procedure.\(^{(4)}\)

**Importance of Dural Invasion**

One of the principal predictors of adverse surgical outcome is lateral extrasellar extension or dural invasion of tumor. In the large surgical series of CD published by Mampalam and colleagues,\(^{(18)}\) 33 of 216 patients had histologically verified tumors and persistent or recurrent hypercortisolism; 24 (73%) of the 33 patients had lateral extrasellar extension or perforation of the sella floor documented at surgery. Overall, in 24 (11%) of the 216 patients dural invasion was evident at surgery, including 13 (76%) of the 17 patients with macroadenomas and persistent or recurrent CD. Among 135 patients with histologically verified microadenomas, 11 (8%) harbored tumors with lateral extrasellar extension and two (1%) had tumors observed at surgery to be associated with perforation of the sella floor. Six of the 11 patients harboring tumors with lateral extrasellar extension had persistent hypercortisolism, four of five patients who experienced remission of Cushing syndrome early after surgery later faced its recurrence, and one of two patients with sella floor perforation had recurrent CD. Thus, at the time of that report, 11 (85%) of the 13 patients who harbored microadenomas associated with dural invasion had persistent or recurrent CD, and all five recurrences among the 135 patients with microadenomas were from lesions with extension into the cavernous sinus or perforation of the sella floor noted at surgery. Thus, the majority of surgical failures were the result of dural invasion by the tumor, and among the 135 microadenomas with dural invasion the ratio of invasion into the medial wall of the cavernous sinus compared with invasion of the dura of the sella floor was 11:2.

In a large and recent study examining the relationship between dural invasion and persistent or recurrent disease, Meij and colleagues\(^{(16)}\) reported a higher incidence of residual endocrinopathy and residual tumor in patients with invasive compared with noninvasive tumors, but found no difference in the incidence of recurrences in patients with invasive compared with noninvasive tumors. The absence of a statistical association of recurrence with dural invasion may be a product of the bias toward inclusion of larger tumors in that study (80% of the previously unoperated tumors included in the study were macroadenomas); with large tumors, other sites of dura frequently may have been invaded by tumor regardless of the nondiagnostic histological findings in the central anterior dura. Furthermore, in most patients with microscopic dural invasion there was also gross evidence of invasion at surgery, including all seven patients who died during the follow-up period. Only 14% of the 354 patients had the combined features of histological evidence of dural invasion and no gross invasion noted at surgery. Because of this, the incidence of persistent and recurrent disease described in that important study primarily reflects the outcome of the combination of gross and microscopic dural invasion, but does not address the issue of patients with microscopic dural involvement that is not evident at surgery.

Our results indicate not only that dural invasion that is evident at surgery is responsible for surgical failure and recurrence, but that dural invasion that is not evident to the surgeon (in the absence of a wide exposure and direct visualization of the lateral margin of the pituitary gland and the medial wall of the cavernous sinus, that is, lateral extension through the pituitary capsule and into the medial wall of the cavernous sinus) is frequently the basis of otherwise undefined surgical failures. Many of these tumors were not evident on high-resolution sellar MR images and in none of them was invasion of the cavernous sinus evident on MR images.

Finally, because of the predominantly lateral location of most types of pituitary tumors and because the incidence of invasion is similar between different types of pituitary tumors,\(^{(1,3,7,9,15,16,23,25,28,29,31,32)}\) it can be anticipated that a similar basis for recurrent endocrinopathy may occur with other types of pituitary tumors.

**References**

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