Physiological growth hormone replacement and rate of recurrence of craniopharyngioma: the Genentech National Cooperative Growth Study

Timothy R. Smith, MD, PhD, MPH,¹ David J. Cote, BS,¹ John A. Jane Jr., MD,² and Edward R. Laws Jr., MD¹

¹Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts; and ²Department of Neurosurgery, University of Virginia, Charlottesville, Virginia

OBJECTIVE The object of this study was to establish recurrence rates in patients with craniopharyngioma postoperatively treated with recombinant human growth hormone (rhGH) as a basis for determining the risk of rhGH therapy in the development of recurrent tumor.

METHODS The study included 739 pediatric patients with craniopharyngioma who were naïve to GH upon entering the Genentech National Cooperative Growth Study (NCGS) for treatment. Reoperation for tumor recurrence was documented as an adverse event. Cox proportional-hazards regression models were developed for time to recurrence, using age as the outcome and enrollment date as the predictor. Patients without recurrence were treated as censored. Multivariate logistic regression was used to examine the incidence of recurrence with adjustment for the amount of time at risk.

RESULTS Fifty recurrences in these 739 surgically treated patients were recorded. The overall craniopharyngioma recurrence rate in the NCGS was 6.8%, with a median follow-up time of 4.3 years (range 0.7–6.4 years.). Age at the time of study enrollment was statistically significant according to both Cox ($p = 0.0032$) and logistic ($p < 0.001$) models, with patients under 9 years of age more likely to suffer recurrence (30 patients [11.8%], 0.025 recurrences/yr of observation, $p = 0.0097$) than those ages 9–13 years (17 patients [6.0%], 0.17 recurrences/yr of observation) and children older than 13 years (3 patients [1.5%], 0.005 recurrences/yr of observation).

CONCLUSIONS Physiological doses of GH do not appear to increase the recurrence rate of craniopharyngioma after surgery in children, but long-term follow-up of GH-treated patients is required to establish a true natural history in the GH treatment era.

<http://thejns.org/doi/abs/10.3171/2016.4.PEDS16112>

KEY WORDS craniopharyngioma; growth hormone; recurrence; oncology

CRANIOPHARYNGIOMAS are histologically benign tumors first described over 150 years ago. They are thought to arise from squamous cells resulting from partial involution of the embryonic vestigial hypophyseal-pharyngeal duct, also known as the “craniopharyngeal duct.”^{30,47} They may represent one end of a spectrum of diseases spanning Rathke's cleft cysts, arachnoid cysts, colloid cysts, cystic pituitary adenomas, epidermoid cysts, and dermoid cysts.⁴⁷ Although benign histologically, their anatomical location, physical characteristics, biological behavior, and associated morbidity and mortality make craniopharyngiomas one of the most destructive lesions of the sellar region.⁴⁰

Craniopharyngiomas comprise approximately 1.2%–4% of all intracranial tumors in children.^{3,20,24,40} They can

be detected at any age, with peak incidence rates in children 5–14 years old and adults 50–74 years of age.²¹ Approximately 340 cases are diagnosed and treated annually in the United States.⁴² The management of craniopharyngiomas continues to be an area of intense controversy in pediatric endocrinology, neurosurgery, and radiation oncology. Major questions exist regarding the optimal surgical goals (for example, gross-total resection vs subtotal resection followed by adjuvant therapy), the ideal timing and modality of radiation therapy, and the role of pituitary hormone replacement therapy.⁵ Some studies have reported that physiological growth hormone (GH) replacement after resection of craniopharyngioma may increase the recurrence rate of these lesions, while others indicate that GH replacement is safe and effective.^{9,11,22,27,31,46}

ABBREVIATIONS GH = growth hormone; NCGS = National Cooperative Growth Study; rhGH = recombinant human GH.

SUBMITTED February 24, 2016. **ACCEPTED** April 5, 2016.

INCLUDE WHEN CITING Published online June 10, 2016; DOI: 10.3171/2016.4.PEDS16112.

TABLE 1. Recurrence rate of craniopharyngioma by age cohort after GH replacement therapy

Cohort Enrollment Age (yrs)	No. of Patients	Mean Time at Risk (yrs) $\pm$ SD	No. of Recurrences	% Patients w/ Recurrence	No. of Recurrences/Yr of Observation
<9	254	4.7 $\pm$ 2.3	30	11.8%	0.025
≥ 9 , <13	281	3.5 $\pm$ 2.0	17	6.0%	0.017
≥ 13	204	2.7 $\pm$ 1.5	3	1.5%	0.005

The Genentech National Cooperative Growth Study (NCGS) was designed to monitor the efficacy and adverse event profile of recombinant human GH (rhGH) therapy in pediatric patients receiving rhGH manufactured by Genentech, Inc. Included in the patients enrolled in the NCGS were those with a history of GH deficiency secondary to surgical treatment for craniopharyngioma. This report is an analysis of the correlation between the recurrence rate of surgically treated craniopharyngiomas in children treated with postoperative physiological rhGH replacement therapy whose data were entered into the NCGS.

Methods

Description of the NCGS

The NCGS core study (registered with the ClinicalTrials.gov database, registration no. NCT00097539) is a multicenter, open-label, observational, postmarketing surveillance study of the Genentech rhGH products Protropin, Nutropin, Nutropin AQ, and Nutropin Depot, which were marketed at different times in the United States and Canada. The study includes male and female patients treated, between 1986 and 2005, with one or more of the aforementioned products for pediatric growth disorders for which GH is indicated. Subjects initiating or receiving therapy with one of these products could be voluntarily enrolled in the study and followed up throughout the course of their treatment. Subjects were excluded from study entry if they were being treated with a non-Genentech rhGH product, had closed epiphyses, or had active neoplasia. Intracranial lesions were required to be inactive (without progression either clinically or radiologically), and antitumor therapy must have been completed for a period of 12 months prior to the institution of rhGH therapy in all included patients. Data for children enrolled in the NCGS with a diagnosis of preexisting craniopharyngioma were extracted for analysis in our study.

Patients

A total of 739 patients who had a craniopharyngioma prior to the initiation of rhGH therapy and who also had follow-up information in the NCGS database were included in this analysis. The data cutoff for the analysis was May 2005. Patients were divided into 3 age groups for study: < 9 years, 9–13 years, and > 13 years. This analysis was restricted to the first 7 years from enrollment because the data were too sparse after this time period. The average dose of rhGH in this patient group was 0.253 ± 0.07 mg/kg/wk. As part of the NCGS follow-up of the children while on rhGH, investigators at the Genentech Department of Medical Information reported adverse events; one of the adverse events reported for patients enrolled

with a craniopharyngioma diagnosis is recurrence of the craniopharyngioma—defined as clinical progression, tumor growth on imaging, or both. Reporting tumor recurrence was mandated by the study protocol. Therefore, the NCGS data provide a reasonable assessment of children diagnosed with craniopharyngioma who are treated with rhGH and subsequently experience recurrence of the craniopharyngioma.

Results

The overall incidence of recurrence in this analysis of 739 patients with craniopharyngioma treated with rhGH replacement was 6.8% (50 recurrences), with a median follow-up of 4.3 years (range 0.7–6.4 years) after initiation of GH therapy (Table 1). Age at the time of study enrollment was statistically significant according to both Cox proportional-hazards ($p = 0.0032$) and multivariate logistic regression ($p < 0.001$) models, with patients under 9 years of age more likely to develop recurrence (30 [11.8%], 0.025 recurrences/yr of observation) than those ages 9–13 years (17 [6.0%], 0.017 recurrences/yr of observation) and those older than 13 years (3 [1.5%], 0.005 recurrences/yr of observation; $p = 0.0097$; Fig. 1). When monitored longer on GH therapy, all age groups were found to be more likely to develop recurrence.

Discussion

After the resection of craniopharyngiomas, many patients retain or develop new endocrine dysfunction. There is some evidence that the most frequent hormone deficiency in all types of central nervous system tumors, regardless of the treatment received, is GH.¹⁷ Often these patients—particularly pediatric patients—require hormone replacement to restore normal physiology. For pediatric patients, GH is perhaps most important to their healthy growth and development, yet its use remains controversial. There is continuing concern that long-term GH replacement may increase the likelihood of craniopharyngioma recurrence after surgery.^{2,8–10,12,26,33,37,39}

It is well known that GH has both mitogenic and antiapoptotic functions.^{4,48} Several studies have independently shown that GH can exert direct antiapoptotic effects on human cancers of various kinds, including breast, brain, colon, and prostate.^{2,4,28,37–39,48} The mitogenic and antiapoptotic properties of GH have led to some concern that long-term GH replacement could increase the recurrence rate or decrease the time to recurrence in patients who have undergone resection of craniopharyngioma. In 1998, an analysis of 488 patients (median follow-up 3.7 years) from the Kabi Pharmacia International Growth Study (KIGS)

FIG. 1. Kaplan-Meier plot of cumulative recurrence of craniopharyngioma in children with GH replacement after resection. Figure is available in color online only.

database and Upjohn International Growth database demonstrated recurrence rates similar to those reported in the present study (54 patients [11.1%], 0.045 recurrences/yr of observation).³¹ Using the same database in 2006, Darendeliler et al. reported similar recurrence rates in 1038 patients treated with rhGH after a median treatment duration of 2.8 years (121 patients [11.6%], 0.036 recurrences/yr of observation).¹⁰ An overview of literature rates of craniopharyngioma recurrence after conventional surgical and adjunctive care is presented in Table 2.^{6,7,11,13,14,18,19,23,32,34,36,41,44,46} Yet recurrence is not the only concern when GH is replaced. A recent study from France described a possible association between GH therapy during childhood among “low-risk patients” (isolated GH deficiency, idiopathic short stature, and small for gestational age) and increased risk for hemorrhagic stroke in young adulthood, though its conclusions have been contested.²⁹

Growth hormone replacement is an effective therapy that often restores normal physiological conditions in patients who otherwise would have severe endocrine deficiencies. In 2003, Gleeson et al. reported that, over the last 25 years, GH therapy in childhood survivors of brain tumors improved final height for patients undergoing both cranial ($r = 0.5$, $p = 0.03$) and craniospinal ($r = 0.6$, $p < 0.001$) operations.¹⁶ Also in 2003, Monson reported that GH replacement helps reduce the significant morbidity associated with GH deficiency by improving central fat mass and reducing serum total and low-density lipoprotein cholesterol.²⁶ He also pointed to GH replacement as an important contributor to psychological well-being that helps resolve some of the psychosocial issues that GH-deficient pediatric patients face.²⁶ Geffner et al. reported excellent linear growth in a series of 199 prepubertal patients undergoing rhGH therapy after resection of a craniopharyngioma; however, they noted that it had

no ameliorative effects on morbid weight gain, a common side effect of resection of tumors in the region of the hypothalamus.¹⁵ Careful dosing and monitoring of rhGH is crucial to the success of GH replacement therapy, as the elevation of GH above physiological levels can have adverse effects.^{1,9,31,33,35,45}

The major limitation of this study is its inclusion criteria. Children followed in this study clearly do not represent all potential GH-treated patients with craniopharyngiomas; one would suspect that patients who fare poorly after surgery or other forms of therapy or who have significant residual tumor after resection might never be considered candidates for GH replacement therapy. Additionally, the timing of the initiation of GH replacement certainly varies from one child to another. The NCGS protocol follows the guidelines of the 2003 Lawson Wilkins Pediatric Endocrine Society by stating that “prudence would dictate waiting one year after completion of tumor therapy with no evidence of further tumor growth before initiating GH therapy.”⁴⁵ Although craniopharyngiomas are not truly malignant, the majority of NCGS patients were treated after at least 1 year from primary therapy; therefore, the rate of recurrence in the 1st year is unlikely to have been captured. Most recurrences have been reported to occur in the first 3 years after surgery.⁴² The actual length of exposure to GH must be considered as one of the factors influencing recurrence in these patients. If there is a relationship between GH replacement and recurrence rates, it would be important to calculate the outcome according to length of exposure and doses of GH. Additional limitations due to the nature of the NCGS relate to missing data, including absent data on possible differences in postoperative adjuvant treatment rates among each cohort, extent of initial resection, and frequency of postoperative MRI monitoring.

TABLE 2. Overall craniopharyngioma recurrence rates in the neurosurgical literature

Authors & Year	No. of Patients	Recurrence Rate	Mean Time to Recurrence (mos)
Katz, 1975	40	12%	48
Shapiro et al., 1979	60	23%	29
Thomsett et al., 1980	42	29%	43
Richmond et al., 1980	32	38%	>60
Carmel et al., 1982	45	50%	67
Clayton et al., 1988	2	0	
Weiss et al., 1989	31	14%	25
Yaşargil et al., 1990	144	7%	—
Fischer et al., 1990	37	57%	—
Hetelekidis et al., 1993	52	25%	45
Fahlbusch et al., 1999	148	11%	<71
Duff et al., 2000	121	17%	—
Gupta et al., 2006	116	13%	16
Schoenfeld et al., 2012	122	25%	12

— = not reported.

Despite these limitations, this report encompasses the largest group of children with craniopharyngiomas ever analyzed for recurrence and provides a valuable resource to assess recurrence specifically in a GH-treated population. The recurrence rates in these children were as low as or lower than those seen in other careful studies of children who have undergone surgical removal of craniopharyngiomas.^{10,27} Specifically, the rate of recurrence of craniopharyngioma after rhGH therapy reported here, 6.8% over 4.3 years of follow-up, compares favorably with the contemporary literature rates of 11%–16%, though a limitation of our study was its relatively shorter median follow-up period.^{10,27} While there is some cell culture evidence showing that craniopharyngioma cell growth is promoted by GH exposure in vitro, perhaps related to the expression of GH receptors and insulin-like growth factor-1 receptors on the tumor, clinical studies do not support this correlation.²⁵ Long-term rhGH replacement therapy does not appear to affect the progression-free survival rate in patients with craniopharyngiomas.^{22,27,37,43}

Conclusions

This analysis provides evidence that there is very low, if any, risk that physiological rhGH replacement therapy given to children who have undergone craniopharyngioma resection facilitates tumor recurrence. This evidence may allow for more systematic and effective GH replacement therapy in these children, for whom the psychosocial aspects of GH deficiency can significantly impede their quality of life.

Acknowledgments

We thank Barbara Lippe, MD; Bert Bakker, MD, PhD; Tom Maneatis, MD; Kevin Connelly; Sumeet Brar; Robert Masi; Joan Jacobs; Winifred Werther; and Jim Frane (Genentech, San Francisco, California) for their contributions to this study.

References

- Arslanian SA, Becker DJ, Lee PA, Drash AL, Foley TP Jr: Growth hormone therapy and tumor recurrence. Findings in children with brain neoplasms and hypopituitarism. **Am J Dis Child** **139**:347–350, 1985
- Barabutis N, Schally AV: Knocking down gene expression for growth hormone-releasing hormone inhibits proliferation of human cancer cell lines. **Br J Cancer** **98**:1790–1796, 2008
- Barkhoudarian G, Laws ER: Craniopharyngioma: history. **Pituitary** **16**:1–8, 2013
- Bogazzi F, Ultimieri F, Raggi F, Russo D, Vanacore R, Guida C, et al: Growth hormone inhibits apoptosis in human colonic cancer cell lines: antagonistic effects of peroxisome proliferator activated receptor-gamma ligands. **Endocrinology** **145**:3353–3362, 2004
- Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. **J Neurosurg** **89**:547–551, 1998
- Carmel PW, Antunes JL, Chang CH: Craniopharyngiomas in children. **Neurosurgery** **11**:382–389, 1982
- Clayton PE, Price DA, Shalet SM, Gattamaneni HR: Craniopharyngioma recurrence and growth hormone therapy. **Lancet** **331**:642, 1988
- Clayton PE, Shalet SM, Gattamaneni HR, Price DA: Does growth hormone cause relapse of brain tumours? **Lancet** **329**:711–713, 1987
- Cowell CT, Dietsch S: Adverse events during growth hormone therapy. **J Pediatr Endocrinol Metab** **8**:243–252, 1995
- Darendeliler F, Karagiannis G, Wilton P, Ranke MB, Albertsson-Wikland K, Anthony Price D: Recurrence of brain tumours in patients treated with growth hormone: analysis of KIGS (Pfizer International Growth Database). **Acta Paediatr** **95**:1284–1290, 2006
- Duff J, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck CD, Scheithauer BW: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery** **46**:291–305, 2000
- Ergun-Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W, et al: Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. **J Clin Endocrinol Metab** **91**:3494–3498, 2006
- Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg** **90**:237–250, 1999
- Fischer EG, Welch K, Shillito J Jr, Winston KR, Tarbell NJ: Craniopharyngiomas in children. Long-term effects of conservative surgical procedures combined with radiation therapy. **J Neurosurg** **73**:534–540, 1990
- Geffner M, Lundberg M, Koltowska-Häggström M, Abs R, Verhelst J, Erfurth EM, et al: Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). **J Clin Endocrinol Metab** **89**:5435–5440, 2004
- Gleeson HK, Stoeter R, Ogilvy-Stuart AL, Gattamaneni HR, Brennan BM, Shalet SM: Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumors receiving GH replacement. **J Clin Endocrinol Metab** **88**:3682–3689, 2003
- Güemes Hidalgo M, Muñoz Calvo MT, Fuente Blanco L, Villalba Castaño C, Martos Moreno GA, Argente J: [Endocrinological outcome in children and adolescents survivors of central nervous system tumours after a 5 year follow-up.] **An Pediatr (Barc)** **80**:357–364, 2014 (Span)
- Gupta DK, Ojha BK, Sarkar C, Mahapatra AK, Sharma BS, Mehta VS: Recurrence in pediatric craniopharyngiomas: analysis of clinical and histological features. **Childs Nerv Syst** **22**:50–55, 2006

19. Hetelekidis S, Barnes PD, Tao ML, Fischer EG, Schneider L, Scott RM, et al: 20-year experience in childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys* **27**:189–195, 1993
20. Jane JA Jr, Laws ER: Craniopharyngioma. *Pituitary* **9**:323–326, 2006
21. Karavitaki N, Cudlip S, Adams CB, Wass JA: Craniopharyngiomas. *Endocr Rev* **27**:371–397, 2006
22. Karavitaki N, Warner JT, Marland A, Shine B, Ryan F, Arnold J, et al: GH replacement does not increase the risk of recurrence in patients with craniopharyngioma. *Clin Endocrinol (Oxf)* **64**:556–560, 2006
23. Katz EL: Late results of radical excision of craniopharyngiomas in children. *J Neurosurg* **42**:86–93, 1975
24. Laws ER Jr, Jane JA Jr: Craniopharyngioma. *J Neurosurg Pediatr* **5**:27–29, 2010
25. Li Q, You C, Liu L, Rao Z, Sima X, Zhou L, et al: Craniopharyngioma cell growth is promoted by growth hormone (GH) and is inhibited by tamoxifen: involvement of growth hormone receptor (GHR) and IGF-1 receptor (IGF-1R). *J Clin Neurosci* **20**:153–157, 2013
26. Monson JP: Long-term experience with GH replacement therapy: efficacy and safety. *Eur J Endocrinol* **148** (Suppl 2):S9–S14, 2003
27. Olsson DS, Buchfelder M, Wiendieck K, Kremenevskaja N, Bengtsson BA, Jakobsson KE, et al: Tumour recurrence and enlargement in patients with craniopharyngioma with and without GH replacement therapy during more than 10 years of follow-up. *Eur J Endocrinol* **166**:1061–1068, 2012
28. Packer RJ, Boyett JM, Janss AJ, Stavrou T, Kun L, Wisoff J, et al: Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. *J Clin Oncol* **19**:480–487, 2001
29. Poidvin A, Touzé E, Ecosse E, Landier F, Béjot Y, Giroud M, et al: Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology* **83**:780–786, 2014
30. Prabhu VC, Brown HG: The pathogenesis of craniopharyngiomas. *Childs Nerv Syst* **21**:622–627, 2005
31. Price DA, Wilton P, Jönsson P, Albertsson-Wikland K, Chatelain P, Cutfield W, et al: Efficacy and safety of growth hormone treatment in children with prior craniopharyngioma: an analysis of the Pharmacia and Upjohn International Growth Database (KIGS) from 1988 to 1996. *Horm Res* **49**:91–97, 1998
32. Richmond IL, Wara WM, Wilson CB: Role of radiation therapy in the management of craniopharyngiomas in children. *Neurosurgery* **6**:513–517, 1980
33. Rohrer TR, Langer T, Grabenbauer GG, Buchfelder M, Glowatzki M, Dörr HG: Growth hormone therapy and the risk of tumor recurrence after brain tumor treatment in children. *J Pediatr Endocrinol Metab* **23**:935–942, 2010
34. Schoenfeld A, Pekmezci M, Barnes MJ, Tihan T, Gupta N, Lamborn KR, et al: The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. *J Neurooncol* **108**:133–139, 2012
35. Shalet SM, Brennan BM, Reddingius RE: Growth hormone therapy and malignancy. *Horm Res* **48** (Suppl 4):29–32, 1997
36. Shapiro K, Till K, Grant DN: Craniopharyngiomas in childhood. A rational approach to treatment. *J Neurosurg* **50**:617–623, 1979
37. Sklar CA, Mertens AC, Mitby P, Occhiogrosso G, Qin J, Heller G, et al: Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* **87**:3136–3141, 2002
38. Stangelberger A, Schally AV, Varga JL, Zarandi M, Szepe-shazi K, Armatas P, et al: Inhibitory effect of antagonists of bombesin and growth hormone-releasing hormone on orthotopic and intraosseous growth and invasiveness of PC-3 human prostate cancer in nude mice. *Clin Cancer Res* **11**:49–57, 2005
39. Swerdlow AJ, Reddingius RE, Higgins CD, Spoudeas HA, Phipps K, Qiao Z, et al: Growth hormone treatment of children with brain tumors and risk of tumor recurrence. *J Clin Endocrinol Metab* **85**:4444–4449, 2000
40. Thapar K, Kohata T, Laws ER, et al: Parasellar lesions other than pituitary adenomas, in Powell MP, Lightman SL, Laws ER (eds): *Management of Pituitary Tumors: The Clinician's Practical Guide*, ed 2. Totowa, NJ: Humana Press, 2003
41. Thomsett MJ, Conte FA, Kaplan SL, Grumbach MM: Endocrine and neurologic outcome in childhood craniopharyngioma: Review of effect of treatment in 42 patients. *J Pediatr* **97**:728–735, 1980
42. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. *J Neurosurg* **97**:3–11, 2002
43. Weiner HL, Wisoff JH, Rosenberg ME, Kupersmith MJ, Cohen H, Zagzag D, et al: Craniopharyngiomas: a clinicopathological analysis of factors predictive of recurrence and functional outcome. *Neurosurgery* **35**:1001–1011, 1994
44. Weiss M, Sutton L, Marcial V, Fowble B, Packer R, Zimmerman R, et al: The role of radiation therapy in the management of childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys* **17**:1313–1321, 1989
45. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, et al: Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *J Pediatr* **143**:415–421, 2003
46. Yaşargil MG, Curcic M, Kis M, Siegenthaler G, Teddy PJ, Roth P: Total removal of craniopharyngiomas. Approaches and long-term results in 144 patients. *J Neurosurg* **73**:3–11, 1990
47. Zada G, Lin N, Ojerholm E, Ramkissoon S, Laws ER: Craniopharyngioma and other cystic epithelial lesions of the sellar region: a review of clinical, imaging, and histopathological relationships. *Neurosurg Focus* **28**(4):E4, 2010
48. Zeitler P, Siriwardana G: Antagonism of endogenous growth hormone-releasing hormone (GHRH) leads to reduced proliferation and apoptosis in MDA231 breast cancer cells. *Endocrine* **18**:85–90, 2002

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: Laws, Smith, Jane. Acquisition of data: Smith, Cote. Analysis and interpretation of data: Cote. Drafting the article: Laws, Cote. Critically revising the article: Laws, Smith, Jane. Reviewed submitted version of manuscript: Laws. Approved the final version of the manuscript on behalf of all authors: Laws. Statistical analysis: Smith. Administrative/technical/material support: Laws, Smith, Cote. Study supervision: Laws, Jane.

Correspondence

Edward R. Laws, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St., PBB3, Boston, MA 02115. email: elaws@partners.org.