Rare TTF-1 positive tumors of the sellar region: Barrow Neurological Institute retrospective case series

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**Introduction**

Granular cell tumors (GCT), pituicytomas (PCT), and spindle cell oncocytomas (SCO) are relatively rare, non-functioning intrinsic pituitary tumors arising in the sellar and suprasellar regions, all recently recognized to share positive staining of thyroid transcription factor-1 (TTF-1). There are limited reports of these tumors to date, and no single institutional report with long-term follow up of all three tumor types.

**Methods**

Our institutional pathology database was queried for the above pathologic diagnoses. Of 16 query results, 11 patients consisting of 4 GCT, 4 PCT, and 3 SCO had complete clinical records for retrospective case series review. Clinical records were assessed for clinical presentation, pre- and post-operative endocrine status, location on imaging, surgical characteristics, pathology results, and tumor recurrence.

**Results**

Although commonly reported to be predominantly female, we found no statistical difference in sex. Presentations were commonly headache (55%),  fatigue (46%), vision changes (64%), and endocrine abnormalities (55%). Granular cell tumors were the only subtype to present exclusively in the infundibulum, as well as undergo a Sylvian approach to resection (n = 2) in our series. There was no significant difference between tumor types or surgical approach in terms of post-operative vision changes; SCOs were more likely to have pre-operative endocrine complications, but less likely to have post-operative worsening of endocrine status (p = 0.056). Contrary to what is commonly reported, none of the tumors were found to bleed excessively intraoperatively. All tumors were positive for TTF-1 staining. Imaging confirmed gross total resection in all 11 cases with no known recurrences at an average follow up of 4.72 ± 3.65 years.

**Conclusions**

We present our institutional series of 4 GCT, 4 PCT, and 3 SCO tumor patients, the largest to date of these three TTF-1 staining tumors of the sellar region. GCTs were reliably found to be exclusively suprasellar at presentation. SCOs tended to present with more endocrine abnormalities, but less likely to have endocrine worsening postoperatively. Gross total resection was achieved in all cases with no known recurrence at nearly 5 years of mean follow up.

# Introduction

Pituicytomas (PCT), granular cell tumors (GCT) and spindle cell oncocytomas (SCO) are rare, intrinsic neoplasms of the sellar region.  As a group, they are classified as non-neuroendocrine World Health Organization Grade I tumors arising from the posterior pituitary (Lopes 2017). Pituicytomas are characterized by their origin from pituicytes, a specialized glial cell found in the neurohypophysis2. Granular cell tumors of the neurohypophysis are masses of uncertain origin, but some studies suggest that these tumors originate from pituicytes3,4. Spindle cell oncocytomas of the adenohypophysis also have unclear cellular origins; however, Roncaroli et al5 suggests that SCOs are derived from folliculostellate cells, which are sustentacular cells of the adenohypophysis. A common histogenetic marker seems to be thyroid transcription factor 1 (TTF-1) expression, which has been recognized6 as positively staining in sellar region tumors, specifically towards pituicytes.

Although all considered benign tumors, their progression can cause symptoms typical of sellar masses including headaches, endocrine abnormalities, and vision loss. When these lesions are symptomatic, treatment is indicated, however there is debate regarding management in the literature. To date there are limited surgical case series of these tumors, and most without long-term follow up. We present a single institutional series reporting clinical presentation, immunohistochemical results, and intraoperative and postoperative findings.

# Methods

We performed a retrospective case series review by querying our institutional pathological database for GCTs, PCTs, and SCOs. Surgical interventions occurred between 1997-2017 on all patients. We received approval from our local Institutional Review Board for this study. Out of 16 patients found, 11 patients (4 GCTs, 4 PCTs, and 3 SCOs) had clinical records sufficient to conduct a retrospective review. Clinic notes from surgical and consulting specialties were used to assess demographics, presenting symptoms, endocrine status, and post-operative complications and health status. Operative reports were reviewed for surgical characteristics. Magnetic resonance imaging (MRI) files, in addition to radiologic reports, were used to assess tumor size, location, and recurrence. Immunohistochemical studies were performed by our institutional neuropathologists using standard techniques. On initiation of this study, all tumor samples were evaluated for TTF-1 staining. Categorical variables were analyzed with a two-tailed Fisher exact tests. Continuous variables were analys

# Results

## Clinical Presentation

Demographic and clinical results are presented in Table 1. Eleven patients with a mean age of 54.7 ± 15.4 years were studied. 45.5% of the patients were female (p = 1.0). There was also no association between either age or sex and tumor type. Visual changes were the most common presenting clinical finding for the three tumors collectively (7/11). The next most common symptoms were headaches (6/11), pre-operative endocrine abnormalities (6/11), and fatigue (5/11). GCTs most commonly presented with headaches (3/4), followed by fatigue/vision changes (2/2) and pre-operative endocrine abnormalities (1/4). PCTs most commonly presented with vision changes (3/4), followed by pre-operative endocrine abnormalities (2/4) and headache/fatigue (1/4). SCOs most commonly presented with pre-operative endocrine abnormalities (3/3), followed by headache, fatigue, and pre-operative endocrine abnormalities (2/4).

Demographics and clinical presentation by tumor type.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | [ALL] N=11 | GCT N=4 | PCT N=4 | SCO N=3 | P value |
| Age | 54.7 (15.4) | 53.8 (6.29) | 56.5 (19.6) | 53.7 (23.3) | 0.97 |
| Sex: |  |  |  |  | 1 |
| F | 5 (45.5%) | 2 (50.0%) | 2 (50.0%) | 1 (33.3%) |  |
| M | 6 (54.5%) | 2 (50.0%) | 2 (50.0%) | 2 (66.7%) |  |
| Headache | 6 (54.5%) | 3 (75.0%) | 1 (25.0%) | 2 (66.7%) | 0.46 |
| Fatigue | 5 (45.5%) | 2 (50.0%) | 1 (25.0%) | 2 (66.7%) | 0.77 |
| Vision changes | 7 (63.6%) | 2 (50.0%) | 3 (75.0%) | 2 (66.7%) | 1 |
| Endocrine abnormality | 6 (54.5%) | 1 (25.0%) | 2 (50.0%) | 3 (100%) | 0.25 |

## Tumor Location and Size

Tumor location, size, and approach findings are presented in Table 2. Of the eleven tumors, GCTs were found exclusively as a part of the suprasellar or infundibular regions (4/4; Table 2), PCTs were found as a part of the infundibular or sellar regions, while SCOs were found in the suprasellar, infundibular, or sellar regions. GCTs were the only tumors to be found exclusively as a part of the infundibular region, as well as exclusively presenting in the suprasellar space. Pre-operative MRI scans were used to determine tumor sizes in the vertical direction and maximum dimensions in the horizontal direction. The average tumor was 1.93 cm at presentation, with GCTs, PCTs, and SCOs averaging 1.48 cm, 2.23 cm, and 2.13 cm respectively (p = 0.3). Figure 1 depicts the relative location and size (scaled relative to the two maximum dimensions) of the eleven different tumors.

Tumor location and approach by tumor type. Location categories are not mutually exclusive.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | [ALL] N=11 | GCT N=4 | PCT N=4 | SCO N=3 | P value |
| Size, Max dimension | 1.93 (0.72) | 1.48 (0.63) | 2.23 (0.79) | 2.13 (0.61) | 0.31 |
| Sellar | 7 (63.6%) | 0 (0.0%) | 4 (100%) | 3 (100%) | 0.01 |
| Suprasellar | 6 (54.5%) | 2 (50.0%) | 3 (75.0%) | 1 (33.3%) | 0.77 |
| Suprasellar including Infundibulum | 9 (81.8%) | 4 (100%) | 3 (75.0%) | 2 (66.7%) | 0.71 |
| Infundibular | 3 (27.3%) | 2 (50.0%) | 0 (0.0%) | 1 (33.3%) | 0.42 |
| Infundibular Only | 2 (18.2%) | 2 (50.0%) | 0 (0.0%) | 0 (0.0%) | 0.27 |
| Approach: |  |  |  |  | 0.1 |
| Endoscopic | 1 (9.09%) | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) |  |
| Microscopic | 8 (72.7%) | 1 (25.0%) | 4 (100%) | 3 (100%) |  |
| Sylvian | 2 (18.2%) | 2 (50.0%) | 0 (0.0%) | 0 (0.0%) |  |



Relative tumor size and location by tumor type with maximum dimension of pre-operative MRI in vertical direction and second largest dimension in horizontal direction. Su = suprasellar space (including infundibulum). In = infundibular. Se = sellar space.

## Operative Findings

Two major surgical approaches, trans-sphenoidal (either endoscopic or microscopic) and Sylvian, were used to resect these tumors. The majority of the tumors were resected with the microscopic technique (8/11), with the PCTs (4/4) and SCOs (3/3) undergoing an exclusively microscopic sphenoidal surgical approach. The Sylvian approach was only used on GCTs (2/4), both of which were infundibular. On review of operative reports, no procedure experienced more than 300 milliliters of blood loss.

Tumor locations, post-operative endocrine complications, vision improvement, and size by surgical approach.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | [ALL] N=11 | Endoscopic N=1 | Microscopic N=8 | Sylvian N=2 | P value |
| Sellar | 7 (63.6%) | 0 (0.0%) | 7 (87.5%) | 0 (0.0%) | 0.02 |
| Suprasellar | 6 (54.5%) | 0 (0.0%) | 5 (62.5%) | 1 (50.0%) | 0.7 |
| Suprasellar + Infundibulum | 9 (81.8%) | 1 (100%) | 6 (75.0%) | 2 (100%) | 1 |
| Infundibulum | 3 (27.3%) | 1 (100%) | 1 (12.5%) | 1 (50.0%) | 0.15 |
| Infundibulum only | 2 (18.2%) | 1 (100%) | 0 (0.0%) | 1 (50.0%) | 0.06 |
| Endocrine complication | 6 (54.5%) | 1 (100%) | 3 (37.5%) | 2 (100%) | 0.3 |
| Vision improved | 4 (36.4%) | 0 (0.0%) | 2 (25.0%) | 2 (100%) | 0.11 |
| Size | 1.93 (0.72) | 0.9 (.) | 2.14 (0.63) | 1.6 (0.85) | 0.22 |

Intraoperative findings showed that most of the tumors had a soft consistency (7/11; Table 4), including all of the SCOs (3/3). These tumors presented in different colors, with a majority appearing gray (7/11), and the rest appearing purple (2/11), tan (1/11), or white (1/11). Regarding specific tumors, we found that the SCOs (3/3) were all gray. The extent of resection for each of these tumors was determined using corroboration between operative reports and post-operative MRI, which demonstrated gross total resection in all cases. Follow-up for the eleven cases was 4.72 ± 3.65 years with no patients with recurrence. Post-operatively four patients with pre-operative visual symptoms had visual improvement while six patients had temporary or long-term worsening of an endocrine complication.

Extent of resection, outcomes, and intraoperative characteristics by tumor type.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | [ALL] N=11 | GCT N=4 | PCT N=4 | SCO N=3 | P value |
| Gross total resection | 11 (100%) | 4 (100%) | 4 (100%) | 3 (100%) | . |
| Endocrine complication | 6 (54.5%) | 4 (100%) | 2 (50.0%) | 0 (0.0%) | 0.06 |
| Vision improved | 4 (36.4%) | 2 (50.0%) | 2 (50.0%) | 0 (0.0%) | 0.42 |
| Follow up, mean (SD) years | 4.72 (3.65) | 5.61 (4.89) | 5.13 (3.8) | 3.0 (1.7) | 0.67 |
| Recurrence | 0 (0%) |  |  |  | . |
| Consistency |  |  |  |  | 0.42 |
| Firm | 4 (36.4%) | 2 (50.0%) | 2 (50.0%) | 0 (0.0%) |  |
| Soft | 7 (63.6%) | 2 (50.0%) | 2 (50.0%) | 3 (100%) |  |
| Color |  |  |  |  | 0.39 |
| Gray | 7 (63.6%) | 2 (50.0%) | 2 (50.0%) | 3 (100%) |  |
| Purple | 2 (18.2%) | 0 (0.0%) | 2 (50.0%) | 0 (0.0%) |  |
| Tan | 1 (9.09%) | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) |  |
| White | 1 (9.09%) | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) |  |

## Histochemistry

Results for our immunohistochemistry are summarized in Table 5. In our eleven tumor cases, we found conflicting results from what has been published in previous literature. Although the literature describes PCTs as generally positive for GFAP staining8, we found that three of the four cases tested for GFAP staining had all reacted negatively. Moreover, EMA staining showed mixed results in GCTs and PCTs, whereas all three SCOs cases reacted positively, which has been shown in the literature9. When testing S100 reactivity, we found that all of the tumors tested (8/8) stained positively, which was shown to be positive in PCTs9,10, but showed both positive and negative results in SCOs9,10. All eleven of the masses, including the three SCO cases, had positive staining for TTF-1.

Immunohistologic staining by tumor type. nd = not done.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | [ALL] N=11 | GCT N=4 | PCT N=4 | SCO N=3 | P value |
| S100 |  |  |  |  | 0.71 |
| + | 8 (72.7%) | 2 (50.0%) | 3 (75.0%) | 3 (100%) |  |
| nd | 3 (27.3%) | 2 (50.0%) | 1 (25.0%) | 0 (0.0%) |  |
| CD68 |  |  |  |  | 0.27 |
| + | 2 (18.2%) | 2 (50.0%) | 0 (0.0%) | 0 (0.0%) |  |
| nd | 9 (81.8%) | 2 (50.0%) | 4 (100%) | 3 (100%) |  |
| PAS |  |  |  |  | 0.18 |
| + | 2 (18.2%) | 2 (50.0%) | 0 (0.0%) | 0 (0.0%) |  |
| - | 2 (18.2%) | 1 (25.0%) | 0 (0.0%) | 1 (33.3%) |  |
| nd | 7 (63.6%) | 1 (25.0%) | 4 (100%) | 2 (66.7%) |  |
| GFAP |  |  |  |  | 0.4 |
| + | 1 (9.09%) | 0 (0.0%) | 0 (0.0%) | 1 (33.3%) |  |
| - | 5 (45.5%) | 1 (25.0%) | 3 (75.0%) | 1 (33.3%) |  |
| nd | 5 (45.5%) | 3 (75.0%) | 1 (25.0%) | 1 (33.3%) |  |
| EMA |  |  |  |  | 0.14 |
| + | 5 (45.5%) | 0 (0.0%) | 2 (50.0%) | 3 (100%) |  |
| - | 2 (18.2%) | 1 (25.0%) | 1 (25.0%) | 0 (0.0%) |  |
| nd | 4 (36.4%) | 3 (75.0%) | 1 (25.0%) | 0 (0.0%) |  |
| Synaptophysin |  |  |  |  | 1 |
| + | 1 (9.09%) | 0 (0.0%) | 1 (25.0%) | 0 (0.0%) |  |
| nd | 10 (90.9%) | 4 (100%) | 3 (75.0%) | 3 (100%) |  |
| Calretinin |  |  |  |  | 1 |
| + | 1 (9.09%) | 0 (0.0%) | 1 (25.0%) | 0 (0.0%) |  |
| nd | 10 (90.9%) | 4 (100%) | 3 (75.0%) | 3 (100%) |  |
| TTF1 + | 11 (100%) | 4 (100%) | 4 (100%) | 3 (100%) | . |

# Discussion

The rarity of these non-endocrine pituitary tumors and relatively small studies in the literature have led to a somewhat conflicting understanding of these tumors and disparate treatment recommendations. Like others in the literature, the currently study is limited by a small number of patients in each tumor category, as well as the retrospective nature of data collection.

In terms of immunohistologic findings, SCOs have been shown to display positive S100 and EMA staining patterns13, which we have also found in our dataset. However, we feel EMA should not be thought of as a method to distinguish SCOs from other lesions6, since PCTs were also positive for EMA staining. Additionally, we found that TTF-1 was expressed in all eleven of our tumors, confirming their histogenetic similarity and likely shared lineage6. Outside of TTF-1 staining, a major limitation of our histologic results is that many stains were not performed on all tumors.

Another observation worthy of discussion revolves around the locations of these tumors. While the literature describes PCTs as purely intrasellar7,8, we found that PCTs may be found in suprasellar or infundibular regions as well. Moreover, our results showed that GCTs were never exclusively found in the intrasellar region, which has also been described by Cohen-Gadol et al15, potentially identifying a reason to exclude these lesions from the differential diagnosis of a purely intrasellar mass. An interesting note regarding the locations of SCOs is that we had one case of a purely intrasellar lesion, showing that it is possible for SCOs to be isolated within the intrasellar region, rather than both intra- and suprasellar7.

Our case series suggests that preoperative endocrine abnormalities, such as hypopituitarism, may be more common in SCOs compared to other tumors, which aligns well with what is currently shown in the literature16. Despite this, we did not find any new or worsening endocrine abnormalities in SCOs, postoperatively.

As far as surgical management and follow-up is concerned, PCTs and SCOs are thought to be highly vascular15,16.The possibility of a massive bleed during surgery has been suggested by some to lead to subtotal resection, perhaps predisposing to recurrence of these tumors (Wolfe, Bruce, and Morcos 2008)(Pirayesh et al. 2012)(Zygourakis et al. 2015). However, our series showed that all eleven of the tumors, regardless of classification, had a gross total resection without encountering significant blood loss due to tumor vascularity.  Furthermore, the high vascularity of these tumors invited support from some groups for a Sylvian, as opposed to an endoscopic, approach in order to preserve vascular integrity17,18; however, we were able to utilize the endoscopic approach safely for these tumors, including for an infundibular GCT case. With a mean follow up of 4.72 ± 3.65 years and no recurrences, we believe that gross total resection is key for management of these tumors.

# Conclusion

We present our institutional series of 4 GCT, 4 PCT, and 3 SCO tumor patients, the largest to date of these three TTF-1 staining tumors of the sellar region. GCTs were reliably found to be exclusively suprasellar at presentation. SCOs tended to present with more endocrine abnormalities, but less likely to have endocrine worsening postoperatively. Gross total resection was achieved in all cases with no known recurrence at nearly 5 years of mean follow up.

## Abbreviations

GCT - granular cell tumor, PCT - pituicytoma, SCO - spindle cell oncocytoma, TTF - thyroid transcription factor,  MRI - magnetic resonance imaging

# References

1.     Louis <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1929165/>

2.     Brat, D. J., et al. (2000). “Pituicytoma: a distinctive low-grade glioma of the neurohypophysis.” Am J Surg Pathol **24**(3): 362-368.

3.     Aquilina, K., et al. (2006). “Granular cell tumour of the neurohypophysis: a rare sellar tumour with specific radiological and operative features.” Br J Neurosurg **20**(1): 51-54.

4.     Saiegh, L., et al. (2013). “Granular cell tumor of the neurohypophysis: case report and review of the literature.” Neuro Endocrinol Lett **34**(5): 331-338.

5.     Roncaroli <https://www.ncbi.nlm.nih.gov/pubmed/12170092>

6.     Lee <https://academic.oup.com/jnen/article/68/5/482/2917042>

7.     Covington, M. F., et al. (2011). “Pituicytoma, spindle cell oncocytoma, and granular cell tumor: clarification and meta-analysis of the world literature since 1893.” AJNR Am J Neuroradiol **32**(11): 2067-2072.

8.     Pirayesh Islamian, A., et al. (2012). “Pituicytoma: overview of treatment strategies and outcome.” Pituitary **15**(2): 227-236.

9.     Mete, O., et al. (2013). “Spindle cell oncocytomas and granular cell tumors of the pituitary are variants of pituicytoma.” Am J Surg Pathol **37**(11): 1694-1699.

10.  Zygourakis, C. C., et al. (2015). “Pituicytomas and spindle cell oncocytomas: modern case series from the University of California, San Francisco.” Pituitary **18**(1): 150-158.

11.  Kleinschmidt-DeMasters, B. K. and M. B. Lopes (2013). “Update on hypophysitis and TTF-1 expressing sellar region masses.” Brain Pathol **23**(5): 495-514.

12.  Mlika <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3047430/>

13.  Borges, M. T., et al. (2011). “Spindle cell oncocytoma with late recurrence and unique neuroimaging characteristics due to recurrent subclinical intratumoral bleeding.” J Neurooncol **101**(1): 145-154.

14.  Cohen-Gadol, A. A., et al. (2003). “Granular cell tumor of the sellar and suprasellar region: clinicopathologic study of 11 cases and literature review.” Mayo Clin Proc **78**(5): 567-573.

15.  Ogiwara, H., et al. (2011). “Spindle cell oncocytoma of the pituitary and pituicytoma: Two tumors mimicking pituitary adenoma.” Surg Neurol Int **2**: 116.

16.  Demssie, Y. N., et al. (2011). “Recurrent spindle cell oncocytoma of the pituitary, a case report and review of literature.” Pituitary **14**(4): 367-370.

17.  Orning, J. L., et al. (2013). “Endoscopic Endonasal Approach for Resection of Infundibular Granular Cell Tumor: Case Report and Literature Review.” J Case Rep Med **2**: 235775.

18.  Nishio <https://www.sciencedirect.com/science/article/pii/S0303846798000171?via%3Dihub>

# References

Lopes, MBS. 2017. “The 2017 World Health Organization Classification of Tumors of the Pituitary Gland: a Summary.”. *Acta Neuropathol* 134: 521–35.

Wolfe, SQ, J Bruce, and JJ Morcos. 2008. “Pituicytoma: Case Report.”. *Neurosurgery* 63: E173–4; discussion E174.

Pirayesh, Islamian A, R Buslei, W Saeger, and R Fahlbusch. 2012. “Pituicytoma: Overview of Treatment Strategies and Outcome.”. *Pituitary* 15: 227–36.

Zygourakis, CC, JD Rolston, HS Lee, C Partow, S Kunwar, and MK Aghi. 2015. “Pituicytomas and Spindle Cell Oncocytomas: Modern Case Series from the University of California, San Francisco.”. *Pituitary* 18: 150–58.