The efficacy and morbidity for transsphenoidal surgery have been well examined for patients undergoing primary surgery for tumors of the pituitary gland as well as other lesions within or near the sella turcica. While transsphenoidal surgery has low morbidity, the degree to which this morbidity increases after reoperation remains unclear. The authors determined the morbidity associated with repeat versus initial transsphenoidal surgery after 1015 consecutive operations.

Methods. The authors conducted a 5-year retrospective review of the first 916 patients undergoing transsphenoidal surgery at their institution after a pituitary center of expertise was established, and they analyzed morbidities.

Results. The authors analyzed 907 initial and 108 repeat transsphenoidal surgeries performed in 916 patients (9 initial surgeries performed outside the authors’ center were excluded). The most common diagnoses were endocrine inactive (30%) or active (36%) adenomas, Rathke’s cleft cysts (10%), and craniopharyngioma (3%). Morbidity of initial surgery versus reoperation included diabetes insipidus (DI) 16% vs 26%; p = 0.03), postoperative hyponatremia (20% vs 16%; p = 0.3), new postoperative hypopituitarism (5% vs 8%; p = 0.3), CSF leak requiring repair (1% vs 4%; p = 0.04), meningitis (0.4% vs 3%; p = 0.02), and length of stay (LOS) (2.8 vs 4.5 days; p = 0.006). Of intraoperative parameters and postoperative morbidities, 1) some (use of lumbar drain and new postoperative hypopituitarism) did not increase with second or subsequent reoperations (p = 0.3–0.9); 2) some (DI and meningitis) increased upon second surgery (p = 0.02–0.04) but did not continue to increase for subsequent reoperations (p = 0.3–0.9); 3) some (LOS) increased upon second surgery and increased again for subsequent reoperations (p < 0.001); and 4) some (postoperative hyponatremia and CSF leak requiring repair) did not increase upon second surgery (p = 0.3) but went on to increase upon subsequent reoperations (p = 0.001–0.02). Multivariate analysis revealed that operation number, but not sex, age, pathology, radiation therapy, or lesion size, increased the risk of CSF leak, meningitis, and increased LOS. Separate analysis of initial versus repeat transsphenoidal surgery on the 2 most common benign pituitary lesions, pituitary adenomas and Rathke’s cleft cysts, revealed that the increased incidence of DI and CSF leak requiring repair seen when all pathologies were combined remained significant when analyzing only pituitary adenomas and Rathke’s cleft cysts (DI, 13% vs 35% [p = 0.001]; and CSF leak, 0.3% vs 9% [p = 0.0009]).

Conclusions. Repeat transsphenoidal surgery was associated with somewhat more frequent postoperative DI, meningitis, CSF leak requiring repair, and greater LOS than the low morbidity characterizing initial transsphenoidal surgery. These results provide a framework for neurosurgeons in discussing reoperation for pituitary disease with their patients.

Key Words • reoperation • pituitary surgery • morbidity • oncology • transsphenoidal surgery

Abbreviations used in this paper: DI = diabetes insipidus; LOS = length of stay.
whose pathologies are representative of the wide spectrum seen in practice and who underwent surgery during the past 5 years after the establishment of our dedicated pituitary center of excellence.

Methods
Study Design, Setting, and Participants
Our institutional Committee on Human Research reviewed and approved this study. We retrospectively reviewed 1015 consecutive endonasal pituitary surgeries performed in the first 916 patients treated in the 5 years since the establishment of the California Center for Pituitary Disorders, a dedicated multidisciplinary center of pituitary expertise. The 1015 operations consisted of 907 first surgeries performed at our center, 99 reoperations performed at our center on patients whose first surgery was also at our center, and 9 reoperations performed at our center on patients whose first surgery was performed elsewhere. Only endonasal procedures were included, and craniotomies were excluded from analysis. Per institutional protocol, patients underwent preoperative and daily sodium checks while hospitalized after surgery, with outpatient checks as needed.

Preoperative Variables Recorded
Parameters recorded for each case included lesion size, patient age and sex, number of prior pituitary surgeries, endonasal surgical approach (966 microscopic operations vs 49 endoscopic), lesion type (endocrine-inactive adenoma, endocrine-active adenoma, Rathke’s cleft cyst, apoplexy, craniopharyngioma, or other), lesion location (sellar, suprasellar, or sellar with suprasellar extension), and the presence of preoperative hypopituitarism as evidenced by low levels of an anterior pituitary lobe lab value.

Postoperative Variables Recorded
Postoperative variables were recorded by 2 independent reviewers to reduce bias. Postoperative hyponatremia was defined as a serum sodium below normal (less than 135 mEq/L) occurring within 30 days of surgery. Diagnosis of diabetes insipidus (DI) was determined based on urine specific gravity (less than 1.005) or treatment with desmopressin. Temporary DI was defined in patients who had a postoperative need to take desmopressin that eventually resolved (longest duration 63 days), while persistent DI was defined as a postoperative need for a patient to take at least daily desmopressin that was still present at the time of last follow-up (median 24 months). Eighteen patients received radiation (1 received radiosurgery and 17 received radiation therapy) a median of 40 days after a surgery and a mean of 21 months before a reoperation. This variable was recorded and analyzed as a risk factor for morbidity of reoperation. New postoperative hypopituitarism was identified as low levels of an anterior pituitary hormone that were normal before surgery. Of note, postoperative pituitary laboratory values were not recorded in 72 patients (61 initial operations and 11 reoperations). Records were retrospectively reviewed to verify length of stay (LOS) after each transsphenoidal surgery, postoperative meningitis confirmed by CSF culture, and postoperative CSF leak requiring surgical repair.

Statistical Analysis
Analysis of variance was used for parametric comparisons of more than 2 variables when the dependent variable was continuous, while a chi-square test was used to compare more than 2 proportions. Parametric comparison between 2 variables was performed using the Student t-test. Fisher’s exact test was used to compare 2 proportions; p values are 2-tailed and p < 0.05 was considered statistically significant. Binary logistic regression was used to correlate preoperative variables with postoperative morbidities, with Bonferroni adjustment used when assessing statistical significance. Multivariate logistic regression was used to correlate preoperative variables with postoperative LOS, with Bonferroni adjustment used when assessing statistical significance.

Results
Participants
The mean age of the 916 patients before the 1015 operations was 46 years (range 3–93 years). There were 513 female patients (56%). The mean lesion size was 1.94 cm (range 3 mm to 6.7 cm). Diagnoses included endocrine inactive (30%) or active (36%) adenomas, craniopharyngioma (3%), Rathke’s cleft cysts (10%), and miscellaneous pathology (20%).

Characteristics of Patients and Lesions Requiring Reoperation
Of 916 patients, 90 patients underwent 108 reoperations (90 second operations; 11 third; 4 fourth; and 3 fifth, sixth, and seventh combined). Reoperations occurred a mean of 49 months after the preceding transsphenoidal operation (median 31 months [range 2–212 months]). Second surgeries occurred a mean of 54 months after the first operation (median 33 months [range 2–212 months]), and third surgeries occurred a mean of 54 months after the first operation (median 36 months [range 14–183 months]). Pathologies at first operation included endocrine active pituitary adenomas in 344 patients (36%), nonfunctional adenomas in 277 patients (30%), Rathke’s cleft cysts in 93 patients (10%), craniopharyngiomas in 27 patients (3%), and miscellaneous pathologies in 185 patients (20%). Pathologies requiring reoperation included endocrine active pituitary adenomas in 19 patients (21%), nonfunctional adenomas in 29 patients (32%), Rathke’s cleft cysts in 7 patients (8%), craniopharyngiomas in 9 patients (10%), and miscellaneous pathologies in 26 patients (29%), with craniopharyngioma and miscellaneous pathologies the only pathologies more frequent among reoperation cases than cases not requiring reoperation (p < 0.05; Fig. 1). Fifty-six percent of patients undergoing reoperation were female (n = 50) with a mean age of 45 years, while 56% of patients never requiring reoperation were female (p = 0.9) and had a mean age of 47 years (p = 0.3) (Table 1). Patients entered their operation with hypopituitarism 27% of the time (269 of 1015 cases), including 26% before first (236 of 907 cas-
es), 30% before second (27 of 90 cases), and 33% before third through seventh operations (6 of 18 cases) (p = 0.5).

Intraoperative and Postoperative Parameters Associated With Initial Surgery Versus Reoperation for All Pathologies

No carotid artery injuries occurred, and there was 1 death within the first 30 postoperative days, which occurred in a patient undergoing initial surgery. Operative time for initial surgeries averaged 121 minutes (range 45–631 minutes), and for reoperations it averaged 129 minutes (range 40–358 minutes) (p = 0.3). Postoperative lumbar drainage was used after 272 initial operations (30%) and after 34 reoperations (31%) (p = 0.7). The mean length of stay increased from 2.8 days after initial transsphenoidal surgery to 4.5 days after repeat transsphenoidal surgery (p = 0.006; Table 2 and Fig. 2).

Morbidity of Reoperation for All Pathologies

Among patients without preoperative DI, transient or permanent DI occurred after 145 (16%) of 905 initial operations, which was less than 20 (25%) of 80 repeat transsphenoidal surgeries leading to postoperative DI (p = 0.04; Table 2 and Fig. 3). Postoperative hypotenatremia occurred with equal frequency after repeat transsphenoidal surgery (20%, n = 22) as after initial transsphenoidal surgery (16%, n = 149) (p = 0.3), but occurred more specifically after the third transsphenoidal surgery and beyond (50%, n = 9; p < 0.001; Table 2). New postoperative hypopituitarism in an endocrine axis documented to be normal prior to the operation in question occurred after 73 initial transsphenoidal surgeries (8%) versus 5 repeat transsphenoidal surgeries (p = 0.3; Table 2 and Fig. 2).

Cerebrospinal fluid leak requiring repair occurred after 9 initial operations (1%), less than the 4% of repeat transsphenoidal surgeries (n = 4) for which postoperative CSF leak repair was needed (p = 0.04; Table 2 and Fig. 2). Postoperative meningitis occurred after 4 initial (0.4%) and 3 repeat transsphenoidal surgeries (3%) (p = 0.02; Table 2 and Fig. 2), with no patients experiencing more than 1 episode of postoperative meningitis.

**TABLE 1: Comparisons between preoperative characteristics of all patients at the time of initial surgery, patients at initial surgery who went on to need reoperation(s), and patients at initial surgery who did not end up needing reoperation*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>Patients Requiring Reop</th>
<th>Patients Undergoing Only 1 Op</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>916 (100)</td>
<td>90 (10)</td>
<td>826 (90)</td>
<td>0.9</td>
</tr>
<tr>
<td>no. of females</td>
<td>513 (56)</td>
<td>50 (56)</td>
<td>463 (56)</td>
<td>0.9</td>
</tr>
<tr>
<td>mean age in yrs (range)</td>
<td>46 (3–93)</td>
<td>45 (3–85)</td>
<td>47 (4–93)</td>
<td>0.3</td>
</tr>
<tr>
<td>mean lesion size in cm (range)</td>
<td>1.9 (0.1–6.7)</td>
<td>2.1 (0.3–6.2)</td>
<td>1.9 (0.3–6.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>type of pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>endocrine active adenoma</td>
<td>334 (36)</td>
<td>19 (21)</td>
<td>315 (38)</td>
<td>0.001</td>
</tr>
<tr>
<td>endocrine inactive adenoma</td>
<td>277 (30)</td>
<td>29 (32)</td>
<td>248 (30)</td>
<td>0.7</td>
</tr>
<tr>
<td>Rathke’s cleft cyst</td>
<td>93 (10)</td>
<td>7 (8)</td>
<td>86 (10)</td>
<td>0.6</td>
</tr>
<tr>
<td>craniopharyngioma</td>
<td>27 (3)</td>
<td>9 (10)</td>
<td>18 (2)</td>
<td>0.0006</td>
</tr>
<tr>
<td>miscellaneous</td>
<td>185 (20)</td>
<td>26 (29)</td>
<td>159 (19)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Values are number of patients (%) unless noted otherwise.
† Patients requiring reoperation versus patients undergoing one (and only one) operation.
A 3-category analysis revealed that mean LOS increased from 2.8 days after initial transsphenoidal surgery to 4.3 days after second transsphenoidal surgery to 6.9 days after third through seventh transsphenoidal surgeries (p < 0.001; Table 2 and Fig. 3). Of CSF leak requiring repair, postoperative DI, postoperative meningitis, postoperative hyponatremia, and new postoperative hypopituitarism, only hyponatremia increased in frequency from the initial operation to the reoperation.
Morbidity of repeat pituitary surgery

first to the second to subsequent transsphenoidal surgeries (p < 0.001; Table 2 and Fig. 3).

We then performed multivariate analyses correlating preoperative risk factors and morbidities. The preoperative risk factors we analyzed were operation number for the patient, pathology, age, sex, lesion size, suprasellar extension, surgical method (microscopic vs endoscopic), and whether the patient received radiation therapy for the sellar pathology prior to surgery. The 4 morbidities we analyzed were DI, LOS, CSF leak, and meningitis. These multivariate analyses revealed that, after adjusting for multiple testing, increasing the number of operations in a patient increased the risk of increased LOS, CSF leak, and meningitis occurring in that patient (Tables 3–6).

Morbidity of Reoperating on Recurrent Pituitary Adenomas and Rathke’s Cleft Cysts

While multivariate analysis suggested that our findings were occurring independent of pathology, to more definitively focus on the typical benign pathologies seen in the pituitary gland, we analyzed the morbidity of the first (n = 698) versus repeat (n = 34) transsphenoidal surgeries performed on the nonfunctional and endocrine inactive pituitary adenomas and Rathke’s cleft cysts taken from this series. While LOS increased from initial surgery to reoperation when all pathologies were combined, the increase was not statistically significant when analyzing only pituitary adenomas and Rathke’s cleft cysts (2.5 vs 2.3 days; p = 0.8; Fig. 4). The increased incidence of meningitis seen with reoperation when all pathologies were combined also was no longer statistically significant when analyzing only pituitary adenomas and Rathke’s cleft cysts (0.3% vs 3%)

TABLE 3: Results of binary logistic regression correlating preoperative variables with the postoperative complication of meningitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>op no.</td>
<td>0.005*</td>
<td>1.6</td>
</tr>
<tr>
<td>sex</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>age at surgery</td>
<td>0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>microscopic vs endoscopic</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>pathological diagnosis</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>preop radiation</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>size</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>suprasellar extension</td>
<td>0.1</td>
<td>11.5</td>
</tr>
</tbody>
</table>

* Operation number met criteria for statistical significance after Bonferroni adjustment (p < 0.006).
The increased DI after repeat transsphenoidal surgery has yet to be examined in detail, making it unclear whether the operation retains its initial excellent safety profile when used for recurrent lesions. We found that, after 1015 pituitary operations, reoperation was associated with an increased incidence of DI, CSF leak, and meningitis, along with increased LOS.

The increased DI after repeat transsphenoidal surgery likely reflects increasing difficulty in preserving the neurovascular structures of the hypothalamus, infundibulum, and neurohypophysis amid the scar tissue found at each subsequent reoperation. Increased meningitis and CSF leak associated with repeat surgery likely reflects increasing difficulty in obtaining a successful resection while preserving the diaphragm sellae, which separates CSF from the resection cavity throughout the immediate postoperative period. Increasing LOS could reflect increasing development of DI delaying discharge or the increased postoperative hypopituitarism we noted to occur after the third transsphenoidal surgery and beyond.

Most previous studies of repeat transsphenoidal surgery have focused on operations for specific hormonally active tumors, like acromegaly or Cushing’s disease. These studies have generally focused on rates of remission and radiographic extent of resection associated with repeat surgery and have usually not commented on the morbidity of repeat surgery, except for a study of repeat surgery for 14 patients with acromegaly in which 2 patients experienced postoperative meningitis and 2 patients experienced new postoperative pituitary deficits. Other studies looked at the use of image guidance to avoid vascular injury during repeat transsphenoidal surgery, and the use of the endoscope at the time of repeat surgery for 12 and 20 patients as a means of increasing the field of view to counteract any challenges associated with repeat surgery, with the latter study reporting CSF leak requiring repair after one of 20 reoperations. A 1985 study of 158 patients undergoing transsphenoidal surgery after prior therapy (including radiation alone) included heterogeneous pathology and found a 3% rate of 30-day postoperative mortality, 1% rate of vascular injury, 1% rate of meningitis, 6% postoperative rate of CSF leak requiring repair, 7% rate of permanent DI, and 8% rate of new hypopituitarism. Our study adds to this literature by specifically comparing the morbidity of repeat surgery with that of first surgeries performed contemporaneously at the same center in a larger number of patients.

In finding somewhat increased morbidity associated with repeat transsphenoidal surgery in a large cohort of patients, our study joins examples of increased morbidity associated with other repeat neurosurgical and nonneurosurgical procedures. Repeat craniotomy for glioblastoma was shown to be more frequently associated with increased infection than was initial craniotomy as part of

**TABLE 4: Results of multivariate linear regression correlating preoperative variables with the postoperative length of stay**

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>op no.</td>
<td>0.002*</td>
<td></td>
</tr>
<tr>
<td>sex</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>age at surgery</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>microscopic vs endoscopic</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>pathological diagnosis</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>preop radiation</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>size</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>suprasellar extension</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

* Operation number and microscopic versus endoscopic met criteria for statistical significance after Bonferroni adjustment (p < 0.006).
Morbidity of repeat pituitary surgery

Similarly, increased morbidity has been demonstrated for revision bariatric surgery. These findings of increased morbidity with repeat transsphenoidal surgery have significant implications on cost and quality assessments for hospitals, insurers, and patients. The factor that we identified to be increased with reoperation that would likely exert the greatest impact on the cost of repeat transsphenoidal surgery is increased length of stay. In our hospital, a non-ICU room costs $1519 per day, making it easy to see how hospital costs can become dramatically higher for repeat transsphenoidal surgery patients. Furthermore, given that many insurance reimbursements are fixed bundled payments, this may translate into an increasing cost that is assumed by the hospital. The other morbidities that are associated with repeat transsphenoidal surgery, like DI or CSF leak, would lead to 30-day readmissions that are not only costly, but are also being increasingly assessed by Medicare and other insurance companies as measures of quality.

While we did not specifically examine the degree to which reoperation provided control of recurrent pituitary lesions, previous work from our group has shown that reoperation provides excellent control of recurrent endocrine inactive adenomas and work from other groups has shown that reoperation provides excellent control of recurrent endocrine active adenomas, suggesting that recurrent adenomas are not significantly more aggressive than at the time of diagnosis.

Based on the excellent control provided by repeat transsphenoidal surgery in these reports, the significant increase in morbidity we identified in repeat transsphenoidal surgery, while worthy of counseling patients about preoperatively, will be unlikely to alter the risk versus benefit considerations for most patients considering repeat transsphenoidal surgery. However, because the benefit of repeat versus initial transsphenoidal surgery and the role of alternative treatments for recurrences like radiation therapy will likely depend on multiple factors specific to each case, deciding whether the benefits of repeat transsphenoidal surgery outweigh the increased risks we identified will likely need to be done on a case-by-case basis.

As with most retrospective studies, the lack of prospective enrollment limits the reliability with which surgical morbidity is documented compared with prospective trials. For example, the lack of prospective enrollment specifically means that postoperative sodium levels were checked until discharge but only in cases in which electrolyte abnormality was suspected after discharge. Furthermore, since our study involves a single institution, it limits the strengths of our conclusions, as some of our findings could be attributable to factors specific to our center.

Our results arise from 2 neurosurgeons performing a total of approximately 200 surgeries per year over a 5-year period.
interval who worked closely with the same endocrinologist during that period. Because our team had experience managing pituitary tumors prior to the formation of the center, our study of cases since the center formed is not equipped to determine the effect of an operative learning curve and the reported role of neurosurgeon experience in reducing the rate of morbidity of repeat pituitary surgery, particularly DI after transsphenoidal surgery. Comparisons of results from multiple sites will be needed to investigate if the recent suggestion that neurosurgeons working with endocrinologists at dedicated pituitary centers of excellence could reduce morbidity is applicable to either first-time or repeat pituitary surgery.

Conclusions

We found that repeat transsphenoidal surgery was associated more frequently with postoperative DI and meningitis and greater LOS, with morbidity increasing with each subsequent operation. These results provide a framework for neurosurgeons discussing reoperation for pituitary disease with their patients. These patients are already familiar with the risks of transsphenoidal surgery, and the information we derived about the degree to which these risks increase with reoperation should be valuable for these patients and their providers.

Disclosure

Arman Jahangiri is a Howard Hughes Medical Institute Research Fellow. 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: Aghi. Acquisition of data: Jahangiri, Wagner, SW Han, SJ Han, Tran, Miller, Tom. Analysis and interpretation of data: Aghi, Jahangiri, Wagner, Zygoarakis. Drafting the article: Aghi, Jahangiri. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Aghi. Statistical analysis: Aghi, Jahangiri.

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