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# Repeat endoscopic transsphenoidal surgery for acromegaly: remission and complications

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**Abstract** Reported biochemical remission rates following surgical intervention for acromegaly range from 38 to 83 %. In patients not achieving surgical remission, few options remain, mostly limited to medical management and radiation therapy. There is debate over whether or not to offer reoperation to patients in whom surgical remission is not achieved with initial resection. Retrospective chart review was undertaken to determine all patients having acromegaly with persistently elevated GH and/or IGF-1 levels after initial pituitary adenoma resection, and who underwent reoperation using endoscopic endonasal approach at a single institution. Biochemical remission was defined as a postoperative GH level <1 ng/mL and a normal postoperative IGF-1 level in the absence of any medical therapy. In total, 14 patients underwent repeat surgical intervention for acromegaly via endoscopic transsphenoidal approach. Of the 14 patients, 8 (57 %) achieved biochemical remission following repeat surgical intervention. Lower preoperative GH levels were associated with greater chance of biochemical remission ($P = 0.048$). New endocrinopathies were seen in 2 patients (14 %), and both were transient diabetes insipidus. Meningitis occurred in 2 patients (14 %); both were aseptic meningitis with no sequelae. No mortality was encountered. Repeat surgical intervention for acromegaly via endoscopic transsphenoidal approach appears safe and effective. With no mortality and minimal morbidity, repeat surgical intervention via endoscopic transsphenoidal approach appears a reasonable option for these hard-to-treat patients and should be considered for patients in whom surgical remission is not achieved with initial surgery.

**Keywords** Acromegaly · Endoscopic endonasal · Pituitary

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## Introduction

Acromegaly is most commonly caused by pituitary adenomas that are growth hormone (GH)-secreting. The consequences of chronic, excessive GH are profound. In fact, acromegalics have a significant reduction in life expectancy, but the standardized mortality ratio returns to that of the normal population if GH levels are normalized [1, 2]. Various methods of treatment have been used for acromegaly including surgical pituitary adenomectomy, radiation therapy, and medical management. In 2010, consensus guidelines were established for defining remission [3]. According to these guidelines, remission is defined as a normal insulin-like growth factor (IGF)-1 level and a GH nadir during oral glucose tolerance testing of less than 0.4 ng/mL or a random GH level of less than 1.0 ng/mL [3].

Surgical intervention with pituitary adenomectomy offers a chance for cure. Reported rates of biochemical remission following surgical intervention vary between 34 and 83 % [4–14]. Across most previous studies, microadenomas have tended to be more responsive to surgical treatment than macroadenomas, though size has not been consistently reported to be predictive of biochemical remission. Factors reported to be associated with increased likelihood of biochemical remission include lower Knosp score, preoperative GH level, and preoperative IGF-1 level [12]. When biochemical remission is not achieved with

initial resection, patients are left with few options. Medical management and radiotherapy are costly and variably effective options. There is continuing debate as to whether a second attempt at resection should be undertaken. In this study, our aim was to examine outcomes for acromegalics undergoing a second attempt at resection utilizing a pure endoscopic endonasal transsphenoidal method after failing to achieve biochemical remission following an initial resection.

## Methods

### Study design

This cohort study was approved by the University of Michigan Institutional Review Board, and data were obtained by retrospective review of medical records including radiographic images. Information technology personnel designed and implemented a search paradigm to query the University of Michigan information systems and electronic medical records to identify all adult patients (18 years of age or older) who underwent transsphenoidal resection of a pituitary adenoma and were diagnosed with acromegaly between January 1, 2003 and April 1, 2012. From this list of patients, the medical records were reviewed to identify all patients who underwent a second attempt at resection utilizing a pure endoscopic endonasal transsphenoidal method after failing to achieve biochemical remission following an initial resection.

### Variables of interest

The following data were abstracted from the medical record or radiographic images: age at time of operation, sex, Knosp score, adenoma size, preoperative GH level, preoperative IGF-1 level, evidence of postoperative biochemical remission, and complications including postoperative pituitary dysfunction, meningitis, intraoperative carotid injury, postoperative visual deficit, and cerebrospinal fluid (CSF) leak. Biochemical remission was defined according to the 2010 consensus guidelines, with a normal IGF-1 level and a GH nadir during oral glucose tolerance testing of less than 0.4 ng/mL or a random GH level of less than 1.0 ng/mL [3]. Knosp scoring was accomplished using preoperative magnetic resonance imaging (MRI) coronal T1-weighted, gadolinium-enhanced sequences [15]. Size was measured using the adenoma's largest dimension on axial, sagittal, or coronal T1-weighted, gadolinium-enhanced MRI sequences.

### Surgical approach

All patients underwent repeat operation via pure endoscopic endonasal transsphenoidal approach using a binarial, 3-hand technique. Frameless stereotactic image-guidance was used in all cases. No CSF diversion was used preoperatively or as routine practice postoperatively.

### Postoperative management

All patients were placed on a standard hydrocortisone taper postoperatively and discharged on maintenance hydrocortisone (10 mg orally every morning and 5 mg orally daily at noon). Hydrocortisone was then discontinued 2 days prior to follow-up and pituitary function was assessed. While in the hospital, patients were closely monitored for diabetes insipidus by following fluid input and output, serum sodium levels, and urinary specific gravity. Patients requiring desmopressin were considered to have diabetes insipidus.

### Statistical analysis

Statistical analysis was performed using commercially available software (SPSS version 18, IBM Corporation, Somers, NY). Univariate comparison of continuous variables with a normal distribution was assessed using 2-sample $t$ tests, and continuous variables not meeting the normality assumption were assessed using the Mann–Whitney $U$ test. All categorical data were assessed by $\chi^2$ test or Fisher exact test, as appropriate. Logistic regression was used to test univariate associations between our variables of interest and the dichotomous outcome of biochemical remission. For all statistical analyses, $P < 0.05$ was considered significant.

## Results

### Baseline characteristics

During the study period, 14 patients underwent repeat operation for acromegaly utilizing the endoscopic endonasal transsphenoidal approach after biochemical remission was not achieved following the first operation. Of these patients, 13 (93 %) underwent initial operation using the microscopic transsphenoidal approach, while only 1 (7 %) patient had a subfrontal craniotomy. Table 1 details baseline preoperative characteristics of the cohort including age, sex, preoperative adenoma size, preoperative Knosp score, preoperative GH level, and preoperative IGF-1 level. Of the 14 patients, 9 (64 %) failed medical management using either lanreotide or octreotide prior to repeat surgical

**Table 1** Baseline demographics and univariate statistics of patients undergoing reoperation for acromegaly utilizing a pure endoscopic endonasal transsphenoidal approach

| Baseline demographics | Entire cohort (N = 14) | Remission (n = 8) | No remission (n = 6) | *P* value |
|---|---|---|---|---|
| Age (years) | 41.4 (13.3) | 45.1 (9.3) | 36.5 (17.0) | 0.244 |
| Sex | | | | 0.640 |
| Female | 8 (57 %) | 5 (63 %) | 3 (50 %) | |
| Male | 6 (43 %) | 3 (37 %) | 3 (50 %) | |
| Adenoma size (mm) | 13.4 (7.8) | 15.3 (9.1) | 10.8 (5.3) | 0.326 |
| Knosp score (median, IQR) | 2 (2) | 2.5 (2) | 2 (3) | 0.344 |
| GH level (ng/mL) | 8.9 (6.1) | 5.3 (4.1) | 13.6 (5.1) | 0.005 |
| IGF-1 level (ng/mL) | 810.5 (425.0) | 544.6 (210.9) | 1 165.0 (378.7) | 0.002 |

*GH* growth hormone, *IGF-1* insulin-like growth factor 1, *IQR* interquartile range

intervention, and 2 (14 %) had radiotherapy prior to repeat surgical intervention.

### Biochemical remission and complications

Of the 14 patients included in the study, 8 (57 %) achieved biochemical remission postoperatively. Age, sex, adenoma size, and Knosp score were similar in those achieving remission and those not achieving remission, while preoperative GH and IGF-1 levels were significantly lower in those patients achieving remission (Table 1). No patients sustained carotid injuries, developed CSF leaks, or had new postoperative visual deficits. New endocrinopathies were seen in 2 patients (14 %); both were transient diabetes insipidus. No permanent new endocrinopathies were seen. Meningitis was seen in 2 patients (14 %); both were found to be aseptic meningitis with no sequelae. There was no mortality seen in these patients.

### Predictors of biochemical remission

Table 2 shows bivariate logistic regression analysis of predictors of biochemical remission. Age, sex, adenoma size, and Knosp score were not associated with increased likelihood of remission. There was a strong trend toward lower preoperative IGF-1 levels being associated with increased likelihood of remission, although this did not reach statistical significance. The only factor significantly associated with increased likelihood of remission was lower preoperative GH levels. In patients achieving remission, 7 of 8 patients (88 %) had a GH level less than 10 ng/mL, compared to 5 of 6 (83 %) patients who did not achieve remission and had a GH level greater than 10 ng/mL.

**Table 2** Predictors of biochemical remission using bivariate logistic regression

| | Odds ratio (95 % confidence interval) | *P* value |
|---|---|---|
| Age | 1.060 (0.962–1.167) | 0.238 |
| Sex | 1.667 (0.195–14.266) | 0.641 |
| Adenoma size | 1.113 (0.899–1.378) | 0.326 |
| Knosp score | 1.618 (0.625–4.188) | 0.322 |
| GH level | 0.672 (0.453–0.997) | 0.048 |
| IGF-1 level | 0.993 (0.986–1.000) | 0.056 |

GH = growth hormone; IGF-1 = insulin-like growth factor 1

## Discussion

Pituitary adenomectomy remains the first-line treatment for most acromegalic patients. However, patients in whom biochemical remission is not achieved following the initial operation have few options. Achieving biochemical remission is important, as patients with normalized GH and IGF-1 levels have their standardized mortality ratio return to that of the normal population [1, 2]. Options for these patients include medical management and radiotherapy, and possibly repeat attempt at surgical intervention. An on-going debate exists concerning the appropriateness of attempting a second resection. In this study, we found that utilizing the endoscopic endonasal transsphenoidal approach for repeat pituitary adenomectomy was associated with rates of biochemical remission similar to that of the initial operation and had low morbidity and mortality.

Radiotherapy is one alternative option to surgery. Previous studies suggest that the rate of biochemical remission following radiotherapy ranges from 5 to 70 % (mean, 45 %). In those who achieve it, the average time to remission ranges between 5 and 10 years [16–23]. Most of these studies were published with less-strict remission criteria than the current consensus guidelines. One risk following radiotherapy is the development of panhypopituitarism. These published studies suggest rates ranging from 8 to 80 % [16–23]. Stereotactic radiosurgery has also become an option as opposed to conventional radiotherapy. Stereotactic radiosurgery has similar remission rates, reportedly ranging from 17 to 96 % (mean, 44.6 %), and are based on less-strict criteria [16, 24–32]. The advantages of stereotactic radiosurgery include faster time to remission

(ranging from 2 to 5 years) and less panhypopituitarism (ranging from 0 to 34 %) [16, 24–32].

Similarly, medical management using somatostatin analogs (lanreotide and octreotide) or GH receptor antagonists (pegvisomant) is an additional alternative for patients who fail to achieve biochemical remission. For all patients on medical therapy, reported biochemical remission rates vary from 38 to 79 % for somatostatin analogs (mean, 44 % with lanreotide and 50 % with octreotide) [16, 33–42]. The most commonly reported side effects are gastrointestinal in nature, including diarrhea, abdominal pain, and cholelithiasis.

Our data indicate that repeat pituitary adenomectomy for patients failing to achieve biochemical remission with initial surgery has remission rates similar to initial surgery and likely better than radiotherapy or medical management when all patients are included. In our study, 57 % of patients achieved biochemical remission when repeat operation utilizing an endoscopic endonasal transsphenoidal approach was undertaken. While achieving similar remission rates, morbidity was low and there was no mortality. Morbidity was particularly low with respect to pituitary function. Only 14 % of patients had temporary endocrinopathies with no permanent endocrinopathies in this series. While in a larger series it is unlikely that no new endocrinopathies will occur, this low rate seems to have a significant advantage over radiotherapy.

While remission rates for repeat operation were similar, it is possible that remission rates would be higher if repeat operation were considered first-line therapy. The current practice pattern is to offer medical management and/or radiotherapy to patients failing to achieve biochemical remission after initial resection. In our series, 64 % of patients failed to achieve biochemical remission with medical management and 14 % failed with radiotherapy. This practice pattern means that the patients undergoing repeat operation are likely the most resistant to therapy. In addition, patients undergoing medical management or radiotherapy that are successful with these therapies never undergo repeat operation and may be the population of patients most likely to respond to repeat resection. Thus, achieving remission rates comparable to initial resection and other treatment modalities in what is likely the most hard-to-treat population while excluding the patients that may be most likely to respond to therapy suggests that if reoperation was the first-line consideration, remission rates may actually be even higher. Further data are needed to evaluate reoperation as first-line therapy for patients failing to achieve biochemical remission with initial operation.

Comparable remission rates and low morbidity and mortality suggest repeat operation using the endoscopic endonasal transsphenoidal approach should be considered. With similar outcomes, cost-effectiveness data also suggest repeat operation should be considered. The average lifetime cost for patients undergoing transsphenoidal resection is $39,311 [16]. Stereotactic radiosurgery is only slightly more expensive with an average lifetime cost of $56,356 [16]. Medical management is markedly more expensive. The average lifetime cost for patients managed with octreotide is $1,667,052, with lanreotide $1,578,567, and with pegvisomant $2,620,833 [16]. Thus, with comparable, and arguably even better, outcomes with transsphenoidal resection, the cost data certainly favors routine utilization of transsphenoidal resection.

Identifying predictors of biochemical remission following repeat transsphenoidal surgery would be useful in counseling patients regarding management options. A number of factors have reportedly been associated with increased likelihood of biochemical remission including lower preoperative GH level, lower preoperative IGF-1 level, lower Knosp score, and smaller size of the adenoma [12]. These data apply to all patients undergoing transsphenoidal resection of a pituitary adenoma for acromegaly and are not specific to those undergoing repeat operation. In this study, we found that a lower preoperative GH level was associated with increased likelihood of biochemical remission. No GH cutoff was found where patients strictly stratified into those achieving remission and those not achieving remission. However, 88 % of patients achieving remission had a GH level less than 10 ng/mL, while 83 % of patients not achieving remission had a GH level greater than 10 ng/mL. Thus, it appears that patients with a GH level of less than 10 ng/mL can be counseled that they have a strong likelihood of achieving biochemical remission. There was a strong trend toward lower IGF-1 levels being associated with increased likelihood of remission, but this did not reach statistical significance and we did not find any association between age, sex, adenoma size, or Knosp score. Additional data are needed to clarify factors associated with increased likelihood of biochemical remission in patients undergoing repeat operation in order to better counsel patients on their options.

## Conclusions

Repeat surgical intervention for acromegaly utilizing the endoscopic transsphenoidal approach appears safe and effective. This approach offers surgical remission rates similar to initial surgical intervention, according to the published literature. With no mortality and minimal morbidity, repeat surgical intervention via the endoscopic transsphenoidal approach appears to be a reasonable option for these often hard-to-treat patients and should be considered part of the clinical armamentarium for patients in whom surgical remission is not achieved with initial surgery.

**Conflict of interest** The authors have no conflicts of interest to report pertaining to the materials or methods used in this study or the findings specified in this paper.

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