Silent corticotroph pituitary adenomas: clinical characteristics, long-term outcomes, and management of disease recurrence

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OBJECTIVE Silent corticotroph adenomas (SCAs) are a distinct subtype of nonfunctioning pituitary adenomas (NFAs) that demonstrate positive immunohistochemistry for adrenocorticotropic hormone (ACTH) without causing Cushing’s disease. SCAs are hypothesized to exhibit more aggressive behavior than standard NFAs. The authors analyzed their institution’s surgical experience with SCAs in an effort to characterize rates of invasion, postoperative clinical outcomes, and patterns of disease recurrence and progression. The secondary objectives were to define the best treatment strategies in the event of tumor recurrence and progression.

METHODS A retrospective analysis of patients treated at the authors’ institution identified 100 patients with SCAs and 841 patients with NFAs of other subtypes who were treated surgically from 2000 to 2019. Patient demographics, tumor characteristics, surgical and neuroimaging data, rates of endocrinopathy, and neurological outcomes were recorded. Cohorts of patients with SCAs and patients with standard NFAs were compared with regard to these characteristics and outcomes.

RESULTS The SCA cohort presented with cranial neuropathy (13% vs 5.7%, p = 0.0051) and headache (53% vs 42.3%, p = 0.042) compared to the NFA cohort, despite similar rates of apoplexy. The SCA cohort included a higher proportion of women (SCA 60% vs NFA 45.8%, p = 0.0071) and younger age at presentation (SCA 50.5 ± 13.3 vs NFA 54.6 ± 14.9 years of age, p = 0.0082). Reoperations were comparable between the cohorts (SCA 16% vs NFA 15.7%, p = 0.98). Preoperative pituitary function was comparable between the cohorts with the exception of higher rates of preoperative panhypopituitarism in NFA patients (2% vs 6.1%, respectively; p = 0.0033). The mean tumor diameter in SCA patients was 24 ± 10.8 mm compared to 26 ± 11.3 mm in NFA patients (p = 0.05). Rates of cavernous sinus invasion were higher in the SCA group (56% vs 49.7%), although this result did not reach statistical significance. There were no significant differences in extent of resection, intraoperative CSF leak rates, endocrine or neurological outcomes, or postoperative complications. Ki-67 rates were significantly increased in the SCA cohort (2.88 ± 2.79) compared to the NFA cohort (1.94 ± 1.99) (p = 0.015). Although no differences in overall rates of progression or recurrence were noted, SCAs had a significantly lower progression-free survival (24.5 vs 51.1 months, p = 0.0011). Among the SCA cohort, progression was noted despite the use of adjuvant radiosurgery in 33% (n = 4/12) of treated tumors. Adequate tumor control was not achieved in half (n = 6) of the SCA progression cohort despite radiosurgery or multiple resections.

CONCLUSIONS In this study, to the authors’ knowledge the largest surgical series to assess outcomes in SCAs to date, the findings suggest that SCAs are more biologically aggressive tumors than standard NFAs. The progression-free survival duration of patients with SCAs is only about half that of patients with other NFAs. Therefore, close neuroimaging and clinical follow-up are warranted in patients with SCAs, and residual disease should be considered for early postoperative adjuvant radiosurgery, particularly in younger patients.

https://thejns.org/doi/abs/10.3171/2020.10.JNS203236

KEYWORDS silent corticotroph adenoma; nonfunctioning pituitary adenoma; pituitary surgery; adenoma recurrence; adjuvant therapy
SILENT corticotroph adenomas (SCAs) are pituitary tumors that stain positive for adrenocorticotropic hormone (ACTH) but do not produce biochemical levels of excess ACTH or cortisol. These tumors account for approximately 20% of all corticotroph adenomas and 5.5% of nonfunctioning pituitary adenomas (NFAs). In 2017, the WHO classified SCAs as a high-risk subtype due to their observed aggressive behavior. The recent reclassification system of pituitary adenomas has described seven morphofunctional types and three lineages, with corticotrophs belonging to the pituitary-restricted transcription factor (TPIT) lineage.

Although SCAs are commonly accepted as a distinct subtype of NFAs, conflicting data have been reported with respect to patient demographics, tumor size, rates of cavernous sinus invasion, and recurrence. As the incidence of SCAs is low and requires immunohistochemistry for diagnosis, much of the reported literature is restricted to small case series. Even fewer studies report results related to SCA recurrence and progression, which are critical to understanding the pathophysiology of this unique subtype of potentially aggressive pituitary adenoma.

We aimed to address these questions by describing our institutional experience at a tertiary academic pituitary center managing patients with SCAs. We report what is to our knowledge the largest single-institution series of SCA patients managed surgically across 2 decades, with a comparison cohort of NFAs. Our objectives were to observe patterns of disease invasion, progression, and recurrence in SCA patients. We further aimed to synthesize best practice strategies in the event of residual tumor or tumor progression.

Methods
Data Collection
We retrospectively identified all adult patients who underwent pituitary tumor resection performed by the two senior authors (M.W. and G.Z.) between January 2000 and December 2019. Patients were included in the study if their underlying histopathology was consistent with either SCA or NFA, SCA was defined as immunoreactivity for ACTH in patients presenting without clinical or laboratory features of hypercortisolism or Cushing’s syndrome. NFA was defined as negative immunoreactivity for ACTH, prolactin, or growth hormone without evidence of hormonal hypersecretion, except hyperprolactinemia consistent with pituitary stalk effect. A neuropathologist reviewed all tumor samples on H&E staining and immunohistochemistry.

Clinical records, hospital charts, and neuroimaging studies were reviewed through the last available follow-up for patients with both SCA and NFA. Medical histories, operative notes, and patient hospital courses were also reviewed. Retrospectively collected data included patient age, sex, presenting symptoms, presenting endocrinopathies, extent of tumor invasion, surgical approach utilized for resection, histopathologic findings, postoperative complications, and cases of tumor recurrence identified based on follow-up imaging. Cavernous sinus invasion was defined by a neuroradiologist using the Knosp criteria, in which tumors with Knosp grades 3 and 4 were considered invasive. Approval for this study was granted by our institutional review board. Given the retrospective nature of this study, informed consent of included patients was not required.

Extent of Resection and Recurrence
All patients underwent preoperative MRI. Postoperative MR images were obtained 3 months after surgery and then annually thereafter. Gross-total resection (GTR) was defined as the absence of enhancing residual tumor on 3-month postoperative MRI. Subtotal resection (STR) was defined as any enhancing residual tumor identified by a radiologist on the 3-month postoperative MRI. In the event of an STR requiring expedited adjuvant radiation or radiosurgery, MRI was obtained during the initial hospitalization. Tumor progression was defined as an increase in tumor volume on follow-up imaging. Tumor recurrence was defined as new tumor identified on MRI following GTR. Progression-free survival (PFS) was defined by the first evidence of radiographic tumor progression or recurrence following initial resection. In the event of tumor progression or recurrence, a weekly multidisciplinary conference including neurosurgery, endocrinology, and radiation oncology physicians was held to decide whether serial observation, additional surgery, or stereotactic radiosurgery (SRS) would be the most advisable treatment.

Endocrine Evaluation
Preoperative endocrine panels including serum levels of cortisol, prolactin, thyroid-stimulating hormone, free thyroxine, follicle-stimulating hormone, luteinizing hormone, and insulin-like growth factor–1 were assessed in all patients. ACTH levels were not routinely tested in the preoperative phase unless the patient had suspected Cushing’s syndrome. In the absence of clinical suspicion, we did not routinely screen patients for Cushing’s syndrome as all patients were suspected to have an NFA at the time of surgery. Our center practices a steroid-sparing protocol in which only patients with hypocortisolism undergo steroid replacement during surgery. Morning cortisol levels were drawn on postoperative day 1 in all patients not already on corticosteroids. Endocrine panels were assessed further in the outpatient setting 6 weeks after surgery and then biannually thereafter.

Statistical Analysis
All statistical analyses were conducted in RStudio (version 1.3.959). Categorical variables for the SCA and NFA tumor groups were reported as frequencies with percentages. Continuous variables were reported as means with standard deviations. Comparisons were made using the chi-square test for categorical variables and the unpaired t-test for continuous variables. Relevant patient variables were binarized and shown as categorical data with number and relative frequency. For group comparisons of independent variables, nonparametric univariate Mann-Whitney U-testing was performed. Statistical analyses of follow-up time, time to recurrence, and time to progression were conducted with Welch two-sample t-testing. All statistical
imputed. MICE to ensure all data were successfully and accurately data types. Post hoc validation was performed following bust and can deal with continuous, binary, and categorical separate model. Models developed through MICE are ro -variable within our data set is individually imputed by a imputation by chained equations (MICE) was performed to fill in missing data.

In total, 100 patients with SCA and 841 patients with NFA patients compared to 26 ± 11.3 mm in NFA patients (p = 0.05). Preoperative MR images were reviewed for evidence of cavernous sinus and suprasellar, infrasellar, and ventricular extension or invasion. There was no significant difference between cavernous sinus invasion, infrasellar or suprasellar extension, or third ventricular involvement. These results are summarized in Table 2. Rates of notable bilateral cavernous sinus invasion were 12% (n = 12) in SCA and 11.1% (n = 94) in NFA patients and were comparable between the cohorts (p = 0.73).

Extent of Extrasellar Extension and Invasion

The mean tumor diameter was 24 ± 10.8 mm in SCA patients compared to 26 ± 11.3 mm in NFA patients (p = 0.05). Preoperative MR images were reviewed for evidence of cavernous sinus and suprasellar, infrasellar, and ventricular extension or invasion. There was no significant difference between cavernous sinus invasion, infrasellar or suprasellar extension, or third ventricular involvement. These results are summarized in Table 2. Rates of notable bilateral cavernous sinus invasion were 12% (n = 12) in SCA and 11.1% (n = 94) in NFA patients and were comparable between the cohorts (p = 0.73).

Surgical Approach and Extent of Resection

The most common surgical technique used to resect tumors in both SCA (48%, n = 48) and NFA (34%, n = 286) patients was the endoscopic endonasal transsphenoidal approach (p = 0.18). Other approaches used to resect these tumors included microscopic sublabial (14% vs 27.9%) and endonasal (31% vs 33.5%) approaches and extended endoscopic endonasal approaches (4% vs 3.1%), as well as pterional craniotomy (3% vs 1.5%). Prior to 2011, all cases were performed microscopically, and since 2011 all cases have been performed using a binostril, four-handed endoscopic endonasal technique.
Intraoperative GTR was achieved in 42% (n = 42) of SCA patients and 48.38% (n = 406) of NFA patients (p = 0.24). These results are summarized in Table 3. Intraoperative CSF leak rates were comparable between cohorts, being identified in 49% (n = 49) of SCA and 46.4% (n = 390) of NFA patients (p = 0.63). Ki-67 rates were significantly increased in the SCA (2.88 ± 2.79) compared to the NFA (1.94 ± 1.99) cohort (p = 0.015).

Postoperative Complications

There were no significant differences in rates of postoperative complications between cohorts. Rates of postoperative CSF leak, hyponatremia, postoperative diabetes insipidus, panhypopituitarism, hypoadrenalism, hypothyroidism, infection, epistaxis, meningitis, and hydrocephalus, deep vein thrombosis or pulmonary embolus, worsening headaches, and worsening visual loss were comparable between the NFA and SCA cohorts and are summarized in Table 4. The SCA cohort included no deaths or carotid artery injuries; however, two internal carotid injuries and two deaths occurred in the NFA cohort.

Tumor Recurrence and Progression

In the available data, the overall follow-up time was longer in the NFA cohort (45.2 months) than in the SCA cohort (34.8 months) (p = 0.039).

Rates of adjuvant radiosurgery were comparable between cohorts. Patients were selected for adjuvant radiosurgery due to cavernous sinus involvement defying attempts at GTR. As such, 23% (n = 23) of SCA and 20.1% (n = 169) of NFA patients underwent some form of radiosurgery or external beam radiation.

There was no incidence of tumor recurrence in the SCA cohort, whereas NFA patients had a 2.1% (n = 18) rate of recurrence (p = 0.15). Further, there was no difference in the groups between rates of progression following STR (p = 0.44). Progression occurred in 12% (n = 12) of SCA patients and 9.9% (n = 83) of NFA patients. However, the SCA cohort was notable for a much more accelerated rate of tumor growth following resection. PFS in the SCA cohort (24.5 months) was less than half of that observed in the NFA cohort (51.1 months) (p = 0.0011). These results are summarized in Table 5 and Fig. 1.

Management of SCA Progression

Twelve SCA patients were noted to have tumor progression at a mean of 24.5 months. No SCA patient developed Cushing’s disease at any time during follow-up. Of the 12 patients with tumor progression, 4 patients underwent adjuvant radiosurgery for residual tumor prior to notable tumor progression (patients 1, 2, 3, and 7; all patient numbers are shown in Table 6). At the time of progression, 11 patients underwent a second form of intervention. All cases of residual tumor were due to cavernous sinus involvement. The remaining patient with tumor progression...
(patient 8) was counseled on further intervention but chose to be observed and had no further progression on serial imaging. Six patients were selected for a second resection based on discussion at a multidisciplinary conference among specialists in neurosurgery, neurooncology, and radiation oncology (patients 2, 3, 5, 7, 11, and 12). In all patients who underwent a secondary surgery, a transsphenoidal approach was used, and they again underwent STR. On the basis of a multidisciplinary conference, 5 patients with progression were referred for either Gamma Knife radiosurgery (GKRS; n = 4; patients 1, 4, 6, and 9) or CyberKnife radiosurgery (n = 1; patient 10).

After the second form of intervention, tumor control was achieved in one-half (n = 6) of the progression cohort (patients 1, 6, 7, 8, 9, and 10). This group included most (n = 4) patients receiving radiosurgery as a secondary means of tumor control, 1 patient who underwent a second STR, and 1 patient undergoing observation. Of those patients noted to have tumor progression despite a second form of intervention, 5 patients were referred for repeated resection (patients 3, 4, 5, and 11) while 1 patient was referred for CyberKnife radiosurgery (patient 12). Patient 3 continued to have progression and ultimately underwent a fourth resection. Patient 11 underwent two further resections and GKRS and was eventually administered temozolomide to successfully curtail progression. Patient 2 was lost to follow-up after progression was noted despite the second resection. There was no significant difference in PFS in SCA patients undergoing STR followed by immediate adjuvant radiosurgery versus STR alone (p = 0.25). Progression and management thereof in the SCA cohort are summarized in Table 6 and Fig. 2.

Discussion

We report the results of a large retrospective cohort of SCA patients with comparison to a time-matched cohort of NFA patients. Our findings suggest that SCAs are relatively aggressive pituitary adenomas with a higher propensity for tumor progression. These data corroborate findings from prior studies, lending support to more proactive intervention using SRS for residual SCA disease, especially in younger patients. Our findings are in agreement with previous results indicating that compared with NFA patients, SCA patients are younger and more likely to be female. The discernable clinical differences between these cohorts were a higher incidence of cranial nerve paresis or headache, higher incidence of amenorrhea, younger age at presentation, and female sex in the SCA cohort, and higher rates of panhypopituitarism in the NFA cohort at the time of presentation. Numerous studies have concluded that there is no significant difference in tumor size at the time of presentation. Although our results are at the verge of significance (p = 0.05), they are at least suggestive of a trend that SCAs tend to be smaller than NFAs at the time of presentation, though both were...
on average classified as macroadenomas. Despite recent criteria by the WHO to classify pituitary adenomas according to transcription factors, with the TPIT corresponding to the corticotroph cell line, a paucity of convincing data still exists in large series showing associations between these factors and clinical behavior. Similarly, we do not have transcription factor data to describe modern null cell adenoma as defined by the new WHO criteria, which may imply a degree of heterogeneity within our NFA cohort. Despite the lack of transcription factor analysis data in our cohort, the several decades of follow-up and comparison to a non-SCA NFA cohort, as categorized by immunohistochemical findings, nevertheless elucidate many important findings related to the clinical and biological behavior of SCAs.

As with many case series spanning across decades, our favored surgical approach transitioned from microscopic to endoscopic techniques. In addition, the rates of developing a postoperative neurological deficit, endocrinopathy, or other complication were similar among cohorts.

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Chemo = chemotherapy.

FIG. 2. Kaplan-Meier plot demonstrating PFS of the SCA cohort ultimately showing tumor progression following STR in patients who underwent immediate adjuvant SRS versus those who underwent STR alone. Figure is available in color online only.
Any discussion on SCA management must focus on the clinical aggression and risk of recurrence/progression. Attention was first brought to SCAs through case reports of aggressive tumors.\textsuperscript{17,18} We failed to demonstrate a difference in rates of recurrence or progression between SCAs and their NFA counterparts. Of interest, however, is the striking contrast in PFS noted in the SCA population. SCA undergoing STR displayed a PFS that was less than half of the NFA population. Further, studies show that SCAs are more likely to invade the cavernous sinus, with pooled estimates being between 25\% and 40\%.\textsuperscript{2,3,15,19,20} Cavernous sinus invasion is estimated to increase the likelihood of progression threefold.\textsuperscript{9,15,16,21} Our results suggest that cavernous sinus invasion may be more common than estimated as 56\% of SCA tumors demonstrated cavernous sinus invasion in this series, though this was comparable to the NFA cohort. Tumor progression following STR is largely explained by cavernous sinus involvement, often precluding GTR. However, there is mounting evidence that SCAs are more biologically active on a molecular level, adding to their observed aggressive nature and more rapid propensity for recurrence or progression.\textsuperscript{16}

One such study divided SCA patients into two groups depending on the degree of ACTH staining. Type I stained diffusely positive for ACTH in a manner similar to Cushing’s disease, while type II stained to a lesser degree.\textsuperscript{16} Key findings included elevated levels of proopiomelanocortin (POMC), the precursor to ACTH, in SCA type I and type II compared to NFA. Further, the enzyme responsible for cleavage of POMC into ACTH, PC1/3, was deficient in SCA compared to Cushing’s disease adenoma, though tenfold higher in type I SCA relative to type II SCA. Type I SCA tended to display a more aggressive clinical course, with a minority eventually developing Cushing’s disease. Another possible explanation for SCA relative aggression has been proposed due to expression of mismatch repair genes \textit{mutS homologs 6/2 (MSH6/2) and programmed cell death 1 ligand 1 (PD-L1)}.\textsuperscript{22} Uraki et al. compared silent adenoma subtypes with respect to expression profile of MSH6/2 as it relates to tumor proliferation and invasiveness.\textsuperscript{22} Knosp grades 1 and 2 were considered noninvasive, while grades 3 and 4 were considered invasive. SCA exhibited significantly lesser expression of MSH6/2 compared to NFA or other silent adenoma subtypes, possibly elucidating a molecular driver to their observed aggression.

In our series, 12\% of SCA patients experienced progression at a median time of 24.5 months. These findings are lower than other large SCA case series described in the literature with comparable follow-up time.\textsuperscript{3,16} In the University of California, San Francisco series, SCA tumor progression was observed in 27\% of SCA cases over a 29-month period.\textsuperscript{16} Similarly, in the Emory series, SCA progression was observed in 47\% of cases over a 36-month period. In such cases, it becomes paramount to monitor tumor status closely in the postoperative period.\textsuperscript{3} Our institution approaches progression with initial discussion at a multidisciplinary conference to discuss further resection versus radiation. Large, nodular components in younger patients are typically referred for repeat resection, depending on the tumor morphology and relationship to the optic chiasm and pituitary gland, and with the intent of often adapting a postoperative target for planned SRS. We have rarely implemented chemotherapeutic agents after a failed second form of intervention, though one such patient required temozolomide in this series.

Recent reports have focused on the use of adjuvant radiation therapy and radiosurgery following resection of recurrent SCAs. While some have shown significant decline in recurrence rates following adjuvant radiation,\textsuperscript{4,10} others have found no difference in outcome. Indeed, one report found an increased rate of recurrence among irradiated patients.\textsuperscript{23} Others have proposed no need for radiation following GTR.\textsuperscript{3,12} We agree with this notion, as none of our SCA patients who underwent GTR experienced recurrence. Of our SCA cohort with progression following STR, 4 patients (33\%) had received adjuvant radiosurgery and yet still failed to achieve tumor control. Our institutional practice reserves adjuvant radiation therapy after a multidisciplinary consensus is reached for patients for whom GTR is not possible to obtain, particularly in cases with extensive cavernous sinus involvement or notable tumor regrowth on postoperative imaging. In situations following initial STR, a multidisciplinary review of the postoperative MRI scan, tumor pathology and markers, and demographic features are discussed. Aggressive tumors with characteristics including ACTH positivity, high Ki-67 labeling index, cavernous sinus invasion, younger age, and patient preferences are all taken into account in the decision to offer adjuvant radiosurgery to the tumor residual versus serial monitoring for progression. We have modified our practice to generally offer early SRS for residual disease in SCA patients, especially in young patients. In the event of serial monitoring, new signs or symptoms prompt earlier imaging and follow-up. Patient education plays a critical role in the successful management of SCA patients. Discussion of presenting symptoms and the risks of recurrence are important to facilitate patient compliance and close follow-up.

\section*{Study Limitations}

Limitations of the current study include being a single-institution retrospective cohort analysis which is in its nature inherent to bias. Further, we made the diagnosis of SCA on immunohistochemical staining but did not assess TPIT expression as described by the most recent guidelines as this was not the standard practice when the study initially began. As the initial experience was prior to routine molecular testing, a sizable portion of our surgical cohort is devoid of expression profiles which will be incorporated in future studies. The SCA cohort had shorter follow-up time compared to the NFA cohort; however, this is a minor limitation given our observation that SCAs tend to have lower PFS. Finally, our institution does not routinely screen patients without presenting features of Cushing’s disease. Though we maintain a low threshold for screening, we withhold such tests in the absence of clinical Cushing’s features. As SCAs are by nature “silent,” these patients lack Cushing’s features and present much more similarly to NFA patients, as seen by symptoms more traditionally caused by mass effect (headache, visual disturbance) and as macro- as opposed to microadenoma.
Conclusions

SCAs comprise a distinct group of NFAs. Given their relatively low prevalence, there is a lack of sufficient data currently available to guide management in cases of disease progression or recurrence, especially as it pertains to transcription factor analysis. Our surgical series marks the largest retrospective review of SCAs treated at a single institution and corroborates prior findings that SCAs exhibit a more aggressive clinical course compared to their NFA counterparts. Specifically, SCAs show markedly lower risk factor for regrowth and recurrence of nonfunctioning pituitary macroadenomas: results from a single Australian centre. Clin Endocrinol (Oxf). 2018;87(3):580–585.


References


Disclosures

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

Conception and design: Strickland, Jackanich, Tavakol, Zada. Acquisition of data: Strickland, Briggs, Jackanich, Tavakol, Shiroishi, Zada. Analysis and interpretation of data: Strickland, Briggs, Jackanich, Shiroishi, Liu, Weiss, Zada. Drafting the article: Strickland, Shahrestani, Briggs, Jackanich, Hurth, Shiroishi, Liu, Carmichael, Weiss, Zada. Reviewed the submitted version of manuscript: Strickland, Carmichael, Weiss, Zada. Approved the final version of the manuscript on behalf of all authors: Strickland. Statistical analysis: Shahrestani, Zada. Study supervision: Zada.

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