Patterns of extrasellar extension in growth hormone–secreting and nonfunctional pituitary macroadenomas

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Object. Growth patterns of pituitary adenomas have been observed to vary by histopathological subtype. The authors aimed to analyze variations in the patterns of extrasellar extension of nonfunctional macroadenomas (NFMA) and growth hormone (GH)–secreting macroadenomas.

Methods. A retrospective review was conducted of data obtained in 75 patients who underwent transsphenoidal operations for histologically confirmed NFMA (50 patients) and GH-secreting macroadenomas (25 patients) at the Brigham and Women’s Hospital over an 18-month period. Patients with microadenomas and prior operations were excluded from the analysis. Preoperative MR images were reviewed to assess patterns of extrasellar extension in the varying tumor subtypes.

Results. The mean maximal tumor diameter in NFMA and GH-secreting macroadenomas was 26 and 16 mm, respectively (p < 0.0001). Extension of the NFMA occurred into the following regions: infrasellar, 23 patients (46%); suprasellar, 41 patients (82%); and cavernous sinus, 20 patients (40%). Extension of GH-macroadenomas occurred into the following regions: infrasellar, 18 patients (72%); suprasellar, 4 patients (16%); and cavernous sinus, 4 patients (16%). Compared with GH-adenomas, NFMA were more likely to develop suprasellar extension (82% vs 16%, p < 0.0001), cavernous sinus extension (40% vs 16%, p = 0.04), and isolated suprasellar extension (30% vs 4%, p = 0.0145). GH-macroadenomas had higher overall rates of infrasellar extension (72% vs 46%, p < 0.05), and isolated infrasellar extension (52% vs 6%, p < 0.0001). Of the 13 GH-macroadenomas with isolated infrasellar extension, 5 (42%) met WHO criteria for atypical adenomas.

Conclusions. Substantial differences in extrasellar growth patterns were observed among varying histological subtypes of pituitary macroadenomas. Despite smaller tumor diameters, GH-macroadenomas demonstrated a preference for infra-sellar extension, whereas NFMA exhibited preferential extension into the suprasellar region.

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Key Words • sella turcica • transsphenoidal surgery • pituitary adenoma • acromegaly • growth hormone • invasion • clivus

Pituitary adenomas are frequently occurring neoplasms of the sellar region that typically become symptomatic due to mass effect on surrounding structures and/or hormonal oversecretion. Invasion of the surrounding dura mater and extension into parasellar compartments occur in a significant proportion of these tumors and have been correlated with patient age, tumor size, and histopathological subtype.12,14,17 The degree of resection, as well as the incidence of subsequent tumor recurrence, has also been reported to correlate, in part, with the degree of invasion into surrounding regions.12,19

In tumors that extend into the cavernous sinuses, supra-sellar space, or clivus, gross-total resection can be challenging, if not impossible, without resulting in significant morbidity. Because subtotal resection is frequently an expected outcome in many patients with tumor invading the para-, infra-, or suprasellar regions, a commonly implemented treatment paradigm is to perform a subtotal tumor resection followed by adjunctive stereotactic radiosurgery and/or continued medical management as a means of achieving long-term control of tumor growth and/or neuroendocrinological remission.18

It has been reported that varying histopathological adenoma subtypes demonstrate preferential growth patterns of dural invasion and extension from their sellar origins.12,16

Abbreviations used in this paper: GH = growth hormone; NFMA = nonfunctional macroadenoma.
For instance, the classic imaging description of a nonfunctional pituitary macroadenoma is a “dumbbell-shaped” tumor with suprasellar extension through the aperture of the diaphragma sellae, resulting in the appearance of a “waist” at this point. Another example is that GH-secreting adenomas are frequently noted to invade the sphenoid sinus and clivus.6,13 In this study, we aimed to analyze patterns of tumor extension on MR imaging studies of these 2 most commonly treated macroadenomas at our institution (GH-secreting and nonfunctional macroadenomas) to better understand the proclivity of these tumors to preferentially invade various parasellar regions.

### Methods

We conducted a retrospective review of the Brigham and Women’s Hospital Pituitary Center database to identify all patients who underwent transsphenoidal surgery performed by the senior author (E.R.L.) between April 2008 and September 2009. Approval for the study was granted by the institutional review board. Of the 177 consecutive transsphenoidal procedures performed for all sellar-region lesions, pathology was consistent with a pituitary adenoma in 111 patients (63%). Patients with microadenomas and a history of transsphenoidal surgery were excluded from the analysis. Furthermore, patients with macroprolactinomas and adrenocorticotrophic hormone macroadenomas were not included due to insufficient sample size. Following exclusion, 75 patients with newly diagnosed GH-secreting (25 patients) and nonfunctional pituitary (50 patients) macroadenomas were included in the analysis. Preoperative MR images were reviewed to assess for the pattern of tumor extension, and findings were subsequently correlated with histopathological diagnosis following tumor resection.

### Imaging Analysis

Based on standard preoperative 3-T MR imaging performed with and without contrast administration, a macroadenoma was defined as a tumor with a maximal diameter of greater than or equal to 10 mm, whereas microadenomas were defined by a maximal diameter of less than 10 mm. Invasion of the cavernous sinuses was defined as extension beyond the line corresponding to the lateral tangents of the 2 components of the intracavernous internal carotid artery, as defined by Knosp et al.8 Suprasellar invasion was defined as clear tumor growth through the diaphragma sellae or above the plane of the inferior optic chiasm. Finally, infrasellar invasion was determined by clear tumor growth through the sellar floor and into the sphenoid sinus or clivus. “Isolated” extension was defined as extrasellar extension into only one of these regions.

### Statistical Analysis

Analysis of the data was performed using GraphPad Statistical Software. Categorical data were compared using a 2-tailed Fisher exact test, and continuous data were analyzed using a 2-tailed unpaired t-test. Statistical significance was defined as p < 0.05.

### Results

Of the 75 patients with GH-secreting macroadenomas and NFMA, overall extension was noted into the following regions: suprasellar, 45 patients (60%); infrasellar, 41 patients (55%); cavernous sinus, 24 patients (32%); and no extension, 9 patients (12%). Sixteen patients (21%) had tumors with isolated infrasellar extension. Of these, 13 (81%) were GH-secreting tumors and 3 (19%) were NFMA. Sixteen patients (21%) had tumors with isolated suprasellar extension. Of these, 15 (94%) were NFMA and 1 (6%) was a GH-secreting tumor. Four patients (5%), all with NFMA, had tumors with isolated cavernous sinus extension.

Of the 25 patients with GH-secreting macroadenomas, extension was noted into the following regions (Table 1): infrasellar, 18 patients (72%); suprasellar, 4 patients (16%); cavernous sinus, 4 patients (16%); and no extension (infrasellar macroadenoma), 6 patients (24%). Compared with nonfunctional macroadenomas, GH-secreting adenomas had significantly higher rates of infrasellar extension (72% vs 46%, respectively; p < 0.05). Patients with GH-secreting adenomas were over 8 times more likely to have isolated infrasellar extension than were patients with NFMA (52% vs 6%, respectively; p < 0.0001) (Fig. 1). Furthermore, of the 13 GH-secreting adenomas with isolated infrasellar extension, 5 (42%) met WHO diagnostic criteria for an atypical pituitary adenoma (MIB-1-labeling index greater than 3%, excessive p53 immunostaining, and high mitotic figures) (Fig. 2).

Of the 50 patients with NFMA, extension was noted into the following regions (Table 1): infrasellar, 23 patients (46%); suprasellar, 41 patients (82%); cavernous sinus, 20 patients (40%); and no extension, 3 patients (6%). Nonfunctional macroadenomas were over 5 times more likely to have suprasellar extension than GH-secreting macroadenomas (82% vs 16%, respectively; p < 0.0001). Addition-
ally, NFMs were more likely to demonstrate cavernous sinus extension than were GH-secreting adenomas (40% vs 16%, respectively; \( p = 0.04 \)). Finally, NFMs were over 7 times more likely to exhibit isolated suprasellar extension than GH-secreting macroadenomas (30% vs 4%, respectively; \( p = 0.0145 \)) (Fig. 3). No statistical differences were noted in the size or patterns of invasion between null-cell adenomas and silent gonadotropin adenomas.

The same analysis was then performed after controlling for tumor size. Patterns of extrasellar extension were analyzed for the 20 largest GH-secreting macroadenomas and 20 smallest NFMs. The mean maximal diameter of the GH group was 17.4 mm and that in the NFMA group was 18.1 mm \( (p > 0.05) \). These groups demonstrated no statistically significant differences in the overall incidence of invasion or that of cavernous sinus invasion. The incidence of suprasellar extension, however, was higher in NFMs than GH-secreting macroadenomas (65% vs 20%, respectively; \( p < 0.01 \)). Furthermore, the incidence of infrasellar extension was higher in GH-secreting macroadenomas than NFMs (70% vs 30%, respectively; \( p < 0.03 \)). Finally, the incidence of isolated infrasellar extension was 5 times higher in GH-secreting macroadenomas than NFMs (50% vs 10%, respectively; \( p < 0.02 \)).

**Discussion**

Extrasellar extension of pituitary macroadenomas into the surrounding supra-, para-, or infrasellar compartments is noted in over 90% of resected macroadenomas. A thorough assessment of the pattern of extrasellar extension on preoperative MR images is mandatory prior to attempting transsphenoidal resection of pituitary adenomas, to define which regions pose the greatest limitation for tumor resection and are likely to retain residual tumor that may cause subsequent disease progression or serve as targets for postoperative radiation. The goal of the current study was to assess whether the 2 most commonly resected macroadenomas at our institution, GH-secreting and nonfunctional subtypes, exhibited preferential patterns of tumor growth into various parasellar compartments. The salient findings of this study are as follows: 1) GH-secreting adenomas, despite being smaller tumors on average, demonstrate preferential extension into the infrasellar region, and the majority of tumors (81%) exhibiting isolated infrasellar extension are GH-secreting adenomas; 2) NFMs demonstrate preferential extension into the suprasellar region, and the majority of tumors (94%) demonstrating isolated suprasellar extension are NFMs; and 3) atypical GH-secreting adenomas have an even higher predisposition for isolated invasion of the infrasellar region. Commensurate with our data is clinical evidence from previous series of patients with GH-secreting adenomas, which have reported visual loss as a presenting symptom in only 9%–14% of patients with acromegaly, compared with 49%–72% of patients with nonfunctioning adenomas.

The implications of these extension patterns of various histopathological subtypes of pituitary adenomas may provide some insight into the tumor biology contributing to the
process of dural and bony invasion, and it remains speculative why GH-secreting adenomas exhibit an increased proclivity for infrasellar invasion. One possibility is that this phenomenon is related to the anatomical topography of somatotrophs in the caudal and lateral aspect of the pituitary gland, which is likely to explain why GH-secreting microadenomas often arise in this location on MR imaging studies. Some authors have suggested that GH may thicken the soft tissue of the diaphragma sellae while enlarging the sellar space, thus making the sellar floor thinner and more prone to tumor penetration. Alternatively, the biology of GH-secreting adenomas may enable them to more easily invade surrounding dural and/or bony structures, perhaps due to differential expression of proteins involved with degradation, such as matrix metalloproteinases. Consistent with this reasoning is that GH-secreting adenomas with a more aggressive inherent tumor biology that met the WHO criteria for atypical adenomas demonstrated especially peculiar patterns of isolated extension through the sellar floor and into the clivus, comprising 5 of the 13 GH-secreting adenomas with such growth. However, non-functional adenomas are typically larger tumors at the time of diagnosis and tend to grow through the diaphragmatic aperture and into the suprasellar cistern without primarily invading bony structures or the cavernous sinus, until they become larger tumors. Atypical nonfunctional adenomas, however, are typically aggressive macroadenomas that often invade multiple surrounding compartments (Fig. 4). From a clinical standpoint, the implications of identifying residual GH-secreting adenoma are of paramount importance. To ultimately achieve normalization of delayed insulin-like growth factor levels following transsphenoidal surgery, many patients with residual GH-secreting tumor may require multimodal management strategies, often consisting of maintained somatostatin-analog therapy, pegvisomant, and/or stereotactic radiosurgery or external beam radiotherapy to treat the residual tumor burden. A priori knowledge of residual tumor in the clivus or sellar floor may aid in the postoperative targeting of residual lesions.

The designation of atypical pituitary adenoma was added to the WHO classification for pituitary adenomas in 2004. It is based on the following criteria: 1) MIB-1 labeling index greater than 3%, 2) increased p53 immunostaining, and 3) increased mitotic figures. In the cur-
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tent study, 5 (39%) of the 13 GH-secreting adenomas demonstrating isolated infrasellar extension were atypical tumors. Although the long-term outcomes of patients harboring atypical adenomas remain to be determined, previous studies have reported a correlation between Ki 67 labeling index and degree of invasion and hormonal remission in patients with acromegaly.4

A previous study by Hagiwara et al.6 compared MR imaging features and growth patterns of GH-secreting and nonfunctional adenomas. The authors also noted increased proportions of infrasellar invasion in GH-adenomas compared with nonfunctional adenomas, but growth patterns based on isolated extension were not reported. The authors used an index called the Suprasellar Extension Index to quantify this growth patterns, which was defined as the height of suprasellar extension minus the depth of infrasellar extension.6 In their study, nonfunctional adenomas had a suprasellar extension value of +5.7 mm, compared with ~0.8 mm in GH-secreting adenomas. The current study lends support to the theory that GH-secreting adenomas have a predisposition for inferior invasion of the bony sellar floor and clivus.

Conclusions

Substantial differences in extrasellar growth patterns are observed among varying histological subtypes of pituitary macroadenomas. Despite their smaller size, GH-macroadenomas demonstrate a propensity for infrasellar extension, whereas NFMAs demonstrate preferential extension into the suprasellar region. Preferential invasion through the bony sellar floor may provide some insight into the tumor biology of GH-secreting adenomas and is important to note as a potential locus for tumor recurrence or targeting for postoperative radiation.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Zada, Laws. Acquisition of data: Zada, Lin. Analysis and interpretation of data: Zada, Lin. Drafting the article: all authors. Critically revising the article: Lin, Laws. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Zada. Study supervision: Laws.

References


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