Research Article
Volume 14:5, 2022

Journal of Cancer Science & Therapy

ISSN: 1948-5956 Open Access

# Endoscopic Transsphenoidal Surgery: Factors Associated with Tumor Progression in Pituitary Adenomas

**Javier Lobato-Polo***

*Department of Neurosurgery, Universidad ICESI, Fundacion Valle Del Lili, Cali, Colombia*

## Abstract

**Objective:** The aim of this study was to measure the incidence of tumor recurrence amongst patients that underwent endoscopic transsphenoidal surgery for pituitary adenomas, as well as the performance of the molecular and radiological factors that are commonly associated with recurrence.

**Methods:** Patients of both adult and pediatric population with pituitary adenomas who were treated for the first time with endoscopic transsphenoidal surgery in a single tertiary care center, between June 2006 and December 2019 were included. Clinical features, laboratory results, imaging findings and molecular tests results were collected. Progression was measured in a follow-up MRI.

**Results:** 88 patients were included. 19.5% presented gonadotroph adenomas and non-functional adenomas, followed by corticotrophs (17.2%) and somatotrophs (13.8%). 20.7% had cellular atypia, 26.2% p53 mutation and up to 79.5% had Ki-67 under 3%. On postoperative MRI (available for 90.9% of patients) 43.8% had tumor residue. Tumor progression occurred in 32 patients (36.4%). Median progression-free survival time was 5.37 years (95%CI= 3.29-N/A). Cellular atypia, Ki-67 elevation, cavernous sinus invasion and tumor residue were suggested as significant prognostic factors. Nonetheless, multivariate time-toevent analysis identified tumor residue as the only factor significantly associated with progression: HR=4.0, 95%CI= 1.56 -10.31.

**Conclusion:** Residual tumor in postoperative imaging aids as a predictor for tumor progression and the invasion of the cavernous sinus, presence of cellular atypia and a proliferation index (Ki-67) above 3% influence the speed at which the recurrence appears, therefore not being a predictive factor but rather a modifier of the recurrence.

**Keywords:** Transsphenoidal surgery • Endoscopic endonasal surgery • Pituitary adenoma • Sellar tumor • Suprasellar tumor • Minimally invasive surgery

## Introduction

Tumoral pathology of the pituitary gland represents 15.3% of the primary neoplasms of the Central Nervous System (CNS). Several types of tumors affect the sellar region; among these are the pituitary carcinoma, pituitary blastoma, tumors of the neurohypophysis, neuronal and paraneuronal tumors, craniopharyngiomas, mesenchymal tumors, adenomas and others. Adenomas are the most common and can induce great morbidity for patients due to their hormonal hypersecretion, mass-effect or invasion of adjacent structures. Nevertheless, they are considered malignant only when they metastasize and not when they recur [1,2].

Prevalence of pituitary adenomas is estimated at 17% [3]. In Europe, the incidence is reported around 3 to 4 of 100,000 new cases per year with a prevalence that oscillates between 78 to 94 of 100,000 people [4]. Patients with these tumors generally have a good clinical response to surgical management, and suitable pharmacology therapy or radiotherapy. Nonetheless, a small proportion of these tumours can have unpredictable behaviour due to an aggressive pathology, and predicting the possibility of tumor progression after surgical resection is of great clinical value [5]. Size, hormonal activity, and invasion of adjacent structures can help establish a tumour's aggressiveness and morbidity, and therefore aid in the decision making process regarding the appropriate treatment for each patient [6-8]. Morbidity usually involves clinical features or entitites secondary to compression of adjacent neurovascular structures or excessive production of specific hormones [9-11].

Higher aggressiveness in a pituitary adenoma increases risk of recurrence, and thus several radiological and molecular markers have been studied in order to estimate likelihood of total resection and predict risk of recurrence at early stages. Regarding biomarkers, expression of p53, the Ki-67 index, oncogenes or microRNAs have been studied. A Ki-67 proliferation index above 3% has been associated with tumour aggressiveness because of increased tumoral growth; invasion of adjacent structures, recurrence and poorer treatment response; and a higher Ki-67 of up to 15% is associated with pituitary carcinoma. However, some studies have failed to find a prognostic value for this proliferation index, and p53 expression has not been directly associated with recurrence but cavernous sinus invasion may be related [1,12-16].

This study aimed to 1) measure the occurrence of tumor recurrence among patients with adenomas treated with transsphenoidal surgery and 2) assess the performance of described molecular and radiological factors associated with recurrence.

## Methods

### Design

This was an analytic cohort based on clinical records that included both adult and pediatric patients with pituitary adenomas that presented to a tertiary care university hospital in Cali, Colombia, and were treated for the first time with endoscopic transsphenoidal surgery, between June 2006 and December 2019. Patients that had previously undergone surgery in other institutions and/

***Address for Correspondence:** Javier Lobato-Polo, Department of Neurosurgery, Universidad ICESI, Fundacion Valle Del Lili, Cali, Colombia; E-mail: Javier.lobato@fvl.org.co*



**Received:** 10 May, 2022; Manuscript No. jcst-22-63644; **Editor Assigned:** 11 May, 2022; PreQC No. P-63644; **Reviewed:** 21 May, 2022; QC No. Q-63644; **Revised:** 24 May, 2022, Manuscript No. R-63644; **Published:** 31 May, 2022, DOI: 10.37421/1948-5956.22.14.530

or for those that prognostic data was not available were excluded. This study was approved by the institutional ethics review board before start.

### Data collection and outcomes of interest

Both physical and electronic clinical records of all patients treated with transsphenoidal surgery within the period of interest were reviewed and screened for inclusion criteria. For included patients, clinical features, laboratory results (including TSH, free T4, growth hormone, prolactin, somatomedin C, ACTH, FSH, LH and cortisol), imaging findings and molecular tests results were collected.

The outcomes of interests were incidence of progression including median progression-free survival time associated with resected pituitary adenomas. Also imaging features and molecular markers were assessed as prognostic factors for tumor progression.

### Statistical analysis

Data was verified with original sources when extreme or missing. A descriptive analysis was performed for all the collected variables. Nominal variables are described with absolute and relative frequencies, and were compared using $Chi^2$. Distribution of continuous variables was assessed with the Shapiro-Wilk test and either means (standard deviation [SD]) or medians (interquartile range [IQR]) were used as suited. The Student's t test or the Mann-Whitney test was used to assess differences in continuous variables according to distribution.

As different follow-up lengths were expected and progression-free survival was of interest, analysis of time to event was planned to describe the incidence of tumor progression. The Kaplan-Meier method and its derived curves were used to provide progression-free survival estimates and assess potential prognostic factors. The log-rank test was used to assess if curves were different. A multivariate Cox-regression model was used to identify independent factors associated with progression and Hazard Ratios (HR) were estimated. A p-value <0.05 was considered to be statistically significant and estimates are accompanied with 95% intervals (95%CI). All analyses were conducted in RStudio version 1.3.10.

## Results

A total of 159 records were screened for eligibility; 88 patients fulfilled selection criteria and were included for analysis. The median age was 50.9 years (IQR 35.3-62.5) and 51.1% were male. Around a third of the patients had a prior history of hypertension (37.5%) or hypothyroidism (30.7%). Most adenomas presented as macroadenomas (68.6%) followed by microadenomas (18.6%) and giant adenomas (12.8%). Cavernous sinus invasion was identified by revision of imaging features and official neuroradiology reports in 34.5% of patients. Table 1 displays these and other clinical characteristics at baseline.

The most frequently altered hormone pre-operatively was prolactin; abnormal in 58.2% of patients, followed by somatomedin C (50%) and cortisol (47.2%). Table 2 displays the frequency of normal, high or low pituitary hormones. Upon histological analysis most lesions were gonadotrophs (19.5%) and non-functional adenomas (19.5%), followed by corticotrophs (17.2%), somatotrophs (13.8%), lactotrophs (12.6%) and plurihormonal adenomas (6.9%). The remaining 10.3% were identified histologically as normal pituitary tissue. Immunohistochemistry showed that 20.7% had cellular atypia, 26.2% p53 mutation and up to 79.5% had Ki-67 fewer than 3%. Tumour sizes were observed to correlate with p53 mutation, as this feature was present in only 13.3% of microadenomas, but in 24.6% and 54% of macroadenomas and giant adenomas, respectively. On post-operative MRI (available for 90.9% of patients) 43.8% had tumour residue. Tumour residue was identified in 28.6% of microadenomas, 49.1% of macroadenomas and 44.4% of giant adenomas. It was associated with Cavernous Sinus Invasion (CSI): 65.5% of patients with CSI had residue *vs.* 34.5% without CSI, *P*- value=0.0046; but not with other molecular or clinical features.

Tumour progression occurred in 32 patients (36.4%). Median progression-free survival time was 5.37 years (95% CI=3.29 - N/A) and is displayed in Figure 1. Figure 2 displays the assessment of different potential prognostic factors for progression through Kaplan-Meier curves; the p value corresponds to the log-rank test. Cellular atypia, Ki-67 elevation, CSI and tumour residue were suggested as significant prognostic factors. Nonetheless, multivariate time-to-event analysis identified tumour residue as the only factor significantly

**Table 1.** Demographic characteristics.

| Clinical Characteristics at Baseline | Result (n=88) |
|---|---|
| Age, Median [IQR] | 50.94 [35.32, 62.46] |
| Sex, masculine, n (%) | 45 (51.1) |
| Hypertension, n (%) | 33 (37.5) |
| Diabetes, n (%) | 13 (14.8) |
| Hypothyroidism, n (%) | 27 (30.7) |
| Smoking, n (%) | 8 (9.1) |
| Adenoma characteristics | |
| Lesion size | |
| Microadenoma, n (%) | 16 (18.6) |
| Macroadenoma, n (%) | 59 (68.6) |
| Giant macroadenoma, n (%) | 11 (12.8) |
| Cavernous sinus invasion, n (%) | 30 (34.5) |
| Cellular atypia | 18 (20.7) |
| Histology | |
| Lactotroph | 11 (12.6) |
| Gonadotroph | 17 (19.5) |
| Corticotroph | 15 (17.2) |
| Somatotroph | 12 (13.8) |
| Plurihormonal | 6 (6.9) |
| Non-functioning | 17 (19.5) |
| Pituitary tissue | 9 (10.3) |
| Ki-67 | |
| <3% | 66 (79.5) |
| ≥ 3% | 17 (20.5) |
| P53 mutation | 22 (26.2) |

**Table 2.** Endocrine profile.

| Pre-Operative Endocrine Profile | Result (n = 88) | | |
|---|---|---|---|
| | Normal | High | Low |
| ACTH, n (%) | 28 (80.0) | 4 (11.4) | 3 (8.6) |
| Cortisol, n (%) | 38 (52.8) | 16 (22.2) | 18 (25.0) |
| FSH, n (%) | 35 (76.1) | 4 (8.7) | 7 (15.2) |
| FT4, n (%) | 49 (66.2) | 2 (2.7) | 23 (31.1) |
| GH, n (%) | 33 (78.6) | 8 (19.0) | 1 (2.4) |
| LH, n (%) | 28 (60.9) | 3 (6.5) | 15 (32.6) |
| PRL, n (%) | 31 (41.9) | 40 (54.1) | 3 (4.1) |
| Somatomedin C, n (%) | 18 (50.0) | 8 (22.2) | 10 (27.8) |
| TSH, n (%) | 57 (73.1) | 13 (16.7) | 8 (10.3) |

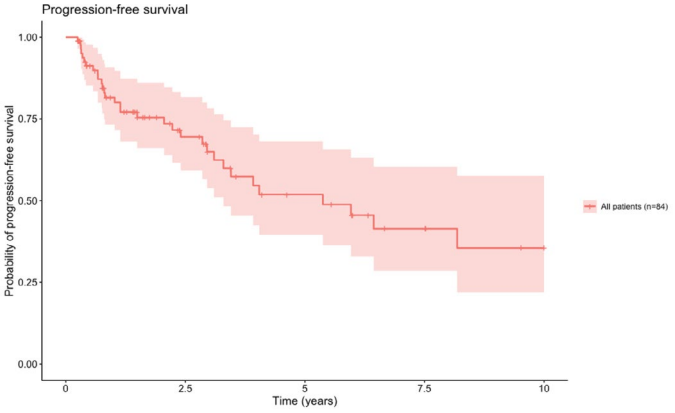


**Figure 1.** Tumour progression occurred in 32 patients (36.4%). Median progression-free survival time was 5.37 years (95% CI=3.29-aN/A).

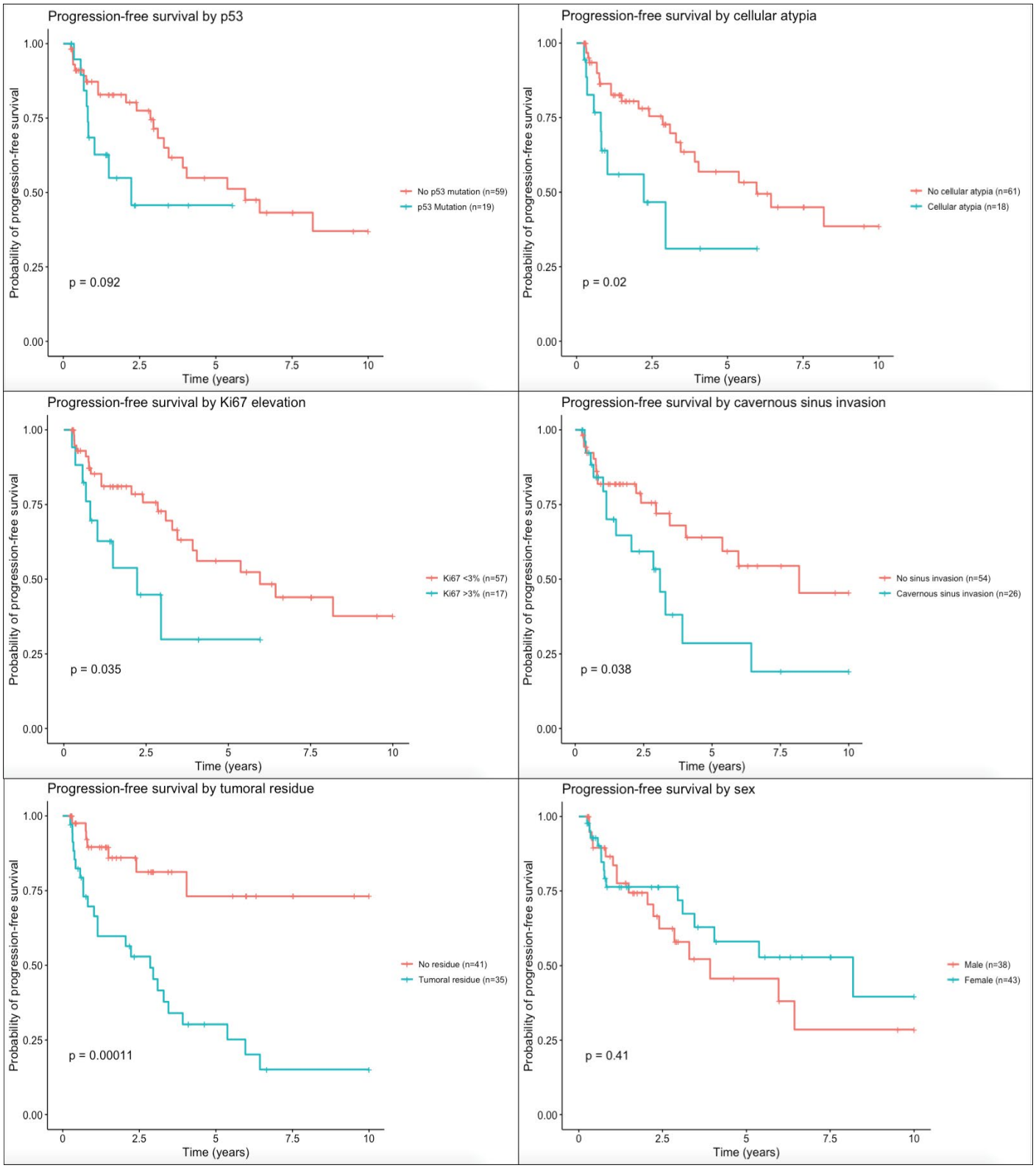


**Figure 2.** Progression-free survival curves according to different potential prognostic factors.

associated with progression: HR=4.0, 95%CI=1.56-10.31. Considering only preoperative factors, CSI was the only factor associated with progression: HR=2.25, 95%CI=1.04-4.93. Sex had no association with tumor progression.

## Discussion

This study found a median progression-free survival of 5.37 years in patients with pituitary adenomas treated with transsphenoidal surgery, and it identified tumor residue as the only prognostic factor for progression. In the first ~4 years after the procedure, 75% of patients with residue had progressed in contrast to those without residue where only 25% progressed. Other molecular, clinical and imaging features that were associated with tumor residue, such as CSI, can be useful in the prognosis for progression if postoperative imaging is not available. CSI is a frequent feature and it precludes complete resection in up to ⅔ of patients.

The histopathological analysis of patients included in this study revealed that up to a quarter of the operated patients presented gonadotroph adenomas, in accordance with what has been observed in studies from Brazil and Canada

[17-19]. Another quarter represented non-functioning adenomas, as it has also been reported previously [20]. The frequency of different histological origins for pituitary adenomas that we report might differ from other reports where usually lactotroph adenomas are the most common. This is explained by our study population which only included patients that required surgical intervention. As lactotroph tumours usually have an adequate response to medical treatment, these are not represented in our study [1,9,21-23].

When reviewed in the available literature, the frequency of CSI in postoperative MRI is similar to the value we report and might affect the speed at which the tumour recurs, most likely associated with the extent of tumour residue [12,13,24,25]. However, it is interesting to highlight that recurrence has been reported to occur in about 50% of pituitary tumours in which gross macroscopic resection is reported; in this cohort it occurred in 22.5% [13].

The presence of p53 mutation has been reported to be associated with CSI but not as an independent predictor of recurrence [12]. A significant association between CSI and p53 mutation was not detected in this study, although the small sample size could explain this discrepancy. Ki-67 was not identified as an independent factor for recurrence, which also differs with the concept that has been previously stated that a proliferation index above 3% is a predictor of malignancy and invasion potential [1,12,14-16].

As seen on the results, when comparing the group that had tumour progression and the ones that did not, the only variable analysed that was statistically significant was the presence of residual tumour on the postoperative MRI as an isolated marker. This does not exclude the possibility of the other variables being risk factors for progression given that our sample was small and does not provide enough statistical power. However, as interesting as it might be, once the time factor was included in the analysis the invasion of the cavernous sinus, presence of cellular atypia and a proliferation index (Ki-67) above 3% show that they do influence the speed at which the recurrence appears, therefore not being a predictive factor but rather a modifier of the recurrence.

## Conclusion

Our study further demonstrates that the presence of residual tumor in postoperative imaging aids as a predictor for tumor progression, and creates an opportunity for larger studies regarding the use of modifying factor for recurrence, such as invasion of the cavernous sinus, presence of cellular atypia and a proliferation index (Ki-67) above 3%, that do not affect whether or not the tumor recurs but that, when it does, how fast will it progress. Multicenter studies are warranted to further assess the usefulness of biological and imaging markers in the prognosis of recurrence after an initial transsphenoidal resection, which in the absence of post-operative MRI could be of value.

## Declaration of Non-duplication

I, Javier Lobato, certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium.

## Conflict of Interest

The authors declare no conflicts of interest.

## References


1. https://link.springer.com/article/10.1007/s12022-017-9498-z
2. Asa, Sylvia L., and Shereen Ezzat. "Aggressive pituitary tumors or localized pituitary carcinomas: Defining pituitary tumors." *Exp RevEndocrinol Metab* 11 (2016): 149-162.
3. Dolecek, Therese A, Jennifer M. Propp, Nancy E. Stroup and Carol Kruchko. "CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009." *Neuro-Oncol* 14 (2012): v1-v49.
4. Solari, Domenico, Francesco Zenga, Filippo F. Angileri and Andrea Barbanera, et al. "A survey on pituitary surgery in Italy." *World Neurosurg* 123 (2019): e440-e449.
5. Asa, Sylvia L. and Ozgur Mete. "What's new in pituitary pathology?" *Histopathol* 72 (2018): 133-141.
6. Juraschka, Kyle, Osaama H. Khan, Bruno L. Godoy and Eric Monsalves, et al. "Endoscopic endonasal transsphenoidal approach to large and giant pituitary adenomas: Institutional experience and predictors of extent of resection." *J Neurosurg* 121 (2014): 75-83.
7. Mehta, Gautam U. and Russell R. Lonser. "Management of hormone-secreting pituitary adenomas." *Neuro-Oncol* 19 (2017): 762-773.
8. Edal, A.L., K. Skjödt and H.J. Nepper-Rasmussen. "SIPAP: A new MR classification for pituitary adenomas." *Acta radiologica* 38 (1997): 30-36.
9. Ezzat, Shereen, Sylvia L. Asa, William T. Couldwell and Charles E. Barr, et al. "The prevalence of pituitary adenomas: A systematic review." *Cancer: Interdiscip Int J Am Cancer Soc* 101 (2004): 613-619.
10. Clayton, R.N., D. Raskauskiene, R.C. Reulen and P.W. Jones. "Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: Audit and meta-analysis of literature." *J Clin Endocrinol Metabo* 96 (2011): 632-642.
11. Dekkers, O. M, N. R. Biermasz, A. M. Pereira and J. A. Romijn, et al. "Mortality in acromegaly: a metaanalysis." *J Clin Endocrinol Metab* 93 (2008): 61-67.
12. Hasanov, Rovshan, Berna İmge Aydoğan, Saba Kiremitçi and Esra Erden, et al. "The prognostic roles of the Ki-67 proliferation index, p53 expression, mitotic index, and radiological tumor invasion in pituitary adenomas." *Endocrine Pathol* 30 (2019): 49-55.
13. Park, Paul, William F. Chandler, Ariel L. Barkan and John J. Orrego, et al. "The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas." *Neurosurg* 55 (2004): 100-107.
14. Zada, Gabriel, Whitney W. Woodmansee, Shakti Ramkissoon and Jordan Amadio, et al. "Atypical pituitary adenomas: Incidence, clinical characteristics, and implications." *J Neurosurg* 114 (2011): 336-344.
15. Matsuyama, Junko. "Ki-67 expression for predicting progression of postoperative residual pituitary adenomas: correlations with clinical variables." *Neurologia Medico-Chirurgica* 52 (2012): 563-569.
16. Thapar, Kamal, Kalman Kovacs, Bernd W. Scheithauer and Lucia Stefaneanu, et al. "Proliferative activity and invasiveness among pituitary adenomas and carcinomas: an analysis using the MIB-1antibody." *Neurosurg* 38 (1996): 99-107.
17. Deng, Yinhui, Yanli Li, Xi Li and Lisha Wu, et al. "Long-term results of gamma knife Radiosurgery for postsurgical residual or recurrent nonfunctioning pituitary adenomas." *Int J Med Sci* 17 (2020): 1532.
18. Mete, Ozgur, Amber Cintosun, Irwin Pressman and Sylvia L. Asa. "Epidemiology and biomarker profile of pituitary adenohypophysial tumors." *Modern Pathol* 31 (2018): 900-909.
19. Gondim, Jackson A., Joao Paulo C. Almeida, Lucas Alverne F. Albuquerque and Michele Schops, et al. "Endoscopic endonasal approach for pituitary adenoma: Surgical complications in 301 patients." *Pituitary* 14 (2011): 174-183.
20. Tjörnstrand, Axel, Kerstin Gunnarsson, Max Evert and Erik Holmberg, et al. "The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011." *European J Endocrinol* 171 (2014): 519-526.
21. Mindermann, Thomas and Charles B. Wilson. "Age-related and gender-related occurrence of pituitary adenomas." *Clin Endocrinol* 41 (1994): 359-364.
22. Han, Yan-Long, Dong-Ming Chen, Cheng Zhang and Miao Pan, et al. "Retrospective analysis of 52 patients with prolactinomas following endoscopic endonasal transsphenoidal surgery." *Med* 97 (2018).
23. Gold, Ellen B. "Epidemiology of pituitary adenomas." *Epidemiologic Rev* 3 (1981): 163-183.
24. Comtois, Ronald, Hugues Beauregard, Maurice Somma and Omar Serri, et al. "The clinical and endocrine outcome to trans-sphenoidal microsurgery of nonsecreting pituitary adenomas." *Cancer* 68 (1991): 860-866.
25. Losa, Marco, Alberto Franzin, Francesca Mangili and Maria Rosa Terreni, et al. "Proliferation index of nonfunctioning pituitary adenomas: Correlations with clinical characteristics and long-term follow-up results." *Neurosurg* 47 (2000): 1313-1319.


**How to cite this article:** Lobato-Polo, Javier. "Endoscopic Transsphenoidal Surgery: Factors Associated with Tumor Progression in Pituitary Adenomas." J Cancer Sci Ther 14 (2022): 530.