Residual Tumor Confers a 10-Fold Increased Risk of Regrowth in Clinically Nonfunctioning Pituitary Tumors

Jelena Maletkovic,[1] Asmaa Dabbagh,[1] Dongyun Zhang,[1] Abdul Zahid,[1] Marvin Bergsneider,[2] Marilene B. Wang,[3] Michael Linetsky,[4] Noriko Salamon,[4] William H. Yong,[5] Harry V. Vinters,[5] and Anthony P. Heaney[1,2]

[1]Department of Medicine, UCLA–David Geffen School of Medicine, Los Angeles, California 90095; [2]Department of Neurosurgery, UCLA–David Geffen School of Medicine, Los Angeles, California 90095; [3]Department of Head & Neck Surgery, UCLA–David Geffen School of Medicine, Los Angeles, California 90095; [4]Department of Neuroradiology, UCLA–David Geffen School of Medicine, Los Angeles, California 90095; and [5]Department of Pathology and Laboratory Medicine, UCLA–David Geffen School of Medicine, Los Angeles, California 90095

ORCiD numbers: 0000-0003-3865-0810 (A. P. Heaney).

Objective: We evaluated tumor recurrence and regrowth rates following endoscopic transnasal transsphenoidal (TNTS) surgical removal in a consecutive series of clinically nonfunctioning pituitary adenomas (CNFTs).

Design: Retrospective chart review of clinical, biochemical, and sellar MRI findings in all TNTS surgeries in patients with CNFT, performed by a single surgeon, between 2008 and 2015 (n = 280).

Patients: Ninety-three patients met eligibility criteria, with complete clinical, biochemical, and imaging follow-up for a 3-year minimum.

Results: Of 85 patients who were not irradiated, 3-month postsurgical MRI demonstrated no residual tumor in 58 of 85 (68.2%), equivocal findings in 12 of 85 (14.1%), and definite residual tumor in 15 of 85 (17.6%) patients. Six of 85 (7.1%) demonstrated tumor regrowth by 3 years, and 2 further patients demonstrated true tumor recurrence at 3 and 6 years after surgery, respectively, for a total recurrence rate of 9.4% (8 of 85). Eight of the 93 patients were irradiated between 3 months and 4 years after pituitary surgery. In 3 patients with tumor regrowth, 2 exhibited residual tumor and 1 had no residual findings at the 3-month postoperative imaging. Overall, Ki-67 labeling index or Knosp grading did not predict recurrence.

Conclusion: Tumor recurrence at 3 years was low (1 of 58; 1.7%) if the 3-month postoperative MRI showed no residual tumor. The findings support a less frequent imaging schedule for this group. Patients with definite residual tumor visible at 3 months harbor the greatest risk for tumor growth, but regrowth does not occur in all patients (6 of 15; 40%).

Freeform/Key Words: pituitary tumor regrowth and recurrence, transnasal transsphenoidal surgery, clinically nonfunctional tumors, radiation therapy, Ki-67

The goals of therapy for pituitary tumors are clinical and biochemical remission and control of tumor growth. In contrast to functioning tumors, for which biochemical markers complement imaging assessment and often suggest tumor recurrence before visible tumor is detected on

Abbreviations: CNFT, clinically nonfunctioning pituitary adenoma; GTR, gross total resection; Ki-67 LI, Ki-67 labeling index; TNTS, transnasal transsphenoidal surgery.

Received 30 April 2019
Accepted 17 July 2019
First Published Online 23 July 2019

ISSN 2472-1972
October 2019 | Vol. 3, Iss. 10
doi: 10.1210/js.2019-00163 | Journal of the Endocrine Society | 1931–1941

imaging, remission and recurrence in clinically nonfunctional tumors (CNFTs) are largely determined by anatomic imaging.

Studies examining long-term recurrence after endoscopic transnasal transsphenoidal (TNTS) pituitary tumor removal often include small numbers of patients with variable follow-up duration. In addition, many are confounded by the concomitant use of routine radiotherapy in the postoperative period for tumor remnants that make clear conclusions on the natural history of these generally benign tumors difficult [1]. One meta-analysis study estimated that the mean early postoperative remission rate was 47.3% in CNFTs [2]. Given the high recurrence rates reported in some studies, some centers submit that most patients with residual postoperative tumor should routinely be offered radiation therapy following surgical resection.

Several studies have demonstrated that the most reliable predictor of tumor regrowth is the presence of residual tumor following pituitary surgery. For example, Chen *et al.* [3] reported a tumor regrowth rate of 12% when no residual tumor was noted after surgery compared with a 46% rate when postoperative residual tumor was noted. Other studies have also suggested that younger age, sex, and initial tumor size may also be contributing factors [4].

Although there is no standard protocol, most pituitary centers typically image in the first 3 to 6 months after pituitary surgery and then annually for 3 to 5 years. Thereafter, MRI is performed less frequently and is guided by the clinical situation in an individualized manner. For example, on the basis of a 2-year follow-up in 51 patients, one study suggested performing postoperative MRI at 4 to 6 months and then 12, 24, and 36 months after surgery, followed by imaging at 5 and 10 years [5]. Currently, we perform MRI of the pituitary 3 and 12 months after surgery and then annually for 3 to 5 years; this equates to an average cost of $5400 per patient for these six MRI studies.

The neurosurgical approach to the sella has changed substantially in the past 10 to 15 years, with the more widespread use of endoscopic approaches. These have enabled direct visualization of tumor and normal pituitary tissue. Some researchers have advocated that the endoscopic approach facilitates more extensive tumor removal, although not all surgeons accept this notion [6]. In light of these advances in surgical technique and the substantial cost and anxiety that imaging studies induce in some patients, we sought to evaluate long-term remission rates in a recent cohort of patients with CNFTs and ask whether our current imaging schedule was appropriate and cost-effective for all patients.

1. Methods

A. Study Design

The institutional review board approved this retrospective chart review study of all patients undergoing first endoscopic TNTS for pathologically confirmed CNFTs (n = 280) between 2008 and 2015 at the UCLA Medical Center by an experienced single surgeon (M.B.), with stable surgical outcomes across the study. Patients' demographic characteristics, endocrinologic evaluation, intraoperative findings, histopathological assessment, and preoperative and serial postoperative MRI studies were reviewed. One hundred eighty-five patients had incomplete clinical, endocrine, and/or imaging assessment for less than the minimum 3-year follow-up period and were excluded, as were 2 patients who underwent surgery for clinically nonfunctioning microadenomas. After exclusions, 93 patients were eligible for study analysis. The core study focused on a mandatory 3-year follow-up for all 93 patients, although we did have longer-term follow-up in 58 of 93 (62%) patients; 4 years, n = 21; 5 years, n = 15; 6 years, n = 12; 7 years, n = 5; 8 years, n = 4; 10 years, n = 1; this was also evaluated in determining recurrence and regrowth rates.

B. Clinical and Endocrine Assessment

Clinically nonfunctioning pituitary adenoma was diagnosed on the basis of clinical history characteristics, physical findings and endocrinologic evaluation results, imaging findings,

and confirmation by histopathology. Early-morning laboratory sampling for prolactin, TSH, free T_4, ACTH, cortisol, LH, FSH, IGF-1, and testosterone (men only) was performed in all patients by using commercially available assays. Endocrine laboratory assessment was performed 2 to 3 months after surgery and then annually unless clinical, biochemical, or imaging evidence of residual disease demanded more frequent biochemical monitoring.

C. Imaging Studies

All MRI studies included pre- and postcontrast T1- and T2-weighted images in sagittal and coronal planes. Cavernous sinus invasion was determined by using the Knosp scale; grades 0, 1, and 2 indicated no invasion; grade 3a, probable invasion; and grades 3b and 4, definite invasion [7]. A 3-month postoperative MRI study was routinely obtained as the baseline comparative study, and findings from that study were categorized into one of three groups: group 1, patients with no residual tumor; group 2, patients who had an equivocal MRI on which the neuroradiologist could not differentiate postoperative change from possible residual tumor; and group 3, patients with definite residual tumor. The subsequent MRI examinations at 1, 2, and 3 years were compared with all prior studies, including the 3-month postoperative baseline study, and were categorized into one of two outcomes: outcome 1, stable compared with 3-month postoperative imaging (no recurrence or no growth); outcome 2, growth of the residual tumor or *de novo* growth (true recurrence).

D. Surgical Technique

All surgeries were performed by a dedicated team consisting of a neurosurgeon (M.B.) and a head and neck surgery skull-base rhinologist (M.B.W.). A binaural endoscopic approach that incorporated a wide sellar exposure was used. Whenever possible, a pseudocapsular dissection technique [8] was used to excise the pituitary tumor. Cavernous sinus exploration was performed in all cases where cavernous sinus invasion was evident.

E. Histopathologic Analysis

Formalin-fixed, paraffin-embedded sections were stained with hematoxylin and eosin. Immunostaining for LH, FSH, TSH, GH, prolactin, and ACTH, as well as Ki-67, was performed on 5-μm sections of the tumor. Ki-67 was scored by the observer estimating percentage of Ki-67–positive nuclei compared with all the nuclei as stained with hematoxylin and eosin. Tumors were classified by using the World Health Organization classification (2004) by our neuropathologists (W.H.Y. and H.V.V.).

F. Statistics

Demographic differences between ages and tumor sizes of the included and excluded patients were assessed by two-sided Student t test, and the difference between sexes was analyzed by a χ^2 tests (Prism 4 software, GraphPad). P values < 0.05 were considered to indicate statistically significant differences.

2. Results

A. Patient Characteristics

Table 1 shows the demographics and tumor characteristics of the study cohort of 93 patients, which were similar to those of the 187 excluded patients and demonstrates similar sex and age distribution and tumor size at presentation. Three of the clinically nonfunctional macroadenomas were so-called giant macroadenomas (>4 cm diameter), 55 were gonadotroph tumors, 6 were "silent" corticotroph tumors, and 32 were null cell tumors. As depicted in Fig. 1A, among 85 nonirradiated patients, pituitary MRI imaging 3 months after surgery

Table 1. Demographic Characteristics and Tumor Size in the 93 Included Patients and 187 Ineligible Patients

Variable	Excluded Patients (n = 187)	Study Patients (n = 93)
Men/women, n/n	84/103	39/54
Age range (mean), y	19–83 (56.2)	21–82 (56.8)
Tumor size range (mean), mm	6–72 (25.6)	10–50 (24.6)

Excluded patients were ineligible because of incomplete clinical, endocrine, and/ or imaging studies or microadenomas (n = 2). Age and tumor size did not significantly differ between groups.

demonstrated no residual tumor in 58 patients (68.2%; group 1), equivocal MRI findings regarding postoperative changes vs residual tumor in 12 patients (14.1%; group 2), and definite residual tumor in the remaining 15 patients (17.6%; group 3). Seven of the 85 patients (8.2%) exhibited tumor growth across the "core" 3-year follow-up imaging study and one patient demonstrated recurrence at 6 years, for a total recurrence rate of 9.4% (8 of 85 patients) over 3 to 10 years. Of these regrowth/recurrent cases, 6 had evidence of residual tumor at 3-months postoperative imaging, whereas no residual tumor was observed in the remaining 2 patients at 3-month postoperative MRI.

Eight of the 93 patients were irradiated between 3 months and 4 years after pituitary surgery, and no tumor growth occurred following radiation therapy (Fig. 1B). Seven of eight patients (87.5%) exhibited residual tumor on the 3-month postoperative imaging study, and no residual findings were noted in the eighth patient. In 3 of these patients, interval tumor growth was documented before radiation administration. The remaining 5 patients did not exhibit tumor growth, and indications for radiation included large-volume residual tumor with (n = 3) or without (n = 2) risk of optic chiasm compression should minimal tumor growth occur.

B. Ki-67 Labeling Index as Predictor of Postoperative Tumor Growth/Recurrence

Ki-67 labeling index (Ki-67 LI) was available in 88 of the 93 patients, as tumors exhibiting substantial apoplexy/necrosis or heavy inflammatory cell infiltrate made assessment of Ki-67 LI unreliable. As depicted in Fig. 2A and 2B, Ki-67 LI ranged from 1% to 12.5% (mean Ki-67 LI ± SD, 2.6% ± 2.1%; n = 88). There was no difference in tumors that exhibited tumor growth of residual (n = 8) or true recurrence (n = 2) (mean Ki-67 LI, 2.9% ± 1.9%; n = 10) compared with those that did not exhibit tumor growth by 3 years (mean Ki-67 LI, 2.6% ± 2.2%; n = 78; P = NS). In addition, Ki-67 LI did not differ in tumors from nonirradiated patients (mean Ki-67 LI, 2.6% ± 2.2%; n = 80) in comparison with tumors from those who received radiation (mean Ki-67 LI, 3.1% ± 2.0%; n = 8; P = NS). The highest KI-67 LI, of 10% to 12.5%, was seen in 2 patients (1 who had no residual at 3 months and 1 who had equivocal findings at 3 months), but neither patient exhibited tumor regrowth across the 3-year follow-up. Twenty-four of our 88 evaluated patients had a Ki-67 LI ≥ 3%, which some studies suggest indicates a higher risk of recurrence. Fourteen of these 24 patients had no residual tumor at 3 months, and none demonstrated true recurrence over 3 years; 4 had an equivocal 3-month MRI study and none of these recurred. Interestingly, of 6 patients who had Ki-67 LI ≥ 3% and had residual tumor at 3 months, 4 exhibited tumor growth over the 3-year follow-up.

C. Knosp Score Prediction of Tumor Resection and Recurrence Risk

In the 59 patients who had a 3-month postoperative MRI showing no residual tumor, Knosp grading of their preoperative MRI (Fig. 3A and 3B) demonstrated that 51 (86%) were noninvasive [G0, n = 16 (27%); G1, n = 24 (41%); and G2, n =11 (19%)], 5 cases (8%) had probable cavernous sinus (CV) invasion (G3a), and 3 tumors (5%) exhibited definite cavernous sinus

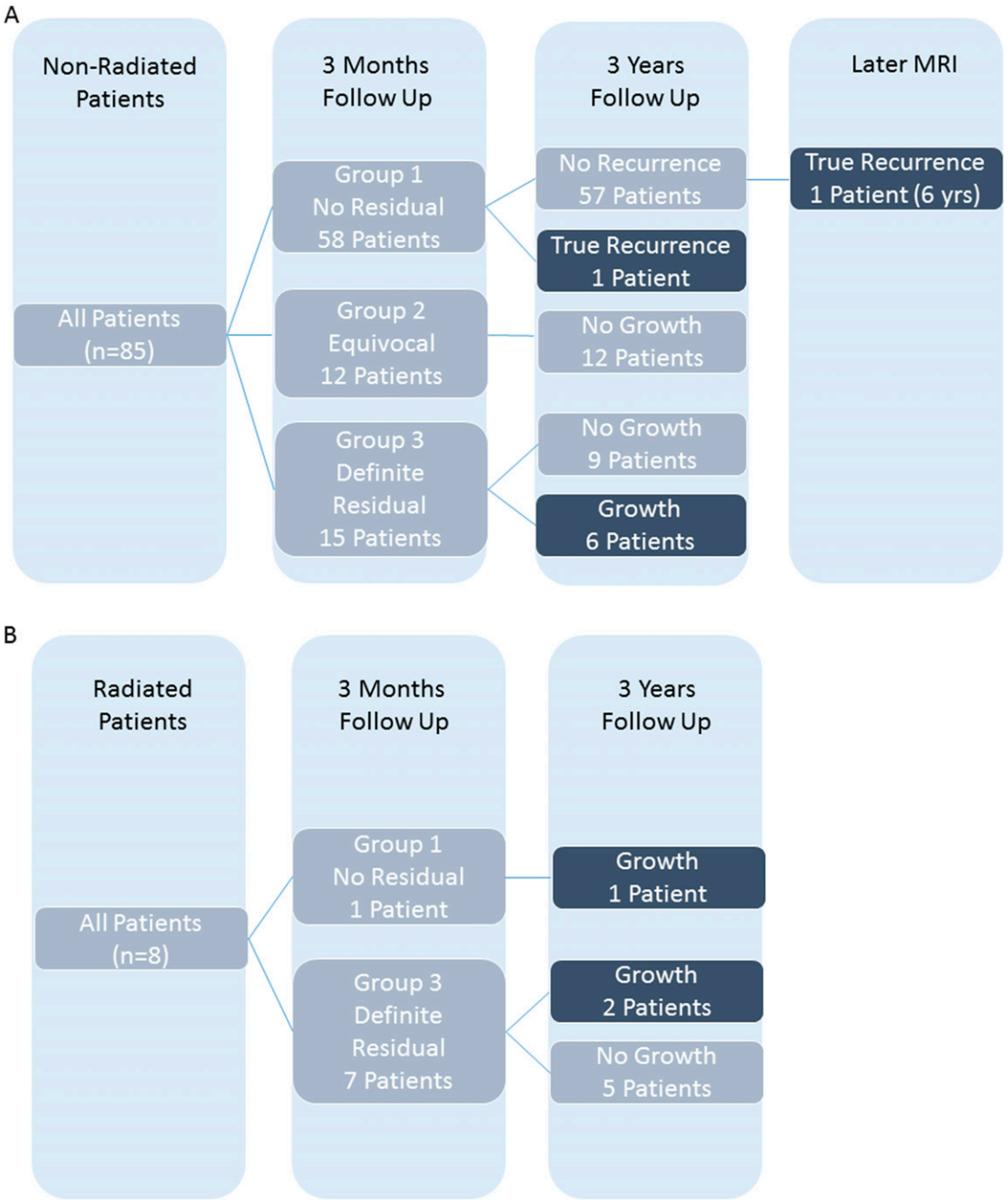

Figure 1. Schematic flowchart of (A) nonirradiated and (B) irradiated patients assigned to groups 1, 2, and 3 based on imaging studies at 3 mo and their imaging study at 3-y follow-up. Group 1, no visible residual tumor on 3-mo postoperative MRI; group 2, equivocal 3-mo postoperative MRI wherein the neuroradiologist could not differentiate postoperative change from possible residual tumor; group 3, definite residual tumor on 3-mo postoperative MRI.

invasion [G4, n = 3 (5%)] (Fig. 3A). In the 22 patients who exhibited definite residual tumor on the 3-month postoperative MRI, Knosp grading indicated 12 (55%) tumors were noninvasive (G0, n = 3; G1, n = 3; G2, n = 6), 5 cases exhibited probable CV invasion (23%, G3a), and 5 tumors were invasive (23%, G4) (Fig. 3A). Of the 8 patients who exhibited growth from residual tumor seen at 3 months across the 3-year follow-up period, 6 were noninvasive (G0, n = 2; G1,

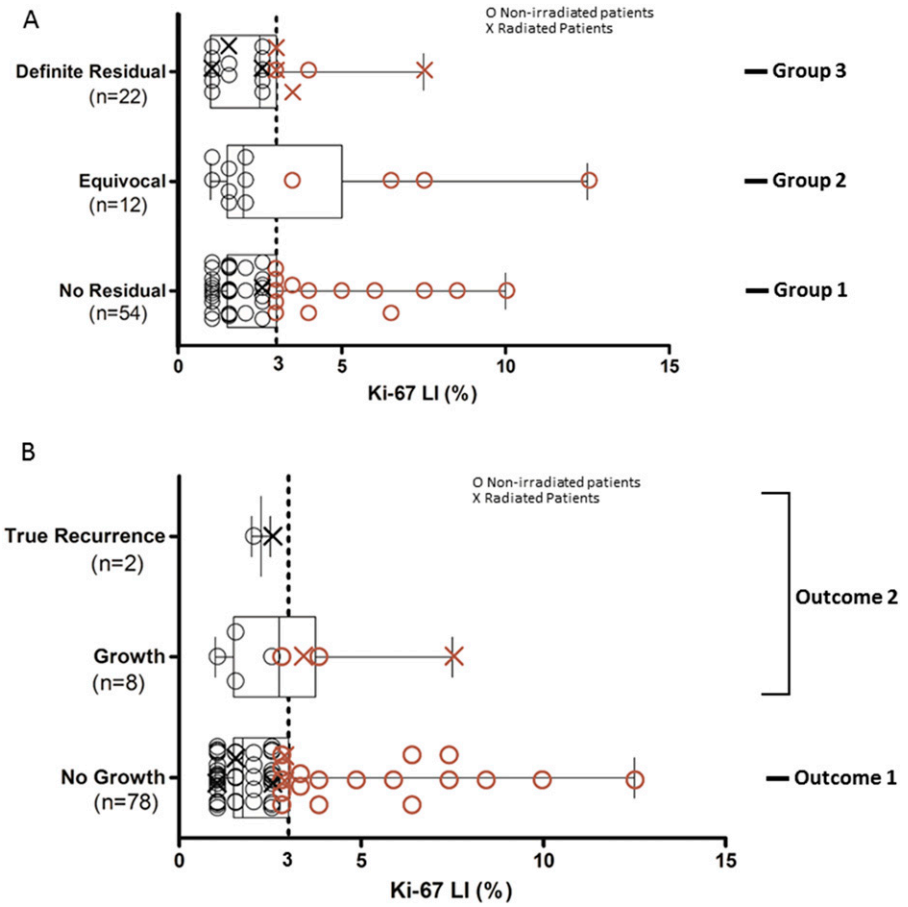

Figure 2. Distribution of Ki-67 LI in 88 of 93 patients based on (A) pituitary MRI at 3 mo postoperatively: definite tumor, equivocal MRI, no residual; and (B) outcome at 3 y after surgery: true recurrence, tumor growth, no tumor growth. The cycle mark indicates nonirradiated patients and cross mark indicates irradiated patients. The red symbols indicate Ki-67 LI ≥3%.

n = 1; G2, n = 3), 1 case had probable CV invasion (G3a), and 1 case had definite CV invasion (G4). Interestingly, in 2 patients who exhibited true recurrence over 3 years (*i.e.*, 3-month postoperative MRI showed no evidence of residual tumor), both tumors were invasive (G4, n = 2) (Fig. 3B).

3. Discussion

Our experience confirms that TNTS is an overall excellent modality for treatment of clinically nonfunctioning pituitary tumors, with an excellent, comparatively low recurrence rate. It also reaffirms the extensive literature that surgical experience is an important factor in attaining initial gross total resection (GTR), which is key to reducing rates of later recurrence in these tumors [3, 9, 10]. We chose to conduct our study in patients who had undergone transsphenoidal surgery by a single surgeon to reduce confounders due to variation in experience and technique. Although this, along with a mandated minimum 3-year careful follow-up, somewhat limited our sample size, it allowed us to obtain complete data for all included patients. As noted, we did assess longer-term follow-up imaging when available in many of our patients, in one case out to 10 years.

In our 85 nonirradiated patients, true recurrence was observed in 1 patient (1.7%) at 3 years; 1 other patient exhibited recurrence at 6 years, for total true recurrence rate of

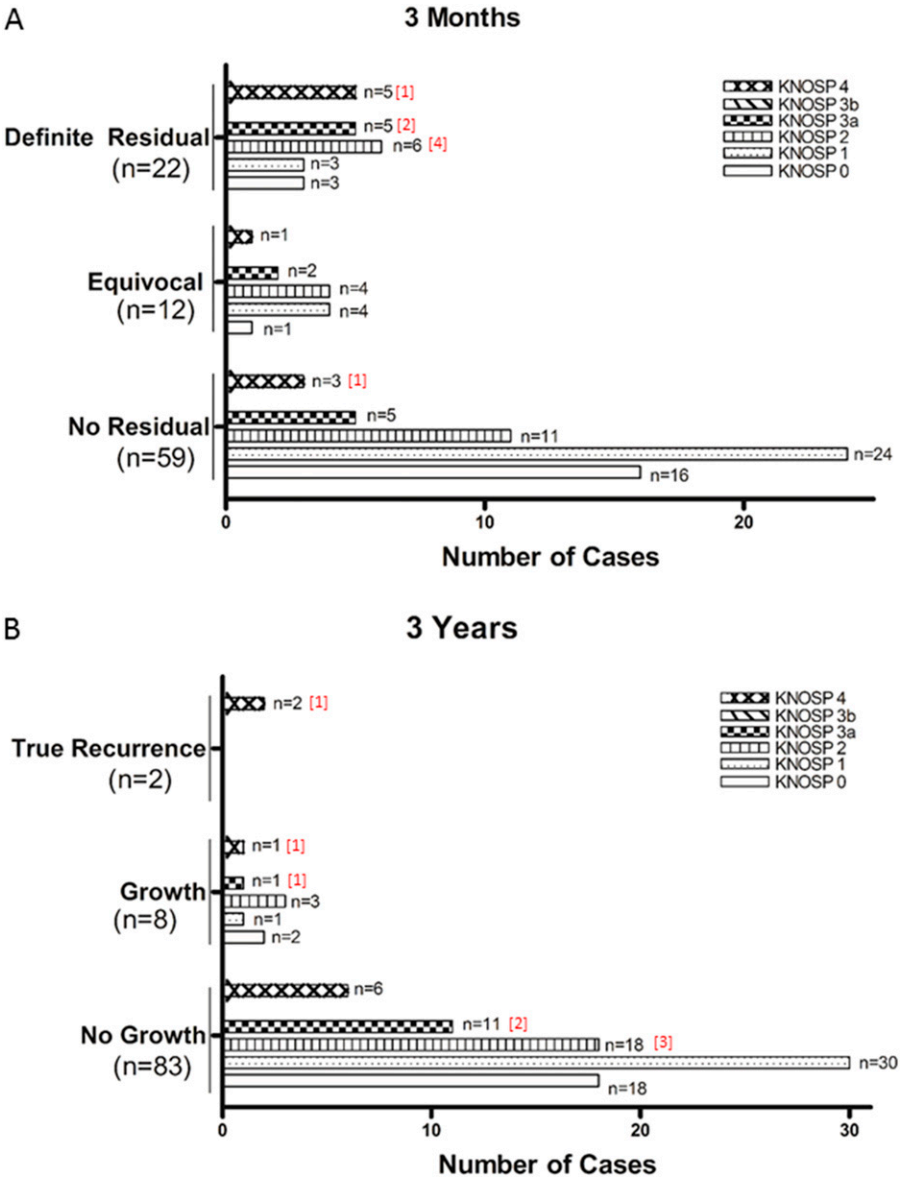

Figure 3. Knosp grading in 93 patients grouped according to (A) pituitary MRI 3 mo postoperatively: definite tumor, equivocal MRI, no residual; and (B) outcome at 3 y after surgery: true recurrence, tumor growth, no tumor growth. Knosp 0, 1, and 2, no cavernous sinus invasion; Knosp 3a, uncertain CV invasion; Knosp 3b and 4, definite CV invasion. Number of irradiated patients is depicted in red brackets.

(3.4%) (2 of 58) across an average follow-up of 4.5 years (range, 3 to 10 years). In 15 patients with definite visible residual tumor at 3 months, regrowth was observed in 6 of 15 (40%) at 3 years; no further patients with tumor growth were noted across the average follow-up period of 4.5 years. In the remaining 8 patients who underwent tumor-directed radiation therapy, 7 had definite residual and 1 exhibited no residual MRI image on 3-month postoperative imaging. Growth of residual tumor before radiation was documented in 3 patients (37.5%), and no patient exhibited tumor growth following radiation therapy. As noted in the Results section, radiation was recommended in the remaining 5 patients because of a significantly sized tumor remnant (n = 4), with eminent risk of optic chiasm compression in 2 of these patients. Considering all patients, both nonradiated and irradiated, we observed an overall regrowth/recurrence rate of 10.7% (10 of 93 patients) at

3 years, with 1 further patient developing true recurrence at 6 years, for total recurrence/regrowth in 11 of 93 (11.8%). This rate is very similar to that reported by others [3, 9]. This latter type of experience understandably has led some centers to routinely recommend radiotherapy in all patients with residual tumor after TNTS [10]. In CNFTs, the goal of surgery is often to decompress structures, such as the optic chiasm and therefore GTR may not be considered as critical as in hormone-secreting tumors, particularly in centers where postoperative radiation is the long-standing practice. In tumors involving the cavernous sinuses, extending to encase the internal carotid arteries and/or extensive suprasellar extension, the risks of a potentially more aggressive surgical effort must be balanced with the morbidity, or lack thereof, of leaving residual nonfunctioning tumor. We believe that careful selection of patients to undergo attempted complete resection of CNFTs is appropriate in certain circumstances where the tumor can be safely fully resected.

The 23-fold difference in recurrence/regrowth rates at 3 years in our patients with no residual tumor (true recurrence, 1 of 58, 1.7%) vs those with definite visible tumor at 3 months (6 of 15, 40%) is striking and not dissimilar to that reported by Dallapiazza *et al.* and others (0% to 6% in patients with no residual), increasing to 42% to 53% with intrasellar remnant tumor and up to 80% with extrasellar tumor, emphasizing that GTR of the tumor itself, as documented by no residual tumor seen on MRI, is the most important determinant of recurrence risk [9–12].

Some studies have suggested that Ki-67 LI may be helpful in predicting pituitary tumor progression. A study in 39 patients reported that pituitary adenomas with progression (regrowth within 5 years after initial surgery) had a higher mean proliferation index (3.66% ± 3.00%; n = 12) than tumors without progression (1.89% ± 1.25%; n = 27; $P < 0.05$) [13]. Other studies have suggested a Ki-67 LI > 3% to be associated with tumor recurrence [14], but others report that although this Ki-67 LI threshold of 3% has a high specificity (89.5%), its sensitivity is comparatively poor (53.8%) [15]. Our study shows that Ki-67 as a standalone parameter is unreliable, in that most of our tumors with high Ki-67 could be fully resected with no visible tumor 3 months after surgery and, therefore, low risk of recurrence. It could be argued that we had inadvertently selected out a group of patients with high potential to regrow early for radiation, and so we also examined that subgroup. Mean Ki-67 LI did not differ between the radiated group (mean Ki-67 LI, 3.1% ± 2.0%; n = 8) and the nonirradiated cohort (mean Ki-67 LI, 2.6% ± 2.2%; n = 80). Overall, our results suggest caution with the use of Ki-67 values alone in guiding clinical decisions, such as indication for radiotherapy after pituitary surgery.

Our study also confirms that persistence of postoperative residual tumor does not always mean regrowth of tumor remnant over time, indicating that other factors, such as the inherent biology of the tumor, play an important role. However, in our series, 4 of 6 tumors (67%) with demonstrable residual tumor at 3 months and a Ki-67 LI > 3% demonstrated recurrence. Therefore, it appears the combined information of postoperative radiologic appearance demonstrating residual tumor and then retrospective review of histopathology in those cases may have the most clinically useful predictive value. This is consistent with findings in a recent prospective study by Raverot *et al.* [16] where several factors regarding the tumor, including radiologic invasion and pathological markers, are combined to offer insight into risk of tumor recurrence. Several tumor subtypes that exhibit increased regrowth/recurrence rates or need for additional surgical or radiation treatments have been proposed [17, 18]. These include so-called silent corticotroph and/or somatotroph tumors, wherein hormones can be detected immunohistochemically in the tumor but clinical signs of hormonal excess are not observed and hormones are not elevated in circulation. More recently, low estrogen receptor α in gonadotroph tumors has been reported to be associated with higher reintervention rates in male patients [19]. All of these studies emphasize the importance of obtaining a complete initial tumor resection in reducing risk of remnant tumor regrowth and in so doing limiting the need for adjuvant therapy, including radiation.

Researchers using a revised Knosp classification have reported that patients with grade 3a tumors had higher GTR rates than did those with grade 3b tumors (85% vs 64%), and the GTR rates in grade 4 tumors was 0%. Using this same modified Knosp classification, we observed that GTR was possible in some patients with grade 4 tumors, whereas in some grade 3 tumors, GTR was not attainable. In some cases, this was at least in part due to adherent properties of the tumor. Our findings also showed that although 2 of 2 (100%) of our patients who exhibited true recurrence over 3 years had invasive tumors (G4) by Knosp grading, 7 of 8 tumors that exhibited growth across the 3-year follow-up period did not have definite evidence of CV invasion on preoperative MRI imaging. Overall, our study indicates that although Knosp grading may be helpful in surgical planning, it has limited value in predicting risk of recurrence. Clearly, in addition to internal carotid artery adhesion and encasement, other anatomic aspects, such as tumor suprasellar extension, can substantially limit gross total pituitary tumor resection.

A strength of our study is that all included patients had a minimum follow-up period of 3 years, with careful, consistent monitoring of clinical, biochemical, and imaging studies. However, given that some studies have estimated the residual tumor volume doubling time to be 3.4 years, the relatively short-term follow-up in some of our patients may have underestimated the ultimate full regrowth and recurrence rates [3, 11, 20]. However, we did have >3 years of follow-up in 58 of 93 patients (62%) (4 years, n = 21; 5 years, n = 15; 6 years, n = 12; 7 years, n = 5; and 8 years, n = 4), with average 4.5 years of follow-up. Furthermore, although 20% of recurrent events may occur at least 10 years after surgery, most are typically observed in the first 3 years. Therefore, our results indicate that if an imaging study at 3 months shows no residual tumor, the risk of subsequent recurrence is reassuringly low at ~1.7% at 3 years and 3.4% overall.

We must acknowledge other limitations in this study, and our conclusions may not be generalizable to all patients who require surgery for pituitary tumors. For example, because we are a tertiary referral center and many of our patients come to us for TNTS alone, thereafter returning to the care of their local endocrinologist, we could capture "complete" follow-up data for only 93 of 280 patients (33%). It is possible that this introduced bias in our outcomes, as we may not have seen all the tumor recurrences. However, generally any patient who does have recurrence will be referred back to our center. Overall, our data affirm the importance of GTR at first surgical attempt in limiting recurrence rates. Ultimately, the skill of the surgeon regardless of the technique (endoscopy vs speculum) is the key determinant of success, as has been emphasized in a recent white paper on pituitary tumor centers of excellence [21].

This study has prompted us to re-evaluate our current imaging schedule. As noted, at 3 months, we observed equivocal postoperative MRI findings in 14% of patients. It may be possible to lower the frequency of indeterminate MRI studies by performing this postoperative MRI first at 6 months and then annually for 3 to 5 years. Using a standardized MRI protocol with the same orientation of coronal sections can also help detect subtle regrowth of tumor remnants. Our data would suggest that if MRI findings are negative at 3 months and 1 year, imaging could then be deferred for at least 2 years and scanning intervals thereafter could be reduced to every 3 to 5 years in most patients unless symptoms suggest otherwise. Additionally, in some patients in whom residual lesions are T2 enhancing, gadolinium injection can be spared and residual tumor monitored without contrast. This strategy of reduced image frequency with sparing use of gadolinium in suitable patients would provide a substantial health care cost saving and lessen test anxiety for patients.

Additional Information

Correspondence: Anthony P. Heaney, MD, PhD, David Geffen School of Medicine, 650 Charles E Yong Drive S, 9240-P Factor Building, Los Angeles, California 90095. E-mail: aheaney@mednet.ucla.edu.

Disclosure Summary: The authors have nothing to disclose.

Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References and Notes

1. Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA. Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation - a follow-up study. *Clin Endocrinol (Oxf).* 1999;**51**(3): 281–284.
2. Roelfsema F, Biermasz NR, Pereira AM. Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis. *Pituitary*. 2012;**15**(1):71–83.
3. Chen Y, Wang CD, Su ZP, Chen YX, Cai L, Zhuge QC, Wu ZB. Natural history of postoperative nonfunctioning pituitary adenomas: a systematic review and meta-analysis. *Neuroendocrinology*. 2012; **96**(4):333–342.
4. Cortet-Rudelli C, Bonneville J-F, Borson-Chazot F, Clavier L, Coche Dequéant B, Desailloud R, Maiter D, Rohmer V, Sadoul JL, Sonnet E, Toussaint P, Chanson P. Post-surgical management of non-functioning pituitary adenoma. *Ann Endocrinol (Paris).* 2015;**76**(3):228–238.
5. Soto-Ares G, Cortet-Rudelli C, Assaker R, Boulinguez A, Dubest C, Dewailly D, Pruvo JP. MRI protocol technique in the optimal therapeutic strategy of non-functioning pituitary adenomas. *Eur J Endocrinol.* 2002;**146**(2):179–186.
6. Mortini P. Cons: endoscopic endonasal transsphenoidal pituitary surgery is not superior to microscopic transsphenoidal surgery for pituitary adenomas. *Endocrine.* 2014;**47**(2):415–420.
7. Micko ASG, Wöhrer A, Wolfsberger S, Knosp E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J Neurosurg.* 2015; **122**:803.
8. Oldfield EH, Vortmeyer AO. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. *J Neurosurg.* 2006;**104**(1):7–19.
9. Dallapiazza RF, Grober Y, Starke RM, Laws ER, Jr, Jane JA, Jr. Long-term results of endonasal endoscopic transsphenoidal resection of nonfunctioning pituitary macroadenomas. *Neurosurgery*. 2015; **76**(1):42–52, discussion 52–53.
10. O'Sullivan EP, Woods C, Glynn N, Behan LA, Crowley R, O'Kelly P, Smith D, Thompson CJ, Agha A. The natural history of surgically treated but radiotherapy-naïve nonfunctioning pituitary adenomas. *Clin Endocrinol (Oxf).* 2009;**71**(5):709–714.
11. Reddy R, Cudlip S, Byrne JV, Karavitaki N, Wass JAH. Can we ever stop imaging in surgically treated and radiotherapy-naive patients with non-functioning pituitary adenoma? *Eur J Endocrinol.* 2011; **165**(5):739–744.
12. O'Reilly MW, Reulen RC, Gupta S, Thompson CA, Dineen R, Goulden EL, Bugg G, Pearce H, Toogood AA, Gittoes NJ, Mitchell R, Thompson CJ, Ayuk J. ACTH and gonadotropin deficiencies predict mortality in patients treated for nonfunctioning pituitary adenoma: long-term follow-up of 519 patients in two large European centres. *Clin Endocrinol (Oxf).* 2016;**85**(5):748–756.
13. Matsuyama J. Ki-67 expression for predicting progression of postoperative residual pituitary adenomas: correlations with clinical variables. *Neurol Med Chir (Tokyo).* 2012;**52**(8):563–569.
14. Kim JS, Lee YS, Jung MJ, Hong YK. The predictive value of pathologic features in pituitary adenoma and correlation with pituitary adenoma recurrence. *J Pathol Transl Med.* 2016;**50**(6):419–425.
15. Righi A, Agati P, Sisto A, Frank G, Faustini-Fustini M, Agati R, Mazzatenta D, Farnedi A, Menetti F, Marucci G, Foschini MP. A classification tree approach for pituitary adenomas. *Hum Pathol.* 2012; **43**(10):1627–1637.
16. Raverot G, Dantony E, Beauvy J, Vasiljevic A, Mikolasek S, Borson-Chazot F, Jouanneau E, Roy P, Trouillas J. Risk of recurrence in pituitary neuroendocrine tumors: a prospective study using a five-tiered classification. *J Clin Endocrinol Metab*. 2017;**102**(9):3368–3374.
17. Bradley KJ, Wass JAH, Turner HE. Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours but do not recur more frequently. *Clin Endocrinol (Oxf).* 2003;**58**(1):59–64.
18. Langlois F, Lim DST, Varlamov E, Yedinak CG, Cetas JS, McCartney S, Dogan A, Fleseriu M. Clinical profile of silent growth hormone pituitary adenomas; higher recurrence rate compared to silent gonadotroph pituitary tumors, a large single center experience. *Endocrine.* 2017;**58**(3):528–534.

19. Øystese KA, Casar-Borota O, Normann KR, Zucknick M, Berg JP, Bollerslev J. Estrogen receptor α, a sex-dependent predictor of aggressiveness in nonfunctioning pituitary adenomas: SSTR and sex hormone receptor distribution in NFPA. *J Clin Endocrinol Metab*. 2017;**102**(9):3581–3590.
20. Brochier S, Galland F, Kujas M, Parker F, Gaillard S, Raftopoulos C, Young J, Alexopoulou O, Maiter D, Chanson P. Factors predicting relapse of nonfunctioning pituitary macroadenomas after neurosurgery: a study of 142 patients. *Eur J Endocrinol*. 2010;**163**:193
21. Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS, Melmed S, Mortini P, Wass J, Giustina A; Pituitary Society, Expert Group on Pituitary Tumors. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): a Pituitary Society Statement [published correction appears in *Pituitary*. 2018 Dec;**21**(6):663]. *Pituitary*. 2017;**20**(5):489–498.