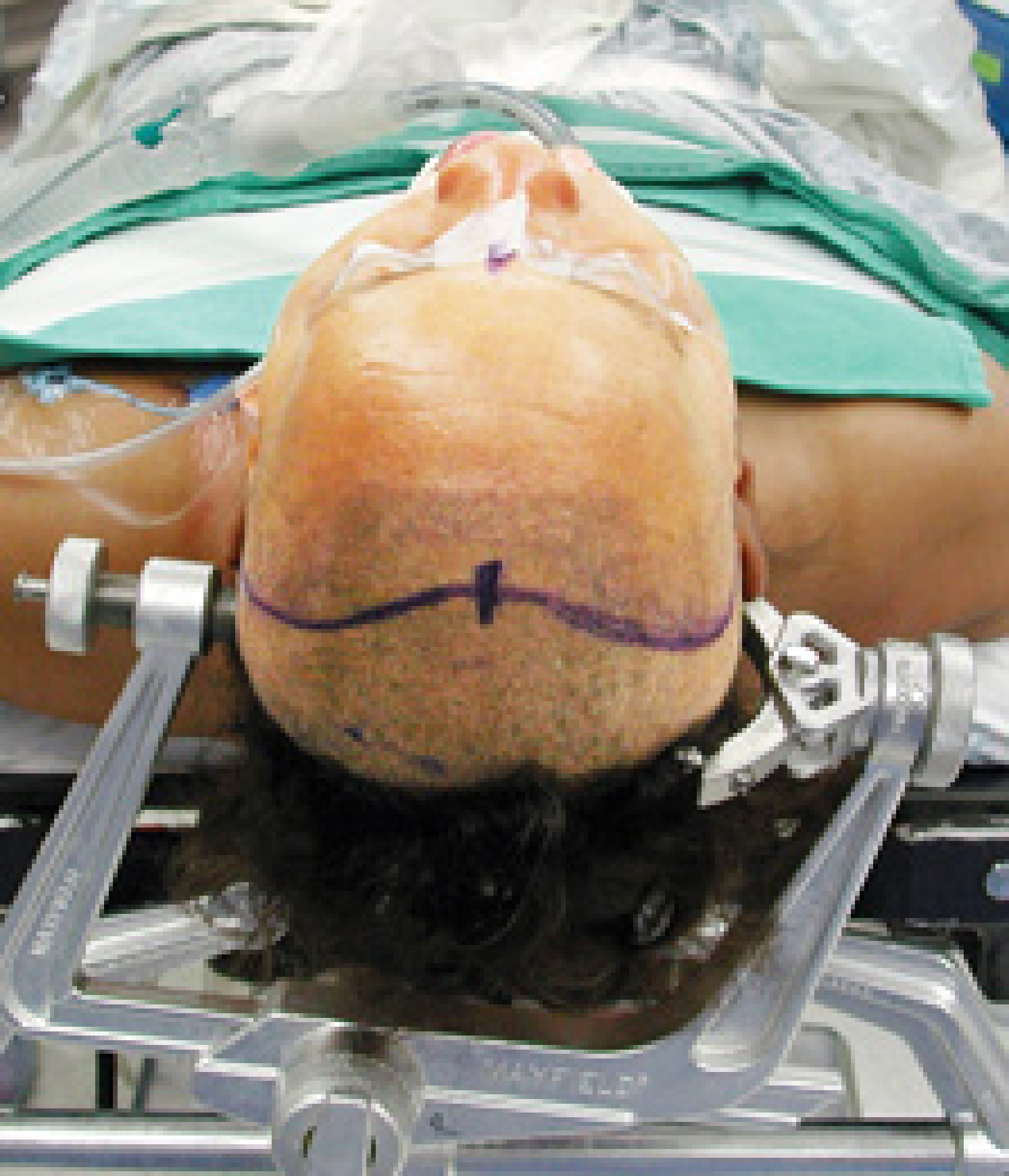

(DOI: 10.3171/2010.3.FOCUS.APR2010.INTRO)

Introduction: Craniopharyngioma

Jeffrey H. Wisoff, M.D.,[1] John A. Jane Jr.,[2] Warren Selman, M.D.,[3] and Rudolf Fahlbusch, M.D., Ph.D.[4]

[1]Division of Pediatric Neurosurgery, New York University Langone Medical Center, New York, New York, [2]Department of Neurosurgery, University of Virginia Health System, Charlottesville, Virginia; [3]Department of Neurological Surgery, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, Ohio; and [4]Neuroendocrine Surgery, International Neuroscience Institute, Hannover, Germany

In the 8 decades since Cushing prophetically described craniopharyngiomas as "one of the most baffling problems to the neurosurgeon,"[2] few subjects in neurosurgery have inspired more controversy than the management of these tumors. The rarity of these tumors has limited both individual neurosurgeons and most institutions from developing experience and expertise in their management: in the US, fewer than 350 craniopharyngiomas are diagnosed annually in the combined pediatric and adult population.[1]

The philosophy of curative treatment in patients with craniopharyngiomas is predicated on patients having unimpeded access to long-term medical care and the personal or societal financial resources for the costs of lifetime hormone replacement therapy. Both partial resection with adjuvant irradiation and primary gross-total resection carry similar rates of long-term disease control and recurrence in high-volume centers.[3,5] This level of care is nearly universally available in North America, Western Europe, Japan, and other industrialized nations but may be extremely limited in other countries. Primary irradiation without resection, intracystic therapies, and palliative strategies may be more appropriate in those settings.

With excellent tumor control available from a variety of treatment paradigms, it is necessary to search for other clinical features or outcome parameters that may differentiate the risks and benefits for individual patients and to help fashion a cohesive therapeutic strategy. The ultimate test of which treatment approach will be appropriate may not depend on initial tumor control but rather the ability to salvage and cure patients with recurrent tumors in conjunction with an assessment of the impact of the treatment modality on the long-term quality of life.[4]

This issue of *Neurosurgical Focus* seeks to enhance our understanding of the biology, risk factors, therapeutic options, and long-term consequences of the management of craniopharyngioma. Four of the original articles provide insights into the pathogenesis and clinicopathology of craniopharyngiomas, describe a novel classification for stratifying the risk of hypothalamic injury in adults, present a proposal for a standardized metric to evaluate pre- and posttreatment functional status, and expand our knowledge of endocrine, ophthalmological, and vascular sequelae of treatment. Nuances of surgical management and an expansion of the results of endoscopic approaches are presented in 3 articles. Contemporary standards for radiation therapy are reviewed by Merchant and Kiehna while the paper by Veeravagu et al. describes advantages of stereotactic radiation techniques. The utilization of intracystic therapies is described by the Vancouver group. Cavalheiro and colleagues' presentation of the results of a multicenter study of intracystic interferon demonstrates both the efficacy of treatment and the necessity for multiinstitutional cooperative trials to provide therapeutic advances in this rare disease.

We hope that this issue of *Neurosurgical Focus* will be stimulating and challenge the reader to reassess his/her understanding of craniopharyngiomas and their treatment

References

1. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. **J Neurosurg 89:**547–551, 1998
2. Cushing H: The craniopharyngiomas, in **Intracranial Tumors—Notes Upon a Series of Two Thousand Verified Cases with Surgical Mortality Percentages Thereto.** Springfield, IL: Charles C Thomas, 1932
3. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
4. Sands SA, Milner JS, Goldberg J, Mukhi V, Moliterno JA, Maxfield C, et al: Quality of life and behavioral follow-up study of pediatric survivors of craniopharyngioma. **J Neurosurg 103:**302–311, 2005
5. Sanford RA: Craniopharyngioma: results of survey of the American Society of Pediatric Neurosurgery. **Pediatr Neurosurg 21:**39–43, 1994

Neurosurg Focus 28 (4):E1, 2010

Molecular pathogenesis of craniopharyngioma: switching from a surgical approach to a biological one

Benedetta Ludovica Pettorini, M.D., Paolo Frassanito, M.D., Massimo Caldarelli, M.D., Gianpiero Tamburrini, M.D., Luca Massimi, M.D., and Concezio Di Rocco, M.D.

Paediatric Neurosurgery Unit, Catholic University of Rome, Italy

Craniopharyngioma has long been considered a benign tumor because of its pathological aspect. This primordial view of craniopharyngioma fit with the primitive treatment attempts based on blind resection of the tumor each time it recurred. The limits of this management strategy were proven early by the high morbidity related to the resection and recurrence risk despite radical lesion removal. Nowadays, craniopharyngioma must be considered a complex molecular disease, and a detailed explanation of the mechanisms underlying its aggressive biological and clinical behavior, despite some benign pathological features, would be the first step toward defining the best management of craniopharyngioma. Indeed, advances in the knowledge of the molecular mechanisms at the base of craniopharyngioma oncogenesis will lead to comprehension of the critical checkpoints involved in neoplastic transformation. The final research target will be the definition of new biological agents able to reverse the neoplastic process by acting on these critical checkpoints. This biological approach will lead to a refined therapy combining higher efficacy and safety with lower morbidity. In this paper the authors reveal state-of-the-art comprehension of the molecular biology of craniopharyngioma and the consequent therapeutic implications. *(DOI: 10.3171/2010.1.FOCUS09300)*

Key Words • **craniopharyngioma** • **molecular biology** • **oncogenetic mechanism**

Craniopharyngioma accounts for 5–10% of childhood tumors. Two histological variants are known: adamantinomatous, typically occurring in the pediatric population, and the squamous papillary form, frequent in adults. These histological forms differ in pathological features, reflecting a distinct oncogenetic origin. Adamantinomatous craniopharyngiomas arise from a neoplastic transformation of the epithelial remnants of the craniopharyngeal duct, involuting during embryological development of the adenohypophysis. The squamous papillary variant arises from a metaplastic process involving the adenohypophyseal cells in the pars tuberalis, leading to the formation of squamous cell nests.

Although a purely surgical approach aimed at total resection has been advocated to cure craniopharyngiomas, this management strategy is often burdened by high morbidity because of the critical relationships of this tumor with neighboring vascular and nervous structures.[21,37] The identification of new therapies would help to comprehend the molecular mechanisms underlying the clinically aggressive behavior of these lesions. Although recent studies have been aimed at clarifying some aspect of neoplastic cell transformation, the molecular pathogenesis of craniopharyngiomas has not been systematically examined in literature. In this paper we attempted to critically review the recent literature on the oncogenetic mechanisms of craniopharyngiomas and their therapeutic implications.

Abbreviations used in this paper: IFN = interferon; MIF = macrophage-inhibiting factor; RAR = retinoic acid receptor; VEGF = vascular endothelial growth factor.

Molecular Pathogenesis

The biological mechanisms at the base of the aggressive neoplastic nature of a lesion are as follows: 1) cellular proliferation depending on failure of the apoptotic pathway and activation of the antiapoptotic pathway or on sensitivity to growth factors, 2) cellular anaplasia, 3) local invasiveness, and 4) neoangiogenesis. These features are as strictly interrelated as the molecular mechanisms underlying them. In addition, every neoplastic lesion has another typical skill—namely, elusion of the immune system, which is essential to its existence. In craniopharyngiomas, the role of the immune response is even more complex, as discussed below.

Cellular Proliferation: Failure of the Apoptotic Pathway and Activation of the Antiapoptotic Pathway

Beta-Catenin and Wnt. Dysregulation of the Wnt signaling pathway could be a molecular mechanism involved in neoplastic cellular transformation. Under physiological conditions, binding of Wnt to a membrane receptor initiates an intracellular signaling cascade resulting in the inactivation of the cytoplasmic glycogen synthase kinase 3β (GSK3beta) complex, including adenomatous polyposis coli, beta-catenin, Axin, and components of

the ubiquitin ligation machinery. Whereas this proteasomal complex is appointed to beta-catenin degradation, and consequently its inactivation, beta-catenin molecules can translocate into the nucleus, where they interact with members of the T cell factor family of transcription factors.[8] Thus, intranuclear beta-catenin accumulation enhances the expression of target genes including c-myc and cyclin D1[14,45] and plays a fundamental role in proliferation as well as pattern formation, morphogenesis, and the evolution of polarity.

Recently, mutations of the glycogen synthase kinase 3β binding domain of beta-catenin were detected in adamantinomatous craniopharyngioma as well as calcifying odontogenic cysts and pilomatricoma.[13,19,38,39,47] These mutations could cause an aberrant and persistent activation of the pathway cited above, leading to an enhanced expression of Axin2 and bone morphogenetic protein 4 in craniopharyngioma.[15] The enhanced expression of Axin can be interpreted as a negative feedback of beta-catenin activity—namely an attempt of the cell to increase production of the component of proteasomal complex appointed to degradation of beta-catenin to decrease its cellular concentration and thus its nuclear activity.

Macrophage Migration Inhibiting Factors and Galectins. Macrophage-inhibiting factor is another molecule probably involved in the oncogenesis of craniopharyngioma. The MIF mRNA and protein are expressed in the normal human epidermis and nerve cells.[31,32,41] The influence of MIF has been described in various pathological conditions of the skin, ranging from inflammatory diseases to epidermal hyperplasia.[10,40,43] In this context MIF could act as a stimulator of tumor and vessel growth.[28,30] In an indirect manner, the role of MIF in tumor cell growth was also demonstrated by evidence that anti-MIF antibodies effectively suppress tumor growth and tumor-associated angiogenesis.[30]

Under physiological conditions, MIF binds to Jab1 in the cell, which induces the phosphorylation of c-Jun and AP-1 and promotes the degradation of p27Kip1; the result is a reduction in the growth-promoting effects of Jab1.[4,20] The MIF expression level seems to correlate with the risk of recurrence in craniopharyngioma, as it was significantly lower in rapidly recurring craniopharyngiomas than in the slowly recurring or nonrecurring lesions.[23]

Moreover, MIF expression in cholesteatomas correlates with an antiapoptotic endogenous lectin, namely, galectin-3. Indeed, mammalian galectins, which are beta-galactoside–binding proteins, can also exert a notable influence on growth regulation through proapoptotic (for example, galectin-1) or antiapoptotic (for example, galectin-3) mechanisms.[9,22,42]

Analogous to MIF, galectin-3 levels of expression were significantly lower in rapidly recurrent craniopharyngiomas.[23] In view of the antiapoptotic role of galectin-3, its low level of expression in recurring craniopharyngiomas seems to be related more to its role in phagocytosis. In this context the low levels of galectin-3 could correlate the oncogenesis of craniopharyngioma with defects in the normal biological elimination of embryonal tissue remnants.[23]

Cellular Proliferation: Sensitivity to Growth Factors

The environment in which craniopharyngiomas arise can play an important role, so that close contact with the pituitary gland and the hypothalamus may influence its growth.

Increased expression of mRNAs for estrogen and progesterone receptors has been observed in the proliferative epithelial component of craniopharyngiomas,[46] and this message from the cytoplasm would be translated into biologically active receptor protein.[16] Moreover, despite the increased expression of mRNA for estrogen receptors, coexpression of the estrogen receptor protein was finally detected on occasion,[46] and the correlation with clinical outcome is not clear.

Estrogen and progesterone receptors could be markers of a high tissue differentiating potential, as their coexpression would be associated with a low risk of tumor regrowth.[18]

Anaplasia: RAR

The correlation of anaplasia with the risk of recurrence is well proved by the expression levels of RAR. Recurrent adamantinomatous craniopharyngiomas are characterized by low levels of RARβ and high levels of RARγ.[25] The RARs belong to a major family of biological regulators that drive maturation in different types of epithelia (including the epidermis), as it is well known that the levels of expression of RAR isotypes differ markedly in relation to levels of maturation and/or differentiation of the epidermis.[6,36]

Invasiveness: Cathepsins

Recent studies have pointed out the role of cathepsins, a class of proteinases acting upstream of metalloproteinases in the proteolytic cascade, enabling tumor cells to invade adjacent normal tissue. Recurrent adamantinomatous craniopharyngiomas are characterized by low levels of cathepsin D and high levels of cathepsin K, and so revealing the same biphasic pattern of expression seen in RAR.[25] On the contrary, although the expression of cathepsin B increases during the malignant progression of primary brain tumors and so is considered a significant prognostic factor,[44] to date its level has not been shown to be related to the aggressiveness of craniopharyngioma.[25]

The mechanism acting downstream remains unclear. Cathepsin D secreted from human prostate carcinoma cells is responsible for the generation of angiostatin, a potent endogenous inhibitor of angiogenesis, and this suggests that it contributes to the prevention of tumor growth and the angiogenesis-dependent growth of metastases.[48] The level of expression of cathepsin D is significantly higher in more differentiated craniopharyngiomas, showing concomitant high levels of RARβ expression than in craniopharyngiomas with lower levels of RARβ expression.[25] The possibility thus remains that, as in the case of human prostate cancer cells, cathepsin D (high in the case of craniopharyngiomas with high levels of RARβ, and so more differentiated) facilitates the generation of angiostatin in craniopharyngiomas and thereby decreases postsurgical regrowth and/or recurrence.

On the other hand, cathepsin K is a cysteine protease of the papain family, which can cleave bone proteins such as Type I collagen, osteopontin, and osteonectin.[52] The knockout of cathepsin K in mice leads to retarded bone matrix degradation and osteopetrosis.[52] A high level of cathepsin K was detected in recurrent craniopharyngiomas.[23] Moreover, this finding seems to be related to cellular undifferentiation, represented by a pattern showing low levels of RARβ and high levels of RARγ.

Neoangiogenesis: VEGF

Neoangiogenesis is a limiting factor for tumor growth. Microvessel density, a measure of angiogenesis, has been proposed as a prognostic indicator correlating with an increased risk of recurrence.[1,50] However, conflicting results on the relationships between microvessel density and the tissutal expression of vascularization stimulatory and inhibitory factors (VEGF and endostatin, respectively)[1,5,50,51] could favor a modification able to enhance the neovascularization stimulus at the cytoplasmic level of postreceptor transduction of the signal or at the membrane level—namely, an increased concentration of a receptor such as VEGFR-2.[7,50] On the other hand, the degree of expression of VEGF seems to play an important role in tumor cyst formation.[49]

Role of Immune System Response: Defensins

After systematic consideration of the molecular mechanisms at the base of the growth of the solid component of craniopharyngiomas, we must specifically discuss cyst formation given that almost 90% of these tumors have a cystic component[2] and that in 60% of cases the cystic portion is predominant. The cystic element is responsible for almost all the symptoms related to mass effect. Moreover, its presence is associated with a major risk of recurrence, and thus suggesting a proliferative mechanism in its genesis and growth.

Much recent research aims to characterize the cyst fluid to understand the mechanism of formation and to refine treatments able to reduce cyst volume and inhibit the formation of new cysts. Indeed, the formation mechanism of cystic fluid has always been debated: it could be the result of blood-brain barrier impairment,[3] but surely an active secretory process takes part in its formation.

Recently, α-defensins 1–3 have been identified as relevant components of cyst fluid.[34] The presence of these antimicrobial peptides would suggest a possible involvement of the innate immune response in the formation and maintenance of the craniopharyngioma-associated cyst. Indeed, human α-defensins 1–3 constitute 30–50% of the total protein content of neutrophil azurophil granules,[11,12] with a well-known powerful antibacterial and antiviral activity. The α-defensin expression is significantly increased in the saliva of patients with oral squamous cell carcinomas,[26] in the fluid of jaw cysts,[27] and in the plasma of patients with sepsis and meningitis.[33] Moreover, the expression of these peptides decreases as a function of the effectiveness of intracystic IFN-α treatment and so correlates with clinical patient outcome. Authors of future studies should clarify whether the reduction in α-defensins derives from a direct antitumoral effect of IFN-α on squamous epithelial cells of the craniopharyngioma cyst or from its immunomodulatory effects on the recruitment of cells of innate immune systems or whether both action mechanisms are implicated.

Conclusions

The term "craniopharyngioma" refers to "kaleidoscopic tumors, solid and cystic, which take origin from epithelial rests ascribable to an imperfect closure of the hypophysis or craniopharyngeal duct."[24] In this primordial view, the craniopharyngioma is a mass exerting compression and the distinction between the cystic and solid components is only grossly understood, but the term "kaleidoscopic" let us suppose that Cushing understood the complexity of this tumor.

Leading surgeons have devoted their efforts to clarifying the true nature of this tumor, namely, its malignant clinical behavior characterized by local invasiveness and a high rate of recurrence, which is in clear contradiction with its benign histological aspect. We hope that the view of this tumor as a complex molecular disease rather than a simple mass can be the first step in defining the best treatment.

Initial efforts have been focused on correlating the mitotic activity of craniopharyngioma with its clinical behavior, unfortunately producing conflicting results.[29,35] These contradictions can be clarified by the current evolution from the "microscopic" view to the "molecular" view. In fact, at the molecular level the cellular proliferation results in multiple failures of the apoptotic pathway combined with persistent activation of the antiapoptotic pathway. The identification of the impaired stages of this circuitry could explain the difference in the incidence of recurrence despite similar mitotic activity.

Besides the cellular proliferation, other cellular physiological functions became abnormal as a result of the neoplastic transformation, and so affected the clinical behavior of craniopharyngioma. Therefore, the terms of the matter are even more complex.

Nowadays, advances in our knowledge of oncogenic mechanisms would lead us to identify critical checkpoints in tumor cell transformation, to drive the definition of specific therapeutic agents able to reverse the neoplastic process at these levels. In this context, this biological approach aims to defeat the tumor by "curing" only the abnormal neoplastic cell. An example of this new approach is the reactivation of the apoptotic pathway—that is, a physiological mechanism in the normal cell that is eluded by the neoplastic cell—as a result of treatment with intracystic IFN.[17]

The final target of this research will be the definition of a tailored therapy combining higher efficacy and safety with lower morbidity. This biological therapy would probably be based on multiple inhibitions that so far have been proved to be more efficient than a single-step inhibition in the treatment of different tumors. On the other hand, considering the immediate future, the definition of molecular markers of malignancy will allow us to stratify patients harboring a craniopharyngioma on the basis of

its biological aggressiveness, and consequently enabling the surgeon to modulate treatment intensity.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: BL Pettorini. Acquisition of data: P Frassanito. Analysis and interpretation of data: BL Pettorini, P Frassanito. Drafting the article: BL Pettorini, P Frassanito. Critically revising the article: BL Pettorini. Reviewed final version of the manuscript and approved it for submission: BL Pettorini, C Di Rocco. Study supervision: BL Pettorini, M Caldarelli, G Tamburrini, L Massimi, C Di Rocco.

References

1. Agozzino L, Ferraraccio F, Accardo M, Esposito S, Agozzino M, Cuccurullo L: Morphological and ultrastructural findings of prognostic impact in craniopharyngiomas. **Ultrastruct Pathol 30:**143–150, 2006
2. Alén JF, Boto GR, Lagares A, de la Lama A, Gómez PA, Lobato RD: Intratumoural bleomycin as a treatment for recurrent cystic craniopharyngioma. Case report and review of the literature. **Neurocirugia (Astur) 13:**479–485, 2002
3. Arefyeva IA, Semenova JB, Zubairaev MS, Kondrasheva EA, Moshkin AV: Analysis of fluid in craniopharyngioma-related cysts in children: proteins, lactate and pH. **Acta Neurochir (Wien) 144:**551–554, 2002
4. Bucala R: Signal transduction. A most interesting factor. **Nature 408:**146–147, 2000
5. Dallago CM, Oliveira MC, Barbosa-Coutinho LM, Ferreira NP: Angiogenesis in craniopharyngiomas: Microvascular density and tissue expression of the vascular endothelial growth factor (VEGF) and endostatin. **Endocr Pathol 16:**355–362, 2005
6. Elder JT, Aström A, Pettersson U, Tavakkol A, Krust A, Kastner P, et al: Retinoic acid receptors and binding proteins in human skin. **J Invest Dermatol 98 (6 Suppl):**36S–41S, 1992
7. Elmaci L, Kurtkaya-Yapicier O, Ekinci G, Sav A, Pamir MN, Vidal S, et al: Metastatic papillary craniopharyngioma: case study and study of tumor angiogenesis. **Neuro Oncol 4:**123–128, 2002
8. Friedrich A, Kullmann F: [Familial adenomatous polyposis syndrome (FAP): pathogenesis and molecular mechanisms.] **Med Klin (Munich) 98:**776–782, 2003 (Ger)
9. Gabius HJ: Animal lectins. **Eur J Biochem 243:**543–576, 1997
10. Gabius HJ: Probing the cons and pros of lectin-induced immunomodulation: case studies for the mistletoe lectin and galectin-1. **Biochimie 83:**659–666, 2001
11. Ganz T, Lehrer RI: Defensins. **Pharmacol Ther 66:**191–205, 1995
12. Ganz T, Selsted ME, Lehrer RI: Defensins. **Eur J Haematol 44:**1–8, 1990
13. Hassanein AM, Glanz SM, Kessler HP, Eskin TA, Liu C: beta-Catenin is expressed aberrantly in tumors expressing shadow cells. Pilomatricoma, craniopharyngioma, and calcifying odontogenic cyst. **Am J Clin Pathol 120:**732–736, 2003
14. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, et al: Identification of c-MYC as a target of the APC pathway. **Science 281:**1509–1512, 1998
15. Hölsken A, Kreutzer J, Hofmann BM, Hans V, Oppel F, Buchfelder M, et al: Target gene activation of the Wnt signaling pathway in nuclear beta-catenin accumulating cells of adamantinomatous craniopharyngiomas. **Brain Pathol 19:**357–364, 2009
16. Honegger J, Renner C, Fahlbusch R, Adams EF: Progesterone receptor gene expression in craniopharyngiomas and evidence for biological activity. **Neurosurgery 41:**1359–1364, 1997
17. Ierardi DF, Fernandes MJS, Silva IR, Thomazini-Gouveia J, Silva NS, Dastoli P, et al: Apoptosis in alpha interferon (IFN-alpha) intratumoral chemotherapy for cystic craniopharyngiomas. **Childs Nerv Syst 23:**1041–1046, 2007
18. Izumoto S, Suzuki T, Kinoshita M, Hashiba T, Kagawa N, Wada K, et al: Immunohistochemical detection of female sex hormone receptors in craniopharyngiomas: correlation with clinical and histologic features. **Surg Neurol 63:**520–525, 2005
19. Kato K, Nakatani Y, Kanno H, Inayama Y, Ijiri R, Nagahara N, et al: Possible linkage between specific histological structures and aberrant reactivation of the Wnt pathway in adamantinomatous craniopharyngioma. **J Pathol 203:**814–821, 2004
20. Kleemann R, Hausser A, Geiger G, Mischke R, Burger-Kentischer A, Flieger O, et al: Intracellular action of the cytokine MIF to modulate AP-1 activity and the cell cycle through Jab1. **Nature 408:**211–216, 2000
21. Komotar RJ, Roguski M, Bruce JN: Surgical management of craniopharyngiomas. **J Neurooncol 92:**283–296, 2009
22. Kopitz J, von Reitzenstein C, André S, Kaltner H, Uhl J, Ehemann V, et al: Negative regulation of neuroblastoma cell growth by carbohydrate-dependent surface binding of galectin-1 and functional divergence from galectin-3. **J Biol Chem 276:**35917–35923, 2001
23. Lefranc F, Chevalier C, Vinchon M, Dhellemmes P, Schüring MP, Kaltner H, et al: Characterization of the levels of expression of retinoic acid receptors, galectin-3, macrophage migration inhibiting factor, and p53 in 51 adamantinomatous craniopharyngiomas. **J Neurosurg 98:**145–153, 2003
24. Lindholm J, Nielsen EH: Craniopharyngioma: historical notes. **Pituitary 12:**352–359, 2009
25. Lubansu A, Ruchoux MM, Brotchi J, Salmon I, Kiss R, Lefranc F: Cathepsin B, D and K expression in adamantinomatous craniopharyngiomas relates to their levels of differentiation as determined by the patterns of retinoic acid receptor expression. **Histopathology 43:**563–572, 2003
26. Lundy FT, Orr DF, Gallagher JR, Maxwell P, Shaw C, Napier SS, et al: Identification and overexpression of human neutrophil α-defensins (human neutrophil peptides 1, 2 and 3) in squamous cell carcinomas of the human tongue. **Oral Oncol 40:**139–144, 2004
27. Mizukawa N, Sugiyama K, Ueno T, Mishima K, Takagi S, Sugahara T: Detection of human α-defensin-1, an antimicrobial peptide, in the fluid of jaw cysts. **Oral Surg Oral Med Oral Pathol 90:**78–81, 2000
28. Nangia-Makker P, Baccarini S, Raz A: Carbohydrate-recognition and angiogenesis. **Cancer Metastasis Rev 19:**51–57, 2000
29. Nishi T, Kuratsu J, Takeshima H, Saito Y, Kochi M, Ushio Y: Prognostic significance of the MIB-1 labeling index for patient with craniopharyngioma. **Int J Mol Med 3:**157–161, 1999
30. Nishihira J: Macrophage migration inhibitory factor (MIF): its essential role in the immune system and cell growth. **J Interferon Cytokine Res 20:**751–762, 2000
31. Nishio Y, Minami A, Kato H, Kaneda K, Nishihira J: Identification of macrophage migration inhibitory factor (MIF) in rat peripheral nerves: its possible involvement in nerve regeneration. **Biochim Biophys Acta 1453:**74–82, 1999
32. Ogata A, Nishihira J, Suzuki T, Nagashima K, Tashiro K: Identification of macrophage migration inhibitory factor mRNA expression in neural cells of the rat brain by in situ hybridization. **Neurosci Lett 246:**173–177, 1998
33. Panyutich AV, Panyutich EA, Krapivin VA, Baturevich EA, Ganz T: Plasma defensin concentrations are elevated in patients with septicemia or bacterial meningitis. **J Lab Clin Med 122:**202–207, 1993

34. Pettorini BL, Caldarelli M, Massimi L, Tamburrini G, Inzitari R, Fanali C, et al: Detection of alpha-defensin 1–3 in cystic craniopharyngioma fluid and their concentration decrease during interferon-alpha treatment. **Childs Nerv Syst 24:**654, 2008
35. Raghavan R, Dickey WT Jr, Margraf LR, White CL III, Coimbra C, Hynan LS, et al: Proliferative activity in craniopharyngiomas: clinicopathological correlations in adults and children. **Surg Neurol 54:**241–248, 2000
36. Redfern CPF, Todd C: Retinoic acid receptor expression in human skin keratinocytes and dermal fibroblasts in vitro. **J Cell Sci 102:**113–121, 1992
37. Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, et al: Craniopharyngioma: the pendulum of surgical management. **Childs Nerv Syst 21:**691–695, 2005
38. Sekine S, Sato S, Takata T, Fukuda Y, Ishida T, Kishino M, et al: Beta-catenin mutations are frequent in calcifying odontogenic cysts, but rare in ameloblastomas. **Am J Pathol 163:**1707–1712, 2003
39. Sekine S, Shibata T, Kokubu A, Morishita Y, Noguchi M, Nakanishi Y, et al: Craniopharyngiomas of adamantinomatous type harbor beta-catenin gene mutations. **Am J Pathol 161:**1997–2001, 2002
40. Shimizu T, Abe R, Ohkawara A, Mizue Y, Nishihira J: Macrophage migration inhibitory factor is an essential immunoregulatory cytokine in atopic dermatitis. **Biochem Biophys Res Commun 240:**173–178, 1997
41. Shimizu T, Ohkawara A, Nishihira J, Sakamoto W: Identification of macrophage migration inhibitory factor (MIF) in human skin and its immmunohistochemical localization. **FEBS Lett 381:**199–202, 1996
42. Sotomayor CE, Rabinovich GA: "Galectin-1 induces central and peripheral cell death: implications in T-cell physiopathology." **Dev Immunol 7:**117–129, 2000
43. Steinhoff M, Meinhardt A, Steinhoff A, Gemsa D, Bucala R, Bacher M: Evidence for a role of macrophage migration inhibitory factor in psoriatic skin disease. **Br J Dermatol 141:**1061–1066, 1999
44. Strojnik T, Kos J, Zidanik B, Golouh R, Lah T: Cathepsin B immunohistochemical staining in tumor and endothelial cells is a new prognostic factor for survival in patients with brain tumors. **Clin Cancer Res 5:**559–567, 1999
45. Tetsu O, McCormick F: Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. **Nature 398:**422–426, 1999
46. Thapar K, Stefaneanu L, Kovacs K, Scheithauer BW, Lloyd RV, Muller PJ, et al: Estrogen receptor gene expression in craniopharyngiomas: an in situ hybridization study. **Neurosurgery 35:**1012–1017, 1994
47. Tsang WY: Only adamantinomatous but not papillary type of craniopharyngioma is associated with beta-catenin mutation. **Adv Anat Pathol 11:**223, 2004
48. Tsukuba T, Okamoto K, Yasuda Y, Morikawa W, Nakanishi H, Yamamoto K: New functional aspects of cathepsin D and cathepsin E. **Mol Cells 10:**601–611, 2000
49. Vaquero J, Zurita M, de Oya S, Coca S, Morales C, Salas C: Expression of vascular permeability factor in craniopharyngioma. **J Neurosurg 91:**831–834, 1999
50. Vidal S, Kovacs K, Lloyd RV, Meyer FB, Scheithauer BW: Angiogenesis in patients with craniopharyngiomas: correlation with treatment and outcome. **Cancer 94:**738–745, 2002
51. Xu J, Zhang S, You C, Wang X, Zhou Q: Microvascular density and vascular endothelial growth factor have little correlation with prognosis of craniopharyngioma. **Surg Neurol 66 (Suppl 1):**S30–S34, 2006
52. Yamashita DS, Dodds RA: Cathepsin K and the design of inhibitors of cathepsin K. **Curr Pharm Des 6:**1–24, 2000

Manuscript submitted December 10, 2009.
Accepted January 5, 2010.

Address correspondence to: Benedetta Ludovica Pettorini, M.D., Paediatric Neurosurgery Unit, Catholic University Medical School, Largo Agostino Gemelli, 8, 00168 Rome, Italy. email: benedettaludovica@virgilio.it.

Neurosurg Focus 28 (4):E2, 2010

Craniopharyngioma Clinical Status Scale: a standardized metric of preoperative function and posttreatment outcome

Robert E. Elliott, M.D.,[1] Stephen A. Sands, Psy.D.,[3] Russell G. Strom, M.D.,[1] and Jeffrey H. Wisoff, M.D.[1,2]

Departments of [1]Neurosurgery and [2]Pediatrics, New York University School of Medicine; and [3]Departments of Pediatrics and Psychiatry, Columbia University College of Physicians and Surgeons, New York, New York

Object. Controversy persists concerning the optimal treatment of craniopharyngiomas in children, and no standard outcome metric exists for comparison across treatment modalities, nor is there one that adequately reflects the multisystem dysfunction that may arise.

Methods. The authors retrospectively analyzed the records of 86 consecutive children who underwent a uniform treatment paradigm of attempted radical resection performed by a single surgeon. Excluding 3 perioperative deaths and 3 patients with inadequate follow-up, 80 children (34 girls and 46 boys; mean age 9.56 years; mean follow-up 9.6 years) composed the study group (53 primary and 27 previously treated/recurrent tumors). Building on existing classification schemes proposed by De Vile for hypothalamic dysfunction and Wen for overall functional outcome, the authors devised a more nuanced classification system (Craniopharyngioma Clinical Status Scale [CCSS]) that assesses outcome across 5 axes, including neurological examination, visual status, pituitary function, hypothalamic dysfunction, and educational/occupational status at last follow-up (there is a 4-tiered grading scale in each domain, with increasing values reflecting greater dysfunction).

Results. There was a significant increase in pituitary dysfunction following treatment—consistent with the high rates of diabetes insipidus and hypopituitarism common to the surgical management of craniopharyngiomas—and less dramatic deterioration in hypothalamic function or cognitive domains. Significant improvement in vision was also demonstrated, with no significant overall change in neurological status. Preoperative CCSS scores predicted postoperative outcome better than clinical characteristics like patient age, sex, tumor size, and the location or presence of hydrocephalus.

Conclusions. Preoperative CCSS scores predicted outcome with higher accuracy than clinical or imaging characteristics. In lieu of randomized trials, the CCSS may provide a useful outcome assessment tool for comparison across treatment paradigms and surgical approaches. Long-term follow-up is critical to the analysis of outcomes of craniopharyngioma treatment, given the often-delayed sequelae of all therapies and the high recurrence rates of these tumors. *(DOI: 10.3171/2010.2.FOCUS09304)*

Key Words • **pediatric tumor** • **craniopharyngioma** • **functional outcome** • **functional assessment**

Craniopharyngiomas are the most common nonglial brain tumor of childhood—comprising 6–8% of pediatric brain tumors—but are relatively rare on a population-wide scale.[3,5,66] They are benign neoplasms thought to arise from embryological remnants of squamous epithelium of the craniopharyngeal duct.[49,65] They most commonly arise in the suprasellar region and have intimate relationships with the circle of Willis, third ventricle, hypothalamus, optic pathways, and pituitary stalk. Although histologically benign, their proximity to such critical structures and their tendency to recur render them potentially dangerous. Children with these tumors are prone to significant deficits prior to or as a result of treatment.

As improvements in surgical technique, RT modalities, and supportive care have resulted in improved overall survival, attention has shifted toward analysis of the quality of survival.[6,7,41,46,50,55,58,61] Although investigators in a handful of studies have attempted to create grading scales to assess functional outcomes and QOL in patients with craniopharyngiomas, each scale has its own limitations. Wen and colleagues[67] developed a 4-tiered outcome

Abbreviations used in this paper: ADLs = activities of daily living; BMI = body mass index; CCSS = Craniopharyngioma Clinical Status Scale; DI = diabetes insipidus; E-CCSS = educational/occupational CCSS; GTR = gross-total resection; H-CCSS = hypothalamic CCSS; N-CCSS = neurological CCSS; NYU = New York University; P-CCSS = pituitary CCSS; QOL = quality of life; RT = radiation therapy; TBI = traumatic brain injury; VA = visual acuity; V-CCSS = visual CCSS; VF = visual field.

TABLE 1: Proposed CCSS

Domain & Score	Criteria
N-CCSS	
1	no deficits or seizures
2	mild deficits (cranial nerve palsy, well-controlled seizures)
3	moderate deficits (mild hemiparesis w/ independent ambulation, moderately controlled seizures)
4	severe deficits (moderate-to-severe hemiparesis, major stroke, significant abulia, or lethargy)
V-CCSS	
1	normal VA & VFs
2	mild acuity deficits or field cut
3	unilat blindness, homonymous hemianopia, or bitemporal hemianopia
4	bilat blindness or nearly functional blindness
P-CCSS	
1	normal anterior & posterior pituitary function
2	mild anterior pituitary dysfunction (1 or 2 hormone supplements)
3	DI w/ or w/o mild anterior pituitary dysfunction (1 or 2 hormone supplements)
4	DI & panhypopituitarism
H-CCSS*	
1	normal hypothalamic function
2	postop obesity (BMI >+2 SD), lack of behavioral/psychological symptoms
3	obesity (BMI >+2 SD) w/ hyperphagia, or memory disturbance or BMI >+3 SD w/o frank hyperphagia behaviors
4	extreme obesity (BMI >+4 SD) & hyperphagia, behavioral disturbances (such as rage episodes), & disturbances of thermoregulation, sleep-wake cycles, or memory
E-CCSS	
1	excellent academic performance &/or occupational success
2	good academic performance at grade level &/or maintaining employment†
3	behind in grade academically, requires significant tutoring, or inability to maintain consistent employment‡
4	completely dependent on others for self-care (cannot perform ADLs), IQ <80, severe cognitive deficits

* Modified version of scale proposed by De Vile et al.[12]
† Meeting or exceeding developmental milestones for preschool-aged children.
‡ Not meeting age-appropriate developmental milestones for preschool-aged children.

scale that addressed overall functional outcome across domains, and De Vile et al.[12] created a grading scale focused on predicting hypothalamic dysfunction to determine the optimal extent of the intended resection. Duff et al.[17] proposed a 2-tiered grading scale that dichotomized outcome into good or poor based on 8 inclusion criteria. Despite these attempts, no assessment tool currently exists that adequately addresses the myriad systems affected by craniopharyngiomas and their treatment, and none has been validated or consistently adopted by other centers.

We propose a system that assesses the following 5 axes of function in children with craniopharyngiomas, to serve as a preliminary attempt at a comprehensive evaluation of pre- and posttreatment status: vision, neurological status, pituitary function, hypothalamic function, and educational/occupational status. Given the persistent debate about the optimal treatment of craniopharyngiomas (namely, radical resection vs limited resection and RT; transcranial vs transsphenoidal approaches), we hope that such a scale could find universal appeal and allow meaningful comparisons across treatment paradigms.

Methods

Patient Population

Between 1986 and 2008, a total of 86 consecutive children younger than 21 years of age underwent 104 operations for excision of craniopharyngiomas by the senior author (J.H.W.) at NYU's Langone Medical Center. Following approval by the NYU Institutional Review Board, data were retrospectively collected by reviewing clinic/office and inpatient records, pre- and postoperative and last follow-up CT and/or MR imaging studies, and operative and pathology reports. Patient characteristics, prior treatments, imaging features, extent of resection, recurrence rate, time to progression, and other oncological treatments were recorded. Long-term follow-up information was obtained between 2006 and 2009 by contacting patients, families, and referring physicians, and from records of the last follow-up office visit. Current follow-up data were not available in 3 patients, and their follow-up duration was censored at the time of last visit (6, 131, and

180 months). Three patients died perioperatively, and in 3 no follow-up data were available. These latter 6 patients were excluded from the study. Primary tumors were those treated at NYU at the time of initial presentation; recurrent tumors were those referred to NYU for surgery after failure of prior treatment at other hospitals. It should be noted that some patients in this series were included in other reports on various aspects of the management of craniopharyngiomas in children.[20–23,58,66,70,71]

A GTR was the primary aim of treatment in all children and was defined as the lack of residual tumor on visual inspection intraoperatively and no residual soft-tissue mass or enhancement suspected to be tumor on postoperative imaging, as determined by an independent neuroradiologist. The outcome variables measured included BMI (weight [in kilograms]/height^2 [in square meters]) with Z scores (SDs),[56] endocrine replacement regimen, VA and VF testing performed pre- and postoperatively by pediatric ophthalmologists, neurological examination pre- and postoperatively, subsequent seizures requiring medications, and highest level of education attained and need for educational assistance.

Children were scored using a 4-tiered grading scale across 5 domains prior to surgery at NYU and at last follow-up (Table 1). The scoring of deficits and function is as follows: 1, normal/excellent function; 2, mild deficit/good function; 3, moderate deficit/fair function; and 4, severe deficit/poor function.

Neurological status was assessed by the neurooncologist, pediatric or adult neurologist, or, less commonly, the senior author. To minimize bias, all possible attempts were made to limit the extent of involvement by the treating neurosurgeon in the neurological evaluation of the patients. Patients with an N-CCSS score of 1 had normal results on neurological examination and were without seizures. Patients receiving an N-CCSS score of 2 had mild deficits like cranial nerve palsy and/or seizures that were well controlled with medications. Patients with an N-CCSS score of 3 had moderate deficits, which included hemiparesis with independent ambulation, or epilepsy. Patients with an N-CCSS score of 4 had significant hemiparesis that prevented ambulation, hemispheric stroke, significant abulia, or abnormal level of consciousness.

All ophthalmological examinations were performed by a pediatric ophthalmologist or neuroophthalmologist, and were composed of detailed VA and VF examinations. Patients with a V-CCSS score of 1 had normal VA and VF function. Patients with a V-CCSS score of 2 had mild deficits in VA (< 20/100) and VF (quadrantanopia or unilateral nasal or temporal field deficit). Patients with a V-CCSS score of 3 had unilateral blindness, bitemporal hemianopia, or homonymous hemianopia. Patients with a V-CCSS score of 4 had bilateral blindness or enough visual compromise in both eyes to be considered functionally blind.

Pituitary function and supplementation needs were assessed by a pediatric endocrinologist. The presence of DI and anterior pituitary deficits were recorded. Patients with a P-CCSS score of 1 had normal anterior and posterior pituitary function and required no supplementation. Patients with a P-CCSS score of 2 had mild anterior pituitary dysfunction requiring supplementation of 1 or 2 hormones. Patients with a P-CCSS score of 3 had DI with or without mild anterior pituitary dysfunction. Patients with a P-CCSS score of 4 had DI and panhypopituitarism (requiring ≥ 3 supplemental hormones).

TABLE 2: Functional classification scale*

Class	Criteria
I	grossly normal & independent
	mild hormonal disturbances
	seizures well controlled w/ medication
II	independent
	panhypopituitarism
	mild-to-moderate visual compromise
	cranial nerve deficits
	mild psychological dysfunction
III	partially dependent
	serious visual compromise
	serious neurological deficits (hemiparesis, refractory seizures)
	learning disabilities or poorly controlled psychological disorders
IV	entirely dependent on others for self-care

* Based on data in the article by Wen et al.

Hypothalamic dysfunction scoring is primarily based on the assessment scale created by De Vile et al.,[12] with only slight modifications for more objective reporting of "obesity" by using BMI with Z scores. In addition to BMI analysis, hypothalamic dysfunction was assessed by parental, family, or primary physician reporting of behavioral disturbances. Patients with an H-CCSS score of 1 exhibited no signs of obesity or behavioral disturbances indicative of hypothalamic injury. Patients with an H-CCSS score of 2 had evidence of postoperative obesity (BMI > +2 SD), but lacked behavioral or psychological symptoms. Patients with an H-CCSS score of 3 exhibited obesity (BMI > +2 SD) with food-seeking behaviors, severe obesity (BMI > +3 SD) without overt hyperphagia, memory disturbance, and no evidence of psychosocial dysfunction. Patients with an H-CCSS score of 4 had one or more of the following signs: extreme obesity (BMI > +4 SD), behavioral disturbances such as rage episodes, severe social isolation, and disturbances of thermoregulation, sleep-wake cycles, or severe memory deficits.

Educational (for school-aged children) and developmental (for preschool-aged children) outcomes were based on neuropsychological testing when available, and on evaluations by pediatric neurologists or primary pediatricians specifically documenting developmental or educational status. Assessments of occupational functioning were obtained from patients, their family members, or their primary medical doctors. Outcomes (E-CCSS) were classified as excellent (E-CCSS score of 1) in children who achieved good or excellent grades at the appropriate level, entered and/or graduated from college, or in adults excelling in their chosen vocation. Good outcomes (E-CCSS score of 2) applied to children who were achieving passing grades at the appropriate level with or without tutoring, in young children meeting or exceeding age-ap-

TABLE 3: Comparison of baseline demographic characteristics of patients with primary and recurrent craniopharyngiomas*

Variable	Primary Group	Recurrent Group	p Value
age (yrs)	8.26 ± 4.5	12.1 ± 4.7	0.001
sex distribution (% M)	58.9	50.0	0.48
tumor size (cm)	4.1 ± 1.5	4.0 ± 1.7	0.91
retrochiasmatic location	43.6%	57.7%	0.34
hydrocephalus present	29.1%	53.8%	0.048
ventriculoperitoneal shunt	14.5%	46.2%	0.005
follow-up (yrs)	11.4 ± 6.5	6.1 ± 5.5	<0.0001

* Values for age, tumor size, and follow-up are given as the mean ± SD.

propriate developmental milestones, and in adults maintaining steady employment. Fair outcomes (E-CCSS score of 3) were cases in which children were behind in school, required special education/tutoring, were not meeting age-appropriate developmental milestones, and in which adults were unable to maintain steady employment. Poor outcomes (E-CCSS score of 4) were those in which patients had severe cognitive deficits, IQ < 80, or required significant assistance with ADLs. For preschool-aged children, those meeting or exceeding their age-appropriate developmental milestones were given an E-CCSS score of 2, and those not meeting milestones were given a score of 3.

In addition to recording neuropsychological, educational, or developmental status at last follow-up, overall functional morbidity—including visual, neurological, hypothalamic, pituitary, and psychosocial dysfunction—was assessed using the 4-tiered classification system proposed by Wen et al.[67] (criteria presented in Table 2). The Wen scores were converted into ordinal numbers for statistical analyses.

Ordinal logistic regression analysis was performed to determine the impact of age at surgery (continuous variable), sex (dichotomous variable), tumor location (dichotomous variable: retro- vs prechiasmatic), tumor size (continuous variable), presence of hydrocephalus (dichotomous variable), prior treatment (dichotomous), and baseline CCSS scoring on the ultimate CCSS outcome after treatment at NYU. Each model was tested for significance by using Cox and Snell pseudo-R^2 testing and model-fitting chi-square testing with p values. A p value < 0.10 on univariate testing was the cutoff for inclusion in the multivariate model.

Averages are expressed as the mean ± SD. The Student t-test was used to compare the following parametric variables: age at time of surgery, maximal tumor diameter, and follow-up duration. The CCSS scores were converted to ordinal numbers for statistical comparisons. The Fisher exact test was used to compare proportions. The Wilcoxon rank-sum test (Mann-Whitney U-test) and paired-sample Wilcoxon signed-rank test were used to compare nonparametric variables between primary and recurrent tumor groups and between pre- and postoperative outcomes, respectively, in the same patients. All statistics were calculated with SSPS software (SSPS 17.0 for Mac; SSPS, Inc.). A p value of < 0.05 on 2-tailed testing was considered statistically significant.

Results

Patients' Demographic Data

Demographic data comparing primary and recurrent tumors are summarized in Table 3. There were 46 males and 34 females in this study group, whose mean age was 9.6 ± 4.8 years at time of surgery (range 9 months–20.5 years). Twenty-seven patients (34%) had received treatment prior to referral to our center, and 53 children (66%) had primary tumors. Thirty-nine tumors (49%) were prechiasmatic, 35 were retrochiasmatic (44%), and 5 large tumors (6%) had both pre- and retrochiasmatic components. One 5-cm tumor was located entirely within the third ventricle. The mean tumor size was 4.1 ± 1.6 cm (range 1.1–8 cm). Thirty patients (37.5%) had preoperative hydrocephalus, and 20 patients (25%) either had ventriculoperitoneal shunts at presentation or required one following resection. The mean follow-up duration was 9.6 ± 6.6 years (range 6 months–23.8 years).

Children with recurrent tumors were older (p = 0.001), were more likely to have hydrocephalus (p = 0.048), were more likely to have or to need ventriculoperitoneal shunts (p = 0.005), and had shorter follow-up (p < 0.0001) compared with the primary tumor group. There was no difference in the sex distribution, distribution of tumor location, or tumor size.

Prior treatments for patients in the recurrent tumor group included one or more resections in 15 children and limited resection plus RT in 10. Two patients had aspirations, followed by Gamma Knife radiosurgery in one child and conventional RT in the other.

Neurological Status

Sixty-four children (80%) were neurologically intact at time of presentation to NYU. Of the 16 patients (20%) with deficits prior to surgery, hemiparesis was the primary deficit in 10 patients and lethargy in 3 patients. Of note, 4 patients with hemiparesis also had either unilateral third cranial nerve palsies or lethargy (2 patients each). The proportion of patients in the primary group (7 [13.2%] of 53) who had preoperative neurological deficits was less than in the recurrent group (9 [33%] of 27; p = 0.04). Preoperative N-CCSS scores are summarized in Fig. 1A. Sixty-four children (80%) had an N-CCSS score of 1; 2 children (2.5%) had a score of 2; 10 (12.5%) had a score

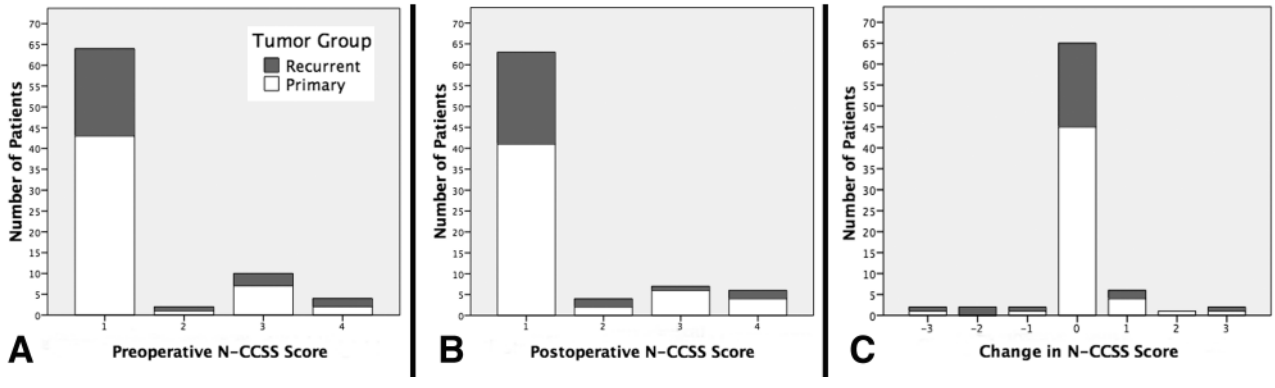

Fig. 1. Histograms summarizing preoperative **(A)**, postoperative **(B)**, and change in **(C)** N-CCSS scores in children with primary and recurrent craniopharyngiomas.

of 3; and 4 (5%) had a score of 4. The mean preoperative N-CCSS score was 1.43 ± 0.90 (median 1). The children with recurrent tumors had a higher N-CCSS score prior to surgery ($p = 0.03$), indicating greater pretreatment neurological dysfunction.

Sixty patients (75%) were either improved (4 patients [5%]) or at their neurological baseline (56 [70%]) in the immediate postoperative period after the initial operation at NYU. Twenty (25%) developed new major (8 patients) and minor (12 patients) neurological deficits in the immediate postoperative period. Four patients (5%) suffered strokes, and another had a mild hemiparesis with nearly complete resolution by 6 months. Three patients had severe lethargy and abulia that either partially or completely resolved by 2 weeks postoperatively. Eleven of these new deficits were cranial nerve palsies, 9 (82%) of which completely resolved by the 6-month follow-up. Two patients required corrective surgery for persistent strabismus. At the last follow-up, 10 patients (12.5%) had permanent postoperative neurological deficits, and 16 (20%) were taking antiepileptic drugs for postoperative seizures. No patient had epilepsy that was refractory to medications. Postoperative N-CCSS scores are summarized in Fig. 1B. Sixty-three children (78.8%) had an N-CCSS score of 1; 4 children (5%) had a score of 2; 7 (8.8%) had a score of 3; and 6 (7.5%) had a score of 4. The mean postoperative N-CCSS score was 1.45 ± 0.94 (median 1). Children with recurrent tumors continued to have higher N-CCSS scores postoperatively; however, the difference was only marginally significant at last follow-up ($p = 0.076$).

Figure 1C demonstrates the change in N-CCSS score following treatment. The mean change in the neurological score was +0.03 ± 0.84 (median 0, range −3 to +3). Overall, there was no significant decline in neurological func-

TABLE 4: Comparison of CCSS scores between primary and recurrent craniopharyngiomas*

Domain	Primary Group	Recurrent Group	p Value
preop score			
N-CCSS	1.26 ± 0.71	1.74 ± 1.13	0.03
V-CCSS	1.79 ± 0.93	2.67 ± 0.78	<0.001
P-CCSS	1.51 ± 0.72	2.78 ± 0.85	<0.001
H-CCSS	1.17 ± 0.64	1.96 ± 1.06	<0.001
E-CCSS	1.55 ± 0.67	1.81 ± 0.79	0.13
postop score			
N-CCSS	1.34 ± 0.85	1.67 ± 1.07	0.076
V-CCSS	1.62 ± 0.81	2.48 ± 0.80	<0.001
P-CCSS	3.23 ± 0.89	3.15 ± 0.72	0.42
H-CCSS	1.55 ± 0.93	2.19 ± 1.00	0.003
E-CCSS	1.79 ± 0.88	2.37 ± 1.12	0.02
change in score			
N-CCSS	0.08 ± 0.70	−0.07 ± 1.07	0.60
V-CCSS	−0.17 ± 0.83	−0.19 ± 0.68	0.82
P-CCSS	1.72 ± 1.04	0.37 ± 0.56	<0.001
H-CCSS	0.38 ± 0.74	0.22 ± 0.58	0.32
E-CCSS	0.25 ± 0.73	0.56 ± 0.70	0.03

* Values are given as the mean ± SD.

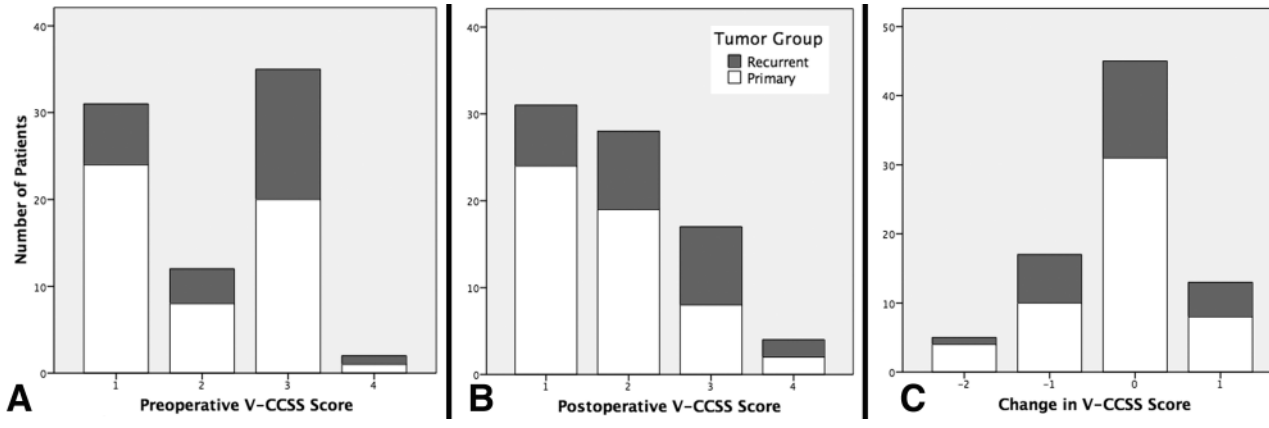

Fig. 2. Histograms summarizing preoperative **(A)**, postoperative **(B)**, and change in **(C)** V-CCSS scores in children with primary and recurrent craniopharyngiomas.

tion as a result of radical resection ($p = 0.42$). There was no difference in the change in N-CCSS score between primary and recurrent tumor groups following treatment ($p = 0.6$). The pre- and postoperative N-CCSS scores and changes following treatment for both primary and recurrent craniopharyngiomas are shown in Table 4.

The ordinal logistic regression model for N-CCSS was significant (pseudo-$R^2 = 0.35$; $p < 0.0005$). Predictors of higher postoperative N-CCSS scores (Table 5) included preoperative N-CCSS score ($p = 0.036$) and giant tumor size ($p = 0.03$).

Visual Status

Two children were too young for formal VA testing and were scored only on gross VF testing results. Forty-three (57.5%) of 80 children had VF deficits, and 31 (40%) of 78 children had VA deficits. Compared with those with primary tumors, a higher proportion of patients with recurrent craniopharyngiomas had VF (23 [43.4%] of 53 vs 20 [74.1%] of 27; $p = 0.01$) and VA (15 [29.4%] of 51 vs 16 [59.3%] of 27; $p = 0.015$) deficits. Two patients were blind prior to surgery at NYU (1 with a primary and 1 with recurrent tumor), 2 had unilateral blindness, and 1 patient had vision limited to the left inferior quadrant, with poor acuity. Preoperative V-CCSS scores are summarized in Fig. 2A. Thirty-two children (40%) had a V-CCSS score of 1; 11 children (13.8%) had a score of 2; 35 (43.8%) had a score of 3; and 2 (2.5%) had a score of 4. The mean preoperative V-CCSS score was 2.09 ± 0.97 (median 2). Children with recurrent tumors had significantly higher preoperative V-CCSS scores in the recurrent tumor group ($p < 0.001$).

Of the 31 patients with VA deficits, improvement occurred in 13 (42%). Deterioration in VA occurred in 12 patients overall, with only 3 patients experiencing monocular blindness. Of these, 1 patient had VA results of 20/40 in the affected eye preoperatively; 1 was too young for preoperative testing, but had decreased vision compared with the unaffected eye prior to surgery; and the final patient had vision only in the left inferior quadrant, with poor VA prior to surgery. None of the 3 patients with preoperative blindness recovered vision. One patient with 20/40 VA bilaterally prior to surgery experienced marked deterioration in his vision postoperatively, and was using Braille for reading at last follow-up.

Of the 43 patients with VF deficits, improvement occurred in 20 (47%). Although VF deficits occurred in 15 patients, only 3 had new deficits that interfered with daily functioning. The most common new immediate postoperative VF deficit was a homonymous hemianopia contralateral to the side of approach (10 left, 1 right). This was most likely due to manipulation of the ipsilateral aspect of the optic chiasm and/or optic tract during tumor removal via the pterional approach. This deficit had resolved in 5 patients by 6 months after resection. Six patients were left with a permanent complete homonymous hemianopia or superior left quadrantanopia (3 each).

Postoperative V-CCSS scores are summarized in Fig. 2B. Thirty-one children (38.8%) had a score of 1; 28 (35%) had a score of 2; 17 (21.3%) had score of 3; and 4 (5%) had a score of 4. The mean postoperative V-CCSS score was 1.9 ± 0.90 (median 2). Children with recurrent tumors continued to have higher V-CCSS scores following surgery ($p < 0.001$).

Figure 2C demonstrates the change in V-CCSS score following treatment. The mean change in score was −0.18 ± 0.78 (median 0, range −2 to +1). There was a significant improvement in V-CCSS score following resection ($p = 0.04$). No patient had more than a 1-point increase (worsening) in V-CCSS score. There was a marginally significant trend toward a higher proportion of VF improvement in primary compared with recurrent tumors (9 [56.3%] of 16 vs 4 [27%] of 15; $p = 0.15$), but no difference in the rate of VF improvement (13 [43.5%] of 23 vs 7 [35%] of 20; $p = 0.22$). There was no difference in rate of VF (9 [17%] of 53 vs 6 [22%] of 27) or VA (7 [14%] of 51 vs 5 [18.5%] of 27) deterioration between primary and recurrent tumor groups following resection. Overall, there was no difference in the change in V-CCSS score between children with primary and recurrent craniopharyngiomas ($p = 0.82$). The pre- and postoperative V-CCSS scores and changes following treatment for both primary and recurrent craniopharyngiomas are shown in Table 4.

The ordinal logistic regression model for V-CCSS was significant (pseudo-$R^2 = 0.56$, $p < 0.0005$). Predictors of higher postoperative V-CCSS scores (Table 5) in-

TABLE 5: Multinomial logistic regression analysis of predictors of postoperative CCSS outcomes*

Variable	p Values for Individual Functional Domains				
	N-CCSS	V-CCSS	P-CCSS	H-CCSS	E-CCSS
age at op	NS	NS	0.07	NS	NS
sex	NS	0.09	NS	NS	NS
giant tumor size	0.03	NS	NS	NS	0.10
recurrent tumor	NS	0.03	0.01	NS	0.06
hydrocephalus	NS	0.07	NS	0.05	0.005
retrochiasmatic location	NS	NS	NS	NS	0.13
preop CCSS score	0.036	<0.0005	<0.0005	<0.0005	<0.0005

* NS = not significant.

cluded preoperative V-CCSS score ($p < 0.0005$) and prior treatment ($p = 0.03$).

Pituitary Function

Twenty-five patients (31.3%) had DI prior to initial surgery at NYU, with or without hypopituitarism. Significantly more patients in the recurrent group (18 [67%] of 27) had preoperative DI compared with the primary group (7 [13%] of 53, $p < 0.001$) prior to surgery at NYU. Preoperative P-CCSS scores are summarized in Fig. 3A. Thirty-three children (41.3%) had a P-CCSS score of 1; 22 (27.5%) had a score of 2; 18 (22.5%) had a score of 3; and 7 (8.8%) had a score of 4. The mean preoperative P-CCSS score was 1.99 ± 1.0 (median 2). Patients with recurrent tumors had significantly higher P-CCSS scores than the primary group ($p < 0.001$).

Postoperatively, 62 patients (77.5%) had DI, including 37 (46.3%) with new-onset DI. Overall, there was no significant difference in the rate of permanent DI between the primary (78%) and recurrent groups (89%). Postoperative P-CCSS scores are summarized in Fig. 3B. Four children (5%) had a score of 1; 9 children (11.3%) had a score of 2; 34 (42.5%) had score of 3; and 33 (41.3%) had a score of 4. The mean postoperative P-CCSS score was 3.2 ± 0.83 (median 3). There was no difference in the postoperative P-CCSS scores between the primary and recurrent tumor groups ($p = 0.42$).

Figure 3C demonstrates the change in P-CCSS score following treatment. The mean change in score was +1.21 ± 1.1 (median 1, range 0 to +3), indicating significant worsening of pituitary function following resection ($p < 0.001$). No patient experienced improvement in pituitary function following treatment. Patients with primary tumors had a greater increase in P-CCSS scores following treatment, indicating a significantly greater decline in pituitary function following resection compared with the recurrent tumor group ($p < 0.001$). The pre- and postoperative P-CCSS scores and changes following treatment for both primary and recurrent craniopharyngiomas are shown in Table 4.

The ordinal logistic regression model for P-CCSS was significant (pseudo-$R^2 = 0.28$; $p = 0.002$). Predictors of higher postoperative P-CCSS scores (Table 5) included preoperative P-CCSS score ($p < 0.0005$) and prior treatment ($p = 0.01$). Of note, no predictors of P-CCSS outcomes were identified when subgroup analysis of children with primary tumors was performed. This was due to the nearly universal endocrinopathy that occurred subsequent to treatment—yielding poor correlations between pre- and postoperative status.

Hypothalamic Function

Hypothalamic disturbance was present in 17 children (21%; 4 primary and 13 recurrent) preoperatively (De Vile classifications: mild in 4, moderate in 9, and severe in 4) and was more prevalent in children in the recurrent

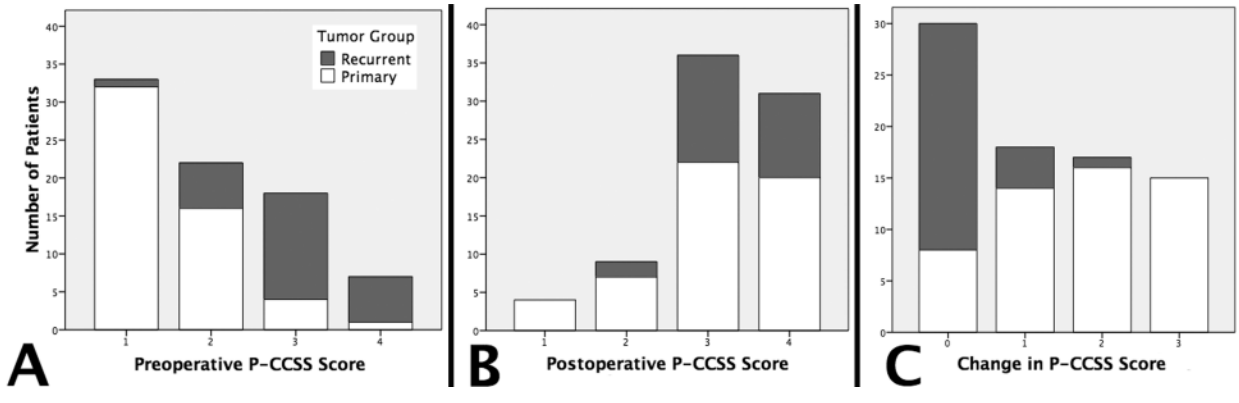

Fig. 3. Histograms summarizing preoperative **(A)**, postoperative **(B)**, and change in **(C)** P-CCSS scores in children with primary and recurrent craniopharyngiomas.

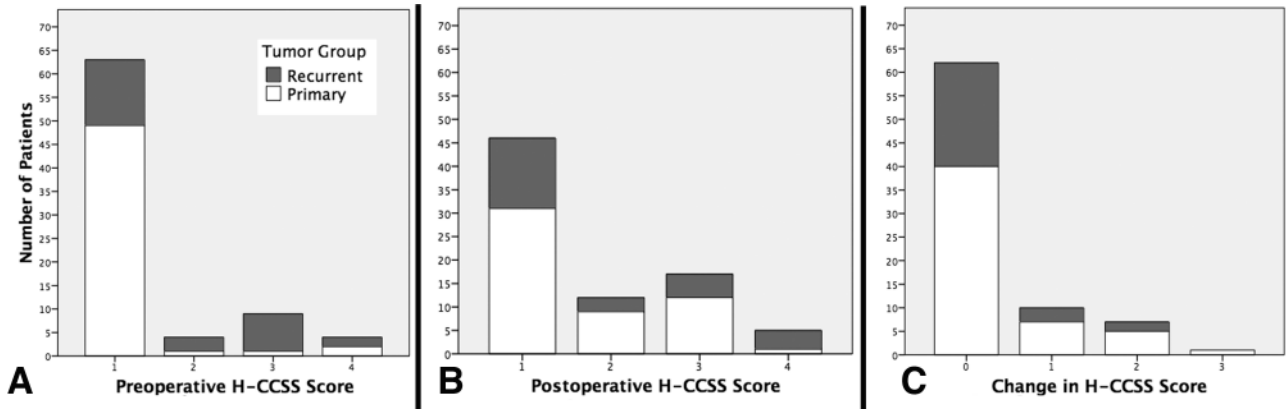

Fig. 4. Histograms summarizing preoperative **(A)**, postoperative **(B)**, and change in **(C)** H-CCSS scores in children with primary and recurrent craniopharyngiomas.

group ($p < 0.001$). Eight patients had mild (5 patients) or moderate (3 patients) dysfunction in short-term memory prior to surgery at NYU. Preoperative H-CCSS scores are summarized in Fig. 4A. Sixty-three children (78.8%) had an H-CCSS score of 1; 4 children (5%) had a score of 2; 9 (11.3%) had a score of 3; and 4 (5%) had a score of 4. The mean preoperative H-CCSS score was 1.42 ± 0.88 (median 1). Patients with recurrent tumors had significantly higher H-CCSS scores than the primary group ($p < 0.001$), indicative of greater pretreatment dysfunction.

Eighteen children (22.5%) developed new or worsened hypothalamic dysfunction postoperatively (mild in 10, moderate in 7, severe in 1). Height and weight measurements were available in 62 patients at the last follow-up (85% of the primary group [45 patients], and 63% of the recurrent group [17]). The mean BMI was +1.18 SDs above normal for the entire cohort (median 1.23, SD 1.4). Although there was a trend toward higher BMI in the recurrent group, this difference was only marginally significant ($p = 0.058$). At last follow-up, 12 patients (19%) had obesity (BMI > +2 SD), 1 (1.6%) had severe obesity (BMI > +3 SD), and 1 had morbid obesity (BMI in this patient, +4.11). The only child with morbid obesity (BMI +4.11) had severe obesity prior to surgery. Two children experienced worsening of their premorbid short-term memory deficits, and another child's deficits improved following resection. Eleven patients experienced new mild (10 children) or moderate (1 child) short-term memory dysfunction postoperatively. Another patient with a 5-cm intraventricular tumor experienced significant lethargy and permanent bulla and cognitive deficits following transcallosal resection. Six of these patients experienced significant improvement in memory function over time. Postoperative H-CCSS scores are summarized in Fig. 4B. Forty-six children (57.5%) had a score of 1; 12 (15%) had a score of 2; 17 (21.3%) had score of 3; and 5 (6.3%) had a score of 4. The mean postoperative H-CCSS score was 1.76 ± 1.0 (median 1). Higher H-CCSS scores persisted following treatment for children with recurrent craniopharyngiomas ($p = 0.003$).

Figure 4C demonstrates the change in H-CCSS score following treatment. The mean change in score was +0.34 ± 0.69 (median 0, range 0 to +3), indicating worse hypothalamic dysfunction following resection ($p < 0.001$). There was no difference in the change in H-CCSS scores following treatment between the primary and recurrent tumor groups ($p = 0.52$). There were no differences in pre- or postoperative hypothalamic dysfunction or BMI in children with pre- and retrochiasmatic tumors. The pre- and postoperative H-CCSS scores and changes following treatment for both primary and recurrent craniopharyngiomas are shown in Table 4.

The ordinal logistic regression model for H-CCSS was significant (pseudo-$R^2 = 0.58$; $p < 0.0005$). Predictors of higher postoperative H-CCSS scores (Table 5) included preoperative H-CCSS score ($p < 0.0005$) and presence of hydrocephalus ($p = 0.05$).

Educational/Occupational Status

Preoperative E-CCSS scores are summarized in Fig. 5A. Thirty-nine children (48.8%) had an E-CCSS score of 1; 32 (40%) had a score of 2; 7 (8.8%) had a score of 3; and 2 (2.5%) had a score of 4. The mean preoperative E-CCSS score was 1.65 ± 0.75 (median 2). There was no significant difference between children with recurrent tumors and the primary group in terms of their E-CCSS scores ($p = 0.136$).

Postoperative E-CCSS scores are summarized in Fig. 5B. Thirty-two children (40%) had a score of 1; 25 (31.3%) had a score of 2; 15 (18.8%) had score of 3; and 8 (10%) had a score of 4. The mean postoperative E-CCSS score was 1.99 ± 1.0 (median 2). Of the poor-outcome group (E-CCSS score of 4), 4 children had significant deficits on formal IQ testing (IQ < 80), and 4 were disabled enough to require significant assistance with ADLs. Seven of the 8 children in this group had preoperative cognitive deficits (mild in 3, moderate in 2, severe in 2). The final patient in this group experienced a midbrain stroke that left him physically dependent but cognitively normal. Among the 15 children who experienced a fair outcome (E-CCSS score of 3), 8 had preoperative cognitive deficits. One child in the fair-outcome group made significant gains in cognition following resection, but social isolation remained prominent. Three children who experienced good

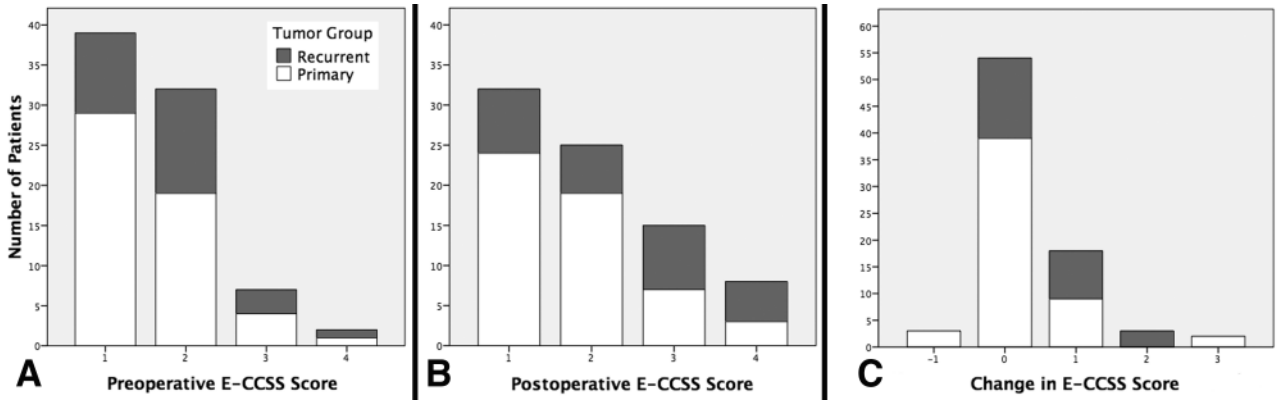

Fig. 5. Histograms summarizing preoperative **(A)**, postoperative **(B)**, and change in **(C)** E-CCSS scores in children with primary and recurrent craniopharyngiomas.

outcomes (E-CCSS score of 2) had mild preoperative deficits that improved postoperatively. No children with excellent outcomes (E-CCSS score of 1) had documented preoperative cognitive deficits, and 3 experienced gains in IQ scores of > 10 points. Thirty-five (73%) of 48 patients 18 years of age or older at the time of last follow-up were either currently attending, had matriculated into, or had graduated from college. Three patients experienced improvement in their social interactive skills, and 1 child worsened in that domain following surgery. Higher E-CCSS scores persisted following treatment for children with recurrent craniopharyngiomas ($p = 0.02$).

Figure 5C demonstrates the change in E-CCSS score following treatment. The mean change in score was +0.34 ± 0.73 (median 0, range −1 to +3), indicating significant worsening of educational/occupational function following resection ($p < 0.001$). Children with recurrent craniopharyngiomas tended to have a greater increase in E-CCSS score at the last follow-up compared with primarily treated patients ($p = 0.017$), indicating a greater decline in overall performance following treatment. The pre- and postoperative E-CCSS scores and changes following treatment for both primary and recurrent craniopharyngiomas are shown in Table 4.

The ordinal logistic regression model for E-CCSS was significant (pseudo-$R^2 = 0.62$; $p < 0.0005$). Predictors of higher postoperative E-CCSS scores (Table 5) included preoperative E-CCSS score ($p < 0.0005$) and presence of hydrocephalus ($p = 0.005$).

Wen Functional Outcome

Preoperatively, patients in the recurrent tumor group had significantly worse functional status compared with the primary group ($p = 0.001$). These differences were mostly attributable to panhypopituitarism and, less so, to visual deficits following initial treatment.

Postoperatively, there was no significant difference in Wen class between the primary and recurrent groups. Following treatment, there was a significant increase in Wen class for children in the primary group, mostly attributable to hypopituitarism and/or DI following surgery ($p < 0.001$). No significant change in Wen class occurred in the recurrent group following surgery, consistent with the fact that many were already Class II due to hypopituitarism, DI, or visual deficits following the original treatment.

Excluding 1 patient who lacked detailed imaging data, subgroup analysis was performed to determine the effects of tumor location and size on functional status before and after surgery. There was no significant difference in good pre- and postoperative functional status between patients with pre- and retrochiasmatic tumors ($p = 0.45$ and $p = 0.85$, respectively). In children with giant tumors, there was a marginally significant trend toward worse functional status before surgery and significantly worse functional outcomes following resection ($p = 0.051$ and $p = 0.03$, respectively).

Discussion

Debate persists regarding the optimal treatment of craniopharyngiomas in children,[4,12,14,20,41,52,54,73] and currently no consistent metric of functional outcome exists to allow meaningful comparisons across treatment paradigms or surgical approaches. We have created a simple grading scale that addresses the clinical status of patients with craniopharyngiomas across the 5 major axes of morbidity, both at presentation and following treatment. We have attempted to overcome the limitations of subjectivity of assessment and excess binning of functional domains to provide a useful metric for intermodality comparison—the CCSS. The criteria for each of the first 4 grades (neurological examination, vision, pituitary function, and hypothalamic function) are objective in nature. Potential for subjectivity exists for our assessment protocol of educational and occupational performance.

In our model, we used a 4-tiered scale to rate educational/occupational success that was based on actual achievement and not formal neuropsychological testing. Starting early on in our series, we advocated for neuropsychological testing in all patients before and after surgery. However, due to financial considerations, poor overall preoperative functional status, need for emergency surgery for high intracranial pressure or vision compromise, poor compliance with follow-up appointments, or logistical reasons, fewer than half of the patients underwent any testing, and only 19% completed both pre- and postoperative testing.

Although neuropsychological testing comprehensively assesses cognitive, attentional, memory, and task-specific performance skills, in our series it did not often predict or correlate with the patient's current level of academic or vocational success and achievement. Defined as performing well at grade level but scoring below the 50th percentile in multiple domains of testing, we noted discrepancies in more than one-third of children tested. Similar findings addressing such "ecological validity" of neuropsychological testing have been noted in patients following TBI—that is, a significant disparity between the deficits noted on formal testing and the patient's performance in school or at work.[39,59,62] In a study of patients with TBI, Sbordone[59] noted that neuropsychological tests "were never designed to predict how these patients were likely to function in real-world settings, live independently, return to work, or maintain competitive employment."

Such discrepancies are probably due to the high sensitivity of formal testing in detecting such specific and task-oriented deficits. We continue to believe that neuropsychological testing is a crucial part of the initial assessment and postoperative follow-up for children with craniopharyngiomas to maximize their educational and vocational potential; however, we believe strongly that their current level of success and achievement should be the ultimate measure of good functional outcomes. Fischer and colleagues[27] shared this belief, and noted that performance after high school is a critically important indicator of overall function.

Compared with preoperative baseline status, we noted a significant increase in pituitary dysfunction following treatment—consistent with the high rates of DI and hypopituitarism common to the surgical management of these tumors—and less dramatic deterioration in hypothalamic function or cognitive domains. Significant improvement in vision was also demonstrated, with no significant overall change in neurological status. Although increasing tumor size, prior treatment, and the presence of hydrocephalus were associated with postoperative deterioration in multiple domains in children with craniopharyngiomas, the preoperative CCSS scores correlated most highly with ultimate outcomes in all domains of function. We believe these results demonstrate the utility of this standardized outcome assessment tool, and can be used to predict morbidity and to offer better counsel to patients, their families, and their primary physicians.

Functional Outcome in Reported Surgical Series

Currently, no Class I or II evidence exists demonstrating the optimal treatment of primary and recurrent craniopharyngiomas in children. Most would agree that complete resection for these benign but tenacious lesions is ideal, but the cost of attempted GTR in all cases has been questioned.[12,29,47,57,63] The 2 major treatment paradigms—complete resection aiming for surgical cure and limited resection followed by RT—offer similar rates of disease control and long-term survival.[4,15,20,29,31,41,44,52,64,73] Given the improved rates of survival with treatment advances over the past few decades, the focus has turned toward functional outcome and QOL metrics.[6,7,41,46,48,50,55,58,61]

Neuropsychological testing of small series of patients has revealed cognitive and intellectual sequelae in as many as 60% of children treated for craniopharyngioma.[6,7,10] Merchant et al.[42] reported increased neurological deficits, increased DI, and statistically insignificant trends toward greater IQ decline and worse QOL in 15 patients in whom attempts at complete resection were made (GTR was successful in 8 of 15), compared with 15 children who underwent limited resection as intended, followed by RT. These differences were small, as were the numbers of children in each group. Prior work by our group demonstrated overall QOL and neuropsychological outcomes following radical resection to be within the normal range seen in children with other chronic diseases. Specific to craniopharyngiomas, however, some children experienced deficits in social function and emotional reactivity. These disturbances were more common in children with retrochiasmatic or recurrent tumors.[58]

In a series of 153 children reported by Zucarro[73] who were treated with the intent of complete removal, all children who underwent GTR (69% of the group) were in school and no more than 1 year behind in grade level, in contrast to only 62% of children who underwent subtotal resection plus RT (31% of the group). Di Rocco and colleagues[15] noted improvement in mean IQ scores following radical resection in 54 children, and all but 2 of 50 surviving patients enjoy a normal social life. Riva et al.[55] reported no instances of cognitive or memory deficits in 12 children who underwent radical resection, but noted increased emotional lability and difficulty with impulse control, possibly related to the subfrontal approach or hypothalamic injury. In a series by Hoffman et al.,[32] 26 of 27 children who underwent aggressive resection had IQ scores at or above average levels. Although 16 children had memory deficits, 14 of them attended regular schools. These authors contend that "memory impairment did not interfere with school progress if intelligence was adequate." A few centers have reported less favorable outcomes and lower rates of functional independence after resection of recurrent compared with primary craniopharyngiomas (58–61% vs 72–78%).[25,72] Habrand et al.[29] described their 25-year experience with limited resection followed by RT, and reported panhypopituitarism in 97% and psychological disturbances and poor school performance in 29% of children. Thus, although these earlier studies are retrospective, lack control groups, and use vaguely defined outcome metrics, it is evident that both treatment paradigms can have deleterious effects on functional outcome in children with craniopharyngiomas.

Functional Outcome Scales for Children With Craniopharyngiomas

Given the limitations and subjectivity of outcome reporting in most series, a few centers have attempted to define specific outcome criteria for craniopharyngiomas. De Vile and colleagues[12] introduced a scale that is similar to ours in addressing these 5 domains of function for children with craniopharyngiomas. These investigators identified the following variables as risk factors for increased morbidity: larger lesion size, hypothalamic involvement of the tumor, clinical signs of hypothalamic dysfunction (namely obesity), and patient younger than 5 years of age.

TABLE 6: Functional outcome grading scale*

Outcome	Criteria
good	alive at follow-up examination
	no major motor deficit related to op or tumor progression
	functional vision
	Katz Grade A (able to perform basic ADLs)
	Karnofsky Performance Scale score ≥80
	no more than 1 yr behind in expected school grade
	employability for adults of working age
	absence of debilitating psychological or emotional problems
poor	all patients not meeting the "good" criteria

* Based on data in the article by Duff et al.

Using these clinical and radiographic findings, they subsequently used the hypothalamic morbidity predicted by their scale to determine preoperatively the optimal surgical plan.[63] Specifically, they treated 23 children with larger tumors and those involving the hypothalamus with intentionally limited resection followed by RT, whereas 25 tumors were deemed completely resectable. Using this paradigm, they reported decreased hypothalamic morbidity, less cognitive decline, improved vision outcomes, and overall less severe morbidity (4 vs 20% compared with their prior series, in which GTR was attempted in all cases).

A few points should be made concerning the morbidity in their series. Using their 1996 study as the aggressive-surgery "control" group,[12] their postoperative morbidity scores are rather high. Severely compromised vision was noted in > 50% of children, 40% of children had major neurological deficits (at least mild-to-moderate motor dysfunction), and 40% had significant cognitive impairment (IQ < 80). These outcomes are worse than those in many published series, and may serve as a poor baseline for comparison as surgical experience and techniques improve over time. Furthermore, severe hypothalamic morbidity still occurred in 20% of children (down from 29% in the original study), and there was no improvement in pituitary function after using the new treatment paradigm (92% still had hypopituitarism, and DI occurred in 73%, compared with 80% in the original series). Although they concluded that their "evidence-based" treatment protocol resulted in improved outcomes, there was little improvement in hypothalamic dysfunction—the purported raison d'être of their new paradigm. Overall, 94% of children were "normal" academically before treatment, and only 62% maintained such normality following treatment—indicative of significant morbidity with even more conservative treatment.[63]

Another concern regarding the De Vile outcome scale is that overall morbidity was determined as a simple sum of the morbidity profiles across each individual axis. However, the functional significance or "weight" of each 1-point score across the different domains is unlikely to be equivalent in terms of subjective morbidity in the patients. We have refrained from creating a composite total score to avoid this pitfall, and are currently attempting to determine the impact on QOL of the individual deficits across domains.

A second major outcome measure was proposed by Wen et al.,[67] consisting of a 4-tiered classification scheme that considers morbidity across all domains (Table 2). The major benefit of this grading scale resides in its simplicity. Its major limitations are its ill-defined terms (such as "learning disabilities" and "psychological disorders") as well as its combining of the deficits in so many disparate domains into a single morbidity class. The former limitation introduces interobserver subjectivity, whereas the latter results in the loss of a more nuanced picture of the deficits in each child.

Duff and colleagues[17] examined the outcomes in 121 adults and children who were treated for craniopharyngiomas, and attempted to identify patients who were "well integrated independent individuals functioning in society." They classified patient outcomes as either good or poor; patients not meeting all 8 criteria (Table 6) were considered to have had poor outcomes. Such dichotomization, however, causes a significant amount of functional data to be lost—limiting the completeness of the assessment and the conclusions that can be drawn when comparing treatment modalities.

Poretti and colleagues[48] used a variety of questionnaires to assess QOL in 25 consecutive children with craniopharyngiomas, including the Pediatric Quality of Life Inventory to address physical, emotional, social, and school functioning; the Youth Self Report scale to assess social and emotional function; the Epworth Sleepiness Scale to assess fatigue and sleepiness during daily activities; and the Child Behavioral Checklist to assess behavioral and emotional problems from the parental perspective. They reported the following as predictors of poor outcome on their QOL analyses: young age, hypothalamic involvement and/or damage, hydrocephalus, and tumor recurrence. Some authors have used the Health Utilities Index Mark 2 to assess health-related QOL.[41,50] This index is used to classify a patient's health across 7 categories (vision, hearing, speech, mobility, emotion, cognition, self-care, pain, and fertility). Obviously, there is some overlap with the predominant deficits children suffer following craniopharyngioma treatment, but many facets of craniopharyngioma morbidity are not addressed. Other scales have been used to assess outcome after resection of brain tumors, including the Glasgow Outcome Scale,[33] the extended Glasgow Outcome Scale,[34] and the modified Rankin Scale.[26,53] All are rather crude measures of outcome; the first and second are used primarily in TBI, and the third is designed to assess patients who have suffered strokes. Furthermore, they all have limitations in terms of interobserver reliability and subjectivity,[51,68,69] and have not been reported or tested in the craniopharyngioma literature.

Expectations Following Treatment of Craniopharyngiomas

Based on large published series, certain generalities can be discussed concerning the expected morbidity following craniopharyngioma treatment. Neurological improvement from resolution of mass effect is common, and the rate of severe injury is low (≤ 15% in most series).

Inadvertent vascular injury appears to be a not insignificant source of acute neurological morbidity, and has been reported with intentionally complete and incomplete resections, and with transcranial and transsphenoidal approaches.[4,11,20,37,38] This complication is probably an unpredictable event, but one that may decrease with a surgeon's experience. Reviewing the major large surgical series of pediatric craniopharyngiomas, vision improvement has been reported in > 50% of cases in the majority of studies, and visual deterioration generally occurs in < 20% of patients.[4,17,20,25,50,57] Higher rates of visual improvement and less deterioration have been reported in many series describing tumors treated transsphenoidally.[8,11,28] Whether this is attributable to patient selection (preponderance of intrasellar tumors) or better technique for optic apparatus decompression awaits comparisons between tumor groups of similar size and location.

As noted by Duff and colleagues,[17] major endocrinopathy following radical surgery is "almost inevitable," and was not a source of significant morbidity in their series. Furthermore, a greater deterioration in pituitary dysfunction and a higher incidence of DI occurred in children with primary tumors. This is accounted for by the fact that most children with recurrent tumors already had panhypopituitarism and DI subsequent to their original (and usually conservative) treatment. Our results corroborate the findings of Duff et al.; patients, families, and primary physicians should be counseled on the very high likelihood of postoperative hypopituitarism and DI. In agreement with De Vile and colleagues,[13] we found that DI, especially in the setting of impaired thirst (adipsia), is more persistently disabling and burdensome to patients and families compared to anterior pituitary dysfunction. With close follow-up, modern endocrinological care is very effective and successful at supplementing endocrine deficiencies, guiding catch-up growth, and nearly eliminating the risk of fatal endocrine crises. The success and safety of all paradigms of craniopharyngioma treatment, however, depend rather heavily on regular postoperative endocrinological support and the familial and societal resources to cope with these nearly universal endocrine deficiencies.[61]

The risk and consequences of hypothalamic dysfunction comprise the main points of contention concerning extent of resection. Hypothalamic dysfunction can manifest as a constellation of disturbances that can include obesity, hyperphagia, memory deficits, thermoregulatory abnormalities, emotionally labile behavior, and sleep-wake cycle disruption.[12,30,43,47,50,57] Standardized assessment and reporting of hypothalamic dysfunction and "obesity" are lacking, and these conditions are poorly reported in the craniopharyngioma literature. Obesity is often undefined in many reports, but is generally < 50% in most surgical series.[4,12,14,17,25,32,35,50,64] In a German multicenter study reported by Müller et al.,[46] in which they failed to describe their treatment protocol, severe obesity (> +3 SD BMI) occurred in 44% of 185 children with long-term "postoperative" follow-up.

As Puget and colleagues[50] noted, the risk of hypothalamic disturbance is heavily dependent on the surgeon's experience. In our series, 43 patients (81%) in the primary group and 15 (56%) in the recurrent group had no or mild hypothalamic dysfunction following surgery, compared with 94 and 63%, respectively, before surgery. Importantly, the majority of the cases of hypothalamic morbidity in children with recurrent craniopharyngiomas occurred subsequent to treatment already received at other centers—mostly consisting of intended subtotal resection plus RT. Furthermore, obesity was rare, and significant hypothalamic disturbance was generally rare in our series, despite a significant proportion of large and retrochiasmatic tumors. We found no significant difference in pre- or postoperative hypothalamic disturbance between children with pre- and retrochiasmatic tumors. Furthermore, mild-to-moderate memory dysfunction accounted for most of the patients with moderate grades of hypothalamic dysfunction postoperatively. As noted previously, memory deficits can often be overcome as long as overall intelligence remains intact.

The aforementioned considerations are most closely associated with surgery-related morbidity, but mention should be made of the effects of RT on children. Radiation therapy has been shown to provide excellent rates of disease control and is the favored option for definitive management in many centers.[29,41,42,52,54] Although most practitioners agree that the risk of complete resection involves the potential for higher rates of acute neurological morbidity and DI, the effects of cranial irradiation are often delayed and unpredictable in onset. More pronounced in younger children,[41,42] side effects of RT include dysfunction of the hypothalamic-pituitary axis, vision decline, benign and malignant radiation-induced CNS tumors, cognitive dysfunction, attentional deficits, cerebrovasculopathy, and moyamoya disease.[1,2,16,18,19,24,36,40,45,60] Prior work by our group[20] and others[54] has shown significantly worse surgical outcomes and survival following tumor progression after failed RT. Given the 20–30% incidence of tumor progression following RT,[9] one must consider the potentially deleterious effects of early irradiation on the safety and efficacy of subsequent treatments.

Study Limitations

The main limitations of this study include the retrospective manner of data collection and the lack of detailed pre- and postoperative neuropsychological testing in many children. Its strengths lie in the large size of the series, lengthy follow-up, and a uniform treatment paradigm in all patients—attempted complete resection for surgical cure. However, the design of any scale involves the neglect of certain data points for the sake of grouping and meaningful comparison and analysis. We have tried to balance these opposing considerations carefully, and have created a 4-tiered classification scheme addressing the 5 major domains of morbidity in children with craniopharyngiomas. Another defect of most classification systems is the lack of direct correlation with or measurement of the effects that each type and extent of deficit may exert on a single child's everyday functioning and QOL. Ideally, we would like to determine further via interviews or questionnaires exactly what are the negative consequences of having deficits of varying degrees in the separate domains. Such a correspondence of each defi-

cit's "weighting" to its impact on QOL would then allow further standardization of an overall morbidity profile (composite CCSS score) that would facilitate improved comparison across centers and treatment modalities. This phase of the project is currently in progress. Finally, the CCSS needs to be externally validated by comparing the results in our series with those of other large series of children with craniopharyngiomas.

Conclusions

We have created a simple grading scale that addresses the clinical status of patients with craniopharyngiomas across the 5 major axes of morbidity at presentation and following treatment. We noted a significant increase in anterior and posterior pituitary dysfunction following treatment—consistent with the high rates of DI and hypopituitarism common to the surgical management of these tumors—and less dramatic deterioration in hypothalamic function or cognitive domains. Significant improvement in vision was also demonstrated in patients with no significant overall change in neurological status. Adoption of this scale by multiple centers may allow a more standardized assessment of pre- and posttreatment functional status, and it may allow meaningful comparisons between the various treatment paradigms. Further work is needed to equate such a grading scale with the subjective quality of survival in children with craniopharyngiomas.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: RE Elliott, JH Wisoff. Acquisition of data: RE Elliott, RG Strom. Analysis and interpretation of data: RE Elliott, SA Sands, RG Strom, JH Wisoff. Drafting the article: RE Elliott, SA Sands, RG Strom, JH Wisoff. Critically revising the article: RE Elliott, SA Sands, RG Strom, JH Wisoff. Reviewed final version of the manuscript and approved it for submission: SA Sands, JH Wisoff. Statistical analysis: RE Elliott.

References

1. Anderson VA, Godber T, Smibert E, Weiskop S, Ekert H: Cognitive and academic outcome following cranial irradiation and chemotherapy in children: a longitudinal study. **Br J Cancer 82:**255–262, 2000
2. Anderson VA, Godber T, Smibert E, Weiskop S, Ekert H: Impairments of attention following treatment with cranial irradiation and chemotherapy in children. **J Clin Exp Neuropsychol 26:**684–697, 2004
3. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. **J Neurosurg 89:**547–551, 1998
4. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C: Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. **Childs Nerv Syst 21:**747–757, 2005
5. Carmel PW, Antunes JL, Chang CH: Craniopharyngiomas in children. **Neurosurgery 11:**382–389, 1982
6. Carpentieri SC, Waber DP, Scott RM, Goumnerova LC, Kieran MW, Cohen LE, et al: Memory deficits among children with craniopharyngiomas. **Neurosurgery 49:**1053–1058, 2001
7. Cavazzuti V, Fischer EG, Welch K, Belli JA, Winston KR: Neurological and psychophysiological sequelae following different treatments of craniopharyngioma in children. **J Neurosurg 59:**409–417, 1983
8. Chakrabarti I, Amar AP, Couldwell W, Weiss MH: Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. **J Neurosurg 102:**650–657, 2005
9. Choux M, Lena G, Genitori L: Le craniopharyngiome de l'enfant de moins de 5 ans. **Neurochirurgie 37 (Suppl 1):**147–150, 1991 (Fr)
10. Clopper RR, Meyer WJ III, Udvarhelyi GB, Money J, Aarabi B, Mulvihill JJ, et al: Postsurgical IQ and behavioral data on twenty patients with a history of childhood craniopharyngioma. **Psychoneuroendocrinology 2:**365–372, 1977
11. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T: Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. **Neurosurgery 55:**539–550, 2004
12. De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, et al: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? **J Neurosurg 85:**73–81, 1996
13. DeVile CJ, Grant DB, Hayward RD, Stanhope R: Growth and endocrine sequelae of craniopharyngioma. **Arch Dis Child 75:**108–114, 1996
14. Dhellemmes P, Vinchon M: Radical resection for craniopharyngiomas in children: surgical technique and clinical results. **J Pediatr Endocrinol Metab 19 (Suppl 1):**329–335, 2006
15. Di Rocco C, Caldarelli M, Tamburrini G, Massimi L: Surgical management of craniopharyngiomas—experience with a pediatric series. **J Pediatr Endocrinol Metab 19 (Suppl 1):**355–366, 2006
16. Dobracki A, Woolf P: Multiple head and neck tumors following treatment for craniopharyngioma. **Pituitary** [epub ahead of print], 2009
17. Duff J, Meyer F, Ilstrup D, Laws E, Schleck C, Scheithauer B: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000
18. Duffner PK: Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. **Neurologist 10:**293–310, 2004
19. Ellenberg L, McComb JG, Siegel SE, Stowe S: Factors affecting intellectual outcome in pediatric brain tumor patients. **Neurosurgery 21:**638–644, 1987
20. Elliott RE, Hsieh K, Hochm T, Belitskaya-Levy I, Wisoff J, Wisoff JH: Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children. **J Neurosurg Pediatr 5:**30–48, 2010
21. Elliott RE, Moshel YA, Wisoff JH: Minimal residual calcification and recurrence after gross-total resection of craniopharyngioma in children. **J Neurosurg Pediatr 3:**276–283, 2009
22. Elliott RE, Moshel YA, Wisoff JH: Surgical treatment of ectopic recurrence of craniopharyngioma. Report of 4 cases. **J Neurosurg Pediatr 4:**105–112, 2009
23. Elliott RE, Wisoff JH: Successful surgical treatment of craniopharyngioma in very young children. **J Neurosurg Pediatr 3:**397–406, 2009
24. Enchev Y, Ferdinandov D, Kounin G, Encheva E, Bussarsky V: Radiation-induced gliomas following radiotherapy for craniopharyngiomas: a case report and review of the literature. **Clin Neurol Neurosurg 111:**591–596, 2009
25. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999

26. Farrell B, Godwin J, Richards S, Warlow C: The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. **J Neurol Neurosurg Psychiatry 54:**1044–1054, 1991
27. 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
28. Gardner PA, Kassam AB, Snyderman CH, Carrau RL, Mintz AH, Grahovac S, et al: Outcomes following endoscopic, expanded endonasal resection of suprasellar craniopharyngiomas: a case series. **J Neurosurg 109:**6–16, 2008
29. Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, et al: The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. **Int J Radiat Oncol Biol Phys 44:**255–263, 1999
30. Hayward R: The present and future management of childhood craniopharyngioma. **Childs Nerv Syst 15:**764–769, 1999
31. 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
32. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI: Aggressive surgical management of craniopharyngiomas in children. **J Neurosurg 76:**47–52, 1992
33. Jennett B, Bond M: Assessment of outcome after severe brain damage. **Lancet 1:**480–484, 1975
34. Jennett B, Snoek J, Bond MR, Brooks N: Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. **J Neurol Neurosurg Psychiatry 44:**285–293, 1981
35. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH: Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. **Med Pediatr Oncol 40:**214–218, 2003
36. Keene DL, Johnston DL, Grimard L, Michaud J, Vassilyadi M, Ventureyra E: Vascular complications of cranial radiation. **Childs Nerv Syst 22:**547–555, 2006
37. Landolt AM, Zachmann M: Results of transsphenoidal extirpation of craniopharyngiomas and Rathke's cysts. **Neurosurgery 28:**410–415, 1991
38. Laws ER Jr: Vascular complications of transsphenoidal surgery. **Pituitary 2:**163–170, 1999
39. LeBlanc JM, Hayden ME, Paulman RG: A comparison of neuropsychological and situational assessment for predicting employability after closed head injury. **J Head Trauma Rehabil 15:**1022–1040, 2000
40. Meadows AT, Gordon J, Massari DJ, Littman P, Fergusson J, Moss K: Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. **Lancet 2:**1015–1018, 1981
41. Merchant TE, Kiehna EN, Kun LE, Mulhern RK, Li C, Xiong X, et al: Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. **J Neurosurg 104 (2 Suppl):**94–102, 2006
42. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984-2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
43. Meuric S, Brauner R, Trivin C, Souberbielle JC, Zerah M, Sainte-Rose C: Influence of tumor location on the presentation and evolution of craniopharyngiomas. **J Neurosurg 103 (5 Suppl):**421–426, 2005
44. Minniti G, Saran F, Traish D, Soomal R, Sardell S, Gonsalves A, et al: Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. **Radiother Oncol 82:**90–95, 2007
45. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE: Late neurocognitive sequelae in survivors of brain tumours in childhood. **Lancet Oncol 5:**399–408, 2004
46. Müller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, et al: Obesity after childhood craniopharyngioma—German multicenter study on pre-operative risk factors and quality of life. **Klin Padiatr 213:**244–249, 2001
47. Pierre-Kahn A, Recassens C, Pinto G, Thalassinos C, Chokron S, Soubervielle JC, et al: Social and psycho-intellectual outcome following radical removal of craniopharyngiomas in childhood. A prospective series. **Childs Nerv Syst 21:**817–824, 2005
48. Poretti A, Grotzer MA, Ribi K, Schönle E, Boltshauser E: Outcome of craniopharyngioma in children: long-term complications and quality of life. **Dev Med Child Neurol 46:**220–229, 2004
49. Prabhu VC, Brown HG: The pathogenesis of craniopharyngiomas. **Childs Nerv Syst 21:**622–627, 2005
50. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106 (1 Suppl):**3–12, 2007
51. Quinn TJ, Dawson J, Walters MR, Lees KR: Reliability of the modified Rankin Scale: a systematic review. **Stroke 40:**3393–3395, 2009
52. Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJ, et al: Craniopharyngioma—a long-term results following limited surgery and radiotherapy. **Radiother Oncol 26:**1–10, 1993
53. Rankin J: Cerebral vascular accidents in patients over the age of 60. II. Prognosis. **Scott Med J 2:**200–215, 1957
54. Regine WF, Kramer S: Pediatric craniopharyngiomas: long term results of combined treatment with surgery and radiation. **Int J Radiat Oncol Biol Phys 24:**611–617, 1992
55. Riva D, Pantaleoni C, Devoti M, Saletti V, Nichelli F, Giorgi C: Late neuropsychological and behavioural outcome of children surgically treated for craniopharyngioma. **Childs Nerv Syst 14:**179–184, 1998
56. Rolland-Cachera MF, Cole TJ, Sempé M, Tichet J, Rossignol C, Charraud A: Body Mass Index variations: centiles from birth to 87 years. **Eur J Clin Nutr 45:**13–21, 1991
57. Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, et al: Craniopharyngioma: the pendulum of surgical management. **Childs Nerv Syst 21:**691–695, 2005
58. Sands SA, Milner JS, Goldberg J, Mukhi V, Moliterno JA, Maxfield C, et al: Quality of life and behavioral follow-up study of pediatric survivors of craniopharyngioma. **J Neurosurg 103 (4 Suppl):**302–311, 2005
59. Sbordone RJ: Limitations of neuropsychological testing to predict the cognitive and behavioral functioning of persons with brain injury in real-world settings. **NeuroRehabilitation 16:**199–201, 2001
60. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, Lange M, Poulsen HS, Müller J: Assessment of the hypothalamo-pituitary-adrenal axis in patients treated with radiotherapy and chemotherapy for childhood brain tumor. **J Clin Endocrinol Metab 88:**3149–3154, 2003
61. Shiminski-Maher T, Rosenberg M: Late effects associated with treatment of craniopharyngiomas in childhood. **J Neurosci Nurs 22:**220–226, 1990
62. Silver CH: Ecological validity of neuropsychological assessment in childhood traumatic brain injury. **J Head Trauma Rehabil 15:**973–988, 2000
63. Thompson D, Phipps K, Hayward R: Craniopharyngioma in childhood: our evidence-based approach to management. **Childs Nerv Syst 21:**660–668, 2005
64. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
65. Wang KC, Hong SH, Kim SK, Cho BK: Origin of craniophar-

yngiomas: implication on the growth pattern. **Childs Nerv Syst 21:**628–634, 2005
66. 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
67. Wen BC, Hussey DH, Staples J, Hitchon PW, Jani SK, Vigliotti AP, et al: A comparison of the roles of surgery and radiation therapy in the management of craniopharyngiomas. **Int J Radiat Oncol Biol Phys 16:**17–24, 1989
68. Wilson JT, Hareendran A, Grant M, Baird T, Schulz UG, Muir KW, et al: Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. **Stroke 33:**2243–2246, 2002
69. Wilson JT, Pettigrew LE, Teasdale GM: Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. **J Neurotrauma 15:**573–585, 1998
70. Wisoff JH: Surgical management of recurrent craniopharyngiomas. **Pediatr Neurosurg 21 (Suppl 1):**108–113, 1994
71. Wisoff JH, Donahue BR: Craniopharyngiomas, in Albright AL, Pollack I, Adelson P (eds): **Principles and Practice of Pediatric Neurosurgery, ed. 2.** Stuttgart: Thieme, 2008
72. 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
73. Zuccaro G: Radical resection of craniopharyngioma. **Childs Nerv Syst 21:**679–690, 2005

Manuscript submitted December 14, 2009.
Accepted January 7, 2010.

Address correspondence to: Jeffrey H. Wisoff, M.D., Division of Pediatric Neurosurgery, New York University Langone Medical Center, 317 East 34th Street, Suite 1002, New York, New York 10016. email: jhw1@nyumc.org.

Magnetic resonance imaging–graded hypothalamic compression in surgically treated adult craniopharyngiomas determining postoperative obesity

Jamie J. Van Gompel, M.D.,[1] Todd B. Nippoldt, M.D.,[2] Dominique M. Higgins, M.S.,[1] and Fredric B. Meyer, M.D.[1]

Departments of [1]Neurosurgery and [2]Endocrinology, Mayo Clinic, Rochester, Minnesota

Object. Obesity as a consequence of management of pediatric craniopharyngioma is a well-described phenomenon related to the degree of hypothalamic involvement. However, weight change and obesity have not been analyzed in adult patients. Therefore, the purpose of this study was 1) to evaluate the pattern of postoperative weight gain related to preoperative body mass index (BMI), 2) determine if postoperative weight gain is an issue in adult patients, and 3) develop an objective MR imaging grading system to predict risk of postoperative weight gain and obesity in adults treated for craniopharyngioma.

Methods. The authors retrospectively screened 296 patients with known craniopharyngioma for the following inclusion criteria: pathologically confirmed craniopharyngioma, index surgery at the authors' institution, and operative weight and height recorded with at least 3 months of follow-up including body weight measurement. Patients aged 18 years or younger were excluded, yielding 28 cases for analysis. Cases of craniopharyngiomas were compared with age- and sex-matched controls (pituitary adenoma patients) to evaluate the pattern and significance of perioperative weight changes.

Results. Mean age was 46 ± 17 years at surgery, and 64% of the patients were male. Complete resection was achieved in 71% of cases. There was no correlation of preoperative BMI and postoperative weight gain testing in a linear model. Sixty-one percent and 46% of patients had postoperative weight gains greater than 4 and 9%, respectively.

Comparing craniopharyngioma patients (cases) to age- and sex-matched controls, the preoperative BMIs were similar ($p = 0.93$) between cases (mean 28.9 [95% CI 30.9–26.9]) and controls (mean 29.3 [95% CI 31.9–26.7]). However, there was a trend to a greater mean postoperative weight change (percentage) in cases (10.1%) than in controls (5.6%) ($p = 0.24$). Hypothalamic T2 signal change and irregular contrast enhancement correlated and predicted higher-grade hypothalamic involvement. Furthermore, they can be used to objectively grade hypothalamic involvement as the authors propose. Progressive hypothalamic involvement correlated with larger postoperative weight gains ($p = 0.022$); however, hypothalamic involvement did not correlate with preoperative BMI ($p = 0.5$).

Conclusions. Postoperative weight gain in adult patients undergoing surgery for craniopharyngioma is a significant problem and correlates with hypothalamic involvement, as it does in pediatric patients. Finally, objective MR imaging criteria can be used to predict risk of postoperative weight gain and aid in grading of hypothalamic involvement. *(DOI: 10.3171/2010.1.FOCUS09303)*

Key Words • **craniopharyngioma** • **weight gain** • **hypothalamus** • **obesity** • **body mass index**

Perioperative weight gain is a substantial issue in pediatric patients undergoing surgery for craniopharyngioma for a plethora of reasons including increased morbidity and poor patient self-perception.[22,24,28] Through the pediatric craniopharyngioma literature, it is becoming clearer that preoperative hypothalamic involvement increases the likelihood of postoperative obesity, and possibly aggressive surgical treatment may increase the likelihood of significant postoperative weight gain.[24] While these observations have been made in children, the adult patients surgically treated for craniopharyngioma have been ignored regarding this important perioperative morbidity.

Progressive hypothalamic involvement has been implicated as a prognostic factor for predicting postoperative weight gain in children.[7,20,22,24,29] Championed by Dr. Sainte-Rose and colleagues, hypothalamic involvement is graded progressively as none (Grade 1), compression (Grade 2), and severe involvement or unidentifiable hypothalamus (Grade 3) (0, 1, and 2 in later publication).[20,22,24] While this grading system intuitively makes sense, as it currently stands, there is reliance on subjective criteria for differentiation between higher grade (1 and 2) patients.

Abbreviations used in this paper: BMI = body mass index; NIH = National Institutes of Health.

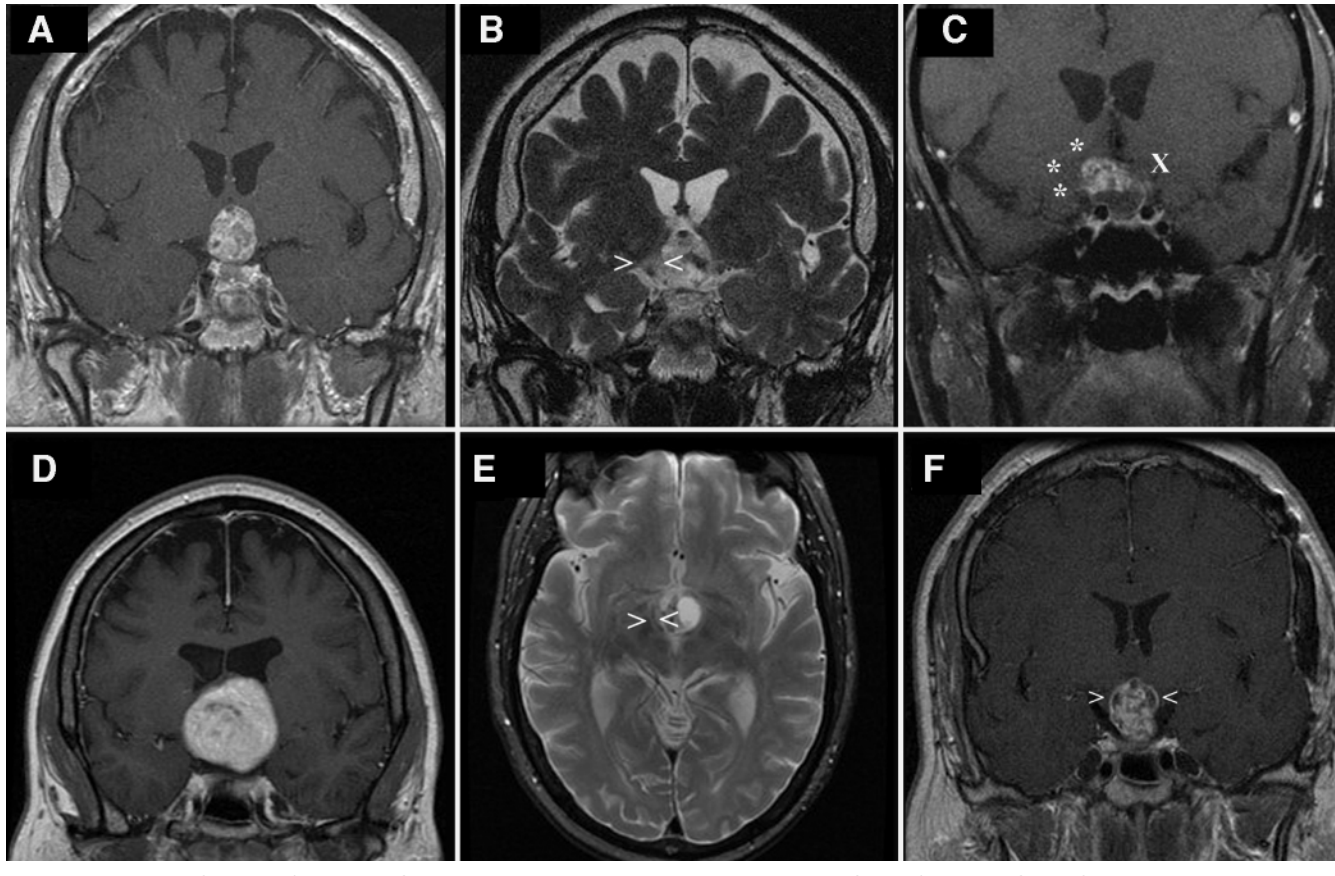

Fig. 1. Coronal T1-weighted Gd-enhanced MR images demonstrating typical Grade 1 **(A)** and Grade 2 **(D)** hypothalamic compression. Coronal **(B)** and axial **(E)** T2-weighted images of typical peritumoral hypothalamic T2 change (between the *open triangles*). Coronal T1-weighted Gd-enhanced images demonstrating irregular contrast enhancement at the right *(asterisks)* and left *(X)* hypothalamic border **(C)**, and in contrast a smooth enhancement (**F** between the *open triangles*).

Furthermore, it is unknown whether there is a difference between higher-grade patients, but preliminary reports suggest that a difference does exist.[20,22] Therefore, if this grading system is to be used to prognosticate postoperative weight gain, additional objective MR imaging findings should be evaluated as additional criteria to define Grade 1 and Grade 2 cases.

Here, we have undertaken a review of data obtained in adult patients with craniopharyngioma to determine the following: 1) the pattern of postoperative weight gain related to preoperative BMI, 2) if postoperative weight gain is an issue in adult patients, and 3) if MR imaging can be used to predict development of postoperative weight gain and obesity in adults treated for craniopharyngioma.

Methods

Inclusion and Exclusion Criteria

We searched the clinical, surgical, and pathological databases of the Mayo Clinic in Rochester for the key word craniopharyngioma in all available fields with a cutoff of January 2009. This search yielded 296 patients. These patients were then screened for this study with the following inclusion criteria: 1) pathologically confirmed craniopharyngioma; 2) first surgery performed at Mayo Clinic; 3) operative weight and height recorded; and 4) at least 3 months of follow-up including body weight measurement.

Age 18 years or younger was an exclusion criterion. Utilizing these criteria, 28 cases treated between August 1998 and January 2009 were identified for analysis. During this period, there were 131 patients overall, and of these there were 94 adult patients undergoing resection. Therefore, 30% of the cases treated from August 1998 to January 2009 were analyzed. The reasons for exclusion were: 165 treatments occurred either before MR imaging was available or did not have preoperative MR imaging; of the 131 patients with MR imaging, 37 were 18 or younger, and 66 either underwent revision surgery or did not have adequate perioperative weight assessments. This study was approved by our institutional review board (study number 05–004448).

Control Individuals

Control individuals were matched for sex and age by searching our surgical database for patients with pathologically confirmed pituitary adenomas undergoing surgery between January 2004 and December 2006. Pituitary adenoma was used as a control because of its sellar location, furthermore it mimics perioperative endocrine

TABLE 1: Weight distribution of preoperative BMI and postoperative weight gain in adult patients with craniopharyngioma*

	Postop Weight Gain								
Preop BMI	<4%	4.01–6%	6.01–8%	8.01–9%	9.01–10%	10.01–15%	15.01–20%	>20.01%	BMI Total
<25	2			1		1	2		6
25–30	6		1		1			4	12
>30	2	1		2	1	2	1	1	10
total	10	1	1	3	2	3	3	5	28
cumulative percentage	36	39	43	54	61	71	82	100	

* The BMI was calculated as described in *Methods*.

changes, and finally there was a robust population available to do case by case age and sex matching. Within this period, 396 controls were identified and sorted according to age and sex. Case by case matching was done with a craniopharyngioma case matched to a pituitary adenoma control case, meeting study inclusion criteria with the exception of pathology.

Weight Recordings

All patients were reviewed for height (cm) and weight (kg). Height was measured using a stadiometer. Body mass index was calculated with the following formula (BMI = [kg weight]/[height in meters]^2) for the initial visit. Weights were recorded for all visits available, but data acquired at 3-, 6-, 9-, and 12-month follow-up were used for analysis. Weights up to 24 months were recorded. After this point, the assumption was that recurrence or adjuvant therapy effects might interfere with this analysis. For initial analysis, preoperative weight categories were subdivided into normal (BMI < 25), overweight (BMI 25–30), and obese (BMI > 30). For simple binary analysis of prognostic outcomes, obesity was defined as a BMI greater than 27.3 kg/m^2 per NIH consortium guidelines.[1]

Interpretation of MR Imaging Findings

Tumor size (cm^3) was calculated using the maximal tumor diameters in 3 dimensions based on the results of MR imaging as documented by the radiologist. Hypothalamic involvement was graded as described by Meuric et al.[20] and modified by Puget et al.[22] under the guidance of Dr. Sainte-Rose and colleagues.[24] Hypothalamic involvement was graded progressively as none (Grade 0), compression (Grade 1), and severe involvement or unidentifiable hypothalamus (Grade 2) (1, 2, and 3 in earlier publication). We assessed the following to make this determination: hypothalamic involvement according to side (right vs left hypothalamus), T2-weighted signal change in the hypothalamus, enhancement (smooth vs indistinct), and invasion (blinded interpretation independently given by F.B.M.). Figure 1 demonstrates examples of these features.

Statistical Analysis

We used JMP 8.0 (SAS Institute, Inc.) and Prism 4.03 for Windows (GraphPad Software, Inc.) to process raw data. A 2-tailed Student t-test (Mann-Whitney analysis) using the assumptions of nonparametric and nonpaired data was used to determine differences between 2 means. One-way ANOVA was used to determine differences between more than 2 means, and the Wilcoxon test was used to estimate the probability value in multiple group analysis.

Results

Demographics

The mean age at surgery for the 28 patients with craniopharyngioma was 45.8 ± 16.7 years; 64% (18 patients) were male. Surgical approach included 23 frontotemporal (either subfrontal or pterional), 3 transnasal-transsphenoidal, 1 interhemispheric, and 1 transcortical. Excluding transnasal procedures, 22 were right sided and 3 were left sided. Complete resection was achieved in 20 patients (71%). One patient presented with preoperative hydrocephalus.

Weight and BMI

Currently, there are no data to define a significant weight gain in patients treated for craniopharyngiomas, especially in adults. Pediatric cases of excessive weight gain are based on 2 SDs above normal child weights for age. While there are extant pediatric papers detailing perioperative weight gain as a problem, they use an arbitrary cutoff to assess this end point. Therefore, in our 28 patients, we have set up gradients according to maximal weight gain in the first 2 postoperative years (Table 1). Furthermore, we subcategorized postoperative weight gain according to preoperative BMI (Table 1). No correlation exists between preoperative BMI and postoperative weight gain. Sixty-one percent and 46% of patients had postoperative weight gains greater than 4 and 9%, respectively (Table 1). Using the NIH consortium guideline to define obesity at a BMI of 27.3, 61%, or 17, of our patients had preoperative BMIs greater than this.[1] There was no association between preoperative BMI and postoperative weight gain ($p = 0.9337$); this, again, is evident when looking at the distribution of these patients in Table 1.

To better understand the significance of preoperative BMI and postoperative weight gain, the patients with craniopharyngioma (cases) were compared with age- and sex-matched control patients undergoing pituitary surgery for pituitary adenomas and fitting the other inclusion criteria. The preoperative BMIs were similar ($p =$

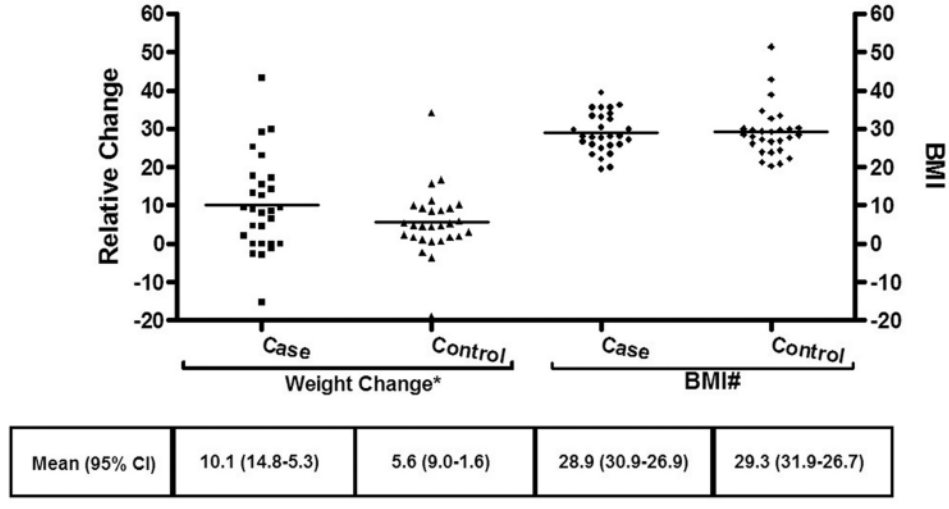

Fig. 2. Side-by-side comparison of weight change (%) of highest postoperative weight compared with surgical weight *(left)* and preoperative BMI *(right)*. *Markers* are individual cases, and *lines* represent group mean. Listed below the figure is the mean of each category and its 95% CI. Although there is a difference in mean of 4.5% weight change between cases (craniopharyngioma) and controls (pituitary adenoma), the Student t-test result was nonsignificant (*p = 0.24). The BMI is similar between cases and controls (#p = 0.93).

0.93) between cases (mean 28.9 [95% CI 30.9–26.9]) and controls (mean 29.3 [95% CI 31.9–26.7]) (Fig. 2). However, there was a trend to a greater mean postoperative weight change in cases (10.1%) than in controls (5.6%) (p = 0.24). The pattern of postoperative weight gain is represented in Fig. 3; here we defined an event as the follow-up date in which there was a greater than 9% weight gain. There was no difference between cases and controls on Kaplan-Meier analysis (p = 0.2). However, notice that approximately 35% of patients achieved a 9% weight gain at 6 months postoperatively. In all cases in which a 9% weight gain was achieved, the weight was gained by 12 months in this study.

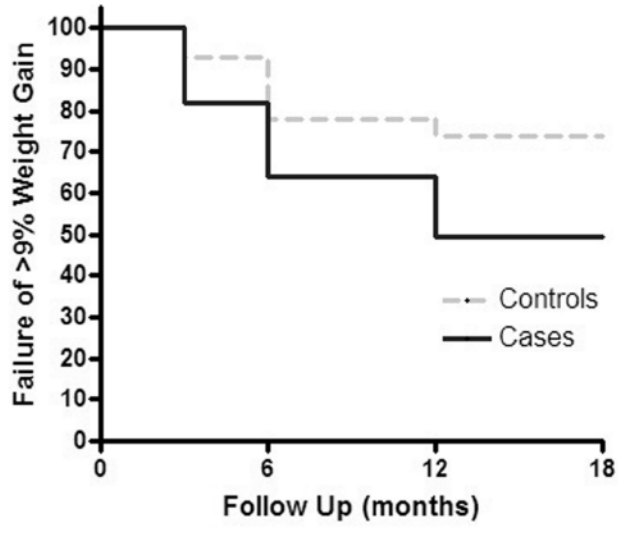

Fig. 3. Kaplan-Meier analysis of time to significant weight gain. Failure Curve demonstrates time after surgery to greater than 9% weight gain. Cases (craniopharyngioma) are compared with controls (pituitary adenoma).

Endocrine Data

Patients with craniopharyngioma required postoperative endocrine replacement more frequently than controls; 57% of the patients and 18% of controls required posterior pituitary replacement (vasopressin). Cortisol replacement, usually provided with hydrocortisone (10 mg twice daily), was required in 68% of cases and 36% of controls. Thyroid and sex hormone replacement were needed in 61 and 50% of craniopharyngioma patients, respectively, and 39% for both in controls (Table 2). No patient received postoperative growth hormone therapy.

Magnetic Resonance Imaging and Hypothalamic Involvement

Progressive hypothalamic involvement (as defined by Sainte-Rose Grade 0–2) correlated with postoperative weight gain (Fig. 4; p = 0.04, Wilcoxon test); however, hypothalamic involvement did not correlate with preoperative BMI (p = 0.5). Left-sided hypothalamic compression correlated with postoperative weight gain (p = 0.006), but right-sided compression did not (p = 0.15). Furthermore, total volume of the tumor correlated with hypothalamic involvement (Fig. 5). Hypothalamic T2 signal change correlated with hypothalamic involvement (p = 0.0008) (Table 3). Invasion, as defined by enhancement without a smooth interface with the hypothalamus was also associated with hypothalamic involvement (p = 0.0009). All patients with Grade 0 hypothalamic involvement had absent T2 signal change and absent invasion, and all patients with Grade 2 hypothalamic involvement had the presence of T2 signal change and invasion. Therefore, the absence of T2 signal change and the absence of invasion were both 100% sensitive in predicting a Grade 0 lesion (Fig. 6). Similarly, the presence of T2 signal change and the presence of invasion were both 100% sensitive in predicting a Grade 2 lesion (Table 3). We then assigned a point for either T2 signal change in the hypothalamus (+ 1) or

TABLE 2: Percentage of patients receiving postoperative endocrine replacement

Replacement Therapy	Patients w/ Craniopharyngioma (%)	Controls (%)
vasopressin	57	18
cortisol	68	36
thyroid	61	39
sex hormone	50	39

TABLE 3: Magnetic resonance imaging prediction of hypothalamic grade

Hypothalamic Involvement (Sainte-Rose Grade)	T2 Signal Change (%)	Invasion/Irregular Enhancement (%)
Grade 0	0	0
Grade 1	57	50
Grade 2	100	100

hypothalamic invasion defined by irregular enhancement into the hypothalamus (+ 1); the addition of these points (0, 1, or 2) correlated strongly with hypothalamic grade ($p < 0.0001$).

Discussion

Obesity associated with or caused by craniopharyngiomas is among the most difficult to treat in medicine and has significant health and long-term impact for the patient.[12,23,25,27,28] The most commonly accepted cause for obesity in these cases is neural injury to the ventromedial hypothalamus, which in animals regulates appetite, satiety, and body fat composition and is thought to do the same in humans.[15–19] In children, there is ongoing debate as to the cause of craniopharyngioma-associated postoperative obesity. It is known that pediatric patients undergoing surgery for craniopharyngioma are shorter both at the time of surgery and thereafter.[8] Thus, one possible cause for postoperative obesity in children with normal eating habits is lack of growth leading to obesity.[8] In an attempt to probe this hypothesis, Geffner et al.[8] treated children postoperatively for 3 years with growth hormone to improve their height; despite statistically significant gains in height, their postoperative obesity was not corrected. Further evidence that this hypothesis is not correct is supported by our present findings. In adults, in whom growth is presumably relatively stable, our data showed that postoperative obesity continues to be a problem for patients with surgically treated craniopharyngiomas where 61 and 46% of patients had a greater than 4 and 9% postoperative weight gain, respectively. We found that postoperative severe obesity was greater than 40%, which is very similar to that in published pediatric case series.[4,5,13,21] Furthermore, postoperative weight gain is a common occurrence after management of craniopharyngioma and has been described in 35–58% of patients in previous studies.[4,6,11,27]

Hypothalamic involvement by tumors and postoperative weight gain do not represent a new concept in pediatrics; however, this has never been shown in adults. The St. Jude experience demonstrates that among an assortment of tumors (astrocytoma, ependymoma, or craniopharyngioma), hypothalamic involvement correlates radically with postoperative weight gain in this pediatric cohort and was independent of pathology.[18] Although not assessed with this study, it may be logical to approach adults as pediatric neurosurgeons do. Although controversial, some authors believe that, in cases of severe hypothalamic involvement, subtotal resection with decompression of the optic apparatus may be a reasonable approach compared with unwavering pursuit of gross-total resection.[3,20,29,30] While it is becoming well accepted that there is an association with hypothalamic compression and perhaps sur-

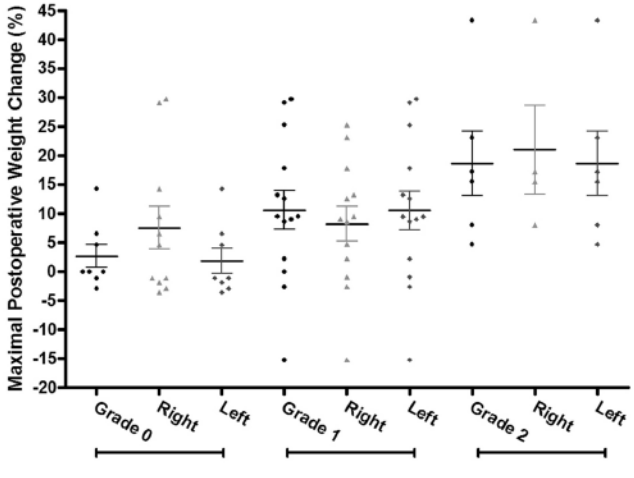

Fig. 4. Maximum postoperative weight change as a function of the hypothalamic compression. *Markers* represent individual patients, *midline* represents mean, and *brackets* represent SEM. First column in each group (0, 1, and 2) represents data for the combined group, followed by distribution for right and left hypothalamic compression, respectively. Overall, compression of the hypothalamus correlated with total postoperative weight gain ($p = 0.04$, Wilcoxon test), as did left-sided compression ($p = 0.006$); however, right-sided compression did not ($p = 0.15$). Means and 95% CIs for combined compression are: Grade 1 (2.7, –2.0 to 7.4), Grade 2 (10.6, 3.4–17.8), and Grade 3 (18.7, 4.2–33.1).

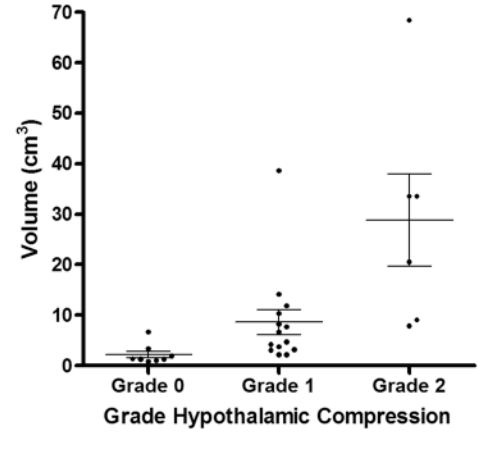

Fig. 5. Spherical volume as a function of the hypothalamic compression. *Markers* represent data points, *midline* represents mean, and *brackets* represent SEM. Means and 95% CIs are: Grade 0 (2.2, 0.5–3.8), Grade 1 (9.0, 3.2–14.0), and Grade 2 (28.8, 5.3–52.3).

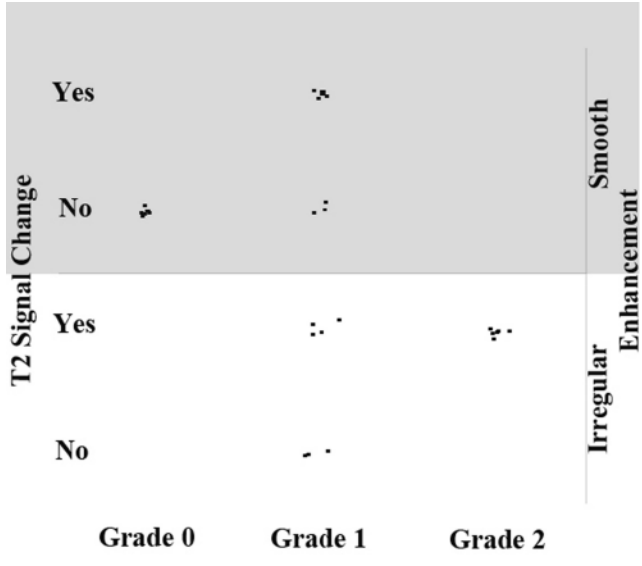

Fig. 6. Scatterplot showing the distribution of cases *(individual markers)* as segregated by T2-weighted MR imaging hyperintensity in the hypothalamus (left y axis, *Yes* is hypothalamic T2 change) and enhancement pattern (smooth vs irregular border) in relation to hypothalamic compression. Note no Grade 0 case has either MR imaging characteristic whereas all Grade 3 cases have both irregular enhancement and hypothalamic hyperintensity.

gical management, both may contribute to postoperative obesity in patients with tumors of this region, and this assumption cannot be directly drawn to include adults,[2] as growth and development are accompanied by significant changes in the hormone milieu in children, in contrast to adults.[9] Unfortunately, we have found in adult patients at risk for postoperative obesity that this perioperative morbidity is a real concern. Furthermore, as we become more aware of this complication, it becomes increasingly important that we focus some of our postoperative care on counseling our patients about its occurrence, detecting this complication, and preventing it.

Importantly, we have attempted to further develop objective grading criteria for hypothalamic involvement, thereby quantifying a descriptive classification proposed by Dr. Sainte-Rose and colleagues, which is summarized in Fig. 7.[20,22] Meuric et al.[20] introduced the concept of grading hypothalamic involvement with a proposed grade of 1–3, later modified to the 0–2 system, reflecting progressive hypothalamic involvement.[20,22,24] Using this grading system, Drs. Puget and Sainte-Rose et al. were prospectively able to avoid any inappropriate postoperative weight gain by performing subtotal resection and avoiding associated operative hypothalamic damage in children.[22] This may or may not be the case in adults; however, this study represents the first step toward this determination, recognizing that hypothalamic involvement is associated with the same complications as in children. Furthermore, objective criteria to differentiate Grade 1 from Grade 2 may be additionally useful in the prognostication of postoperative obesity. First, peritumoral edema can be evaluated preoperatively with T2-weighted and FLAIR imaging. Previously this has been suggested as a significant harbinger of complications and was named "moustache appearance" by Higashi et al.[10] in a description of perifocal hypothalamic edema in 2 patients with craniopharyngioma. The existence of hypothalamic edema in this study was strongly associated with progressive hypothalamic involvement. Furthermore, irregular enhancement suggestive of invasion was associated with more severe hypothalamic involvement. This concept has not been previously described; however, Shi et al.[26] have discussed the importance of maintenance of the tiny perforating vessels that supply the hypothalamic nuclei, and perhaps irregular enhancement suggests that these vessels are parasitized or congested and therefore at risk.

Our results have provided a rather curious finding, in that it appears in this small group that left-sided hypothalamic compression statistically is more important than right-sided compression in relation to postoperative weight gain. We recognize, given our limited data, that this is inconclusive; however, the brain in most circum-

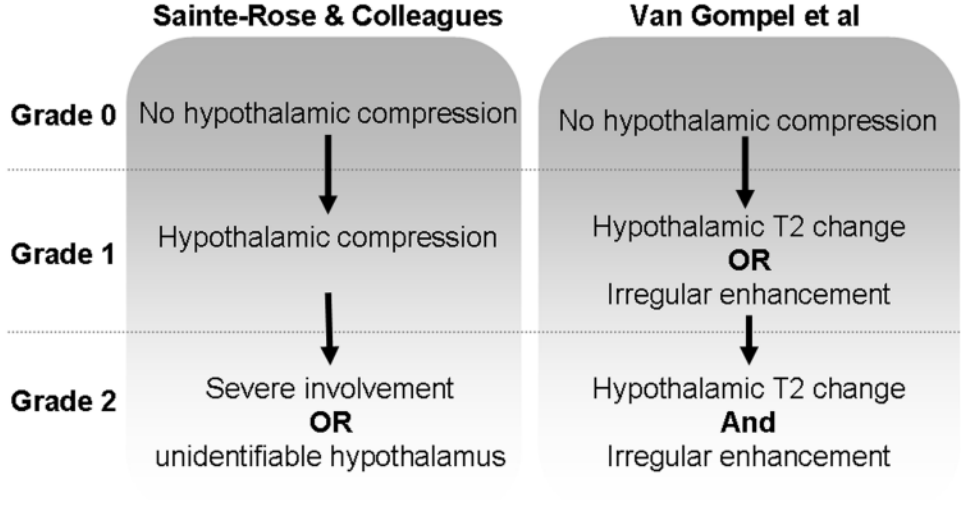

Fig. 7. Flow diagram of hypothalamic compression grading system, as described by Drs. Meuric, Puget, and Sainte-Rose (see text), compared with this study's proposed objective MR imaging criteria.

stances is organized with dominant and nondominant paired structures. Further, the endocrine consequences in these patients may also influence postoperative weight gain. Growth hormone deficit and consequent low levels of insulin-like growth factor are a well-known complicating factor of weight gain in patients with anterior pituitary origin and hypothalamic involvement.[14] Although growth hormone deficiency appears to be important, Kendall-Taylor et al.[14] have implicated hypothalamic involvement, in patients with combined hypothalamic involvement and growth hormone failure, as the major cause of obesity in these patients.[8] None of our patients received postoperative growth hormone replacement. Therefore, because the effects of treatment with growth hormone on adult patients are unknown it may be reasonable to attempt this as a treatment to prevent postoperative obesity in these patients.

The inclusion criteria used in this study may impose a bias in relation to patients at risk for developing postoperative obesity. The assumption here is that those at risk for weight gain were the ones that were followed with weight recordings. Therefore, 39% (> 9% change) to 57% (> 4% change) of these patients with significant postoperative obesity may not represent the true percentage of all presenting patients because, in the present study, this represents only 30% of the patients in that time period. Consequently, the external validity of this study is poor. However, to evaluate our initial study questions we believed that our excessive inclusion criteria were important to analyze the impact of hypothalamic involvement and weight changes in adult patients undergoing surgery for craniopharyngioma. Furthermore, although there was no statistically significant difference in postoperative weight gain between craniopharyngioma patients and pituitary adenoma patients, it is likely that one does exist. Due to the variability of weight recordings, a standardized effect of likely 0.4 could be used, coupled with a power of 80% and alpha of 5%; we would need approximately 148 patients in each group to detect a difference between cases and controls.

Conclusions

Although this has been long recognized in children, this series suggests that we must consider postoperative obesity an important morbidity in adult patients undergoing surgery for craniopharyngioma. Furthermore, we are then obligated to consider alterations in established therapies and interventions for these patients. In preoperative counseling, it will be vital to inform the patient of the real risk of obesity postoperatively if certain imaging findings are present. We conclude here, as has been concluded in pediatric cases, that the degree of hypothalamic involvement, as evaluated preoperatively by MR imaging, may predict postoperative obesity. As surgeons, we need to continue to improve patient outcomes, and this study serves as a starting point to do so in adult patients with craniopharyngiomas.

Disclosure

The project described in this article was supported by a grant (No. 1 UL1 RR024150) from the National Center for Research Resources (NCRR), a component of the NIH, and the NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Reengineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov.

Author contributions to the study and manuscript preparation include the following. Conception and design: JJ Van Gompel, TB Nippoldt, FB Meyer. Acquisition of data: JJ Van Gompel, DM Higgins, FB Meyer. Analysis and interpretation of data: JJ Van Gompel, FB Meyer. Drafting the article: JJ Van Gompel, TB Nippoldt, DM Higgins, FB Meyer. Critically revising the article: JJ Van Gompel, TB Nippoldt, DM Higgins, FB Meyer. Reviewed final version of the manuscript and approved it for submission: JJ Van Gompel, TB Nippoldt, DM Higgins, FB Meyer. Statistical analysis: JJ Van Gompel. Study supervision: TB Nippoldt, FB Meyer.

Acknowledgments

The authors would further like to recognize: Steven D. Thalacker for his work in database and internal review board preparation, Bruce Kall for database preparation, Wanda Winchschitl, and Nicolee Fode Thomas for their excellent care of these patients. The authors would further like to thank Drs. J. L. D. Atkinson, C. Raffel, D. Piepgras, and M. Link for care of their patients included in this series.

References

1. Anonymous (NIH Technology Assessment Conference Panel): Methods for voluntary weight loss and control. **Ann Intern Med 116:**942–949, 1992
2. Ahmet A, Blaser S, Stephens D, Guger S, Rutkas JT, Hamilton J: Weight gain in craniopharyngioma—a model for hypothalamic obesity. **J Pediatr Endocrinol Metab 19:**121–127, 2006
3. Boop FA: Craniopharyngioma. **J Neurosurg 106 (1 Suppl):**1–2, 2007
4. Curtis J, Daneman D, Hoffman HJ, Ehrlich RM: The endocrine outcome after surgical removal of craniopharyngiomas. **Pediatr Neurosurg 21 (Suppl 1):**24–27, 1994
5. de Vile CJ, Grant DB, Hayward RD, Kendall BE, Neville BG, Stanhope R: Obesity in childhood craniopharyngioma: relation to post-operative hypothalamic damage shown by magnetic resonance imaging. **J Clin Endocrinol Metab 81:**2734–2737, 1996
6. Duff JM, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck CD, Scheithauer BW: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000
7. Garnett MR, Puget S, Grill J, Sainte-Rose C: Craniopharyngioma. **Orphanet J Rare Dis 2:**18, 2007
8. 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
9. Gleeson H, Amin R, Maghnie M: 'Do no harm': management of craniopharyngioma. **Eur J Endocrinol 159 (Suppl 1):**S95–S99, 2008
10. Higashi S, Yamashita J, Fujisawa H, Yamamoto Y, Kadoya M: "Moustache" appearance in craniopharyngiomas: unique magnetic resonance imaging and computed tomographic findings of perifocal edema. **Neurosurgery 27:**993–996, 1990
11. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI: Aggressive surgical management of craniopharyngiomas in children. **J Neurosurg 76:**47–52, 1992
12. Inge TH, Pfluger P, Zeller M, Rose SR, Burget L, Sundararajan S, et al: Gastric bypass surgery for treatment of hypo-

thalamic obesity after craniopharyngioma therapy. **Nat Clin Pract Endocrinol Metab 3:**606–609, 2007
13. Karavitaki N, Brufani C, Warner JT, Adams CBT, Richards P, Ansorge O, et al: Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. **Clin Endocrinol (Oxf) 62:**397–409, 2005
14. Kendall-Taylor P, Jönsson PJ, Abs R, Erfurth EM, Koltowska-Häggström M, Price DA, et al: The clinical, metabolic and endocrine features and the quality of life in adults with childhood-onset craniopharyngioma compared with adult-onset craniopharyngioma. **Eur J Endocrinol 152:**557–567, 2005
15. Lustig RH: Hypothalamic obesity: causes, consequences, treatment. **Pediatr Endocrinol Rev 6:**220–227, 2008
16. Lustig RH: The neuroendocrinology of obesity. **Endocrinol Metab Clin North Am 30:**765–785, 2001
17. Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kaste SC, Schreiber RE, et al: Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. **J Clin Endocrinol Metab 88:**2586–2592, 2003
18. Lustig RH, Post SR, Srivannaboon K, Rose SR, Danish RK, Burghen GA, et al: Risk factors for the development of obesity in children surviving brain tumors. **J Clin Endocrinol Metab 88:**611–616, 2003
19. Lustig RH, Rose SR, Burghen GA, Velasquez-Mieyer P, Broome DC, Smith K, et al: Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. **J Pediatr 135:**162–168, 1999
20. Meuric S, Brauner R, Trivin C, Souberbielle JC, Zerah M, Sainte-Rose C: Influence of tumor location on the presentation and evolution of craniopharyngiomas. **J Neurosurg 103 (5 Suppl):**421–426, 2005
21. Müller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, et al: Obesity after childhood craniopharyngioma—German multicenter study on pre-operative risk factors and quality of life. **Klin Padiatr 213:**244–249, 2001
22. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106 (1 Suppl):**3–12, 2007
23. Roth C, Wilken B, Hanefeld F, Schröter W, Leonhardt U: Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. **Eur J Endocrinol 138:**89–91, 1998
24. Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, et al: Craniopharyngioma: the pendulum of surgical management. **Childs Nerv Syst 21:**691–695, 2005
25. Schultes B, Ernst B, Schmid F, Thurnheer M: Distal gastric bypass surgery for the treatment of hypothalamic obesity after childhood craniopharyngioma. **Eur J Endocrinol 161:**201–206, 2009
26. Shi XE, Wu B, Zhou ZQ, Fan T, Zhang YL: Microsurgical treatment of craniopharyngiomas: report of 284 patients. **Chin Med J (Engl) 119:**1653–1663, 2006
27. Sorva R: Children with craniopharyngioma. Early growth failure and rapid postoperative weight gain. **Acta Paediatr Scand 77:**587–592, 1988
28. Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT: Features of the metabolic syndrome after childhood craniopharyngioma. **J Clin Endocrinol Metab 89:**81–86, 2004
29. Trivin C, Busiah K, Mahlaoui N, Recasens C, Souberbielle JC, Zerah M, et al: Childhood craniopharyngioma: greater hypothalamic involvement before surgery is associated with higher homeostasis model insulin resistance index. **BMC Pediatr 9:**24, 2009
30. Vinchon M, Weill J, Delestret I, Dhellemmes P: Craniopharyngioma and hypothalamic obesity in children. **Childs Nerv Syst 25:**347–352, 2009

Manuscript submitted December 14, 2009.
Accepted January 13, 2010.

Address correspondence to: Fredric B. Meyer, M.D., Department of Neurosurgery, Mayo Clinic and Mayo College of Medicine, 200 First Street SW, Rochester, Minnesota 55905. email: meyer.fredric@mayo.edu.

Neurosurg Focus 28 (4):E4, 2010

Craniopharyngioma and other cystic epithelial lesions of the sellar region: a review of clinical, imaging, and histopathological relationships

Gabriel Zada, M.D.,[1] Ning Lin, M.D.,[1] Eric Ojerholm, B.S.E.,[1] Shakti Ramkissoon, M.D., Ph.D.,[2] and Edward R. Laws, M.D.[1]

Departments of [1]Neurosurgery and [2]Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Object. Cystic epithelial masses of the sellar and parasellar region may be difficult to differentiate on a clinical, imaging, or even histopathological basis. The authors review the developmental relationships and differentiating features of various epithelial lesions of the sellar region.

Methods. The authors performed a review of the literature to identify previous studies describing the etiological relationships and differentiating features of various cystic sellar lesions, including craniopharyngioma (CP), Rathke cleft cyst, xanthogranuloma, and dermoid and epidermoid cysts.

Results. There is significant evidence in the literature to support a common ectodermal origin of selected sellar and suprasellar cystic lesions, which may account for the overlap of features and transitional states observed in some cases. Research obtained from animal studies and reports of transitional cystic epithelial masses or lesions crossing over from typical to more aggressive pathological subtypes have collectively provided a solid foundation for this theory. Histological features that signify transitional entities beyond simple benign Rathke cleft cysts include squamous metaplasia, stratified squamous epithelium, and ciliated or mucinous goblet cells in squamous-papillary CPs. Several studies have identified key clinical, imaging, and histopathological features that can be used in the differentiation of these lesions.

Conclusions. The pattern of embryological formation of the hypothalamic-pituitary axis plays a major role in its propensity for developing cystic epithelial lesions. Subsequent inflammatory, metaplastic, and neoplastic processes may promote further progression along the pathological continuum, ranging from benign epithelial cysts to aggressive neoplastic cystic CPs. Selected clinical, imaging, and histopathological features can be used collectively to help differentiate these lesions and assign a formal diagnosis, thus accurately guiding further treatment. *(DOI: 10.3171/2010.2.FOCUS09318)*

Key Words • **craniopharyngioma** • **Rathke cleft cyst** • **epithelial cyst** • **embryology** • **magnetic resonance imaging**

Differentiation of cystic lesions of the sellar and parasellar region may pose a diagnostic dilemma to neurosurgeons, radiologists, and pathologists involved in treating patients with these entities. As a result of the pattern of embryological development of the adenohypophysis from its stomodeal origin, as well as subsequent inflammatory, metaplastic, and neoplastic processes that can occur, the potential exists for the formation of a variety of cystic lesions in the sellar and parasellar region. The spectrum of cystic pathology occurring in the sellar region includes CPs, RCCs, colloid cysts, arachnoid cysts, cystic pituitary adenomas, xanthogranulomas, epidermoid cysts, dermoid cysts, and several others.[15,60] In the majority of cases, a straightforward diagnosis of typical cystic lesions is established with little difficulty based on the lesion's clinical, imaging, and histopathological characteristics. In some cases, however, a significant degree of overlap in these features occurs and may preclude the assignment of a definitive diagnosis. Establishing an accurate working diagnosis for sellar region pathology is critical in formulating appropriate surgical goals, predicting the likelihood of lesion recurrence, and guiding postoperative adjunctive management.

In 1994, Harrison and colleagues[34] reported 19 cases of cystic epithelial lesions, in which overlapping radiological and histopathological features were evident in almost half, rendering 3 lesions without a formal diagnosis. Their study, in addition to several others, posited that cystic epithelial lesions may comprise varying entities along a continuum of pathology derived from a common ectodermal origin in the primitive craniopharyngeal duct,

Abbreviations used in this paper: CP = craniopharyngioma: RCC = Rathke cleft cyst.

thus accounting for the overlapping features observed in selected lesions.[2,25,30,32,34,69,70,113] At one end of this pathological spectrum are benign RCCs, which are nonneoplastic lesions generally accepted to be derived from the remnant of the Rathke pouch. At the other end are CPs, which are neoplastic, often aggressive lesions thought to arise from squamous epithelial cell rests occurring anywhere along the region of the primitive stomodeum, from the sella to the infundibulum to the tuber cinereum and floor of the third ventricle.

In this summary, a current analysis of the developmental and clinicopathological relationships among CPs, RCCs, and other cystic epithelial derivatives of the sellar region is provided. The embryological development of the hypothalamic-pituitary region and various reasons for its particular predisposition to developing a variety of cystic lesions is discussed. Furthermore, we review the evidence favoring a common ectodermal origin, in contrast to alternative nonectodermal hypotheses, for the origin of cystic epithelial lesions. Finally, we review the typical and atypical features of RCCs and CPs, as well as the clinical, imaging, and histopathological features that have proved to be most useful in differentiating these lesions.

Craniopharyngiomas: Typical Features

Craniopharyngiomas can arise anywhere along the vestiges of the stomodeal diverticulum, but they most frequently originate in the region of the infundibulum, where squamous epithelial rests are known to occur.[49,52,84] In rare cases, CPs arise in less typical locations along the remnants of the primitive craniopharyngeal duct, including the nasopharynx, sphenoid bone, or as primary intraventricular lesions.[11,20,46,49] Overall, CPs comprise approximately 3% of all intracranial tumors, yet this proportion is notably higher in the pediatric population (10% of all pediatric brain tumors).[23,48,49,51] The estimated incidence of craniopharyngiomas is 0.13 per 100,000 cases per year.[12] Historically, CPs present in a bimodal age distribution with peak ages at the time of presentation of 5–14 years and then 50–74 years.[12] However, these lesions may present in patients of all ages. The clinical presentation of CPs at any age frequently includes headache, vision loss, and hypopituitarism.[16,52] In children, growth and sexual retardation, obesity, and hydrocephalus are frequently observed as well.[51,59] Many patients with CPs suffer from chronic obesity, which is thought to develop secondary to hypothalamic dysfunction. Memory loss and cognitive deficits are more common findings in older patients.[37] Diabetes insipidus is seen on presentation in 6–38% of new cases.[38,52]

The 2 major pathological subtypes of CP are the adamantinomatous and squamous-papillary varieties, although mixed-type lesions have been reported.[20,22] These 2 generalized tumor subtypes vary in age at presentation, tumor location, consistency, imaging characteristics, and histopathological features.[1,92,109]

Typical Imaging Features of CP

From an imaging standpoint, CPs are typically described as calcified, solid, and/or cystic lesions, typically

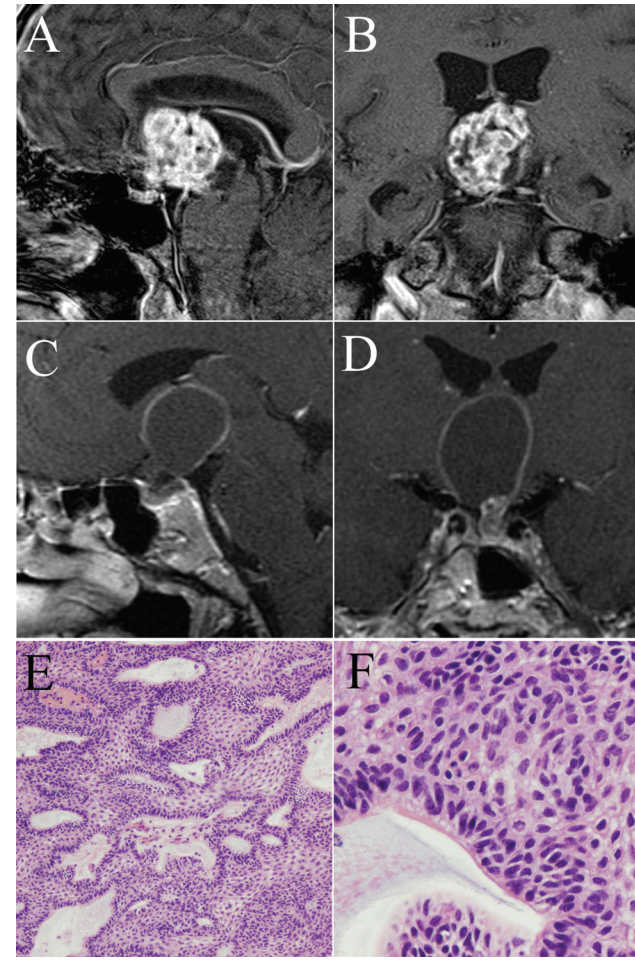

Fig. 1. Imaging and histopathological examples of typical adamantinomatous craniopharyngiomas. **A and B:** Sagittal and coronal Gd-enhanced MR images obtained in a patient with a primarily solid suprasellar craniopharyngioma. **C and D:** Coronal Gd-enhanced MR images acquired in a patient with a mixed solid and cystic suprasellar craniopharyngioma. **E and F:** Photomicrographs of typical adamantinomatous craniopharyngioma composed of squamous epithelium arranged in sheets, lobules, and anastomosing trabeculae lined by palisaded columnar epithelium. H & E, original magnification × 100 **(E)** and 400 **(F).**

with a lobular shape and diameter of 20–40 mm (Fig. 1).[1,26,109] The majority of CPs involve the suprasellar space, with 40–53% of cases exhibiting some intrasellar involvement.[51,105] Craniopharyngiomas occasionally extend into the anterior, middle, or posterior fossa and may invade the floor or walls of the third ventricle.[26,105] Hydrocephalus is observed in up to 38% of cases and is a more common finding in children.[51,109]

On standard CT scanning, calcification is evident in 60% of tumors and is more common in pediatric cases and the adamantinomatous subtype.[1,52,92,109] The majority of adamantinomatous CPs are mixed solid-cystic or predominantly cystic tumors with a lobulated appearance (Fig. 1).[1,92,109] On MR imaging, the solid elements are usually iso- or hypointense on T1-weighted images, exhibit inhomogeneous high intensity on T2-weighted images, and heterogeneously enhance following Gd administra-

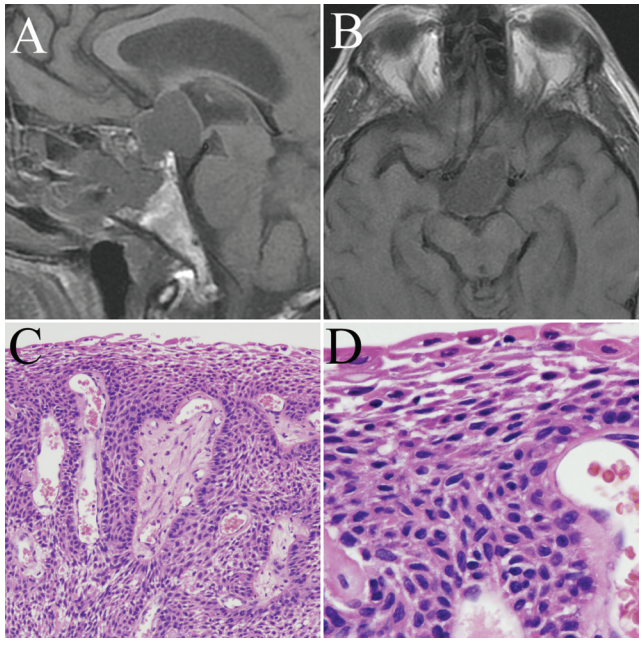

Fig. 2. Imaging and histopathological examples of papillary CP. **A and B:** Sagittal and axial MR images. **C and D:** Photomicrographs of typical papillary CP composed of well-differentiated squamous epithelium supported by a network of fibrovascular cores. H & E, original magnification × 100 **(C)** and 400 **(D)**.

tion.[17,92] The cystic elements of adamantinomatous CPs typically display a high intensity on T1-weighted images, high or mixed intensity on T2-weighted images, and contrast enhancement of the cyst wall.[92] The squamous-papillary subtype is found in approximately one-third of adult CP cases and rarely shows calcification.[1,20,92,109] The majority of squamous-papillary CPs are predominantly solid or mixed solid-cystic tumors with a spherical shape, and usually exhibit low intensity on T1-weighted images, high intensity on T2-weighted images, and enhancement of the cyst wall after addition of Gd (Fig. 2).[1,20,92] The MR imaging appearance of the solid regions is frequently similar to those of the adamantinomatous variety.

Typical Histopathological Features of CP

Histologically, adamantinomatous CPs are thought to arise from squamous embryonic rests and bear similarity to adamantinomas or ameloblastomas of the jaw with the potential for enamel production (Fig. 1). The epithelium is often stratified squamous or adamantinoid type, frequently with evidence of wet keratin nodules. The cystic components are often described as having a characteristic "machine-oil" interior, containing desquamated squamous epithelium and comprised mainly of keratin and cholesterol.

The papillary subtype of CP is known to occur more commonly in adults than children (14–50% of craniopharyngioma in adults compared with only 2% of CP in children).[20] Papillary CPs usually bear similarity to oropharyngeal mucosa and rarely exhibit calcification. The cyst contents are typically yellow and viscous. Histopathological analysis frequently demonstrates squamous

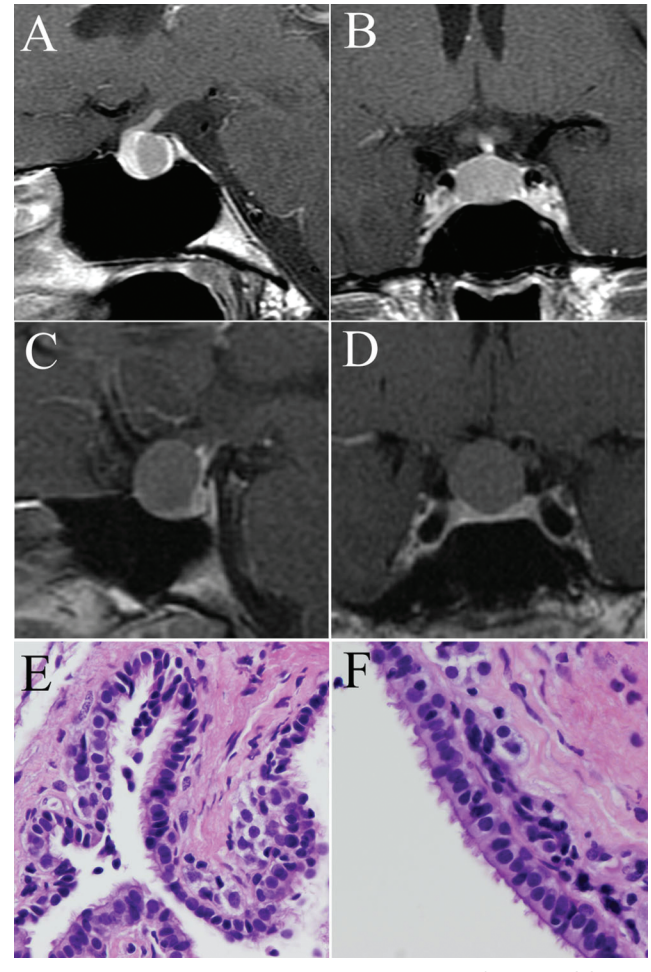

Fig. 3. Imaging and histopathological examples of typical RCCs. **A and B:** Sagittal and coronal Gd-enhanced MR images obtained in a patient with an intrasellar RCC located between the anterior and posterior pituitary gland. **C and D:** Sagittal and coronal Gd-enhanced MR images obtained in a patient with an intra- and suprasellar RCC. **E and F:** Photomicrographs of typical RCC lined by a single layer of columnar, ciliated epithelium. H & E, original magnification × 100 **(E)** and 400 **(F)**.

epithelium forming pseudopapillae, without discrete nodules of wet keratin or calcium. There has been some debate as to whether adamantinomatous CPs demonstrate a higher potential for recurrence, although recent analyses have reported similar or slightly higher rates than their papillary counterparts.[1,20,109] Several investigators have argued that papillary and adamantinomatous CPs may also represent 2 distinct entities that are located at opposing ends of a pathological continuum.[22,109] It has been reported that various markers, including KL-1 or cytokeratin 7, can be used to distinguish the adamantinomatous and papillary varieties of CP.[58]

Rathke Cleft Cysts: Typical Features

Rathke cleft cysts are benign, cystic remnants of the craniopharyngeal duct that are typically located in the sellar and suprasellar region.[19,50] They are often discovered incidentally and have been identified in up to 22% of the population according to routine examination of

autopsy specimens.[100] Despite their relatively high prevalence, they result in clinical symptoms in a minority of patients, comprising only 5–9% of all surgically resected sellar lesions.[2,56,108,115,116] Typical symptoms associated with RCCs include headache, endocrine dysfunction, and visual loss.[2,45] Less frequently, RCCs can present with chemical meningitis, abscess, lymphocytic hypophysitis, or intracystic hemorrhage and apoplexy.[56,96] Although the peak age at the time of clinical presentation is generally 40–50 years,[2,7,56] RCCs can also cause symptoms in children, potentially resulting in somatic and/or sexual retardation in addition to the more common symptoms described above.[114]

Typical Imaging Features of RCCs

On MR imaging, RCCs often appear as well-circumscribed, centrally located spherical or ovoid lesions of the sellar region. The majority of these smooth contoured cysts are unilobar with a diameter ranging between 5–40 mm (mean approximately 17 mm) (Fig. 3).[56,75,97] They are often identified as having an epicenter located between the anterior and posterior pituitary gland in the region of the pars intermedia. The vast majority of lesions are intrasellar or intra- and suprasellar, with reports of purely suprasellar lesions occurring in a minority of patients.[6,110] The normal pituitary gland may be displaced in any direction by an RCC, including circumferentially if the cyst arises in and remains encased within the gland.[10,86]

In the majority of cases, administration of Gd contrast material demonstrates little or no enhancement of the cyst wall or contents on MR imaging.[7,8,14] A thin peripheral rim of enhancement has been attributed to inflammation or squamous metaplasia of the cyst wall, or to a circumferential rim of displaced pituitary gland.[10,56] The MR imaging signal intensity of cyst contents demonstrates high variability on T1- and T2-weighted sequences and has been reported to correlate with the nature of the cystic contents.[4,35,102] In the series by Kim et al.,[56] the 3 most common signal patterns were a high intensity on both T1- and T2-weighted images, a low intensity on T1-weighted images with a high intensity on T2-weighted images, and a high intensity on T1-weighted images with a low intensity on T2-weighted images. Rathke cleft cysts filled with thin, CSF-like fluid generally exhibit a low intensity on T1-weighted images and a high intensity on T2-weighted images, while cysts with more proteinaceous, mucoid fluid correlate with higher intensity on T1-weighted images.[10,17,35,90] Although most RCCs display a homogeneous signal intensity, up to 40% contain a waxy intracystic nodule composed of protein and cellular debris that typically fails to enhance following contrast administration.[8,10,14]

Typical Histopathological Features of RCCs

Histopathologically, RCCs typically demonstrate simple columnar or cuboidal epithelium, often with ciliated or mucinous goblet cells (Fig. 3). Pseudostratified columnar cells are also commonly observed in specimens of RCCs. Squamous metaplasia of RCCs has been noted in 9–39% of patients and is associated with higher rates of cyst recurrence.[2,56,63] Similarly, stratified squamous epithelium occurs in a minority of RCCs and is thought to pose a higher risk for cyst recurrence.[56]

There is a tendency for RCCs to develop attachment to the pituitary stalk, which plays a major in the development of postoperative diabetes insipidus and pituitary insufficiency following complete cyst removal.[50,61,73] Overall long-term recurrence rates following RCC fenestration or resection have varied from 3–33% and have been reported to correlate with several factors, including the radiological enhancement pattern of the cyst wall, the presence of squamous metaplasia or stratified epithelium, the aggressiveness of cyst wall resection, and the placement of an abdominal fat graft.[2,7,54,56,71]

Epidermoid Cysts: Typical Features

Epidermoid lesions can occur anywhere in the intracranial cavity. They most commonly arise as extradural lesions or as intracerebral masses in the region of the cerebellopontine angle, but they may also present in the sellar and parasellar region.[9,40,76,91,99,107] Epidermoid cysts often arise in a paramedian location, in contrast to typically midline dermoid cysts.[91] Sellar and parasellar epidermoid tumors make up only 0.2–0.7% of major transsphenoidal series.[27,89] Epidermoid tumors typically present in middle-aged patients with symptoms of mass effect, such as headache and vision loss.[31,74,112] Some reports have also described an uncommon clinical presentation mimicking that of pituitary apoplexy.[91,104] The cyst contents of epidermoid cysts, and many other epithelial sellar region cysts, can be caustic to the surrounding tissue, often resulting in hypophysitis, meningitis, or neurological deficits. Standard MR imaging cannot be reliably used in all cases to definitively establish a diagnosis of epidermoid or dermoid tumors, on account of their nonspecific MR imaging features. Demonstration of restricted diffusion on diffusion weighted imaging, however, has been shown to play a useful role in allowing the differentiation of epidermoid lesions from other types of cystic pathology, in particular arachnoid cysts.[103]

Intraoperatively, epidermoid cysts can often be adhesive lesions not universally amenable to a gross-total resection. The cyst capsule and contents cannot consistently be dissected away from key vascular and nervous structures to achieve an acceptable outcome with minimal morbidity. Histologically, epidermoid cysts are characterized by a squamous epithelium, keratohyaline granule layers, and stratifications of "dry" keratin (Fig. 4). Gross-total resection of intradural epidermoid tumors has been reported in 42% of cases, with a long-term recurrence rate of 26%.[31] Resection remains the most effective modality, as no adjunctive measures have been proven to be of significant benefit in the management of these lesions.

Embryologic Development and Origins of Cystic Epithelial Lesions of the Sellar Region

Elucidation of the developmental processes accounting for the formation of the hypothalamic-pituitary system and related cystic lesions occurred as a result of several investigators over the course of several decades.[67] Martin

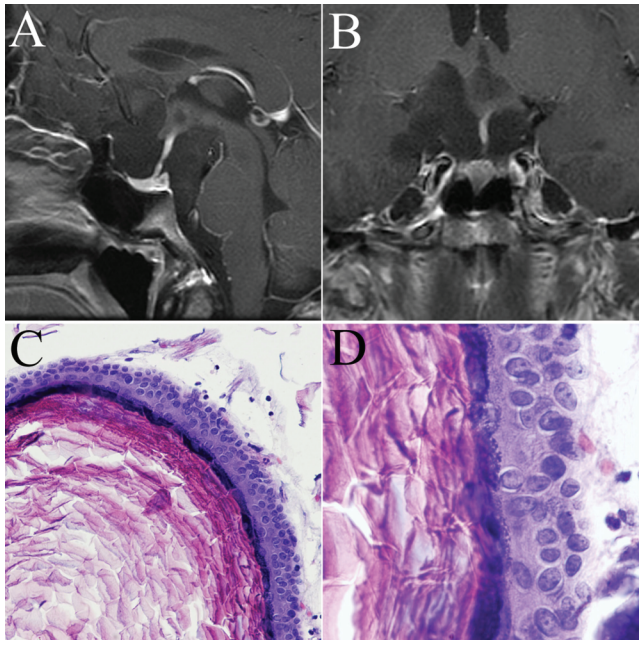

Fig. 4. Imaging and histopathological examples of a suprasellar epidermoid tumor. **A and B:** Sagittal and coronal Gd-enhanced MR images. **C and D:** Photomicrographs of typical epidermoid cyst lining composed of keratinizing stratified squamous epithelium with germinal, granular, and corneal layers with abundant acellular keratin debris. Dermal appendages are not present. H & E, original magnification × 100 **(C)** and 400 **(D)**.

Rathke[85] was the first to describe the evagination process of the anterior foregut in 1838. In 1860, Huber von Luschka[66] was the first to describe the presence of squamous epithelial rests occurring along the axis of the pituitary gland and infundibulum. Although Babinksi[5] and Frohlich[28] each described epithelial suprasellar tumors at around the turn of the century, Jakob Erdheim[24] first indicated that these lesions, which we now refer to as craniopharyngiomas, arise from squamous cell rests occurring in the region of the remnant hypophyseal/pharyngeal duct.

Embryological Development of the Hypothalamic-Pituitary Region

The pituitary gland can be divided into 2 distinct anatomical compartments with different ectodermal origins. The adenohypophysis is ultimately formed by an ectodermal outpouching of the stomodeum (primitive oral cavity) located immediately anterior to the oropharyngeal membrane, known as the Rathke pouch. The neurohypophysis, on the other hand, develops from a downward extension of neuroectodermal tissue originating from the diencephalon, called the infundibulum.[49,62,88]

The onset of neurulation begins with the primitive streak and node, which first appear on the dorsal aspect of the embryonic disc at approximately the 3rd week of gestational life. Once the neural tube is formed, transverse segmentation occurs at the midbrain, pons, and cervical levels, and a series of evaginations of the neural tube walls eventually produces several important structures in the CNS. The Rathke pouch (also known as the hypophysial diverticulum at this stage) is first noted to appear as an outpouching from the roof of the oral cavity at the 4th week of gestation. During the following weeks, this diverticulum gradually elongates and becomes constricted at its attachment site to the oral epithelium. At 6–8 weeks of life, the pouch loses its connection with the oral cavity and has grown in close contact with the infundibulum dorsally. Between the 3rd and 5th months of gestation, cells in the anterior wall of the Rathke pouch proliferate rapidly to form the pars anterior, whereas cells in the posterior wall do not divide significantly to form abundant glandular tissue. Instead, cells from this less active posterior wall form the pars intermedia, which is frequently not a prominent structure in the adult pituitary gland. Meanwhile, the infundibulum gives rise to the median eminence, the pituitary stalk, and the pars nervosa, or the posterior lobe of the pituitary gland. A small extension of the pars anterior, known as the pars tuberalis, extends superoventrally along the stalk and eventually surrounds it by the 16th week of gestation.

The extensive proliferation of the anterior wall of the hypophysial diverticulum eventually reduces its lumen size to that of a narrow cleft that is not typically recognizable in the adult pituitary. It is likely that CPs, RCCs, and other cystic epithelial lesions originate from remnants of this ectodermal cleft and the associated derivatives of the primitive stomodeum, where squamous cell rests are known to reside. In the past, 2 generalized theories have been proposed to explain the origins of CPs in this region. The "embryogenic theory" states that when the Rathke pouch is detached from the oral epithelium, remnants of ectopic craniopharyngeal duct may be deposited within the sellar region. The craniopharyngeal duct contains ectoblastic cells, which are derived from parts of the stomodeum and could be the origin of adamantinomatous craniopharyngiomas.[24,29,80] The "metaplastic theory," on the other hand, proposes that squamous epithelial cell rests that are found in the adenohypophysis and infundibulum can undergo metaplasia, thus giving rise to the papillary subtype of CP tumors.[80,84,93] Evidence supporting and refuting the various theories for both ectodermal and nonectodermal origins of cystic epithelial lesions is further discussed below. It is certainly possible that developmental as well as subsequent metaplastic and neoplastic processes can each play a role in the formation of various lesions along a spectrum of related pathology.

Evidence Lending Support to a Common Ectodermal Origin of Cystic Epithelial Lesions

The evidence lending support to the prevailing theory of a common ectodermal origin for many cystic epithelial lesions of the sellar region is derived from several sources. These sources include animal laboratory investigations, observational reports of transitional lesions containing features of multiple histopathological lesions, and case reports of progression from one lesion type to another, all of which have provided a credible basis for this viewpoint.

In a study by VanGilder and Inukai[106] in 1973, oral mucosa was transplanted into the brains of 50 baby rats. The transplanted cells differentiated into a spectrum of

TABLE 1: Histological characteristics, incidence, and recurrence rates of various cystic epithelial lesions and their subtypes*

Lesion Type	Pathological Features	Incidence	Recurrence Rate
RCC			
typical[2,7,56,97]	simple cuboidal or columnar cells	28–54% of RCCs	3–19%
	pseudostratified columnar	23–49% of RCCs	3–19%
"transitional"[2,7,41,56,63,68,69,91,108,113]	squamous epithelium, including squamous metaplasia; chronic inflammation	9–39% of RCCs	32–39%
CP			
ciliated or goblet papillary[30,70,77–79,97]	ciliated or mucinous goblet cells	infrequent case reports	unknown
squamous-papillary[1,20,109]	stratified squamous epithelium, pseudopapillae	28–33% in adults, 2% in children	0–12%
adamantinomatous[1,26,109]	adamantoid epithelium, wet keratin	66–68% in adults, 96–100% in children	13–22%
xanthogranuloma[63,83]	xanthogranulomatous component, little epithelium (usually squamous)	34% of suspected CPs	unknown
epidermoid cyst[20,31,112]	squamous epithelium, dry keratin, keratohyaline granules	<1% of primary CNS lesions	0–26%

* Superscripted numbers indicate studies discussing the respective lesion.

histopathological subtypes characterized by stratified squamous, cuboidal, and transitional epithelium as well as cholesterol clefts, calcification, and bone. The authors concluded that similar progenitor cells may differentiate into the spectrum of cystic epithelial lesions observed in the developing human brain. In another study, Iwata et al.[47] performed a microscopic analysis of the hypophysis in rats. The authors found evidence of epithelial craniopharyngeal derivatives in approximately 0.16% of rats, and they suggested developmental rather than neoplastic origins of RCCs and related cystic epithelial lesions. Similarly, Schaetti and colleagues[94] examined pituitary specimens in rats and reported finding epithelial craniopharyngeal derivatives consisting of cuboidal or columnar epithelium with goblet cells or stratified squamous epithelium. The authors of this study supported a heterotopic, nonneoplastic origin for many of these various epithelial cystic masses as well.

Several varieties of "transitional" or "crossover" cystic epithelial lesions with nonspecific features have been reported in the literature, collectively providing additional support for a theory of sequential progression in epithelial cystic lesions (Table 1).[30,34,69,70,107,113] Although RCCs are considered nonneoplastic cystic lesions, recurrence rates following surgical intervention have been reported to be as high, or higher, than in some series following resection of CPs.[2,16,26,54,71] More aggressive, or "transitional," subtypes of RCCs have been reported to comprise a significant proportion of these recurrences and are frequently characterized by less typical histopathological features (Fig. 5). A theory of acute and chronic inflammatory processes, perhaps incited by repeated cyst leakage or microhemorrhage, has been implicated in inciting the process of squamous metaplasia identified in some RCCs.[33] Between 9 and 39% of RCCs demonstrate evidence of squamous metaplasia, which has been independently associated with higher rates of cyst recurrence.[2,7,56,63,108] The higher recurrence rates observed in RCCs with squamous metaplasia support the idea that these are likely more aggressive lesions that more closely approach the natural history of CP.[2] The presence of stratified squamous epithelial cells in a minority of RCCs, as well as the higher MIB-1 labeling indexes associated with these lesions, also lends support to the theory that at least a subset of CPs may develop from such transitional intermediaries.[41,69] A theory by Ikeda and Yoshimoto[41] proposed that squamous epithelial cells in aggressive RCCs with higher proliferative indexes eventually outgrow and displace simple epithelium cell types.

More evidence for this hypothesis comes from reports of transitional-type pathology, consisting of histological features falling along different points of this histopathological continuum and occurring within the same lesion.[34,87] In such cases, the intrasellar portion typically demonstrates features consistent with an RCC, whereas the suprasellar portion usually demonstrates features that are more typical for CP. Furthermore, numerous cases of ciliated epithelial cells or mucin-containing goblet cells occurring in squamous-papillary craniopharyngiomas have been reported and implicated as providing further support for a common ectodermal origin and transitional entity between RCCs and CPs.[30,34,68,77,78] As these rare lesions' epithelial cells undergo transformation and no longer exhibit ciliation, it has been proposed that they develop into the more characteristic stratified squamous cell epithelial cells traditionally observed in the squamous-papillary subtype of CP.[30,79]

Finally, several cases of ciliated squamous-papillary CPs have been reported to arise directly from preexisting RCCs.[79,82,93] In one of these studies, Park et al.[82] reported a case of an RCC with negative β-catenin accumulation that transitioned into a CP with positive β-catenin accumulation.[82] A major limitation of these reports, however, is that for any given case it cannot been proven with certainty that a CP neoplasm actually arose from a preexisting RCC. The possibilities of coexisting lesions or dif-

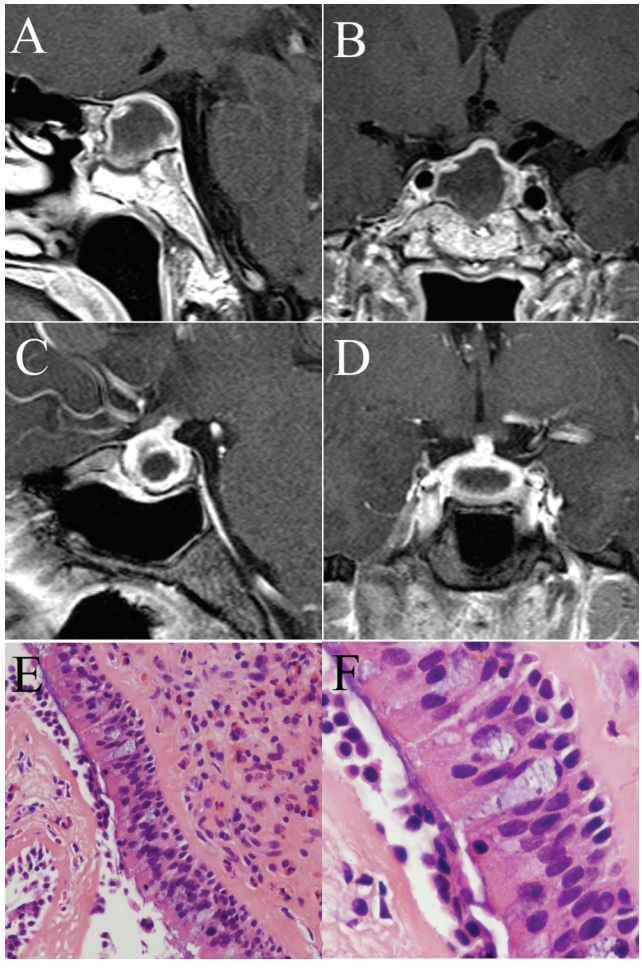

Fig. 5. Imaging and histopathological examples of atypical RCCs. **A and B:** Sagittal and coronal Gd-enhanced MR images acquired in a patient with a recurrent RCC and thickening of the cyst wall. **C and D:** Sagittal and coronal Gd-enhanced MR images obtained in a patient with an RCC, demonstrating significant wall thickening and enhancement. **E and F:** Photomicrographs of an atypical RCC lined by columnar epithelium with frequent goblet cells and mucin production. H & E, original magnification × 100 **(E)** and 400 **(F)**.

ferences in biopsy technique and tissue analysis can be alternative explanations for this phenomenon.

Another noteworthy histological category with features resembling those of both CPs and RCCs is the sellar xanthogranuloma. These lesions tend to occur in younger patients (mean 27 years), have a smaller diameter, and remain primarily intrasellar with infrequent calcification.[83] Although they have been reported to comprise a distinct entity, it remains unknown whether they are derived from RCCs or CPs following extensive inflammation and metaplasia, to the point that no epithelium is readily identifiable.[63,83] Le and coworkers[63] reported that the features of xanthogranuloma were more consistent with RCCs than CPs and demonstrated a high association with squamous metaplasia of these lesions.

Evidence Supporting Nonectodermal Origins of Cystic Epithelial Sellar Lesions

In the past, some investigators have favored theories supporting nonectodermal origins of various cystic epithelial sellar lesions. One alternative explanation is a theory that RCCs and related epithelial sellar and parasellar cysts, including neurenteric cysts and colloid cysts, are derived from an endodermal origin.[32,43,44,81] The presence of histological features such as ciliation, goblet cells, and mucin associated with each of these lesions has provided the main argument in favor of this theory.[42] As Harrison and colleagues[34] described, however, similar histological findings can be identified in a variety of epithelial tumors located throughout the cerebrum. Furthermore, the same authors argued that the contents of the sella are purely ectodermal, with no valid explanation in place for how endodermal derivatives may arise here later during development, including theories of dysraphism.[34] Another theory for the origin of cystic epithelial lesions in this region is that they are derived instead from neuroepithelial sources such as the neural crest, as supported by the finding of amyloid stroma in some examples.[18,21,65,98] A third alternative theory suggests that cystic epithelial lesions are derived from metaplasia of anterior pituitary cells.[3,39,95] Some authors have reported RCCs or CPs occurring in conjunction with pituitary adenomas as transitional or collision lesions.[53,55] However, no evidence for a direct metaplastic origin of these cystic lesions from adenomas, or vice versa, has been proven as an alternative to a purely coincidental hypothesis.[53]

Differentiation of Cystic CP and RCC

Although RCCs and CPs may represent 2 poles of a pathological spectrum, they are for the most part distinct entities, and according to Thapar and Kovacs,[101] have "differences that are much more compelling than are their similarities." Several previous reports have attempted to identify the clinical, radiological, and histopathological parameters that are most useful in accurately differentiating cystic sellar region pathology. In this section, these key characteristics are reviewed (Table 2).

Clinical Features

The majority of studies report overlapping clinical features for RCCs and CPs in adults, with regard to age distribution and sex.[36] Similarly, presenting clinical features such as headache, endocrine deficits, visual deficits, and diabetes insipidus have not been reliably demonstrated to allow differentiation of CPs from RCCs.[36,97] The only clinical features that have been reliably correlated with the diagnosis of CP over RCC, according to one study, were a significantly higher incidence of amenorrhea and neuropsychiatric deficits associated with CP.[97]

Imaging Features

In many cases, imaging modalities can be used to more reliably differentiate RCCs from CPs and other cystic lesions. In some cases, this differentiation can be quite challenging, as the majority of studies have been unable to reliably do so based solely on T1- and T2-weighted intensity (Fig. 6).[17,36,97] Calcification on CT imaging is often a useful characteristic for differentiat-

TABLE 2: Summary of clinical, imaging and histopathological characteristics that have been demonstrated to benefit in differentiating CPs and RCCs*

Feature	All CPs		RCCs
	Adamantinomatous	Papillary	
clinical			
psychiatric deficits[97]	+	+	–
amenorrhea[97]	+	+	+/–
imaging			
calcification (CT)[1,20,36,97]	++	–	–
size (>20 mm)[1,17,20,36,97]	+	+	+/–
location			
suprasellar only[17,36,97]	+	++	+/–
compressing 3rd ventricle[17,97]	+	+	–
ovoid shape[17,97]	+/–	+	++
cyst wall enhancement[17]	+	+	+/–
single-shot fast spin echo diffusion weighted imaging[57]	+	+	–
histopathology			
calcification[20,97]	+	–	–
epithelial lining			
adamantinomatous[1,33]	++	–	–
squamous[36,56,97]	+	++	+/–
simple columnar[36,97]	–	–	+
simple cuboidal[36,97]	–	–	+
pseudostratified columnar[36,97]	–	–	+
ciliated[36,97]	–	–	++
mucinous/goblet cells[1,36,97]	–	+	++
keratin nodules[36,97]	++	+/–	–
chronic inflammation[56,97]	+	NA	+/–
markers			
CK 8[63,111]	+/–	+/–	++
CK 20[63,111]	–	–	+
nuclear β–catenin accumulation[36]	++	–	–

* Superscripted numbers indicate studies discussing the respective feature. Abbreviations: NA = not applicable; ++ = quite common; + = more common; +/– = less likely; – = rare or absent.

ing RCCs from CPs. In previous studies, 42–87% of CPs exhibited calcification, compared with only 0–13% of RCCs.[36,97] It is important to note, however, that several cases of RCCs have been reported to occur with ossification and no evidence of neoplastic features, and that the presence of calcium is not necessarily pathognomonic for CP.[64,72]

In 2006, Hofmann and colleagues[36] reported that the imaging parameters that can be used to support a diagnosis of CP over RCC include: greater tumor diameter (> 2 cm), suprasellar location, and presence of calcification. In another study by Choi et al.,[17] MR imaging features were reviewed for RCCs, CPs, and cystic pituitary adenomas. Radiological parameters that supported a diagnosis of RCC were an ovoid shape, small cyst volume, and thin or no cyst wall enhancement. Conversely, a radiological diagnosis of CP was supported by features such as superior tumor lobulation, larger tumor volume, compression of the third ventricle, and a reticular enhancement pattern of the solid tumor portion. Kunii et al.[57] used single-shot fast spin echo diffusion weighted MR imaging to differentiate cystic sellar and suprasellar lesions. They reported that RCCs could be identified using this imaging modality because of the lesion's increased regional apparent diffusion coefficient values, in contrast with those of CPs and hemorrhagic pituitary adenomas. However, this modality was less useful in differentiating RCCs from cystic pituitary adenomas.

Histopathological Features

The most reliable methods of distinguishing cystic epithelial lesions are clearly based on histopathological

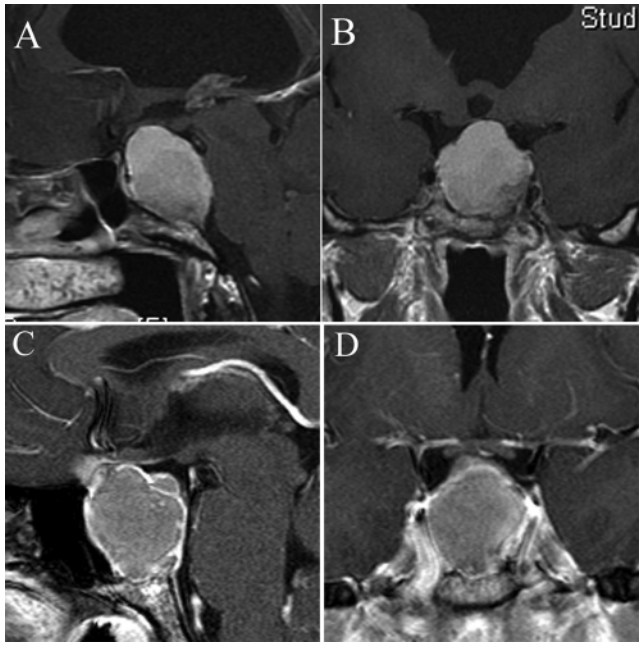

Fig. 6. Imaging examples demonstrating the potential difficulty in differentiating atypical CPs and RCCs. **A and B:** Sagittal and coronal Gd-enhanced MR images obtained in a patient with a recurrent RCC, demonstrating suprasellar, clival, and retrosellar extension. **C and D:** Sagittal and coronal Gd-enhanced MR images obtained in a patient with a cystic CP, also demonstrating suprasellar and infrasellar extension.

and molecular markers, representing the gold standard for diagnosis. However, even at a microscopic and molecular level the differentiation of these lesions is often not clear cut, which perhaps further elucidates why the clinical and radiological features are often indistinguishable.

In a report by Shin and associates,[97] the histopathological features of RCCs and CPs were reviewed to identify those that correlated significantly with each lesion type. The authors determined that the characteristics correlating significantly with a diagnosis of RCC were simple columnar or cuboidal epithelium, pseudostratified columnar epithelium, and ciliation. Conversely, features supporting a diagnosis of CP included stratified squamous epithelium, calcification, keratin nodules, and chronic inflammation.

Nuclear immunohistochemical staining for β-catenin accumulation has been used as a reliable method of differentiation of some cystic sellar region lesions and has been shown to demonstrate immunoreactivity exclusively in CPs.[36] A similar study demonstrated β-catenin immunoreactivity in 77% of CPs, particularly of the adamantinomatous subtype.[13] Although useful, the downside of this modality is that it cannot be used to reliably differentiate squamous-papillary CPs from transitional RCCs, which is often the more formidable challenge.[36]

The expression patterns of various cytokeratins have also been reported to aid in the differentiation of RCCs from CPs yet with less consistency. In a study reviewing cytokeratin expression in 15 patients with cystic sellar lesions, Xin et al.[111] reported that RCCs demonstrate expression of cytokeratins 8 and 20, whereas CP did not. However, a similar study in 2007 by Le and coworkers[63] failed to demonstrate as reliable of a pattern, in which cytokeratin 8 reactivity occurred in all cases of RCC and CP.

Conclusions

Varying subtypes of sellar and parasellar epithelial cystic masses may be difficult to differentiate on a clinical, imaging, or even histopathological basis. There is significant evidence to support a common ectodermal origin of such entities, which may account for the overlap of features and transitional states observed in some cases. The pattern of embryological formation of the hypothalamic-pituitary axis plays a major role in its susceptibility to the development of such cystic epithelial lesions. Subsequent inflammatory, metaplastic and neoplastic processes may promote further progression along a pathological continuum ranging from benign epithelial cysts to aggressive neoplastic CPs. Research obtained from animal studies, reports of transitional cystic epithelial masses with nonspecific features, and reports of lesions crossing over from typical to more aggressive pathological subtypes have collectively provided a solid foundation for this idea. Selected clinical, imaging, and histopathological features can be used to aid in differentiating these lesions and assigning a formal diagnosis to guide further treatment.

Acknowledgement

The authors would like to thank Dr. Peter Chiarelli for assistance with journal collection.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: G Zada, N Lin, ER Laws. Acquisition of data: G Zada, E Ojerholm, S Ramkissoon. Analysis and interpretation of data: G Zada, S Ramkissoon, ER Laws. Drafting the article: G Zada, N Lin, E Ojerholm, S Ramkissoon, ER Laws. Critically revising the article: G Zada, N Lin, E Ojerholm, S Ramkissoon, ER Laws. Reviewed final version of the manuscript and approved it for submission: G Zada, N Lin, E Ojerholm, S Ramkissoon, ER Laws. Study supervision: ER Laws.

References

1. Adamson TE, Wiestler OD, Kleihues P, Yaşargil MG: Correlation of clinical and pathological features in surgically treated craniopharyngiomas. **J Neurosurg 73:**12–17, 1990
2. Aho CJ, Liu C, Zelman V, Couldwell WT, Weiss MH: Surgical outcomes in 118 patients with Rathke cleft cysts. **J Neurosurg 102:**189–193, 2005
3. Asa SL, Kovacs K, Bilbao JM: The pars tuberalis of the human pituitary. A histologic, immunohistochemical, ultrastructural and immunoelectron microscopic analysis. **Virchows Arch A Pathol Anat Histopathol 399:**49–59, 1983
4. Asari S, Ito T, Tsuchida S, Tsutsui T: MR appearance and cyst content of Rathke cleft cysts. **J Comput Assist Tomogr 14:**532–535, 1990
5. Babinski J: Tumeur du corps pituitaire sans acromegalie et avec arrêt développementdes organes génitaux. **Rev Neurol 9:**531–533, 1900 (Fr)
6. Barrow DL, Spector RH, Takei Y, Tindall GT: Symptomatic

Rathke's cleft cysts located entirely in the suprasellar region: review of diagnosis, management, and pathogenesis. **Neurosurgery 16:**766–772, 1985
7. Benveniste RJ, King WA, Walsh J, Lee JS, Naidich TP, Post KD: Surgery for Rathke cleft cysts: technical considerations and outcomes. **J Neurosurg 101:**577–584, 2004
8. Binning MJ, Gottfried ON, Osborn AG, Couldwell WT: Rathke cleft cyst intracystic nodule: a characteristic magnetic resonance imaging finding. **J Neurosurg 103:**837–840, 2005
9. Boggan JE, Davis RL, Zorman G, Wilson CB: Intrasellar epidermoid cyst. Case report. **J Neurosurg 58:**411–415, 1983
10. Brassier G, Morandi X, Tayiar E, Riffaud L, Chabert E, Heresbach N, et al: Rathke's cleft cysts: surgical-MRI correlation in 16 symptomatic cases. **J Neuroradiol 26:**162–171, 1999
11. Brunel H, Raybaud C, Peretti-Viton P, Lena G, Girard N, Paz-Paredes A, et al: [Craniopharyngioma in children: MRI study of 43 cases.] **Neurochirurgie 48:**309–318, 2002 (Fr)
12. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. **J Neurosurg 89:**547–551, 1998
13. Buslei R, Nolde M, Hofmann B, Meissner S, Eyupoglu IY, Siebzehnrübl F, et al: Common mutations of beta-catenin in adamantinomatous craniopharyngiomas but not in other tumours originating from the sellar region. **Acta Neuropathol 109:**589–597, 2005
14. Byun WM, Kim OL, Kim D: MR imaging findings of Rathke's cleft cysts: significance of intracystic nodules. **AJNR Am J Neuroradiol 21:**485–488, 2000
15. Cavallo LM, Prevedello D, Esposito F, Laws ER Jr, Dusick JR, Messina A, et al: The role of the endoscope in the transsphenoidal management of cystic lesions of the sellar region. **Neurosurg Rev 31:**55–64, 2008
16. Chakrabarti I, Amar AP, Couldwell W, Weiss MH: Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. **J Neurosurg 102:**650–657, 2005
17. Choi SH, Kwon BJ, Na DG, Kim JH, Han MH, Chang KH: Pituitary adenoma, craniopharyngioma, and Rathke cleft cyst involving both intrasellar and suprasellar regions: differentiation using MRI. **Clin Radiol 62:**453–462, 2007
18. Concha S, Hamilton BP, Millan JC, McQueen JD: Symptomatic Rathke's cleft cyst with amyloid stroma. **J Neurol Neurosurg Psychiatry 38:**782–786, 1975
19. Couldwell WT, Weiss MH: Nonadenomatous lesions of the pituitary, in Krisht A, Tindall, GT (eds): **Pituitary Disorders.** Baltimore, MD: Lipincott Williams & Wilkins, 1999
20. Crotty TB, Scheithauer BW, Young WF Jr, Davis DH, Shaw EG, Miller GM, et al: Papillary craniopharyngioma: a clinicopathological study of 48 cases. **J Neurosurg 83:**206–214, 1995
21. Diengdoh JV, Scott T: Electron-microscopical study of a Rathke's cleft cyst. **Acta Neuropathol 60:**14–18, 1983
22. Eldevik OP, Blaivas M, Gabrielsen TO, Hald JK, Chandler WF: Craniopharyngioma: radiologic and histologic findings and recurrence. **AJNR Am J Neuroradiol 17:**1427–1439, 1996
23. Elliott RE, Wisoff JH: Successful surgical treatment of craniopharyngioma in very young children. **J Neurosurg Pediatr 3:**397–406, 2009
24. Erdheim J: Über Hypophysenganggeschwülste und Hirncholesteatome. **Sitzungsber Kaiserliche Akad Wiss (Wien) 113 (sect3):**537–726, 1904
25. Fager CA, Carter H: Intrasellar epithelial cysts. **J Neurosurg 24:**77–81, 1966
26. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
27. Fatemi N, Dusick JR, de Paiva Neto MA, Kelly DF: The endonasal microscopic approach for pituitary adenomas and other parasellar tumors: a 10-year experience. **Neurosurgery 63 (4 Suppl 2):**244–256, 2008
28. Frohlich A: Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie. **Wien Klin Rundschau 15:**883–886, 903–906, 1901
29. Goldberg GM, Eshbaugh DE: Squamous cell nests of the pituitary gland as related to the origin of craniopharyngiomas. A study of their presence in the newborn and infants up to age four. **Arch Pathol 70:**293–299, 1960
30. Goodrich JT, Post KD, Duffy P: Ciliated craniopharyngioma. **Surg Neurol 24:**105–111, 1985
31. Gormley WB, Tomecek FJ, Qureshi N, Malik GM: Craniocerebral epidermoid and dermoid tumours: a review of 32 cases. **Acta Neurochir (Wien) 128:**115–121, 1994
32. Graziani N, Dufour H, Figarella-Branger D, Donnet A, Bouillot P, Grisoli F: Do the suprasellar neurenteric cyst, the Rathke cleft cyst and the colloid cyst constitute a same entity? **Acta Neurochir (Wien) 133:**174–180, 1995
33. Hama S, Arita K, Nishisaka T, Fukuhara T, Tominaga A, Sugiyama K, et al: Changes in the epithelium of Rathke cleft cyst associated with inflammation. **J Neurosurg 96:**209–216, 2002
34. Harrison MJ, Morgello S, Post KD: Epithelial cystic lesions of the sellar and parasellar region: a continuum of ectodermal derivatives? **J Neurosurg 80:**1018–1025, 1994
35. Hayashi Y, Tachibana O, Muramatsu N, Tsuchiya H, Tada M, Arakawa Y, et al: Rathke cleft cyst: MR and biomedical analysis of cyst content. **J Comput Assist Tomogr 23:**34–38, 1999
36. Hofmann BM, Kreutzer J, Saeger W, Buchfelder M, Blümcke I, Fahlbusch R, et al: Nuclear beta-catenin accumulation as reliable marker for the differentiation between cystic craniopharyngiomas and Rathke cleft cysts: a clinico-pathologic approach. **Am J Surg Pathol 30:**1595–1603, 2006
37. Honegger J, Barocka A, Sadri B, Fahlbusch R: Neuropsychological results of craniopharyngioma surgery in adults: a prospective study. **Surg Neurol 50:**19–29, 1998
38. Honegger J, Buchfelder M, Fahlbusch R: Surgical treatment of craniopharyngiomas: endocrinological results. **J Neurosurg 90:**251–257, 1999
39. Hunter IJ: Squamous metaplasia of cells of the anterior pituitary gland. **J Pathol Bacteriol 69:**141–145, 1955
40. Iaconetta G, Carvalho GA, Vorkapic P, Samii M: Intracerebral epidermoid tumor: a case report and review of the literature. **Surg Neurol 55:**218–222, 2001
41. Ikeda H, Yoshimoto T: Clinicopathological study of Rathke's cleft cysts. **Clin Neuropathol 21:**82–91, 2002
42. Ikeda H, Yoshimoto T, Suzuki J: Immunohistochemical study of Rathke's cleft cyst. **Acta Neuropathol 77:**33–38, 1988
43. Inoue T, Matsushima T, Fukui M, Iwaki T, Takeshita I, Kuromatsu C: Immunohistochemical study of intracranial cysts. **Neurosurgery 23:**576–581, 1988
44. Ishii T, Yamasaki T, Tanaka J, Tanaka S, Hori T, Muraoka K: [Rathke's cleft cyst—report of three cases.] **No Shinkei Geka 15:**451–456, 1987 (Japanese)
45. Isono M, Kamida T, Kobayashi H, Shimomura T, Matsuyama J: Clinical features of symptomatic Rathke's cleft cyst. **Clin Neurol Neurosurg 103:**96–100, 2001
46. Iwasaki K, Kondo A, Takahashi JB, Yamanobe K: Intraventricular craniopharyngioma: report of two cases and review of the literature. **Surg Neurol 38:**294–301, 1992
47. Iwata H, Hosoi M, Miyajima R, Yamamoto S, Mikami S, Yamakawa S, et al: Morphogenesis of craniopharyngeal derivatives in the neurohypophysis of Fisher 344 rats: abnormally developed epithelial tissues including parotid glands derived from the stomatodeum. **Toxicol Pathol 28:**568–574, 2000
48. Jagannathan J, Dumont AS, Jane JA Jr, Laws ER Jr: Pediatric

sellar tumors: diagnostic procedures and management. **Neurosurg Focus 18 (6A):**E6, 2005
49. Jane JA Jr, Laws ER: Craniopharyngioma. **Pituitary 9:**323–326, 2006
50. Kanter AS, Sansur CA, Jane JA Jr, Laws ER Jr: Rathke's cleft cysts. **Front Horm Res 34:**127–157, 2006
51. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, et al: Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. **Clin Endocrinol (Oxf) 62:**397–409, 2005
52. Karavitaki N, Cudlip S, Adams CB, Wass JA: Craniopharyngiomas. **Endocr Rev 27:**371–397, 2006
53. Karavitaki N, Scheithauer BW, Watt J, Ansorge O, Moschopoulos M, Llaguno AV, et al: Collision lesions of the sella: coexistence of craniopharyngioma with gonadotroph adenoma and of Rathke's cleft cyst with corticotroph adenoma. **Pituitary 11:**317–323, 2008
54. Kasperbauer JL, Orvidas LJ, Atkinson JL, Abboud CF: Rathke cleft cyst: diagnostic and therapeutic considerations. **Laryngoscope 112:**1836–1839, 2002
55. Kepes JJ: Transitional cell tumor of the pituitary gland developing from a Rathke's cleft cyst. **Cancer 41:**337–343, 1978
56. Kim JE, Kim JH, Kim OL, Paek SH, Kim DG, Chi JG, et al: Surgical treatment of symptomatic Rathke cleft cysts: clinical features and results with special attention to recurrence. **J Neurosurg 100:**33–40, 2004
57. Kunii N, Abe T, Kawamo M, Tanioka D, Izumiyama H, Moritani T: Rathke's cleft cysts: differentiation from other cystic lesions in the pituitary fossa by use of single-shot fast spin-echo diffusion-weighted MR imaging. **Acta Neurochir (Wien) 149:**759–769, 2007
58. Kurosaki M, Saeger W, Lüdecke DK: Immunohistochemical localisation of cytokeratins in craniopharyngioma. **Acta Neurochir (Wien) 143:**147–151, 2001
59. Laws ER: Craniopharyngiomas in children and young adults. **Prog Exp Tumor Res 30:**335–340, 1987
60. Laws ER: Endoscopic surgery for cystic lesions of the pituitary region. **Nat Clin Pract Endocrinol Metab 4:**662–663, 2008
61. Laws ER, Kanter AS: Rathke cleft cysts. **J Neurosurg 101:**571–572, 2004
62. Laws ER, Weiss MH, White WL: Craniopharyngioma. **Skull Base 13:**55–58, 2003
63. Le BH, Towfighi J, Kapadia SB, Lopes MB: Comparative immunohistochemical assessment of craniopharyngioma and related lesions. **Endocr Pathol 18:**23–30, 2007
64. Lee CH, Seo EK, Cho YJ, Kim SJ: Large ossified Rathke's cleft cyst—a case report and review of the literature. **J Korean Neurosurg Soc 44:**256–258, 2008
65. Leech RW, Olafson RA: Epithelial cysts of the neuraxis: presentation of three cases and a review of the origins and classification. **Arch Pathol Lab Med 101:**196–202, 1977
66. Luschka Hv: **Der Hirnanhang u.d. Steissdruse d. Menschen.** Berlin, 1860
67. Maartens N, Kaye A: Transsphenoidal resection of craniopharyngiomas, in Laws ER, Lanzino G (eds): **Transsphenoidal Surgery.** Philadelphia: Elsevier, 2006
68. Maruki C, Shimoji T, Kijima H, Matsumoto M, Maeda M: Ciliated epithelial cell cluster in Rathke's cleft cyst—report of two cases. **Neurol Med Chir (Tokyo) 31:**92–95, 1991
69. Matsushima T, Fukui M, Fujii K, Kinoshita K, Yamakawa Y: Epithelial cells in symptomatic Rathke's cleft cysts. A light- and electron-microscopic study. **Surg Neurol 30:**197–203, 1988
70. Matsushima T, Fukui M, Ohta M, Yamakawa Y, Takaki T, Okano H: Ciliated and goblet cells in craniopharyngioma. Light and electron microscopic studies at surgery and autopsy. **Acta Neuropathol 50:**199–205, 1980
71. Mukherjee JJ, Islam N, Kaltsas G, Lowe DG, Charlesworth M, Afshar F, et al: Clinical, radiological and pathological features of patients with Rathke's cleft cysts: tumors that may recur. **J Clin Endocrinol Metab 82:**2357–2362, 1997
72. Nakasu Y, Nakasu S, Nakajima M, Itoh R, Matsuda M: Atypical Rathke's cleft cyst associated with ossification. **AJNR Am J Neuroradiol 20:**1287–1289, 1999
73. Nemergut EC, Zuo Z, Jane JA Jr, Laws ER Jr: Predictors of diabetes insipidus after transsphenoidal surgery: a review of 881 patients. **J Neurosurg 103:**448–454, 2005
74. Netsky MG: Epidermoid tumors. Review of the literature. **Surg Neurol 29:**477–483, 1988
75. Nishioka H, Haraoka J, Izawa H, Ikeda Y: Magnetic resonance imaging, clinical manifestations, and management of Rathke's cleft cyst. **Clin Endocrinol (Oxf) 64:**184–188, 2006
76. Oge K, Ozgen T: Transsphenoidal removal of an intra- and suprasellar epidermoid cyst. **Neurochirurgia (Stuttg) 34:**94–96, 1991
77. Oka H, Kawano N, Yagishita S, Kobayashi I, Saegusa H, Fujii K: Ciliated craniopharyngioma indicates histogenetic relationship to Rathke cleft epithelium. **Clin Neuropathol 16:**103–106, 1997
78. Oka H, Kawano N, Yagishita S, Suwa T, Yoshida T, Maezawa H, et al: Origin of ciliated craniopharyngioma: pathological relationship between Rathke cleft cyst and ciliated craniopharyngioma. **Noshuyo Byori 12:**97–103, 1995
79. Okada T, Fujitsu K, Miyahara K, Ichikawa T, Takemoto Y, Niino H, et al: Ciliated craniopharyngioma—case report and pathological study. **Acta Neurochir (Wien) 152:**303–307, 2010
80. Oskouian RJ, Samii A, Laws ER Jr: The craniopharyngioma. **Front Horm Res 34:**105–126, 2006
81. Palma L, Celli P: Suprasellar epithelial cyst. Case report. **J Neurosurg 58:**763–765, 1983
82. Park YS, Ahn JY, Kim DS, Kim TS, Kim SH: Late development of craniopharyngioma following surgery for Rathke's cleft cyst. **Clin Neuropathol 28:**177–181, 2009
83. Paulus W, Honegger J, Keyvani K, Fahlbusch R: Xanthogranuloma of the sellar region: a clinicopathological entity different from adamantinomatous craniopharyngioma. **Acta Neuropathol 97:**377–382, 1999
84. Prabhu VC, Brown HG: The pathogenesis of craniopharyngiomas. **Childs Nerv Syst 21:**622–627, 2005
85. Rathke H: Ueber die Entstehung der Glandula pituitaria. **Arch Anat Physiol Wiss Med 5:**482–485, 1838
86. Ross DA, Norman D, Wilson CB: Radiologic characteristics and results of surgical management of Rathke's cysts in 43 patients. **Neurosurgery 30:**173–179, 1992
87. Russell D, Rubinstein L: **Pathology of Tumours of the Nervous System, ed 5**: Williams & Wilkins, 1989
88. Sadler T: **Langman's Medical Embryology.** Philadelphia: Lippincott Williams & Wilkins, 2009, p 414
89. Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S: Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. **Eur J Endocrinol 156:**203–216, 2007
90. Saeki N, Sunami K, Sugaya Y, Yamaura A: MRI findings and clinical manifestations in Rathke's cleft cyst. **Acta Neurochir (Wien) 141:**1055–1061, 1999
91. Sani S, Smith A, Leppla DC, Ilangovan S, Glick R: Epidermoid cyst of the sphenoid sinus with extension into the sella turcica presenting as pituitary apoplexy: case report. **Surg Neurol 63:**394–397, 2005
92. Sartoretti-Schefer S, Wichmann W, Aguzzi A, Valavanis A: MR differentiation of adamantinous and squamous-papillary craniopharyngiomas. **AJNR Am J Neuroradiol 18:**77–87, 1997
93. Sato K, Oka H, Utsuki S, Kondo K, Kurata A, Fujii K: Ciliated craniopharyngioma may arise from Rathke cleft cyst. **Clin Neuropathol 25:**25–28, 2006
94. Schaetti P, Argentino-Storino A, Heinrichs M, Mirea D, Popp A,

Karbe E: Aberrant craniopharyngeal structures within the neurohypophysis of rats. **Exp Toxicol Pathol 47:**129–137, 1995
95. Shanklin WM: The histogenesis and histology of an integumentary type of epithelium in the human hypophysis. **Anat Rec 109:**217–231, 1951
96. Shimoji T, Shinohara A, Shimizu A, Sato K, Ishii S: Rathke cleft cysts. **Surg Neurol 21:**295–310, 1984
97. Shin JL, Asa SL, Woodhouse LJ, Smyth HS, Ezzat S: Cystic lesions of the pituitary: clinicopathological features distinguishing craniopharyngioma, Rathke's cleft cyst, and arachnoid cyst. **J Clin Endocrinol Metab 84:**3972–3982, 1999
98. Shuangshoti S, Netsky MG, Nashold BS Jr: Epithelial cysts related to sella turcica. Proposed origin from neuroepithelium. **Arch Pathol 90:**444–450, 1970
99. Tatagiba M, Iaconetta G, Samii M: Epidermoid cyst of the cavernous sinus: clinical features, pathogenesis and treatment. **Br J Neurosurg 14:**571–575, 2000
100. Teramoto A, Hirakawa K, Sanno N, Osamura Y: Incidental pituitary lesions in 1,000 unselected autopsy specimens. **Radiology 193:**161–164, 1994
101. Thapar K, Kovacs K: Cystic lesions of the sellar region, in Bigner D, McLendon R, Bruner J (eds): **Russell and Rubinsteins's Pathology of Tumors of the Central Nervous System, ed 6.** New York: Oxford University Press, 1998, Vol 2, pp 650–652
102. Tominaga JY, Higano S, Takahashi S: Characteristics of Rathke's cleft cyst in MR imaging. **Magn Reson Med Sci 2:**1–8, 2003
103. Tsuruda JS, Chew WM, Moseley ME, Norman D: Diffusion-weighted MR imaging of the brain: value of differentiating between extraaxial cysts and epidermoid tumors. **AJR Am J Roentgenol 155:**1059–1068, 1990
104. Tuna H, Torun F, Torun AN, Erdogan A: Intrasellar epidermoid cyst presenting as pituitary apoplexy. **J Clin Neurosci 15:**1154–1156, 2008
105. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
106. VanGilder JC, Inukai J: Growth characteristics of experimental intracerebrally transplanted oral epithelium. **J Neurosurg 38:**608–615, 1973
107. Verkijk A, Bots GT: An intrasellar cyst with both Rathke's cleft and epidermoid characteristics. **Acta Neurochir (Wien) 51:**203–207, 1980
108. Voelker JL, Campbell RL, Muller J: Clinical, radiographic, and pathological features of symptomatic Rathke's cleft cysts. **J Neurosurg 74:**535–544, 1991
109. 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
110. Wenger M, Simko M, Markwalder R, Taub E: An entirely suprasellar Rathke's cleft cyst: case report and review of the literature. **J Clin Neurosci 8:**564–567, 2001
111. Xin W, Rubin MA, McKeever PE: Differential expression of cytokeratins 8 and 20 distinguishes craniopharyngioma from Rathke cleft cyst. **Arch Pathol Lab Med 126:**1174–1178, 2002
112. Yaşargil MG, Abernathey CD, Sarioglu AC: Microneurosurgical treatment of intracranial dermoid and epidermoid tumors. **Neurosurgery 24:**561–567, 1989
113. Yoshida J, Kobayashi T, Kageyama N, Kanzaki M: Symptomatic Rathke's cleft cyst. Morphological study with light and electron microscopy and tissue culture. **J Neurosurg 47:**451–458, 1977
114. Zada G, Ditty B, McNatt SA, McComb JG, Krieger MD: Surgical treatment of Rathke cleft cysts in children. **Neurosurgery 64:**1132–1038, 2009
115. Zada G, Kelly DF, Cohan P, Wang C, Swerdloff R: Endonasal transsphenoidal approach for pituitary adenomas and other sellar lesions: an assessment of efficacy, safety, and patient impressions. **J Neurosurg 98:**350–358, 2003
116. Zada G, Liu CY, Fishback D, Singer PA, Weiss MH: Recognition and management of delayed hyponatremia following transsphenoidal pituitary surgery. **J Neurosurg 106:**66–71, 2007

Manuscript submitted December 15, 2009.
Accepted February 23, 2010.
Address correspondence to: Gabriel Zada, M.D., Department of Neurosurgery, Brigham and Women's Hospital, 15 Francis Street, PBB3, Boston, Massachusetts 02115. email:gzada@usc.edu.

Neurosurg Focus 28 (4):E5, 2010

Craniopharyngioma: a comparison of tumor control with various treatment strategies

Isaac Yang, M.D.,[1] Michael E. Sughrue, M.D.,[1] Martin J. Rutkowski, B.A.,[1] Rajwant Kaur, B.S.,[1] Michael E. Ivan, M.D.,[1] Derick Aranda, M.D.,[1] Igor J. Barani, M.D.,[2] and Andrew T. Parsa, M.D., Ph.D.[1]

Departments of [1]Neurological Surgery, and [2]Radiation Oncology, University of California, San Francisco, California

Object. Craniopharyngiomas have a propensity to recur after resection, potentially causing death through their aggressive local behavior in their critical site of origin. Recent data suggest that subtotal resection (STR) followed by adjuvant radiotherapy (XRT) may be an appealing substitute for gross-total resection (GTR), providing similar rates of tumor control without the morbidity associated with aggressive resection. Here, the authors summarize the published literature regarding rates of tumor control with various treatment modalities for craniopharyngiomas.

Methods. The authors performed a comprehensive search of the English language literature to identify studies publishing outcome data on patients undergoing surgery for craniopharyngioma. Rates of progression-free survival (PFS) and overall survival (OS) were determined through Kaplan-Meier analysis.

Results. There were 442 patients who underwent tumor resection. Among these patients, GTR was achieved in 256 cases (58%), STR in 101 cases (23%), and STR+XRT in 85 cases (19%). The 2- and 5-year PFS rates for the GTR group versus the STR+XRT group were 88 versus 91%, and 67 versus 69%, respectively. The 5- and 10-year OS rates for the GTR group versus the STR+XRT group were 98 versus 99%, and 98 versus 95%, respectively. There was no significant difference in PFS (log-rank test) or OS with GTR (log-rank test).

Conclusions. Given the relative rarity of craniopharyngioma, this study provides estimates of outcome for a variety of treatment combinations, as not all treatments are an option for all patients with these tumors. *(DOI: 10.3171/2010.1.FOCUS09307)*

Key Words • **craniopharyngioma** • **surgery** • **gross-total resection** • **radiotherapy** • **tumor control**

Craniopharyngiomas are the most common pituitary masses in children. They represent 6–13% of all childhood brain lesions and are classified as intracranial tumors of benign or unspecified behavior by pediatric cancer registries.[32,98] The Childhood Cancer Registry of Piedmont, Italy, has postulated an estimated incidence of 1.4 cases per million children per year with similar estimates provided by other cancer registries in Western countries.[32] Epidemiologically, craniopharyngiomas have a bimodal age distribution pattern with a peak between 5 and 14 years and in adults older than 65 years, although the tumor has been reported in all age groups.[125,274] Over the past few years Haupt et al.[98] have documented dramatic improvements in survival, but craniopharyngiomas continue to pose a challenge for management teams, who must struggle to find that delicate balance between tumor control and the posttreatment quality of life in young children.

Craniopharyngiomas have a propensity to recur after resection, and if left untreated, these recurrences can cause death through their aggressive local behavior in their critical site of origin. For many years, GTR was regarded as the treatment of choice; however, more recent data have suggested that tissue-sparing STR followed by fXRT might be an appealing substitute for GTR, providing similar rates of tumor control without the endocrine and behavioral morbidity associated with aggressive resection. Regardless of the ideal, not all therapies are always available to address every one of these frequently challenging tumors, given the relative intolerance of very young children to radiotherapy and the frequent infeasibility of GTR in cases of extensive tumor invasion. Furthermore, radiosurgery is not an option in many cases because of the proximity of some tumors to the optic apparatus or the large size of some tumors at presentation. In this review, we compared the efficacy of different

Abbreviations used in this paper: fXRT = focal fractionated adjuvant radiotherapy; GTR = gross-total resection; OS = overall survival; PFS = progression-free survival; SRS = stereotactic radiosurgery; STR = subtotal resection; XRT = adjuvant radiotherapy.

treatment paradigms in providing baseline outcomes in patients with craniopharyngiomas.

Methods

Article Selection

Articles were identified via a PubMed search using the key phrases "craniopharyngioma" alone and in combination with "tumor control," "recurrence," "survival," and "morbidity." Inclusion criteria were as follows: 1) all patients had to have available follow-up data, and 2) articles had to have enough information for each patient to be disaggregated. Exclusion criteria involved the following: 1) articles that combined the outcomes of patients harboring craniopharyngiomas with those of patients harboring other childhood tumors were excluded, unless there was a clear distinction between the 2 separate groups of patients; and 2) Rathke pouch tumors were excluded from this study. After reviewing these articles, we thoroughly evaluated all referenced sources.

All references that contained disaggregated data specifically addressing tumor control or reporting progression with adequate follow-up in patients who had undergone resection with or without fXRT or SRS, as adjuvant therapy or monotherapy, were included in our analysis. Any paper that did not provide some follow-up imaging data on these patients was excluded, as the absence of such data would not facilitate a Kaplan-Meier analysis.

Data Extraction

Our searches yielded 274 studies[1–31,33–56,59–97,99–124,126–218,220–251,253–273,275–277,279–282] reporting data for 8058 nonduplicated patients with craniophayngiomas, the majority of whom were presented in aggregated data sets. Disaggregated data useable for survival and progression analysis was presented for 800 patients. The median largest tumor dimension and median tumor volume were not reportable or analyzable in our analysis, as studies did not consistently report either value. Data were stratified into 5 groups based on the treatment paradigm: STR alone, GTR alone, STR followed by XRT (STR+XRT), biopsy followed by fXRT (fXRT), or biopsy followed by radiosurgery alone (SRS). We hypothesized that tumors treated with SRS or radiotherapy without resection were probably anatomically and volumetrically different from those subjected to some form of surgery. This proposition is supported by the significantly smaller tumor sizes in patients undergoing fXRT. To control for this confounder, we did not directly compare the radiation-only groups (that is, the SRS and fXRT groups) with the surgically treated patients.

Tumor control data were included if adequate radiographic follow-up data were presented in the study, whether demonstrating evidence of recurrence or continued tumor control. The time to progression or recurrence (for simplicity, this idea from this point forward is referred to as "progression" regardless of the extent of resection) was defined as the time from diagnosis to radiographic evidence of progression. Progression-free survival and OS were calculated at the 1- and 5-year time points. Studies that did not present patient data in a way that these variables could be reliably determined were excluded from further analysis.

TABLE 1: Clinical characteristics of the study group*

Characteristic	GTR	STR	STR+XRT
no. of patients	256	101	85
sex (M/F)	127:129	45:56	34:51
mean age in yrs†	23 ± 1.3	22 ± 1.9	26 ± 2.0
mean tumor size†	3.0 ± 0.2	3.7 ± 0.8	3.5 ± 0.2

* The p value was not significant for any of the variables.
† Values are expressed as the means ± SEs.

Statistical Analysis

The Pearson chi-square test was used to analyze for differences in categorical factors. The Fisher exact test was applied if there were fewer than 5 values per cell. Analysis of variance was used to evaluate for statistical differences in preoperative continuous factors, including age and tumor size. Post hoc between-group analyses were performed using the Tukey test when the ANOVA demonstrated a $p < 0.05$. Kaplan-Meier estimates were used to generate time-to-progression curves. Differences in time to progression were analyzed using the log-rank test. Analyses were performed with SPSS, version 16.0 (SPPS, Inc.).

Results

Clinical Characteristics of Included Patients

As stated above, data for 800 patients were available for survival analysis. We limited our analysis to patients reported in studies since 1990, which limited us to 442 patients undergoing surgery (Table 1). Among these patients, GTR was achieved in 256 cases (58%), STR alone in 101 cases (23%), and STR+XRT in 85 cases (19%). Surgical patients in different cohorts did not differ in their mean age at the time of surgery, sex distribution, or preoperative tumor size.

The mean overall follow-up for all patients in these studies was 54 ± 1.8 months.

Gross-Total Resection Provides Improved Tumor Control Compared with STR

To determine the impact of the extent of resection on tumor control rates, we compared rates of progression and OS in patients who underwent STR with rates in patients who underwent GTR. There were no significant differences between the 2 groups in terms of sex distribution (male sex 49 vs 46%, chi-square test), age (23 ± 1.3 vs 22 ± 1.9 years, ANOVA), or tumor size (3.0 ± 0.2 vs 3.7 ± 0.8 cm, ANOVA Tukey test). The 2- and 5-year PFS rates for the GTR group versus the STR group were 88 versus 67%, and 67 versus 34%, respectively. The 5- and 10-year

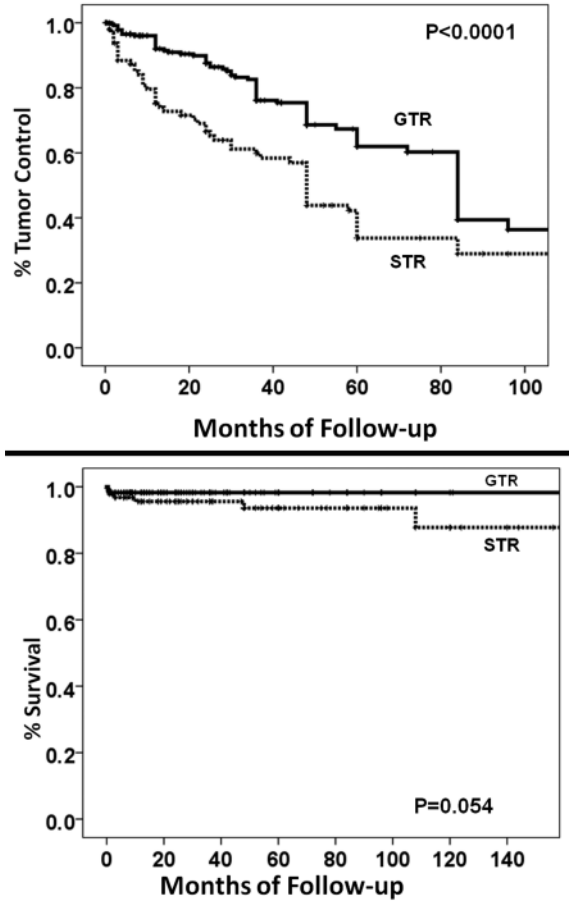

Fig. 1. Comparison of PFS **(upper)** and overall survival **(lower)** between patients treated with GTR versus those treated with STR.

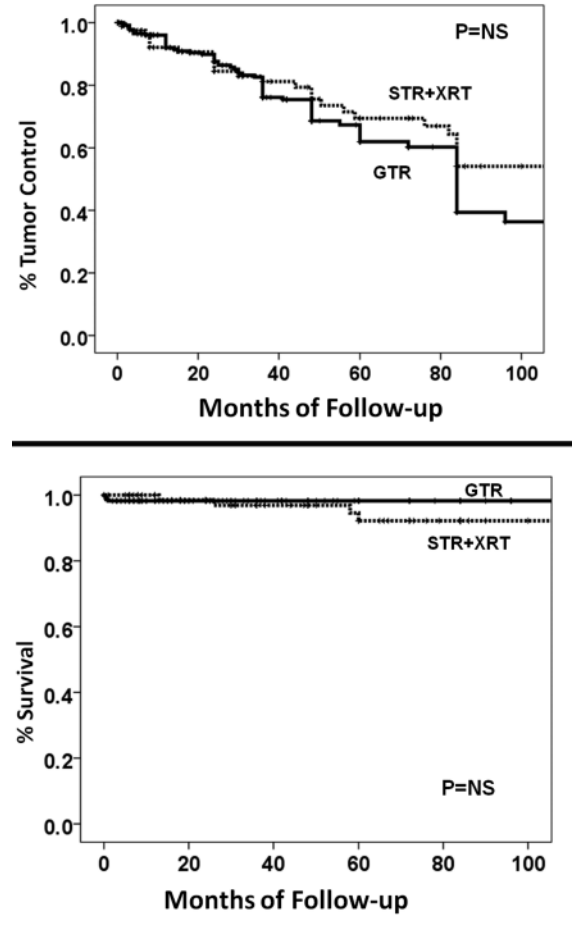

Fig. 2. Comparison of PFS **(upper)** and overall survival **(lower)** between patients treated with GTR compared with STR+XRT. NS = not significant.

OS rates for the GTR group versus the STR group were 98 versus 96%, and 98 versus 93%, respectively. These values represented a statistically significant improvement in PFS ($p < 0.0001$, log-rank test), and a trend toward improved OS ($p = 0.054$, log-rank test; Fig. 1).

Subtotal Resection With Radiotherapy Can Replace GTR for Tumor Control

To determine the impact of the addition of radiotherapy to STR on tumor control rates, we compared rates of progression and OS in patients who underwent STR+XRT with the rates in patients who underwent GTR. There were no significant differences between the 2 groups in terms of sex distribution (male sex 49 vs 40%, chi-square test), age (23 ± 1.3 vs 26 ± 2.0 years, ANOVA), or tumor size (3.0 ± 0.2 vs 3.5 ± 0.2 cm, ANOVA Tukey test). The 2- and 5-year PFS rates for the GTR group versus the STR+XRT group were 88 versus 91%, and 67 versus 69%, respectively. The 5- and 10-year OS rates for the GTR group versus the STR+XRT group were 98 versus 99%, and 98 versus 95%, respectively. There was no significant difference in PFS (log-rank test) or OS with GTR (log-rank test; Fig. 2).

Discussion

Craniopharyngioma is a locally aggressive sellar/suprasellar mass with a high propensity for recurrence. This lesion is associated with decreased survival, demonstrating a 3–6 times higher mortality rate than the general population.[31,198] The negative effect of tumor recurrence on the mortality rate is well documented[31,124,252] with 10-year survival rates ranging between 29 and 70% depending on what modality of treatment is implemented.[125] While there are few definitive studies regarding management strategies for these tumors, the general philosophy toward the treatment of these lesions has shifted toward less aggressive resection in appropriate circumstances, with tumor control after STR being achieved with radiotherapy or radiosurgery, if possible.

In this study, we systematically reviewed the published literature and summarized the rates of tumor control following various surgical and radiation-based treatments. We found that while GTR provides improved tumor control compared with STR alone, the addition of XRT to STR can provide tumor control rates essentially similar to those for GTR.

These data seem to support the idea that STR+XRT is a reasonable approach to achieve tumor control while

limiting hypothalamic and hypophyseal morbidity associated with aggressive resection. Many investigators have associated very aggressive attempts at total tumor removal with markedly increased rates of anterior hypopituitarism, diabetes insipidus, growth disturbances, and behavioral and feeding abnormalities. For example, diabetes insipidus has been reported in 59–93% of cases following surgery.[70,219,260,278] Panhypopituitarism occurs in 75–100% of patients who undergo resection.[58,122] Hypothalamic obesity occurs in ~ 40% of patients postoperatively. It is important to consider these complications especially in young patients, who compose a large fraction of those with craniopharyngioma and for whom significant endocrinological problems can yield dramatic adverse effects. While radiotherapy is often not a reasonable option in very young children, when possible, it is generally believed to cause less local hypothalamic/hypohyseal morbidity—and based on our analysis it seems to provide similar rates of tumor control.

Study Limitations

While these findings represent a helpful summary of the published literature on this topic, an analysis of the data is only as good as the composite studies and may reflect source study biases. It is impossible for us to control for the quality of data reported in the literature, and an overly stringent definition of tumor recurrence in some studies may overestimate rates of tumor control in other studies. Furthermore, subjectively defined variables, such as histological grade, extent of resection, and adequacy of radiation therapy, probably vary among studies, and we cannot independently confirm the validity of these definitions in other investigators' studies. Moreover, our use of the Kaplan-Meier analysis largely precludes the use of formal meta-analysis, including the calculation of a Q-statistic, which allows one to determine how heterogeneous the data are. The inability to study this by using meta-analysis methods prevents us from addressing this limitation in a statistically meaningful way. Finally, given the diverse range of data presentation, the number of variables capable of being studied and controlled for is limited. Variables that might be of interest that are inconsistently presented across studies cannot be reviewed.

Additionally, we cannot analyze the effect of differences in treatment philosophies between institutions. Given that the extent of resection for craniopharyngiomas is frequently presented as a binary variable (that is, GTR or STR) in the literature, we cannot accurately deduce whether all GTRs were, in fact, GTRs. Furthermore, STRs performed by surgeons with the goal of achieving GTRs were probably more extensive resections than those performed by surgeons who sought to perform STRs only. Given that the goals of surgery for a given clinician are inconsistently published, we cannot control for this factor.

Conclusions

In summary, we reported the results of a review of the published literature on control rates of craniopharyngioma after treatment with various modalities. Thus, while we cannot absolutely guarantee that these data definitively predict the expected outcomes of patients undergoing these treatment paradigms, we think that our review provides a useful summary of the existing literature and that analysis of the data can yield useful insights on which to base future inquiries.

Disclosure

Dr. Parsa is supported in part by the Reza and Georgiana Khatib endowed chair in skull base tumor surgery. Dr. Sughrue is supported by the American Association of Neurological Surgeons' Neurosurgery Research and Education Foundation. Mr. Rutkowski is supported by the Doris Duke foundation.

Conception and design: AT Parsa, ME Sughrue, D Aranda. Acquisition of data: ME Sughrue, D Aranda. Analysis and interpretation of data: I Yang, ME Sughrue, R Kaur, D Aranda. Drafting the article: AT Parsa, I Yang, ME Sughrue, ME Ivan. Critically revising the article: AT Parsa, I Yang, ME Sughrue, MJ Rutkowski, R Kaur, ME Ivan, IJ Barani. Reviewed final version of the manuscript and approved it for submission: AT Parsa, I Yang, ME Sughrue, MJ Rutkowski, R Kaur, ME Ivan, D Aranda, IJ Barani. Statistical analysis: ME Sughrue, R Kaur, D Aranda. Administrative/technical/material support: ME Sughrue, D Aranda.

Acknowledgment

The authors thank statistician Mei Polley for her helpful input on methodological issues associated with systematic reviews of the literature.

References

1. Abe T, Lüdecke DK: Transnasal surgery for infradiaphragmatic craniopharyngiomas in pediatric patients. **Neurosurgery 44:**957–964, 1999
2. Adamson TE, Wiestler OD, Kleihues P, Yaşargil MG: Correlation of clinical and pathological features in surgically treated craniopharyngiomas. **J Neurosurg 73:**12–17, 1990
3. Adeloye A, Nottidge VA, Udi J: Craniopharyngioma in Nigerian children. **Childs Nerv Syst 4:**128–134, 1988
4. Agozzino L, Ferraraccio F, Accardo M, Esposito S, Agozzino M, Cuccurullo L: Morphological and ultrastructural findings of prognostic impact in craniopharyngiomas. **Ultrastruct Pathol 30:**143–150, 2006
5. Al-Mefty O, Ayoubi S, Kadri PA: The petrosal approach for the total removal of giant retrochiasmatic craniopharyngiomas in children. **J Neurosurg 106 (2 Suppl):**87–92, 2007
6. al-Mefty O, Kersh JE, Routh A, Smith RR: The long-term side effects of radiation therapy for benign brain tumors in adults. **J Neurosurg 73:**502–512, 1990
7. Albright AL, Hadjipanayis CG, Lunsford LD, Kondziolka D, Pollack IF, Adelson PD: Individualized treatment of pediatric craniopharyngiomas. **Childs Nerv Syst 21:**649–654, 2005
8. Amendola BE, Gebarski SS, Bermudez AG: Analysis of treatment results in craniopharyngioma. **J Clin Oncol 3:**252–258, 1985
9. Amendola BE, Wolf A, Coy SR, Amendola MA: Role of radiosurgery in craniopharyngiomas: a preliminary report. **Med Pediatr Oncol 41:**123–127, 2003
10. Ammirati M, Samii M, Sephernia A: Surgery of large retrochiasmatic craniopharyngiomas in children. **Childs Nerv Syst 6:**13–17, 1990
11. Anderson CA, Wilkening GN, Filley CM, Reardon MS, Kleinschmidt-DeMasters BK: Neurobehavioral outcome in pediatric craniopharyngioma. **Pediatr Neurosurg 26:**255–260, 1997
12. Apuzzo ML, Chikovani OK, Gott PS, Teng EL, Zee CS, Gian-

notta SL, et al: Transcallosal, interfornicial approaches for lesions affecting the third ventricle: surgical considerations and consequences. **Neurosurgery 10:**547–554, 1982
13. Aydin Y, Can SM, Gŭlkilik A, Tŭrkmenoglu O, Alatli C, Ziyal I: Rapid enlargement and recurrence of a preexisting intrasellar craniopharyngioma during the course of two pregnancies. Case report. **J Neurosurg 91:**322–324, 1999
14. Barajas MA, Ramírez-Guzmán G, Rodríguez-Vázquez C, Toledo-Buenrostro V, Velásquez-Santana H, del Robles RV, et al: Multimodal management of craniopharyngiomas: neuroendoscopy, microsurgery, and radiosurgery. **J Neurosurg 97 (5 Suppl):**607–609, 2002
15. Barlas O, Bayindir C, Can M: Interstitial irradiation for craniopharyngioma. **Acta Neurochir (Wien) 142:**389–395, 2000
16. Bartlett JR: Craniopharyngiomas—a summary of 85 cases. **J Neurol Neurosurg Psychiatry 34:**37–41, 1971
17. Barua KK, Ehara K, Kohmura E, Tamaki N: Treatment of recurrent craniopharyngiomas. **Kobe J Med Sci 49:**123–132, 2003
18. Baskin DS, Wilson CB: Surgical management of craniopharyngiomas. A review of 74 cases. **J Neurosurg 65:**22–27, 1986
19. Behari S, Banerji D, Mishra A, Sharma S, Sharma S, Chhabra DK, et al: Intrinsic third ventricular craniopharyngiomas: report on six cases and a review of the literature. **Surg Neurol 60:**245–253, 2003
20. Belen D, Er U, Yigitkanli K, Bolay H: Delayed neurotoxic complication of intracavitary bleomycin therapy for craniopharyngioma in a child who had previously undergone radiosurgery. Case report. **J Neurosurg 106 (5 Suppl):**391–393, 2007
21. Berlis A, Vesper J, Ostertag C: Stent placement for intracranial cysts by combined stereotactic/endoscopic surgery. **Neurosurgery 59 (4 Suppl 2):**ONS474–ONS480, 2006
22. Bhagwati SN, Deopujari CE, Parulekar GD: Lamina terminalis approach for retrochiasmal craniopharyngiomas. **Childs Nerv Syst 6:**425–429, 1990
23. Bianco Ade M, Madeira LV, Rosemberg S, Shibata MK: Cortical seeding of a craniopharyngioma after craniotomy: case report. **Surg Neurol 66:**437–440, 2006
24. Bin-Abbas B, Mawlawi H, Sakati N, Khafaja Y, Chaudhary MA, Al-Ashwal A: Endocrine sequelae of childhood craniopharyngioma. **J Pediatr Endocrinol Metab 14:**869–874, 2001
25. Blackburn TP, Doughty D, Plowman PN: Stereotactic intracavitary therapy of recurrent cystic craniopharyngioma by instillation of 90yttrium. **Br J Neurosurg 13:**359–365, 1999
26. Boch AL, van Effenterre R, Kujas M: Craniopharyngiomas in two consanguineous siblings: case report. **Neurosurgery 41:**1185–1187, 1997
27. Bohn D, Davids MR, Friedman O, Halperin ML: Acute and fatal hyponatraemia after resection of a craniopharyngioma: a preventable tragedy. **QJM 98:**691–703, 2005
28. Bremer AM, Nguyen TQ, Balsys R: Therapeutic benefits of combination chemotherapy with vincristine, BCNU, and procarbazine on recurrent cystic craniopharyngioma. A case report. **J Neurooncol 2:**47–51, 1984
29. Broggi G, Franzini A, Cajola L, Pluchino F: Cell kinetic investigations in craniopharyngioma: preliminary results and considerations. **Pediatr Neurosurg 21 (Suppl 1):**21–23, 1994
30. Buhl R, Nabavi A, Fritsch M, Mehdorn HM: Nasopharyngeal extension of a craniopharyngioma in a 4 year old girl. **Acta Neurochir (Wien) 143:**1283–1285, 2001
31. Bülow B, Attewell R, Hagmar L, Malmström P, Nordström CH, Erfurth EM: Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. **J Clin Endocrinol Metab 83:**3897–3904, 1998
32. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. **Neurosurg Focus 3(6):**e1, 1997
33. Burkey BB, Speyer MT, Maciunas RJ, Fitzpatrick JM, Galloway RL Jr, Allen GS: Sublabial, transseptal, transsphenoidal approach to the pituitary region guided by the ACUSTAR I system. **Otolaryngol Head Neck Surg 118:**191–194, 1998
34. Cabezudo JM, Vaquero J, Areitio E, Martinez R, de Sola RG, Bravo G: Craniopharyngiomas: a critical approach to treatment. **J Neurosurg 55:**371–375, 1981
35. Cáceres A: Intracavitary therapeutic options in the management of cystic craniopharyngioma. **Childs Nerv Syst 21:**705–718, 2005
36. Caldarelli M, di Rocco C, Papacci F, Colosimo C Jr: Management of recurrent craniopharyngioma. **Acta Neurochir (Wien) 140:**447–454, 1998
37. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C: Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. **Childs Nerv Syst 21:**747–757, 2005
38. Calvo FA, Hornedo J, Arellano A, Sachetti A, de la Torre A, Aragon G, et al: Radiation therapy in craniopharyngiomas. **Int J Radiat Oncol Biol Phys 9:**493–496, 1983
39. Cavalheiro S, Dastoli PA, Silva NS, Toledo S, Lederman H, da Silva MC: Use of interferon alpha in intratumoral chemotherapy for cystic craniopharyngioma. **Childs Nerv Syst 21:**719–724, 2005
40. Cavazzuti V, Fischer EG, Welch K, Belli JA, Winston KR: Neurological and psychophysiological sequelae following different treatments of craniopharyngioma in children. **J Neurosurg 59:**409–417, 1983
41. Chakrabarti I, Amar AP, Couldwell W, Weiss MH: Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. **J Neurosurg 102:**650–657, 2005
42. Chen C, Okera S, Davies PE, Selva D, Crompton JL: Craniopharyngioma: a review of long-term visual outcome. **Clin Experiment Ophthalmol 31:**220–228, 2003
43. Chiou SM, Lunsford LD, Niranjan A, Kondziolka D, Flickinger JC: Stereotactic radiosurgery of residual or recurrent craniopharyngioma, after surgery, with or without radiation therapy. **Neuro Oncol 3:**159–166, 2001
44. Chung WY, Pan DH, Shiau CY, Guo WY, Wang LW: Gamma knife radiosurgery for craniopharyngiomas. **J Neurosurg 93 (Suppl 3):**47–56, 2000
45. Chung WY, Pan HC, Guo WY, Shiau CY, Wang LW, Wu HM, et al: Protection of visual pathway in gamma knife radiosurgery for craniopharyngiomas. **Stereotact Funct Neurosurg 70 (Suppl 1):**139–151, 1998
46. Cinalli G, Spennato P, Cianciulli E, Fiorillo A, Di Maio S, Maggi G: The role of transventricular neuroendoscopy in the management of craniopharyngiomas: three patient reports and review of the literature. **J Pediatr Endocrinol Metab 19 (Suppl 1):**341–354, 2006
47. Clayton PE, Price DA, Shalet SM, Gattemaneni HR: Craniopharyngioma recurrence and growth hormone therapy. **Lancet 1:**642, 1988
48. Colangelo M, Ambrosio A, Ambrosio C: Neurological and behavioral sequelae following different approaches to craniopharyngioma. Long-term follow-up review and therapeutic guidelines. **Childs Nerv Syst 6:**379–382, 1990
49. Combs SE, Thilmann C, Huber PE, Hoess A, Debus J, Schulz-Ertner D: Achievement of long-term local control in patients with craniopharyngiomas using high precision stereotactic radiotherapy. **Cancer 109:**2308–2314, 2007
50. Connolly ES Jr, Winfree CJ, Carmel PW: Giant posterior fossa cystic craniopharyngiomas presenting with hearing loss. Report of three cases and review of the literature. **Surg Neurol 47:**291–299, 1997
51. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI,

Fukushima T: Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. **Neurosurgery 55:**539–550, 2004
52. Crotty TB, Scheithauer BW, Young WF Jr, Davis DH, Shaw EG, Miller GM, et al: Papillary craniopharyngioma: a clinicopathological study of 48 cases. **J Neurosurg 83:**206–214, 1995
53. Danoff BF, Cowchock FS, Kramer S: Childhood craniopharyngioma: survival, local control, endocrine and neurologic function following radiotherapy. **Int J Radiat Oncol Biol Phys 9:**171–175, 1983
54. Dashora U, Mathias D, James A, Zammit-Maempel I, Perros P: Management of recurrent pituitary cysts with pituitary-nasal drain. **Pituitary 5:**225–233, 2002
55. Davies MJ, King TT, Metcalfe KA, Monson JP: Intraventricular craniopharyngioma: a long-term follow-up of six cases. **Br J Neurosurg 11:**533–541, 1997
56. Day JD, Giannotta SL, Fukushima T: Extradural temporopolar approach to lesions of the upper basilar artery and infrachiasmatic region. **J Neurosurg 81:**230–235, 1994
57. DeVile CJ, Grant DB, Hayward RD, Stanhope R: Growth and endocrine sequelae of craniopharyngioma. **Arch Dis Child 75:**108–114, 1996
58. De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, et al: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? **J Neurosurg 85:**73–81, 1996
59. Delitala A, Brunori A, Chiappetta F: Purely neuroendoscopic transventricular management of cystic craniopharyngiomas. **Childs Nerv Syst 20:**858–862, 2004
60. Demaerel P, Moseley IF, Scaravilli F: Recurrent craniopharyngioma invading the orbit, cavernous sinus and skull base: a case report. **Neuroradiology 35:**261–263, 1993
61. Dhellemmes P, Vinchon M: Radical resection for craniopharyngiomas in children: surgical technique and clinical results. **J Pediatr Endocrinol Metab 19 (Suppl 1):**329–335, 2006
62. Di Rocco C, Caldarelli M, Tamburrini G, Massimi L: Surgical management of craniopharyngiomas—experience with a pediatric series. **J Pediatr Endocrinol Metab 19 (Suppl 1):**355–366, 2006
63. Djordjević M, Djordjević Z, Janićijević M, Nestorović B, Stefanović B, Ivkov M: Surgical treatment of craniopharyngiomas in children. **Acta Neurochir Suppl (Wien) 28:**344–347, 1979
64. Duff JM, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck C, Scheithauer BW: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000
65. Economos D: Systemic shunting of residual intraparenchymatous cystic craniopharyngioma. **Acta Neurochir Suppl (Wien) 28:**363–366, 1979
66. el Gammal T, Brooks BS, Hoffman WH: MR imaging of the ectopic bright signal of posterior pituitary regeneration. **AJNR Am J Neuroradiol 10:**323–328, 1989
67. Eldevik OP, Blaivas M, Gabrielsen TO, Hald JK, Chandler WF: Craniopharyngioma: radiologic and histologic findings and recurrence. **AJNR Am J Neuroradiol 17:**1427–1439, 1996
68. Elwatidy SM, Jamjoom ZA, Jamjoom AB, Yakoub AO: Craniopharyngioma. Analysis of factors that affect the outcome. **Saudi Med J 23:**34–38, 2002
69. Erşahin Y, Yurtseven T, Ozgiray E, Mutluer S: Craniopharyngiomas in children: Turkey experience. **Childs Nerv Syst 21:**766–772, 2005
70. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
71. 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
72. Fisher PG, Jenab J, Gopldthwaite PT, Tihan T, Wharam MD, Foer DR, et al: Outcomes and failure patterns in childhood craniopharyngiomas. **Childs Nerv Syst 14:**558–563, 1998
73. Fitzek MM, Linggood RM, Adams J, Munzenrider JE: Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. **Int J Radiat Oncol Biol Phys 64:**1348–1354, 2006
74. Flickinger JC, Deutsch M, Lunsford LD: Repeat megavoltage irradiation of pituitary and suprasellar tumors. **Int J Radiat Oncol Biol Phys 17:**171–175, 1989
75. Flickinger JC, Lunsford LD, Singer J, Cano ER, Deutsch M: Megavoltage external beam irradiation of craniopharyngiomas: analysis of tumor control and morbidity. **Int J Radiat Oncol Biol Phys 19:**117–122, 1990
76. Fraioli MF, Santoni R, Fraioli C, Contratti F: "Conservative" surgical approach and early postoperative radiotherapy in a patient with a huge cystic craniopharyngioma. **Childs Nerv Syst 22:**151–163, 2006
77. Frank G, Pasquini E, Doglietto F, Mazzatenta D, Sciarretta V, Farneti G, et al: The endoscopic extended transsphenoidal approach for craniopharyngiomas. **Neurosurgery 59 (1Suppl 1):**ONS75–ONS83, 2006
78. Freeman CR, Souhami L, Caron JL, Villemure JG, Olivier A, Montes J, et al: Stereotactic external beam irradiation in previously untreated brain tumors in children and adolescents. **Med Pediatr Oncol 22:**173–180, 1994
79. Frisén L, Sjöstrand J, Norrsell K, Lindgren S: Cyclic compression of the intracranial optic nerve: patterns of visual failure and recovery. **J Neurol Neurosurg Psychiatry 39:**1109–1113, 1976
80. Garcia-Uria J: Surgical experience with craniopharyngioma in adults. **Surg Neurol 9:**11–14, 1978
81. Ghatak NR, White BE: Delayed radiation necrosis of the hypothalamus. Report of a case simulating recurrent craniopharyngioma. **Arch Neurol 21:**425–430, 1969
82. Gil Z, Constantini S, Spektor S, Abergel A, Khafif A, Beni-Adani L, et al: Skull base approaches in the pediatric population. **Head Neck 27:**682–689, 2005
83. Giller CA, Berger BD, Pistenmaa DA, Sklar F, Weprin B, Shapiro K, et al: Robotically guided radiosurgery for children. **Pediatr Blood Cancer 45:**304–310, 2005
84. Gomez-Daspet J, Elko L, Grebenev D, Vesely DL: Survival with serum sodium level of 180 mEq/L: permanent disorientation to place and time. **Am J Med Sci 324:**321–325, 2002
85. Gonc EN, Yordam N, Ozon A, Alikasifoglu A, Kandemir N: Endocrinological outcome of different treatment options in children with craniopharyngioma: a retrospective analysis of 66 cases. **Pediatr Neurosurg 40:**112–119, 2004
86. Gsponer J, De Tribolet N, Déruaz JP, Janzer R, Uské A, Mirimanoff RO, et al: Diagnosis, treatment, and outcome of pituitary tumors and other abnormal intrasellar masses. Retrospective analysis of 353 patients. **Medicine (Baltimore) 78:**236–269, 1999
87. Guidetti B, Fraioli B: Craniopharyngiomas. Results of surgical treatment. **Acta Neurochir Suppl (Wien) 28:**349–351, 1979
88. 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
89. Gupta K, Kuhn MJ, Shevlin DW, Wacaser LE: Metastatic craniopharyngioma. **AJNR Am J Neuroradiol 20:**1059–1060, 1999
90. Gürkaynak M, Ozyar E, Zorlu F, Akyol FH, Atahan IL: Results of radiotherapy in craniopharyngiomas analysed by the linear quadratic model. **Acta Oncol 33:**941–943, 1994
91. Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C,

Pierre-Kahn A, et al: The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. **Int J Radiat Oncol Biol Phys 44:**255–263, 1999
92. Hader WJ, Steinbok P, Hukin J, Fryer C: Intratumoral therapy with bleomycin for cystic craniopharyngiomas in children. **Pediatr Neurosurg 33:**211–218, 2000
93. Hafez MA, ElMekkawy S, AbdelBadie H, Mohy M, Omar M: Pediatric craniopharyngioma—rationale for multimodal management: the Egyptian experience. **J Pediatr Endocrinol Metab 19 (Suppl 1):**371–380, 2006
94. Hamamoto Y, Niino K, Adachi M, Hosoya T: MR and CT findings of craniopharyngioma during and after radiation therapy. **Neuroradiology 44:**118–122, 2002
95. Hamlat A, Morandi X, Riffaud L, Carsin-Nicol B, Haegelen C, Helal H, et al: Transtemporal-transchoroidal approach and its transamygdala extension to the posterior chiasmatic cistern and diencephalo-mesencephalic lesions. **Acta Neurochir (Wien) 150:**317–328, 2008
96. Hargrave DR: Does chemotherapy have a role in the management of craniopharyngioma? **J Pediatr Endocrinol Metab 19 (Suppl 1):**407–412, 2006
97. Hasegawa T, Kondziolka D, Hadjipanayis CG, Lunsford LD: Management of cystic craniopharyngiomas with phosphorus-32 intracavitary irradiation. **Neurosurgery 54:**813–820, 2004
98. Haupt R, Magnani C, Pavanello M, Caruso S, Dama E, Garrè ML: Epidemiological aspects of craniopharyngioma. **J Pediatr Endocrinol Metab 19 (Suppl 1):**289–293, 2006
99. Hoff JT, Patterson RH Jr: Craniopharyngiomas in children and adults. **J Neurosurg 36:**299–302, 1972
100. Hoffman HJ: Craniopharyngiomas. **Can J Neurol Sci 12:**348–352, 1985
101. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI: Aggressive surgical management of craniopharyngiomas in children. **J Neurosurg 76:**47–52, 1992
102. Honegger J, Buchfelder M, Fahlbusch R: Surgical treatment of craniopharyngiomas: endocrinological results. **J Neurosurg 90:**251–257, 1999
103. Hoogenhout J, Otten BJ, Kazem I, Stoelinga GB, Walder AH: Surgery and radiation therapy in the management of craniopharyngiomas. **Int J Radiat Oncol Biol Phys 10:**2293–2297, 1984
104. Hukin J, Steinbok P, Lafay-Cousin L, Hendson G, Strother D, Mercier C, et al: Intracystic bleomycin therapy for craniopharyngioma in children: the Canadian experience. **Cancer 109:**2124–2131, 2007
105. Hukin J, Visser J, Sargent M, Goddard K, Fryer C, Steinbok P: Childhood craniopharyngioma: Vancouver experience. **Childs Nerv Syst 21:**758–765, 2005
106. Im SH, Wang KC, Kim SK, Chung YN, Kim HS, Lee CH, et al: Transsphenoidal microsurgery for pediatric craniopharyngioma: special considerations regarding indications and method. **Pediatr Neurosurg 39:**97–103, 2003
107. Inoue HK, Fujimaki H, Kohga H, Ono N, Hirato M, Ohye C: Basal interhemispheric supra- and/or infrachiasmal approaches via superomedial orbitotomy for hypothalamic lesions: preservation of hypothalamo-pituitary functions in combination treatment with radiosurgery. **Childs Nerv Syst 13:**250–256, 1997
108. Isaac MA, Hahn SS, Kim JA, Bogart JA, Chung CT: Management of craniopharyngioma. **Cancer J 7:**516–520, 2001
109. Israel ZH, Pomeranz S: Intracranial craniopharyngioma seeding following radical resection. **Pediatr Neurosurg 22:**210–213, 1995
110. Ito M, Jamshidi J, Yamanaka K: Does craniopharyngioma metastasize? Case report and review of the literature. **Neurosurgery 48:**933–936, 2001
111. Ivkov M, Ribarić I, Slavik E, Antunović V, Samardzić M, Djordjević M: Surgical treatment of craniopharyngiomas in adults. **Acta Neurochir Suppl (Wien) 28:**352–356, 1979
112. Jackson AS, St George EJ, Hayward RJ, Plowman PN: Stereotactic radiosurgery. XVII: Recurrent intrasellar craniopharyngioma. **Br J Neurosurg 17:**138–143, 2003
113. Jakacki RI, Cohen BH, Jamison C, Mathews VP, Arenson E, Longee DC, et al: Phase II evaluation of interferon-alpha-2a for progressive or recurrent craniopharyngiomas. **J Neurosurg 92:**255–260, 2000
114. Jeong IH, Lee JK, Moon KS, Joo SP, Kwak HJ, Kim TS, et al: Ectopic recurrence of craniopharyngioma: a case report and review of the literature. **J Neurooncol 79:**191–195, 2006
115. Jialal I, Reddi K, Omar MA, Van Dellen JR, Joubert SM: Pituitary tumours in African and Indian patients. **Trop Geogr Med 38:**175–179, 1986
116. Joki T, Oi S, Babapour B, Kaito N, Ohashi K, Ebara M, et al: Neuroendoscopic placement of Ommaya reservoir into a cystic craniopharyngioma. **Childs Nerv Syst 18:**629–633, 2002
117. Jooma R, Kendall BE: Intracranial tumours in the first year of life. **Neuroradiology 23:**267–274, 1982
118. Julow J, Backlund EO, Lányi F, Hajda M, Bálint K, Nyáry I, et al: Long-term results and late complications after intracavitary yttrium-90 colloid irradiation of recurrent cystic craniopharyngiomas. **Neurosurgery 61:**288–296, 2007
119. Julow J, Lányi F, Hajda M, Simkovics M, Arany I, Tóth S, et al: The radiotherapy of cystic craniopharyngioma with intracystic installation of 90Y silicate colloid. **Acta Neurochir (Wien) 74:**94–99, 1985
120. Kabil MS, Shahinian HK: Application of the supraorbital endoscopic approach to tumors of the anterior cranial base. **J Craniofac Surg 16:**1070–1075, 2005
121. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH: Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. **Med Pediatr Oncol 40:**214–218, 2003
122. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH: Clinical outcome in children with recurrent craniopharyngioma after primary surgery. **Cancer J 6:**388–393, 2000
123. Kang JK, Song JU: Results of the management of craniopharyngioma in children. An endocrinological approach to the treatment. **Childs Nerv Syst 4:**135–138, 1988
124. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, et al: Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. **Clin Endocrinol (Oxf) 62:**397–409, 2005
125. Karavitaki N, Cudlip S, Adams CB, Wass JA: Craniopharyngiomas. **Endocr Rev 27:**371–397, 2006
126. Katz EL: Late results of radical excision of craniopharyngiomas in children. **J Neurosurg 42:**86–93, 1975
127. Kawaguchi T, Fujimura M, Shirane R, Shoji T, Watanabe M, Tominaga T: Ectopic recurrence of craniopharyngioma. **J Clin Neurosci 12:**307–309, 2005
128. Keohane C, Hally M, Ryder DQ, Buckley TF: Late recurrence of craniopharyngioma in the cerebellopontine angle in a fertile woman. **J Neurol Neurosurg Psychiatry 57:**873–874, 1994
129. Khafaga Y, Jenkin D, Kanaan I, Hassounah M, Al Shabanah M, Gray A: Craniopharyngioma in children. **Int J Radiat Oncol Biol Phys 42:**601–606, 1998
130. Kim MS, Lee SI, Sim SH: Brain tumors with cysts treated with Gamma Knife radiosurgery: is microsurgery indicated? **Stereotact Funct Neurosurg 72 (Suppl 1):**38–44, 1999
131. Kim SD, Park JY, Park J, Lee JB, Kim SH, Lim DJ: Radiological findings following postsurgical intratumoral bleomycin injection for cystic craniopharyngioma. **Clin Neurol Neurosurg 109:**236–241, 2007
132. Kim SK, Wang KC, Shin SH, Choe G, Chi JG, Cho BK: Radical excision of pediatric craniopharyngioma: recurrence pattern and prognostic factors. **Childs Nerv Syst 17:**531–537, 2001
133. Kobayashi T, Kida Y, Mori Y, Hasegawa T: Long-term results of gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. **J Neurosurg 103 (6 Suppl):**482–488, 2005

134. Kobayashi T, Tanaka T, Kida Y: Stereotactic gamma radiosurgery of craniopharyngiomas. **Pediatr Neurosurg 21 (Suppl 1):**69–74, 1994
135. Kodama T, Matsukado Y, Uemura S: Intracapsular irradiation therapy of craniopharyngiomas with radioactive gold: indication and follow-up results. **Neurol Med Chir (Tokyo) 21:**49–58, 1981
136. Kondziolka D, Nathoo N, Flickinger JC, Niranjan A, Maitz AH, Lunsford LD: Long-term results after radiosurgery for benign intracranial tumors. **Neurosurgery 53:**815–822, 2003
137. König A, Lüdecke DK, Herrmann HD: Transnasal surgery in the treatment of craniopharyngiomas. **Acta Neurochir (Wien) 83:**1–7, 1986
138. Konovalov AN, Gorelyshev SK: Surgical treatment of anterior third ventricle tumours. **Acta Neurochir (Wien) 118:**33–39, 1992
139. Kramer S, Southard M, Mansfield CM: Radiotherapy in the management of craniopharyngiomas: further experiences and late results. **Am J Roentgenol Radium Ther Nucl Med 103:**44–52, 1968
140. Kranzinger M, Jones N, Rittinger O, Pilz P, Piotrowski WP, Manzl M, et al: Malignant glioma as a secondary malignant neoplasm after radiation therapy for craniopharyngioma: report of a case and review of reported cases. **Onkologie 24:**66–72, 2001
141. Kristopaitis T, Thomas C, Petruzzelli GJ, Lee JM: Malignant craniopharyngioma. **Arch Pathol Lab Med 124:**1356–1360, 2000
142. Kulkarni V, Daniel RT, Pranatartiharan R: Spontaneous intraventricular rupture of craniopharyngioma cyst. **Surg Neurol 54:**249–253, 2000
143. Kuwabara S, Seo H, Ishikawa S: Huge, dense, cystic craniopharyngioma with unusual extensions—case report. **Neurol Med Chir (Tokyo) 27:**37–41, 1987
144. Lange M, Kirsch CM, Steude U, Oeckler R: Intracavitary treatment of intrasellar cystic craniopharyngeomas with 90-Yttrium by trans-sphenoidal approach—a technical note. **Acta Neurochir (Wien) 135:**206–209, 1995
145. Lapras C, Patet JD, Mottolese C, Gharbi S, Lapras C Jr: Craniopharyngiomas in childhood: analysis of 42 cases. **Prog Exp Tumor Res 30:**350–358, 1987
146. Larijani B, Bastanhagh MH, Pajouhi M, Kargar Shadab F, Vasigh A, Aghakhani S: Presentation and outcome of 93 cases of craniopharyngioma. **Eur J Cancer Care (Engl) 13:**11–15, 2004
147. Laws ER Jr: Transsphenoidal removal of craniopharyngioma. **Pediatr Neurosurg 21 (Suppl 1):**57–63, 1994
148. Laws ER Jr, Morris AM, Maartens N: Gliadel for pituitary adenomas and craniopharyngiomas. **Neurosurgery 53:**255–260, 2003
149. Lena G, Paz Paredes A, Scavarda D, Giusiano B: Craniopharyngioma in children: Marseille experience. **Childs Nerv Syst 21:**778–784, 2005
150. Lessell S: Unilateral exophthalmos. Occurrence after treatment for perichiasmatic neoplasms. **JAMA 234:**305–306, 1975
151. Lichter AS, Wara WM, Sheline GE, Townsend JJ, Wilson CB: The treatment of craniopharyngiomas. **Int J Radiat Oncol Biol Phys 2:**675–683, 1977
152. Lin KL, Wang HS, Lui TN: Diagnosis and follow-up of craniopharyngiomas with transcranial Doppler sonography. **J Ultrasound Med 21:**801–806, 2002
153. Lippens RJ, Rotteveel JJ, Otten BJ, Merx H: Chemotherapy with Adriamycin (doxorubicin) and CCNU (lomustine) in four children with recurrent craniopharyngioma. **Eur J Paediatr Neurol 2:**263–268, 1998
154. Liu JM, Garonzik IM, Eberhart CG, Sampath P, Brem H: Ectopic recurrence of craniopharyngioma after an interhemispheric transcallosal approach: case report. **Neurosurgery 50:**639–645, 2002
155. Locatelli D, Levi D, Rampa F, Pezzotta S, Castelnuovo P: Endoscopic approach for the treatment of relapses in cystic craniopharyngiomas. **Childs Nerv Syst 20:**863–867, 2004
156. Long DM, Chou SN: Transcallosal removal of cranio-pharyngiomas within the third ventricle. **J Neurosurg 39:**563–567, 1973
157. Lonjon M, Dran G, Casagrande F, Vandenbos F, Mas JC, Richelme C: Prenatal diagnosis of a craniopharyngioma: a new case with radical surgery and review. **Childs Nerv Syst 21:**177–180, 2005
158. Lunsford LD, Pollock BE, Kondziolka DS, Levine G, Flickinger JC: Stereotactic options in the management of craniopharyngioma. **Pediatr Neurosurg 21 (Suppl 1):**90–97, 1994
159. Luu QT, Loredo LN, Archambeau JO, Yonemoto LT, Slater JM, Slater JD: Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. **Cancer J 12:**155–159, 2006
160. Lyen KR, Grant DB: Endocrine function, morbidity, and mortality after surgery for craniopharyngioma. **Arch Dis Child 57:**837–841, 1982
161. Madhavan M, Jain GP, Abdullah Jafri J, Idris Z: Intraventricular squamous papillary craniopharyngioma: report of a case with intraoperative imprint cytology. **Acta Cytol 49:**431–434, 2005
162. Maira G, Anile C, Albanese A, Cabezas D, Pardi F, Vignati A: The role of transsphenoidal surgery in the treatment of craniopharyngiomas. **J Neurosurg 100:**445–451, 2004
163. Maira G, Anile C, Colosimo C, Cabezas D: Craniopharyngiomas of the third ventricle: trans-lamina terminalis approach. **Neurosurgery 47:**857–865, 2000
164. Maira G, Anile C, Rossi GF, Colosimo C: Surgical treatment of craniopharyngiomas: an evaluation of the transsphenoidal and pterional approaches. **Neurosurgery 36:**715–724, 1995
165. Maira G, Di Rocco C, Anile C, Roselli R: Hyperprolactinemia as the first symptom of craniopharyngioma. **Childs Brain 9:**205–210, 1982
166. Malik JM, Cosgrove GR, VandenBerg SR: Remote recurrence of craniopharyngioma in the epidural space. Case report. **J Neurosurg 77:**804–807, 1992
167. Maniatis AK, Simmons JH, Zeitler PS: Hypothalamic obesity in a patient with craniopharyngioma: dysregulation of neurohormonal control of energy balance. **Curr Opin Pediatr 17:**275–279, 2005
168. Maniker AH, Krieger AJ: Rapid recurrence of craniopharyngioma during pregnancy with recovery of vision: a case report. **Surg Neurol 45:**324–327, 1996
169. Mark RJ, Lutge WR, Shimizu KT, Tran LM, Selch MT, Parker RG: Craniopharyngioma: treatment in the CT and MR imaging era. **Radiology 197:**195–198, 1995
170. Mason PW, Krawiecki N, Meacham LR: The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. **Arch Pediatr Adolesc Med 156:**887–892, 2002
171. Matarazzo P, Genitori L, Lala R, Andreo M, Grossetti R, de Sanctis C: Endocrine function and water metabolism in children and adolescents with surgically treated intra/parasellar tumors. **J Pediatr Endocrinol Metab 17:**1487–1495, 2004
172. Matson DD, Crigler JF Jr: Management of craniopharyngioma in childhood. **J Neurosurg 30:**377–390, 1969
173. Matthew DJ, Levin M: Pulmonary thromboembolism in children. **Intensive Care Med 12:**404–406, 1986
174. McMurry FG, Hardy RW Jr, Dohn DF, Sadar E, Gardner WJ: Long term results in the management of craniopharyngiomas. **Neurosurgery 1:**238–241, 1977
175. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984-2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
176. Minamida Y, Mikami T, Hashi K, Houkin K: Surgical management of the recurrence and regrowth of craniopharyngiomas. **J Neurosurg 103:**224–232, 2005

177. Minniti G, Saran F, Traish D, Soomal R, Sardell S, Gonsalves A, et al: Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. **Radiother Oncol 82:**90–95, 2007
178. Moon SH, Kim IH, Park SW, Kim I, Hong S, Park CI, et al: Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas—a study in single institute. **Childs Nerv Syst 21:**799–807, 2005
179. Mori K, Handa H, Murata T, Takeuchi J, Miwa S, Osaka K: Results of treatment for craniopharyngioma. **Childs Brain 6:**303–312, 1980
180. Mottolese C, Stan H, Hermier M, Berlier P, Convert J, Frappaz D, et al: Intracystic chemotherapy with bleomycin in the treatment of craniopharyngiomas. **Childs Nerv Syst 17:**724–730, 2001
181. Mottolese C, Szathmari A, Berlier P, Hermier M: Craniopharyngiomas: our experience in Lyon. **Childs Nerv Syst 21:**790–798, 2005
182. Mudgil AV, Repka MX: Childhood optic atrophy. **Clin Experiment Ophthalmol 28:**34–37, 2000
183. Müller-Scholden J, Lehrnbecher T, Müller HL, Bensch J, Hengen RH, Sörensen N, et al: Radical surgery in a neonate with craniopharyngioma. report of a case. **Pediatr Neurosurg 33:**265–269, 2000
184. Murphy M, Worth RD, Norris JS: 'Disappearing' recurrent craniopharyngioma. **Br J Neurosurg 18:**65, 2004
185. Nimsky C, Ganslandt O, Hofmann B, Fahlbusch R: Limited benefit of intraoperative low-field magnetic resonance imaging in craniopharyngioma surgery. **Neurosurgery 53:**72–81, 2003
186. Nishioka H, Ito H, Haraoka J, Hashimoto T, Kato Y: Repeated hemorrhage in ciliated craniopharyngioma—case report. **Neurol Med Chir (Tokyo) 40:**324–328, 2000
187. Niu DM, Guo WY, Pan HC, Wong TT: Rapid enlargement of a residual craniopharyngioma during short-term growth hormone replacement. **Childs Nerv Syst 18:**164–165, 2002
188. Nomura H, Kurimoto M, Nagai S, Hayashi N, Hirashima Y, Tsukamoto E, et al: Multiple intracranial seeding of craniopharyngioma after repeated surgery—case report. **Neurol Med Chir (Tokyo) 42:**268–271, 2002
189. Norris JS, Pavaresh M, Afshar F: Primary transsphenoidal microsurgery in the treatment of craniopharyngiomas. **Br J Neurosurg 12:**305–312, 1998
190. Novegno F, Di Rocco F, Colosimo C Jr, Lauriola L, Caldarelli M: Ectopic recurrences of craniopharyngioma. **Childs Nerv Syst 18:**468–473, 2002
191. Nyffeler T, Regard M: Kleptomania in a patient with a right frontolimbic lesion. **Neuropsychiatry Neuropsychol Behav Neurol 14:**73–76, 2001
192. Ohmori K, Collins J, Fukushima T: Craniopharyngiomas in children. **Pediatr Neurosurg 43:**265–278, 2007
193. Onoyama Y, Ono K, Yabumoto E, Takeuchi J: Radiation therapy of craniopharyngioma. **Radiology 125:**799–803, 1977
194. Palaoğlu S, Akbay A, Mocan G, Onol B, Ozcan OE, Ozgen T, et al: Ossified adamantinous type craniopharyngiomas. A series of 13 patients. **Acta Neurochir (Wien) 127:**166–169, 1994
195. Pan DH, Lee LS, Huang CI, Wong TT: Stereotactic internal irradiation for cystic craniopharyngiomas: a 6-year experience. **Stereotact Funct Neurosurg 54–55:**525–530, 1990
196. Park DH, Park JY, Kim JH, Chung YG, Lee HK, Lee KC, et al: Outcome of postoperative intratumoral bleomycin injection for cystic craniopharyngioma. **J Korean Med Sci 17:**254–259, 2002
197. Pemberton LS, Dougal M, Magee B, Gattamaneni HR: Experience of external beam radiotherapy given adjuvantly or at relapse following surgery for craniopharyngioma. **Radiother Oncol 77:**99–104, 2005
198. Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, van Thiel SW, et al: High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. **Clin Endocrinol (Oxf) 62:**197–204, 2005
199. Plowman PN, Wraith C, Royle N, Grossman AB: Stereotactic radiosurgery. IX. Craniopharyngioma: durable complete imaging responses and indications for treatment. **Br J Neurosurg 13:**352–358, 1999
200. Pollock BE, Lunsford LD, Kondziolka D, Levine G, Flickinger JC: Phosphorus-32 intracavitary irradiation of cystic craniopharyngiomas: current technique and long-term results. **Int J Radiat Oncol Biol Phys 33:**437–446, 1995
201. Pollock BE, Natt N, Schomberg PJ: Stereotactic management of craniopharyngiomas. **Stereotact Funct Neurosurg 79:**25–32, 2002
202. Pomeranz HD, Aldrich EF: Intrachiasmal craniopharyngioma: treatment with a cisternal catheter drainage and radiation. **J Neuroophthalmol 24:**27–30, 2004
203. Pritz MB: Ruptured true posterior communicating artery aneurysm and cystic craniopharyngioma. **Acta Neurochir (Wien) 144:**937–939, 2002
204. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106 (1 Suppl):**3–12, 2007
205. Ragel BT, Bishop FS, Couldwell WT: Recurrent infrasellar clival craniopharyngioma. **Acta Neurochir (Wien) 149:**729–730, 2007
206. Ragoowansi AT, Piepgras DG: Postoperative ectopic craniopharyngioma. Case report. **J Neurosurg 74:**653–655, 1991
207. Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJ, et al: Craniopharyngioma—a long-term results following limited surgery and radiotherapy. **Radiother Oncol 26:**1–10, 1993
208. Rajan B, Ashley S, Thomas DG, Marsh H, Britton J, Brada M: Craniopharyngioma: improving outcome by early recognition and treatment of acute complications. **Int J Radiat Oncol Biol Phys 37:**517–521, 1997
209. Ramnarayan R, Sreehari NR, Ninan GK, John KM: Delayed postoperative extradural hematoma. **Pediatr Neurosurg 43:**113–114, 2007
210. Regine WF, Mohiuddin M, Kramer S: Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. **Radiother Oncol 27:**13–21, 1993
211. Rehman HU, Atkin SL: Sleep disturbances and cardiac arrhythmia after treatment of a craniopharyngioma. **J R Soc Med 92:**585–586, 1999
212. Richmond IL, Wara WM, Wilson CB: Role of radiation therapy in the management of craniopharyngiomas in children. **Neurosurgery 6:**513–517, 1980
213. Richmond IL, Wilson CB: Parasellar tumors in children. II. Surgical management, radiation therapy, and follow-up. **Childs Brain 7:**85–94, 1980
214. Rilliet B, Vernet O, Pica A: The Geneva and Lausanne (French-speaking Switzerland) experience: in favor of the transsphenoidal approach when feasible. **Childs Nerv Syst 21:**725–728, 2005
215. Rodriguez FJ, Scheithauer BW, Tsunoda S, Kovacs K, Vidal S, Piepgras DG: The spectrum of malignancy in craniopharyngioma. **Am J Surg Pathol 31:**1020–1028, 2007
216. Rudnick EF, DiNardo LJ: Image-guided endoscopic endonasal resection of a recurrent craniopharyngioma. **Am J Otolaryngol 27:**266–267, 2006
217. Sääf M, Thorén M, Bergstrand CG, Norén G, Rähn T, Tallstedt L, et al: Treatment of craniopharyngiomas—the stereotactic approach in a ten to twenty-three years' perspective. II. Psychosocial situation and pituitary function. **Acta Neurochir (Wien) 99:**97–103, 1989
218. Samuels MH, Henry P, Kleinschmidt-Demasters B, Lillehei K, Ridgway EC: Pulsatile prolactin secretion in hyperprolactinemia due to presumed pituitary stalk interruption. **J Clin Endocrinol Metab 73:**1289–1293, 1991
219. Sanford RA: Craniopharyngioma: results of survey of the

American Society of Pediatric Neurosurgery. **Pediatr Neurosurg 21 (Suppl 1):**39–43, 1994
220. Schefter JK, Allen G, Cmelak AJ, Johnson M, Toms S, Duggan D, et al: The utility of external beam radiation and intracystic 32P radiation in the treatment of craniopharyngiomas. **J Neurooncol 56:**69–78, 2002
221. Schulz-Ertner D, Frank C, Herfarth KK, Rhein B, Wannenmacher M, Debus J: Fractionated stereotactic radiotherapy for craniopharyngiomas. **Int J Radiat Oncol Biol Phys 54:**1114–1120, 2002
222. Scott RM, Hetelekidis S, Barnes PD, Goumnerova L, Tarbell NJ: Surgery, radiation, and combination therapy in the treatment of childhood craniopharyngioma—a 20-year experience. **Pediatr Neurosurg 21 (Suppl 1):**75–81, 1994
223. Sener RN, Kismali E, Akyar S, Selcuki M, Yalman O: Large craniopharyngioma extending to the posterior cranial fossa. **Magn Reson Imaging 15:**1111–1112, 1997
224. Sepehrnia A, Samii M, Tatagiba M: Management of intracavernous tumours: an 11-year experience. **Acta Neurochir Suppl (Wien) 53:**122–126, 1991
225. Shapiro K, Till K, Grant DN: Craniopharyngiomas in childhood. A rational approach to treatment. **J Neurosurg 50:**617–623, 1979
226. Shi XE, Wu B, Zhou ZQ, Fan T, Zhang YL: Microsurgical treatment of craniopharyngiomas: report of 284 patients. **Chin Med J (Engl) 119:**1653–1663, 2006
227. Shinohara O, Shinagawa T, Kubota C, Oi S: Spontaneous reduction of a recurrent craniopharyngioma in an 8-year-old female patient: case report. **Neurosurgery 41:**1188–1190, 1997
228. Shirane R, Ching-Chan S, Kusaka Y, Jokura H, Yoshimoto T: Surgical outcomes in 31 patients with craniopharyngiomas extending outside the suprasellar cistern: an evaluation of the frontobasal interhemispheric approach. **J Neurosurg 96:**704–712, 2002
229. Shirane R, Hayashi T, Tominaga T: Fronto-basal interhemispheric approach for craniopharyngiomas extending outside the suprasellar cistern. **Childs Nerv Syst 21:**669–678, 2005
230. Shuman AG, Heth JA, Marentette LJ, Blaivas M, Muraszko KM: Extracranial nasopharyngeal craniopharyngioma: case report. **Neurosurgery 60:**E780–E781, 2007
231. Siomin V, Spektor S, Beni-Adani L, Constantini S: Application of the orbito-cranial approach in pediatric neurosurgery. **Childs Nerv Syst 17:**612–617, 2001
232. Smith AR, Elsheikh TM, Silverman JF: Intraoperative cytologic diagnosis of suprasellar and sellar cystic lesions. **Diagn Cytopathol 20:**137–147, 1999
233. Smith D, Finucane F, Phillips J, Baylis PH, Finucane J, Tormey W, et al: Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. **Clin Endocrinol (Oxf) 61:**273–279, 2004
234. Snow A, Gozal E, Malhotra A, Tiosano D, Perlman R, Vega C, et al: Severe hypersomnolence after pituitary/hypothalamic surgery in adolescents: clinical characteristics and potential mechanisms. **Pediatrics 110:**e74, 2002
235. Sorva R, Heiskanen O: Craniopharyngioma in Finland. A study of 123 cases. **Acta Neurochir (Wien) 81:**85–89, 1986
236. Sorva R, Heiskanen O, Perheentupa J: Craniopharyngioma in adults. **Ann Clin Res 19:**339–343, 1987
237. Sorva R, Jääskinen J, Heiskanen O, Perheentupa J: Postoperative computed tomographic control of 38 patients with craniopharyngioma. **Surg Neurol 29:**115–119, 1988
238. Sosa IJ, Krieger MD, McComb JG: Craniopharyngiomas of childhood: the CHLA experience. **Childs Nerv Syst 21:**785–789, 2005
239. Srinivasan J, Dailey AT, Berger MS: The bifrontal olfactory nerve-sparing approach to lesions of the suprasellar region in children. **Pediatr Neurosurg 30:**245–252, 1999
240. Stahnke N, Grubel G, Lagenstein I, Willig RP: Long-term follow-up of children with craniopharyngioma. **Eur J Pediatr 142:**179–185, 1984
241. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, et al: Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. **Int J Radiat Oncol Biol Phys 58:**714–720, 2004
242. Sung DI: Suprasellar tumors in children: a review of clinical manifestations and managements. **Cancer 50:**1420–1425, 1982
243. Sutton LN, Gusnard D, Bruce DA, Fried A, Packer RJ, Zimmerman RA: Fusiform dilatations of the carotid artery following radical surgery of childhood craniopharyngiomas. **J Neurosurg 74:**695–700, 1991
244. Svien HJ: Surgical experiences with craniopharyngiomas. **J Neurosurg 23:**148–155, 1965
245. Sweet WH: Radical surgical treatment of craniopharyngioma. **Clin Neurosurg 23:**52–79, 1976
246. Symon L: An approach to radical excision of craniopharyngioma by the temporal route. **Pediatr Neurosurg 21 (Suppl 1):**64–68, 1994
247. Symon L: Microsurgery of the hypothalamus with special reference to craniopharyngioma. **Neurosurg Rev 6:**43–49, 1983
248. Symon L, Pell MF, Habib AH: Radical excision of craniopharyngioma by the temporal route: a review of 50 patients. **Br J Neurosurg 5:**539–549, 1991
249. Symon L, Sprich W: Radical excision of craniopharyngioma. Results in 20 patients. **J Neurosurg 62:**174–181, 1985
250. Taguchi Y, Tanaka K, Miyakita Y, Sekino H, Fujimoto M: Recurrent craniopharyngioma with nasopharyngeal extension. **Pediatr Neurosurg 32:**140–144, 2000
251. Takahashi H, Yamaguchi F, Teramoto A: Long-term outcome and reconsideration of intracystic chemotherapy with bleomycin for craniopharyngioma in children. **Childs Nerv Syst 21:**701–704, 2005
252. Tarbell NJ, Barnes P, Scott RM, Goumnerova L, Pomeroy SL, Black PM, et al: Advances in radiation therapy for craniopharyngiomas. **Pediatr Neurosurg 21 (Suppl 1):**101–107, 1994
253. Tavangar SM, Larijani B, Mahta A, Hosseini SM, Mehrazine M, Bandarian F: Craniopharyngioma: a clinicopathological study of 141 cases. **Endocr Pathol 15:**339–344, 2004
254. Tena-Suck ML, Salinas-Lara C, Arce-Arellano RI, Rembao-Bojórquez D, Morales-Espinosa D, Sotelo J, et al: Clinicopathological and immunohistochemical characteristics associated to recurrence/regrowth of craniopharyngiomas. **Clin Neurol Neurosurg 108:**661–669, 2006
255. Thomas RF, Monacci WT, Mair EA: Endoscopic image-guided transethmoid pituitary surgery. **Otolaryngol Head Neck Surg 127:**409–416, 2002
256. Thompson D, Phipps K, Hayward R: Craniopharyngioma in childhood: our evidence-based approach to management. **Childs Nerv Syst 21:**660–668, 2005
257. Thompson IL, Griffin TW, Parker RG, Blasko JC: Craniopharyngioma: the role of radiation therapy. **Int J Radiat Oncol Biol Phys 4:**1059–1063, 1978
258. 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
259. Tomita T, Bowman RM: Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. **Childs Nerv Syst 21:**729–746, 2005
260. Tomita T, McLone DG: Radical resections of childhood craniopharyngiomas. **Pediatr Neurosurg 19:**6–14, 1993
261. Trejos H, Caceres A, Segura JL: Monstrous craniopharyngioma. Case presentations and term proposal. **Childs Nerv Syst 21:**1049–1055, 2005
262. Ulfarsson E, Lindquist C, Roberts M, Rähn T, Lindquist M, Thorén M, et al: Gamma knife radiosurgery for craniopharyngiomas: long-term results in the first Swedish patients. **J Neurosurg 97 (5 Suppl):**613–622, 2002

263. Usanov EI, Hatomkin DM, Nikulina TA, Gorban NA: Craniopharyngioma of the pineal region. **Childs Nerv Syst 15:**4–7, 1999
264. Van den Berge JH, Blaauw G, Breeman WA, Rahmy A, Wijngaarde R: Intracavitary brachytherapy of cystic craniopharyngiomas. **J Neurosurg 77:**545–550, 1992
265. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
266. Varlotto JM, Flickinger JC, Kondziolka D, Lunsford LD, Deutsch M: External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. **Int J Radiat Oncol Biol Phys 54:**492–499, 2002
267. Villani RM, Tomei G, Bello L, Sganzerla E, Ambrosi B, Re T, et al: Long-term results of treatment for craniopharyngioma in children. **Childs Nerv Syst 13:**397–405, 1997
268. Voges J, Sturm V, Lehrke R, Treuer H, Gauss C, Berthold F: Cystic craniopharyngioma: long-term results after intracavitary irradiation with stereotactically applied colloidal beta-emitting radioactive sources. **Neurosurgery 40:**263–270, 1997
269. Vrionis FD, Saatman D, Sorenson J, Brem S: Microscopic paraseptal sphenoidotomy approach for pituitary tumors. **Cancer Control 9:**223–231, 2002
270. Vyramuthu N, Benton TF: The management of craniopharyngioma. **Clin Radiol 34:**629–632, 1983
271. Wara WM, Sneed PK, Larson DA: The role of radiation therapy in the treatment of craniopharyngioma. **Pediatr Neurosurg 21 (Suppl 1):**98–100, 1994
272. 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
273. 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
274. Wellons JC III, Tubbs RS: Staged surgical treatment of a giant neonatal craniopharyngioma. Case illustration. **J Neurosurg 105 (1 Suppl):**76, 2006
275. Wen BC, Hussey DH, Staples J, Hitchon PW, Jani SK, Vigliotti AP, et al: A comparison of the roles of surgery and radiation therapy in the management of craniopharyngiomas. **Int J Radiat Oncol Biol Phys 16:**17–24, 1989
276. Xu JG, You C, Cai BW, Jiang S, Sun H, Guo FY, et al: Microsurgical resection of craniopharyngioma of the third ventricle via an improved transventricular approach. **Chin Med J (Engl) 118:**806–811, 2005
277. Yamada Y, Haraoka J, Akimoto J: Ectopic recurrence of craniopharyngioma. **Neurol Med Chir (Tokyo) 46:**598–600, 2006
278. 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
279. Yu X, Liu Z, Li S: Combined treatment with stereotactic intracavitary irradiation and gamma knife surgery for craniopharyngiomas. **Stereotact Funct Neurosurg 75:**117–122, 2000
280. Zona G, Spaziante R: Management of cystic craniopharyngiomas in childhood by a transsphenoidal approach. **J Pediatr Endocrinol Metab 19 (Suppl 1):**381–388, 2006
281. Zuccaro G: Radical resection of craniopharyngioma. **Childs Nerv Syst 21:**679–690, 2005
282. Zuccaro G, Jaimovich R, Mantese B, Monges J: Complications in paediatric craniopharyngioma treatment. **Childs Nerv Syst 12:**385–391, 1996

Manuscript submitted December 14, 2009.
Accepted January 5, 2010.

Address correspondence to: Andrew T. Parsa, M.D., Ph.D., Department of Neurological Surgery, University of California, San Francisco, 400 Parnassus Avenue, A808, San Francisco, California 94143-0350. email: parsaa@neurosurg.ucsf.edu.

Neurosurg Focus 28 (4):E6, 2010

Surgical nuances for removal of retrochiasmatic craniopharyngiomas via the transbasal subfrontal translamina terminalis approach

James K. Liu, M.D., Lana D. Christiano, M.D., Gaurav Gupta, M.D., and Peter W. Carmel, M.D.

Department of Neurological Surgery, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Neurological Institute of New Jersey, Newark, New Jersey

Giant craniopharyngiomas in the retrochiasmatic space are challenging tumors, given the location and surrounding vital structures. Surgical removal remains the first line of therapy and offers the best chance of cure. For tumors with extension into the retrochiasmatic space, the authors use the translamina terminalis corridor via the transbasal subfrontal approach. Although the lamina terminalis can be accessed via anterolateral approaches (pterional or orbitozygomatic), the surgical view of the optic chiasm is oblique and prevents adequate visualization of the ipsilateral wall of the third ventricle. The transbasal subfrontal approach, on the other hand, offers the major advantage of direct midline orientation and access to the third ventricle through the lamina terminalis. This provides the significant advantage of visualization of both walls of the third ventricle and hypothalamus as well as inferior midline access to the interpeduncular cistern to permit safe neurovascular dissection and total tumor removal. In this report, the authors describe the transbasal subfrontal translamina terminalis approach, with specific emphasis on technical surgical nuances in removing retrochiasmatic craniopharyngiomas. An illustrative video demonstrating the technique is also presented. *(DOI: 10.3171/2010.1.FOCUS09309)*

Key Words • **retrochiasmatic craniopharyngioma** • **transbasal subfrontal approach** • **lamina terminalis** • **surgical approach**

Retrochiasmatic craniopharyngiomas comprise approximately 11–46%[3,14,18,24,36,38] of all craniopharyngiomas, and are difficult tumors to remove because of their anatomical location. Surgical removal of these lesions has been associated with a high rate of surgery-related morbidity and mortality, as has incomplete removal resulting in higher recurrence rates.[13,29,31,36] Because they are thought to arise from a supradiaphragmatic origin,[38] retrochiasmatic craniopharyngiomas are hidden behind the optic chiasm, and often can extend superiorly into the third ventricle and inferiorly into the interpeduncular cistern and retrosellar region.[13,32,36] Surgical exposure attained using conventional operative corridors through the subchiasmatic (interoptic) or optico-carotid cisterns allows only limited and inadequate visualization of the infra- and retrochiasmatic regions, because these tumors are hidden behind an anteriorly displaced or prefixed chiasm.[2,36] In essence, the optic nerves and chiasm are situated between the tumor and the surgeon, and therefore obstruct visualization and access to the retrochiasmatic region.

This has led to the development of transcranial approaches through the lamina terminalis to access retrochiasmatic craniopharyngiomas, which include midline (unilateral subfrontal, bifrontal, bifrontal interhemispheric) and anterolateral (pterional, orbitopterional, orbitozygomatic) routes. Other approaches to retrochiasmatic craniopharyngiomas also include transsphenoidal, extended transsphenoidal, endoscopic expanded endonasal, and posterior petrosal approaches. Each has its own advantages and disadvantages. The primary disadvantages of anterolateral approaches to the lamina terminalis include loss of midline orientation, lack of visualization of the ipsilateral wall of the third ventricle and hypothalamus (blind spot), limited oblique visualization superiorly into the third ventricle, limited visualization inferiorly into the interpeduncular cistern, and narrowing of the lamina terminalis working corridor when coming in from a lateral projection.

In our experience, we have favored midline transcranial approaches, particularly the transbasal subfrontal route, to the lamina terminalis, which addresses the disadvantages of anterolateral approaches. By coming in from a midline projection and orientation, the working corridor of the lamina terminalis is maximized and both walls of the third ventricle and hypothalamus can be adequately visualized, thereby eliminating the blind spot. There is also more superior access to the top of the third ventricle, and midline visualization inferiorly into the interpeduncular cistern. If the Liliequist membrane has not been breached by the tumor, it acts as a favorable plane of

Abbreviations used in this paper: ACA = anterior cerebral artery; BA = basilar artery; ICA = internal carotid artery; PCA = posterior cerebral artery; PCoA = posterior communicating artery; SSS = superior sagittal sinus.

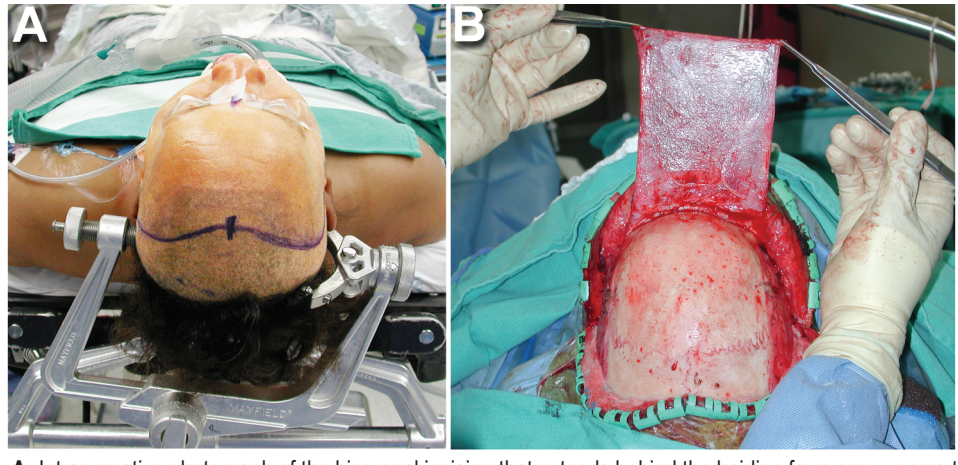

Fig. 1. **A:** Intraoperative photograph of the bicoronal incision that extends behind the hairline from one zygoma to the other, no more than 1 cm anterior to the tragus. **B:** Intraoperative photograph of the vascularized pedicled pericranial flap that is elevated as a separate layer for later reconstruction and closure. The posterior margin of the galeal incision is undermined posteriorly to provide additional length, to maximize the length of the pericranial flap.

dissection for removing the inferior limit of tumor in the interpeduncular cistern and retrosellar region. We believe that the transbasal subfrontal approach to the lamina terminalis is an ideal one for removing giant retrochiasmatic craniopharyngiomas that have significant intraventricular extension. In this report, we describe our technique and its operative nuances in removing these difficult lesions. An illustrative video demonstrating the technique is also presented in this report (Video 1).

Video 1. Illustrative video demonstrating the surgical technique for removing retrochiasmatic craniopharyngiomas by using the transbasal subfrontal translamina terminalis approach.

Surgical Technique

Patient Positioning

A lumbar drain is placed at the start of the operation and is clamped off until further CSF drainage is needed to facilitate brain relaxation during intradural exposure of the tumor. Our neuroanesthesia team uses total intravenous anesthesia (primarily intravenous propofol and remifentanil) rather than inhalational agents, to promote further reduction of intracranial pressure and a decrease in cerebral swelling.[10] The patient is positioned supine on the operating table and the head is fixed in a 3-point head holder. The bed is slightly flexed into a lounge chair position, with the patient's head and trunk elevated approximately 15–20° to facilitate venous return. The neck is extended to allow the frontal lobe to fall away from the anterior skull base.

Skin Incision and Harvest of Vascularized Pericranial Flap

A bicoronal incision is used that extends behind the hairline from one zygoma to the other, no more than 1 cm anterior to the tragus (Fig. 1A). The scalp is elevated in a 2-layer fashion (galea and pericranial layers). Using the skin knife, the scalp is incised through the galea aponeu-

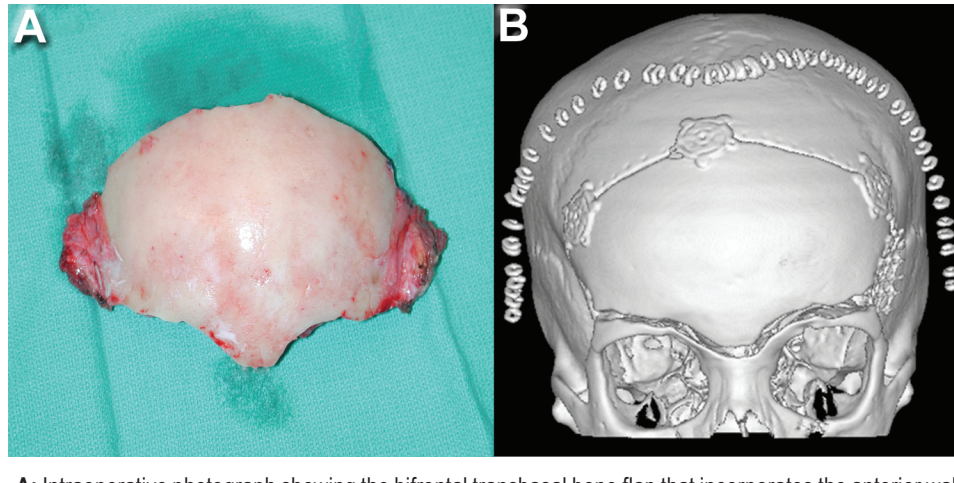

Fig. 2. **A:** Intraoperative photograph showing the bifrontal transbasal bone flap that incorporates the anterior wall of the frontal sinus. The inferior margin of the osteotomy is made at the nasofrontal suture and extends laterally over both orbital rims. This allows the bone flap to extend as low as possible by following the contour of the anterior skull base in the coronal orientation. **B:** A 3D reconstructed CT scan of the skull demonstrating the bifrontal transbasal bone flap.

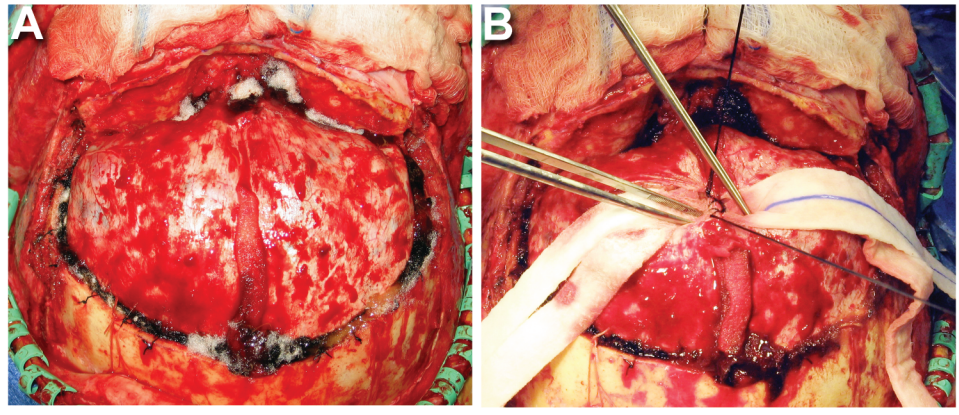

Fig. 3. **A:** Intraoperative photograph of the bifrontal transbasal exposure. The bone flap has been removed. The exposure is flush with the floor of the anterior skull base in the coronal orientation, and there is no bone overhang to obstruct the surgeon's line of sight to the anterior skull base. **B:** Intraoperative photograph demonstrating the bifrontal dural opening. Cottonoid patties are used to protect the frontal lobes during ligation and division of the SSS and falx cerebri.

rosis while sparing the pericranium. The galea layer is elevated along with the scalp anteriorly, while leaving the pericranium and temporalis muscle and fascia attached to the skull. The superficial temporal fat pad is elevated up with the galeal skin flap by using the interfascial dissection technique, as described by Yasargil et al.,[41] to preserve the frontotemporal branch of the facial nerve. Extreme care is taken to preserve the supraorbital nerve and artery as the galeal elevation approaches near the supraorbital rim. The posterior margin of the galeal incision is undermined posteriorly to provide additional length, to maximize the length of the pericranial flap. The pericranium is then incised above the superior temporal line on both sides and elevated as a separate layer attached to its vascular pedicle for later reconstruction and closure (Fig. 1B). Elevation of this layer allows exposure of the frontal

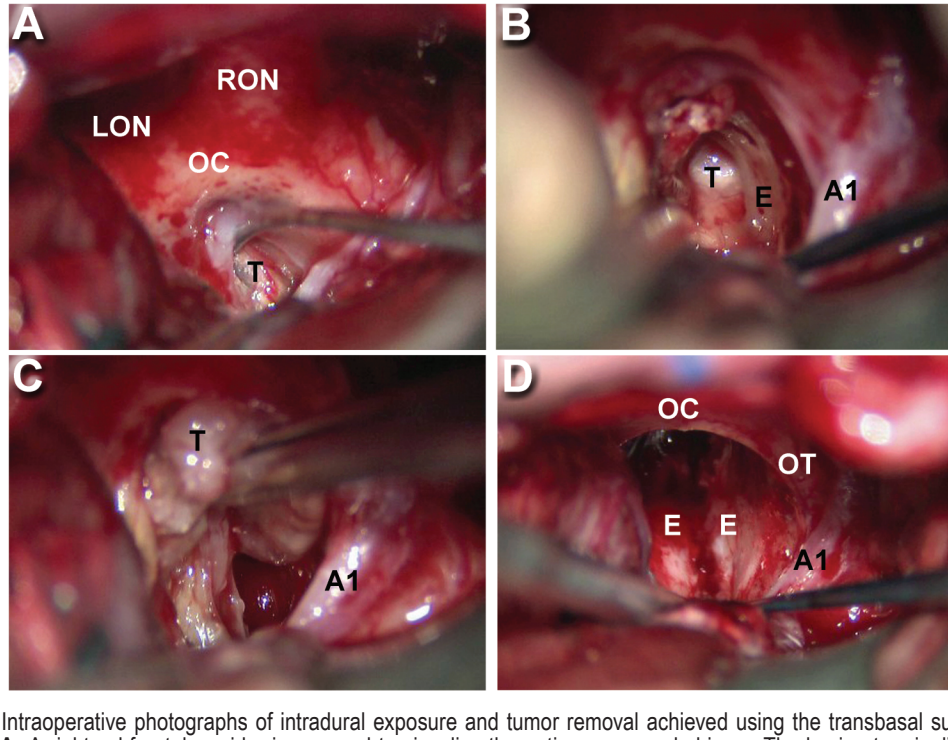

Fig. 4. Intraoperative photographs of intradural exposure and tumor removal achieved using the transbasal subfrontal approach. **A:** A right subfrontal corridor is exposed to visualize the optic nerves and chiasm. The lamina terminalis is opened sharply to identify the tumor capsule within the third ventricle. **B:** The ependyma of the ipsilateral wall of the third ventricle is well visualized from the midline orientation. This allows for dissection of the tumor capsule from the ependymal wall under direct visualization. **C:** The tumor capsule is gently delivered from a superior to inferior direction into the lamina terminalis corridor. **D:** After complete removal of the tumor, both ependymal surfaces of the third ventricle and hypothalamus are well visualized in the midline orientation. A1 = A_1 branch of right ACA; E = ependymal wall of the third ventricle; LON = left optic nerve; OC = optic chiasm; OT = right optic tract; RON = right optic nerve; T = tumor.

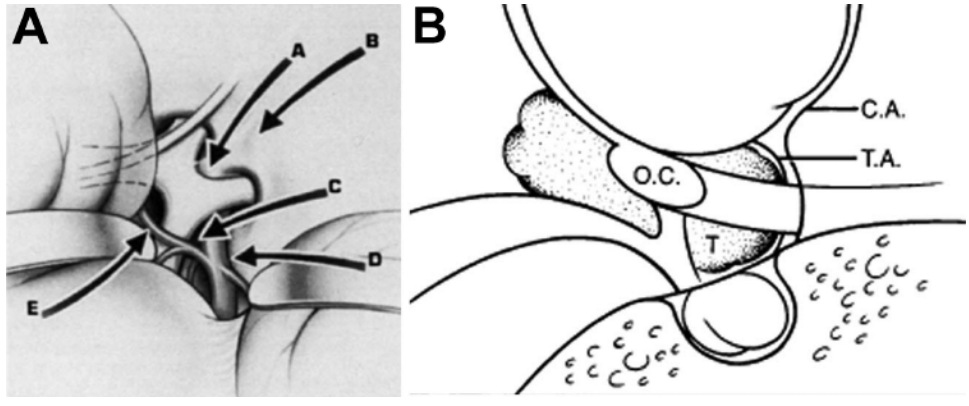

Fig. 5. **A:** Illustration showing the various corridors used to access craniopharyngiomas with the subfrontal approach, including subchiasmatic *(A)*, extension of the subchiasmatic by removing the tuberculum sellae and planum sphenoidale *(B)*, optico-carotid *(C)*, carotid-oculomotor *(D)*, and lamina terminalis *(E)*. **B:** Schematic drawing showing a sagittal view of tumor (T) arising in the suprasellar region, appearing beneath the optic chiasm (O.C.). The tumor is invested by a layer of arachnoid (T.A.) and is covered by cisternal arachnoid (C.A.). As the tumor grows, the layers may become fused over some or even most of the lesion's surface. The safest plane of dissection is between the tumor capsule and the tumor arachnoid. (Reprinted with permission from Carmel PW: Craniopharyngiomas, in Winn R (ed): **Youmans Neurological Surgery, 5th ed.** Philadelphia: W. B. Saunders, 2003. Copyright Elsevier.)

bone down to the orbital rims and nasion. The pericranial flap is wrapped in wet sponge to prevent dehydration, and reflected along with the scalp with the aid of hooks and rubber bands.

Craniotomy Procedure

A modified bifrontal transbasal craniotomy that incorporates the anterior wall of the frontal sinus is performed (Fig. 2). The inferior margin of the osteotomy is made through the anterior wall of the frontal sinus, starting at the nasofrontal suture and extending laterally over both orbital rims. This technique allows the bifrontal bone flap to extend as low as possible by following the contour of the anterior skull base in the coronal orientation. This modification provides an excellent line of sight to the anterior skull base, without any obstruction from bone overhang (Fig. 3). There is also an increased inferior-to-superior angle of attack to access the third ventricle. This also

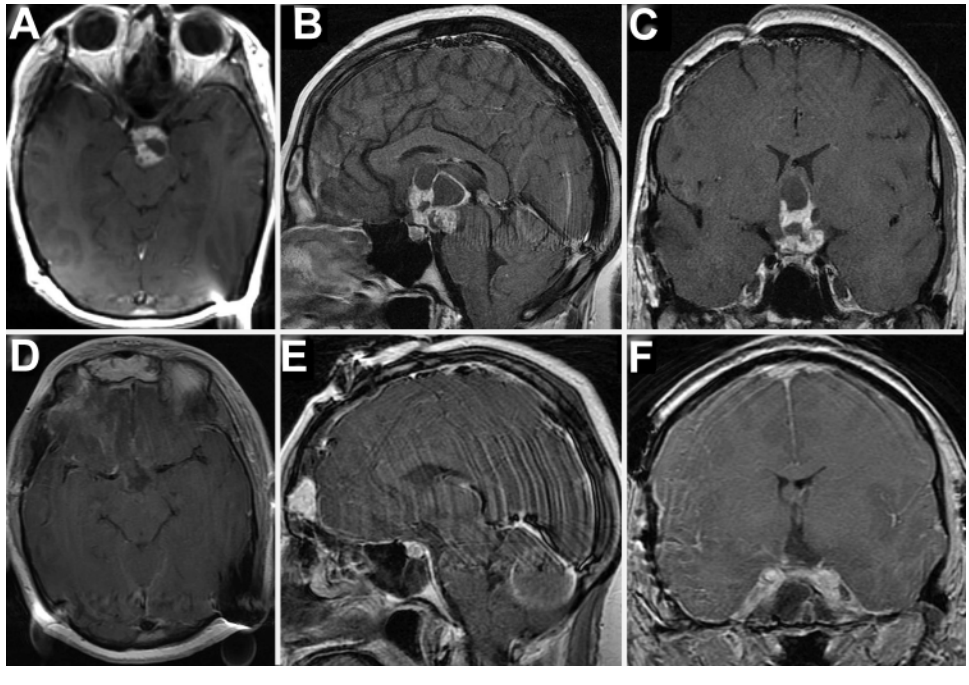

Fig. 6. Preoperative T1-weighted MR images with addition of Gd (**A**, axial; **B**, sagittal; **C**, coronal views) demonstrating a large retrochiasmatic craniopharyngioma with solid and cystic components. The tumor extends superiorly to the top of the third ventricle and inferiorly into the interpeduncular cistern and retrosellar region. Postoperative T1-weighted MR images with addition of Gd (**D**, axial; **E**, sagittal; **F**, coronal views) showing gross-total removal of the tumor after a transbasal subfrontal approach to the lamina terminalis.

obviates the need for any supraorbital rim removal, while minimizing brain retraction. The frontal sinus mucosa is exenterated and cranialized by removing the posterior wall of the frontal sinus. The nasofrontal ducts are packed with Betadine-soaked Gelfoam pledgets. Alternatively, autologous fat or muscle can be used here as well.

Dural Opening

The dura mater is incised on both sides of the SSS in a lateral-to-medial direction near the frontal base (Fig. 3). Care is taken not to violate any bridging veins. The frontal lobes are protected with cottonoid patties and the falx cerebri is identified. The anterior and inferior extent of the SSS is ligated using a pair of 2-0 silk suture ligatures, and then sharply divided toward the incisura of the falx cerebri. This allows final release of the bifrontal dura from the crista galli.

Intradural Exposure and Tumor Removal

A right subfrontal corridor is exposed to visualize the optic nerves and chiasm (Fig. 4). This is generally more advantageous for most right-handed surgeons, while sparing retraction on the contralateral frontal lobe. Although a unilateral subfrontal corridor is used, having a bifrontal craniotomy up front with division of the falx provides additional exposure to maximize the midline viewing angle, and increases the working corridor and angles of attack to the tumor. This also provides interhemispheric or bifrontal exposure to the lamina terminalis as alternative options.

The right frontal lobe is gently elevated and protected with cottonoid patties to identify the right olfactory tract, which is dissected from its attachments to the frontal lobe. The optic nerve and chiasm are identified and the chiasmatic and optico-carotid cisterns are opened up by using sharp dissection. The ICA and ACAs are identified. Care is taken to preserve the perforating vessels on the A_1 segment of the ACA. Adequate brain relaxation for the subfrontal corridor is achieved with intravenous mannitol, total intravenous anesthesia, and intraoperative removal of CSF from the cisterns during arachnoid dissection. If necessary, the lumbar drain can be opened for additional removal of CSF. The left frontal lobe will naturally fall away from the anterior skull base with the aforementioned brain relaxation techniques.

At this juncture, all possible routes to the tumor (including subchiasmatic, optico-carotid, and carotid-oculomotor) should be routinely inspected to see if there are any favorable corridors for tumor removal prior to opening the lamina terminalis (Fig. 5). In giant retrochiasmatic craniopharyngiomas that extend superiorly into the third ventricle, the tumor is often hidden from view behind the optic chiasm, and subsequent opening of the lamina terminalis is required. Tumor filling the third ventricle displaces the optic chiasm anteriorly and the optic tracts laterally, which can create the appearance of a prefixed chiasm.[8,9]

The lamina terminalis is opened sharply to identify the tumor capsule within the third ventricle (Fig. 4). A plane is then developed between the tumor capsule and the ependyma of the third ventricle. To deliver giant tumors through a relatively small window such as the lamina terminalis without injury to the visual apparatus, the surgeon must "make the tumor smaller" and deliver it in a piecemeal fashion. For solid components of the tumor, this can be accomplished with a precision-tip ultrasonic aspirator for central debulking and decompression of the tumor. For cystic portions of the tumor, gentle incremental aspiration of intracystic fluid allows decompression of the capsule while maintaining enough turgor of the cyst wall to separate the tumor capsule from the walls of the third ventricle. Once the tumor has been adequately debulked and decompressed, the tumor capsule can be gently delivered from a superior to inferior direction through the lamina terminalis (Fig. 4). The microsuction device in the surgeon's nondominant hand is used to help push the tumor down into the field and dissect the lesion off of the walls of the third ventricle while holding gentle traction on the capsule with tumor forceps in the dominant hand. Once the ventricular walls are identified, microcottonoid patties are used to protect the walls and maintain the plane of dissection between the ependyma and the tumor capsule. It is important not to amputate the tumor capsule prematurely and "lose the handle," whereby a remnant of the capsule will retract upward out of view from the lamina terminalis window. If the superior aspect of the lesion fails to deliver from the third ventricle, a transcallosal or transcortical transventricular approach can be used to remove the remaining intraventricular tumor.

Once the superior and posterior extensions of the intraventricular tumor have been delivered, attention is then directed to the remaining lesion within the infrachiasmatic and interpeduncular cistern. The Liliequist membrane forms the inferior boundary of the tumor in the interpeduncular cistern and becomes an important plane of dissection. Here, it is important to identify the "double" arachnoid layer and to distinguish the tumor arachnoid plane from the cisternal arachnoid plane (Fig. 5). The optimal and safest plane of dissection is between the tumor capsule and the tumor arachnoid, not the cisternal arachnoid plane. Early identification and preservation of this plane will facilitate the best chance at total removal of the lesion, and will spare the BA, PCAs, and P_1 perforating vessels, which are protected by the Liliequist membrane. We therefore avoid bipolar cautery on the tumor capsule to prevent annealing of the arachnoid layers, and to preserve the subarachnoid plane of dissection.

The remaining portions of tumor are dissected from the undersurface of the optic apparatus by using sharp dissection. This area is often a blind spot for the surgeon working from this approach. Angled dental mirrors and angled endoscopes can be used to inspect the undersurface of the chiasm and median eminence for residual tumor. If tumor remnants or calcium fragments are densely adherent to the chiasm or the hypothalamus, these residual lesions are left behind to avoid risk of injury to these structures. Attempts should be made to identify and preserve the pituitary stalk. Although the stalk may be displaced, it can be located where it penetrates the diaphragma sellae to reach the pituitary gland. The stalk also has a unique striated appearance that represents the

long portal veins that run parallel along its surface.[8,9] At the end of the resection, one should be able to visualize the pituitary stalk, the oculomotor nerve, and bilateral P_1 segments of the PCAs through the opening of the lamina terminalis.

Wound Closure

The dura mater is reapproximated in a watertight fashion. After sectioning the SSS and falx cerebri, the dura often retracts posteriorly, and an interpositional dural graft substitute is used for closure. It is important to provide some redundant dura to accommodate for frontal lobe reexpansion and to prevent restriction if there is frontal lobe edema postoperatively. The Betadine-soaked Gelfoam pledgets are left in the nasofrontal ducts and cranialized frontal sinus. The vascularized pedicled pericranial flap is rotated posteriorly to occlude the frontal sinus cavity. The flap can be tacked down to the frontobasal dura with several interrupted dural sutures. The remaining redundant portion of the pericranium is unraveled to provide coverage over the frontal dural closure. The edges of the pericranium can be tacked to the bony edges of the craniotomy to hold it in place. When replacing the bone flap, care is taken not to constrict the vascular supply of the pericranium at the inferior margin of the bone flap. The remainder of the closure is performed in the standard fashion.

Illustrative Case With Online Surgical Video

History and Examination. This 29-year-old woman presented with 2 episodes of transient visual loss in both eyes. She had undergone a prior ventriculoperitoneal shunt placement and subtotal resection of a retrochiasmatic craniopharyngioma via an orbitozygomatic approach at another institution approximately 1 year previously. On examination, she exhibited no neurological deficits. A formal neuroophthalmological examination demonstrated no evidence of any visual field or visual acuity deficits. She was receiving hormone replacement therapy, including hydrocortisone, levothyroxine, and desmopressin acetate.

Magnetic resonance imaging (Fig. 6) demonstrated a large, recurrent, retrochiasmatic craniopharyngioma, with extension superiorly into the third ventricle up to the foramen of Monro, and extension inferiorly into the interpeduncular cistern. The tumor comprised both solid and cystic components and was primarily supradiaphragmatic in origin. There was no evidence of shunt malfunction or hydrocephalus.

Operation. The patient underwent a transbasal subfrontal craniotomy, as described above. A right-sided unilateral subfrontal approach to the lamina terminalis was performed. The lamina terminalis was opened up sharply to expose the tumor capsule. Initial decompression of the lesion was achieved by aspirating the fluid from its cystic portion. Further decompression was accomplished using ultrasonic aspiration for internal debulking of the solid components of the tumor. Once the tumor was adequately debulked, its capsule was carefully dissected away from both ependymal walls of the third ventricle and hypothalamus under direct visualization. The superior extent of the tumor capsule was brought down through the lamina terminalis with careful dissection. The remaining lesion in the interpeduncular cistern and infrachiasmatic region was carefully dissected off of the Liliequist membrane, with preservation of the BA and PCAs. A gross-total removal of the tumor was accomplished entirely through the lamina terminalis corridor, and both walls of the third ventricle were well visualized at the end of the surgery (Fig. 4).

Postoperative Course. Postoperatively, the patient was awake and alert, with no evidence of any neurological or visual deficits. Her endocrine status remained unchanged, requiring the same doses of hormones as had been prescribed preoperatively for replacement therapy. Postoperative MR imaging demonstrated gross-total removal of the tumor (Fig. 6).

Discussion

Choice of Surgical Approach

Several approaches have been proposed for removing retrochiasmatic craniopharyngiomas. These include midline transcranial (bifrontal transbasal, subfrontal, bifrontal interhemispheric), midline transnasal (transsphenoidal, extended transsphenoidal, endoscopic expanded endonasal), anterolateral (pterional, orbitopterional, orbitozygomatic), and posterior petrosal approaches (retrolabyrinthine, partial labyrinthine petrous apicetomy, translabyrinthine). Choosing the appropriate approach depends primarily on the location of the lesion and amount of tumor extension, and also to some degree on the surgeon's preference, comfort, and familiarity with the approach. The approach should provide adequate exposure that creates the shortest distance to the tumor with minimal brain retraction. Variations of each approach can be tailored to the individual patient by modifying the degree of bone removal. One should be ready to perform a combination of approaches for extensive lesions that cannot be adequately accessed via a single approach. For example, for craniopharyngiomas with significant intraventricular extension, a transcallosal or transcortical transventricular approach may be required in addition to a basal approach to the suprasellar region.

Retrochiasmatic craniopharyngiomas present a formidable surgical challenge because of their location behind and underneath the optic chiasm. Superior extension into the third ventricle and inferior extension into the interpeduncular cistern further increases the risk and complexity of the resection. With anterolateral approaches to the lamina terminalis, either pterional or orbitozygomatic, the angle of attack to the optic chiasm and lamina terminalis is oblique, and therefore prohibits visualization of the ipsilateral wall of the third ventricle and hypothalamus. This increases the risk of hypothalamic injury if adherent tumor is removed blindly without the ability to dissect the tumor off the hypothalamus under direct visualization. The superior viewing angle to the top of the third ventricle is also limited, although it is somewhat

improved with an orbitozygomatic approach.[15,25,33] In addition, access to the interpeduncular cistern and infrachiasmatic region through the optico-carotid and carotid-oculomotor corridors can be narrow and is sometimes obstructed by perforating arteries.[2]

A transbasal subfrontal approach maximizes the lamina terminalis working corridor by maintaining a direct midline trajectory to the optic chiasm. In contrast to anterolateral approaches, in which the ipsilateral wall of the third ventricle is not well visualized, a midline transbasal approach provides excellent visualization of both walls of the third ventricle and hypothalamus (Fig. 4). Therefore, the tumor can be safely dissected from the ependymal walls under direct visualization. By maintaining a midline orientation, the tumor can be followed inferiorly into the interpeduncular cistern through the lamina terminalis exposure. Identification of the Liliequist membrane is critical because dissection between the tumor capsule and the tumor arachnoid permits total removal while preserving the arteries and perforating vessels that are protected by the Liliequist membrane.

Our modification of the bifrontal transbasal craniotomy (transbasal transglabellar) incorporates the anterior wall of the frontal sinus so that the inferior margin of the osteotomy extends as low as possible by following the contour of the anterior skull base in the coronal orientation (Fig. 4). By making the osteotomy at the nasofrontal suture below the glabella, there is no bone overhang that obstructs the line of sight to the midline anterior skull base. This exposure increases the inferior-to-superior viewing angle into the top of the third ventricle through the lamina terminalis, and minimizes the degree of brain retraction. By performing a bifrontal craniotomy and also bifrontal dural incision with division of the SSS and falx, the surgeon's line of sight is directly in the midline. The contralateral frontal lobe is spared from retraction, but will naturally fall away from the skull base during the operation, thereby increasing the working corridor and angles of attack to the tumor without obstruction by the falx cerebri. In unilateral subfrontal dural openings, the exposure is slightly off midline and slightly oblique because of the limitations of the falx. The area that is most difficult to visualize when using the subfrontal translamina terminalis approach is the region directly beneath the optic chiasm and nerves. Visualization of this area can be achieved with angled dental mirrors or angled endoscopes.

The transnasal transsphenoidal approach, on the other hand, can provide visualization of the infrachiasmatic area that is hidden from a transcranial view. This approach has generally been reserved for craniopharyngiomas that are primarily subdiaphragmatic in origin and accompanied by an enlarged sella turcica.[13,36,40] However, with advancements in transnasal approaches, such as extended transsphenoidal[11,20,23,27] and endoscopic expanded endonasal approaches,[7,22] suprasellar supradiaphragmatic craniopharyngiomas can be safely removed. Nevertheless, retrochiasmatic and also retroinfundibular craniopharyngiomas remain challenging to remove transnasally.[22] They are often densely adherent to the diaphragm, major arteries, and perforating vessels, the pituitary stalk, and the walls of the third ventricle. Careful microdissection of these vital neurovascular structures via a transnasal approach can be difficult and at times precarious.[36] Division of the diaphragma sellae increases the risk of a CSF leak;[13,36] however, this has been largely reduced by using a vascularized nasoseptal flap for CSF leak repair.[21] In addition, the pituitary gland often must be mobilized to improve suprasellar and supradiaphragmatic visualization, thereby increasing the risk of endocrine dysfunction.[13,22]

The transpetrosal approach to retrochiasmatic craniopharyngiomas was pioneered by Hakuba et al.[17] and Al-Mefty and colleagues.[1,2] These authors have favored this approach because it allows an upward projection to be used to dissect the upper pole of the tumor, with direct visualization of the hypothalamus and pituitary stalk.[1,2] The disadvantages of this approach are prolonged temporal lobe retraction, potential injury to the vein of Labbé, technical difficulty in performing a mastoidectomy in young children with a nonpneumatized mastoid sinus, and also the aforementioned disadvantages associated with coming in from a lateral projection.

Avoiding Complications

Thorough knowledge of and attention to vital anatomical structures is of paramount importance to successful surgical removal of these tumors. Craniopharyngiomas can be densely adherent to the major arteries of the circle of Willis.[8,13] They receive their blood supply from perforating vessels of the PCoA and branches of the ICA that also supply the pituitary stalk.[8,40] The infundibulum can be significantly displaced, and should be identified on preoperative imaging during development of the surgical plan. Occasionally, however, the tumor arises from within the infundibulum and obliterates the stalk completely.[22] Third ventricular anatomy can also be notably altered. Particular attention should be paid to the hypothalamus, mammillary bodies, velum interpositum, Liliequist membrane, and interpeduncular cistern.

Endocrinological dysfunction,[4,17,30] hypothalamic dysfunction,[2,34] death,[2,29] and blindness[4,40] are substantial adverse outcomes that must be discussed with the patient and family prior to surgery. Adequate hormone replacement is fundamental in decreasing morbidity, because the pituitary stalk is often intimately involved with the tumor capsule.[4–6,12,16,19,26,28,35,39]

Significant morbidity can result from overly aggressive resection. Determining the extent of resection is a difficult task, but may save the patient from significant morbidity. Factors precluding complete resection include adherence to or invasion of the hypothalamus,[13,36] location of the tumor,[13,36] size of the tumor,[13,37] consistency of the tumor,[25,36] and more than 10% calcification.[13] Despite the primary goal of total removal, it is important to know when to perform a subtotal resection after recognizing the aforementioned intraoperative findings that may risk permanent injury to critical neurovascular structures.

Standard microsurgical techniques should be used during the dissection of craniopharyngiomas. Maintaining the arachnoid planes will assist the surgeon in the dissection of the tumor capsule away from the neurovascular structures. The optimal plane of dissection is between the

capsule and the tumor arachnoid. Additionally, optimal tumor debulking and cyst aspiration prior to dissection allows for greater mobility of the capsule wall and safer dissection, particularly when delivering large tumors through a relatively small window, such as the lamina terminalis.

Conclusions

The transbasal subfrontal approach provides direct midline access to the lamina terminalis for removal of retrochiasmatic craniopharyngiomas with third ventricular extension. By maintaining a midline orientation, excellent visualization of both walls of the third ventricle and hypothalamus as well as access to the interpeduncular cistern and retrosellar region can be achieved to permit total removal of these formidable tumors. The plane of dissection should be maintained between the capsule and the tumor arachnoid.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: JK Liu, LD Christiano. Acquisition of data: LD Christiano, G Gupta. Analysis and interpretation of data: JK Liu. Drafting the article: JK Liu, LD Christiano, G Gupta. Critically revising the article: JK Liu, LD Christiano, PW Carmel. Reviewed final version of the manuscript and approved it for submission: JK Liu, LD Christiano, G Gupta, PW Carmel. Study supervision: JK Liu, PW Carmel.

References

1. Al-Mefty O, Ayoubi S, Kadri PA: The petrosal approach for the resection of retrochiasmatic craniopharyngiomas. **Neurosurgery 62 (5 Suppl 2):**ONS331–ONS336, 2008
2. Al-Mefty O, Ayoubi S, Kadri PA: The petrosal approach for the total removal of giant retrochiasmatic craniopharyngiomas in children. **J Neurosurg 106 (2 Suppl):**87–92, 2007
3. Ammirati M, Samii M, Sephernia A: Surgery of large retrochiasmatic craniopharyngiomas in children. **Childs Nerv Syst 6:**13–17, 1990
4. Baskin DS, Wilson CB: Surgical management of craniopharyngiomas. A review of 74 cases. **J Neurosurg 65:**22–27, 1986
5. Bertherat J, Carel JC, Adamsbaum C, Bougnères PF, Chaussain JL: [Endocrine evaluation and evolution of intrasellar craniopharyngioma (CPIS): study of 8 cases.] **Arch Pediatr 1:**886–893, 1994 [Fr]
6. Brauner R, Malandry F, Rappaport R, Pierre-Kahn A, Hirsch JF: [Craniopharyngioma in children. Endocrine evaluation and treatment. Apropos of 37 cases.] **Arch Fr Pediatr 44:**765–769, 1987 [Fr]
7. Cappabianca P, Cavallo LM, Colao A, Del Basso De Caro M, Esposito F, Cirillo S, et al: Endoscopic endonasal transsphenoidal approach: outcome analysis of 100 consecutive procedures. **Minim Invasive Neurosurg 45:**193–200, 2002
8. Carmel PW: Craniopharyngiomas, in Winn R (ed): **Youmans Neurological Surgery, 5th ed.** Philadelphia: W. B. Saunders Company, 2003
9. Carmel PW: Tumours of the third ventricle. **Acta Neurochir (Wien) 75:**136–146, 1985
10. Cole C, Gottfried O, Gupta D, Couldwell W: Total intravenous anesthesia: advantages for intracranial surgery. **Neurosurgery 61:**369–377, 2007
11. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T: Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. **Neurosurgery 55:**539–550, 2004
12. de Vries L, Lazar L, Phillip M: Craniopharyngioma: presentation and endocrine sequelae in 36 children. **J Pediatr Endocrinol Metab 16:**703–710, 2003
13. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
14. Garcia-Uria J: Surgical experience with craniopharyngioma in adults. **Surg Neurol 9:**11–14, 1978
15. Golshani KJ, Lalwani K, Delashaw JB, Selden NR: Modified orbitozygomatic craniotomy for craniopharyngioma resection in children. **J Neurosurg Pediatr 4:**345–352, 2009
16. Gonc EN, Yordam N, Ozon A, Alikasifoglu A, Kandemir N: Endocrinological outcome of different treatment options in children with craniopharyngioma: a retrospective analysis of 66 cases. **Pediatr Neurosurg 40:**112–119, 2004
17. Hakuba A, Nishimura S, Inoue Y: Transpetrosal-transtentorial approach and its application in the therapy of retrochiasmatic craniopharyngiomas. **Surg Neurol 24:**405–415, 1985
18. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI: Aggressive surgical management of craniopharyngiomas in children. **J Neurosurg 76:**47–52, 1992
19. Honegger J, Buchfelder M, Fahlbusch R: Surgical treatment of craniopharyngiomas: endocrinological results. **J Neurosurg 90:**251–257, 1999
20. Kaptain G, Vincent D: Sheehan J, Laws ER, Jr.: Transsphenoidal approaches for the extracapsular resection of midline suprasellar and anterior cranial base lesions. **Neurosurg 62:**1264–1271, 2008
21. Kassam A, Thomas A, Carrau RL, Snyderman C, Vescan A, Prevedello D, et al: Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. **Neurosurg 63 (1 Suppl):**ONS44–ONS53, 2008
22. Kassam AB, Gardner PA, Snyderman CH, Carrau RL, Mintz AH, Prevedello DM: Expanded endonasal approach, a fully endoscopic transnasal approach for the resection of midline suprasellar craniopharyngiomas: a new classification based on the infundibulum. **J Neurosurg 108:**715–728, 2008
23. Kouri JG, Chen MY, Watson JC, Oldfield EH: Resection of suprasellar tumors by using a modified transsphenoidal approach. Report of four cases. **J Neurosurg 92:**1028–1035, 2000
24. Lehrnbecher T, Müller-Scholden J, Danhauser-Leistner I, Sörensen N, von Stockhausen HB: Perioperative fluid and electrolyte management in children undergoing surgery for craniopharyngioma. A 10-year experience in a single institution. **Childs Nerv Syst 14:**276–279, 1998
25. Liu JK, Cole CD, Kestle JR, Brockmeyer DL, Walker ML: Cranial base strategies for resection of craniopharyngioma in children. **Neurosurg Focus 18(6A):**E9, 2005
26. Lyen KR, Grant DB: Endocrine function, morbidity, and mortality after surgery for craniopharyngioma. **Arch Dis Child 57:**837–841, 1982
27. Maira G, Anile C, Albanese A, Cabezas D, Pardi F, Vignati A: The role of transsphenoidal surgery in the treatment of craniopharyngiomas. **J Neurosurg 100:**445–451, 2004
28. Maira G, Anile C, Colosimo C, Cabezas D: Craniopharyngiomas of the third ventricle: trans-lamina terminalis approach. **Neurosurgery 47:**857–865, 2000
29. Maira G, Anile C, Rossi GF, Colosimo C: Surgical treatment of craniopharyngiomas: an evaluation of the transsphenoidal and pterional approaches. **Neurosurgery 36:**715–724, 1995
30. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thomp-

son SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
31. Patterson RH Jr, Danylevich A: Surgical removal of craniopharyngiomas by the transcranial approach through the lamina terminalis and sphenoid sinus. **Neurosurgery 7:**111–117, 1980
32. Rutka JT: Craniopharyngioma. **J Neurosurg 97:**1–2, 2002
33. Schwartz MS, Anderson GJ, Horgan MA, Kellogg JX, McMenomey SO, Delashaw JB Jr: Quantification of increased exposure resulting from orbital rim and orbitozygomatic osteotomy via the frontotemporal transsylvian approach. **J Neurosurg 91:**1020–1026, 1999
34. Scott RM: Craniopharyngioma: a personal (Boston) experience. **Childs Nerv Syst 21:**773–777, 2005
35. Sklar CA: Craniopharyngioma: endocrine sequelae of treatment. **Pediatr Neurosurg 21 (Suppl 1):**120–123, 1994
36. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
37. Villani RM, Tomei G, Bello L, Sganzerla E, Ambrosi B, Re T, et al: Long-term results of treatment for craniopharyngioma in children. **Childs Nerv Syst 13:**397–405, 1997
38. Wang KC, Kim SK, Choe G, Chi JG, Cho BK: Growth patterns of craniopharyngioma in children: role of the diaphragm sellae and its surgical implication. **Surg Neurol 57:**25–33, 2002
39. Wang L, Zhao SF, Zhang W, Zhang MZ: Treatment of alternated water-electrolyte balance and endocrine status after removal of craniopharyngioma in adults. **Chin Med J (Engl) 119:**1348–1352, 2006
40. 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
41. Yaşargil MG, Reichman MV, Kubik S: Preservation of the frontotemporal branch of the facial nerve using the interfascial temporalis flap for pterional craniotomy. Technical article. **J Neurosurg 67:**463–466, 1987

Manuscript submitted December 14, 2009.
Accepted January 14, 2010.

Address correspondence to: James K. Liu, M.D., Department of Neurological Surgery, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, 90 Bergen Street, Suite 8100, Newark, New Jersey 07101. email: james.liu@umdnj.edu.

Neurosurg Focus 28 (4):E7, 2010

Amaurosis in infancy due to craniopharyngioma: a not-exceptional but often misdiagnosed symptom

Alberto Feletti, M.D.,[1] Elisabetta Marton, M.D.,[1] Grazia Marina Mazzucco, M.D.,[1] Shanna Fang, B.S.,[2] and Pierluigi Longatti, M.D.[1]

[1]Department of Neurosurgery, Treviso Regional Hospital–University of Padova, Treviso, Italy; and [2]Department of Neurological Surgery, University of California, San Francisco, California

Since children may not be able to complain of progressive reduction in optic acuity, visual assessment in infancy may present practical difficulties. The authors report a case of craniopharyngioma, which led a young child to early blindness before the correct diagnosis could be made. Similar to other reported cases, the authors found that surgery did not substantially modify the preoperative visual deficit. They conclude that minimal improvement in visual acuity can be expected despite successful microsurgical removal of the tumor. *(DOI: 10.3171/2010.1.FOCUS09262)*

Key Words • **craniopharyngioma** • **amaurosis** • **childhood** • **misdiagnosis** • **visual outcome**

Craniopharyngiomas are rare brain tumors that cause visual impairments and symptoms in almost all cases. Visual disturbances are notoriously misleading in infancy since ophthalmological symptoms are difficult to detect, and they commonly result in incorrect differential diagnoses. Furthermore, it is not easy to determine the indication for neuroradiological assessment in children whose visual symptoms are unclear.

Although rarely, pediatric patients may undergo neurosurgical evaluation when amaurosis is already present. The reported case illustrates how the rare but insidious craniopharyngioma can cause amaurosis to be misdiagnosed as more benign visual impairments.

Case Report

This 2-year-old girl presented with a 9-month history of progressive divergent strabismus, which began initially in the left eye, and then progressed to bilateral strabismus. The pediatric ophthalmologist, diagnosing the patient with congenital strabismus, prescribed the usual occlusion therapy to avoid amblyopia and continued with patient follow-up. After some months, however, the child's relatives noted some gait uncertainty, with disequilibrium, frequent falls, and difficulty in evaluating the distances of objects. The little girl walked up the stairs, touching the steps one by one; when the floor changed color, she stopped walking, squatted down, and felt her way along the floor to determine if there was a step in front of her. This behavior frightened her parents who brought their daughter to our hospital for an urgent evaluation. At admission, the child's hypothalamus-pituitary axis function was unimpaired, but fundus oculi examination revealed an atrophic papilla (Fig. 1). Magnetic resonance imaging showed the presence of an expansive sellar lesion of 3.8-cm maximum diameter, with severe compression of the optic chiasm, suggesting a diagnosis of craniopharyngioma (Fig. 2). Visual evoked potentials demonstrated a complete absence of cortical signal (Fig. 3).

The tumor, found to be adherent to the optic nerves, was radically removed through a frontobasal interhemispheric approach with preservation of the pituitary stalk. Pathological examination confirmed the diagnosis of adamantinomatous craniopharyngioma (WHO Grade I). Aside from transient polydipsia, the patient's postoperative recovery was uneventful, although she continues to experience subtotal visual deficit and unstable gait. An MR imaging examination 1 year after surgery confirmed complete removal of the tumor (Fig. 2).

Discussion

The child whose case is reported above developed visual disturbances without anyone noticing it until an almost complete amaurosis: the ophthalmologist focused on the strabismus, disregarding the progressive loss of visual acuity. It is surprising that in this era a benign tumor like craniopharyngioma could be detected only after such serious damage to the optic nerves.

Despite the vast amount of literature on craniopha-

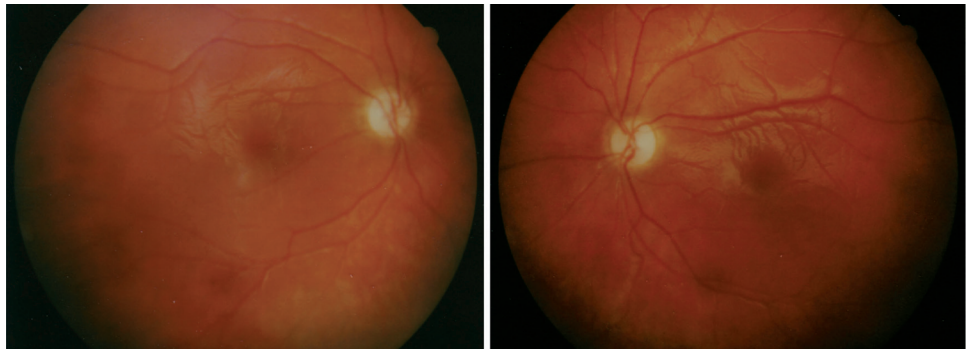

Fig. 1. Fundus oculi revealing an atrophic papilla.

ryngiomas, the incidence of amaurosis due to this benign tumor in the pediatric population has not yet been established. We reviewed the literature to identify all cases of craniopharyngiomas causing blindness in children and found an incidence of amaurosis ranging from 0 to 33% (Table 1). It is remarkable that the highest incidences often correspond to series of patients from developing countries,[2,16] or from specific subpopulations such as giant craniopharyngiomas.[3] It is likely that amaurosis is not that unusual a symptom in infants with craniopharyngioma, but its prevalence is probably underestimated. The high variability in reported incidence rates may be due to difficulty in assessing visual acuity in very young children, who are usually unable to communicate these important visual changes. The reported frequency of visual disturbances due to craniopharyngioma is higher in the adult population than in children,[26] probably because of frequent misdiagnosis in pediatric patients. Furthermore, young age at diagnosis and the presence of visual symptoms are unfavorable predictors of visual outcome since

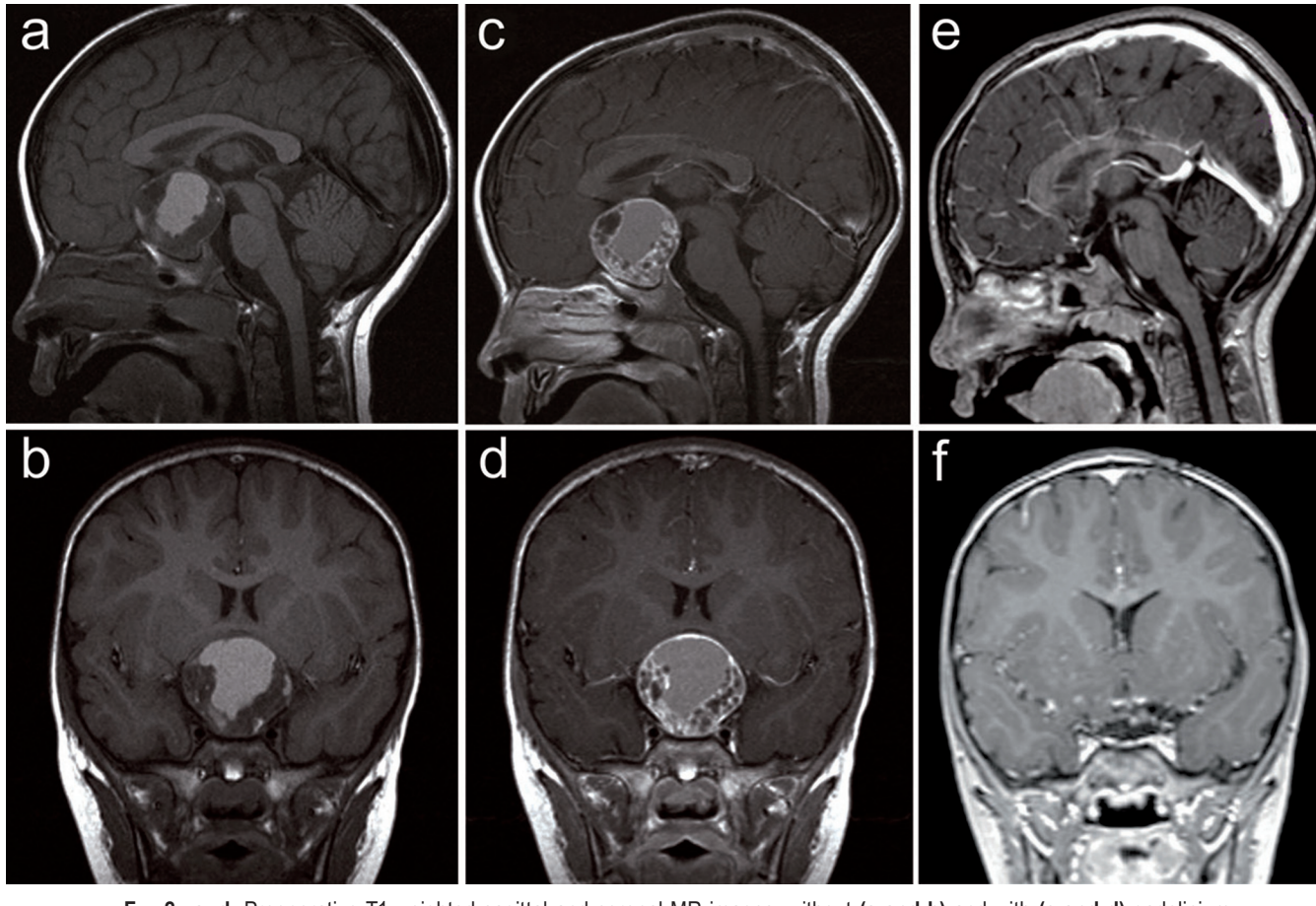

Fig. 2. a–d: Preoperative T1-weighted sagittal and coronal MR images, without **(a and b)** and with **(c and d)** gadolinium, demonstrating the presence of an expansive sellar lesion of 3.8-cm maximum diameter, with considerable compression of the optic chiasm. **e and f:** Postoperative Gd-enhanced T1-weighted sagittal and coronal MR images obtained 1 year after surgery confirming complete removal of the tumor and absence of any recurrence.

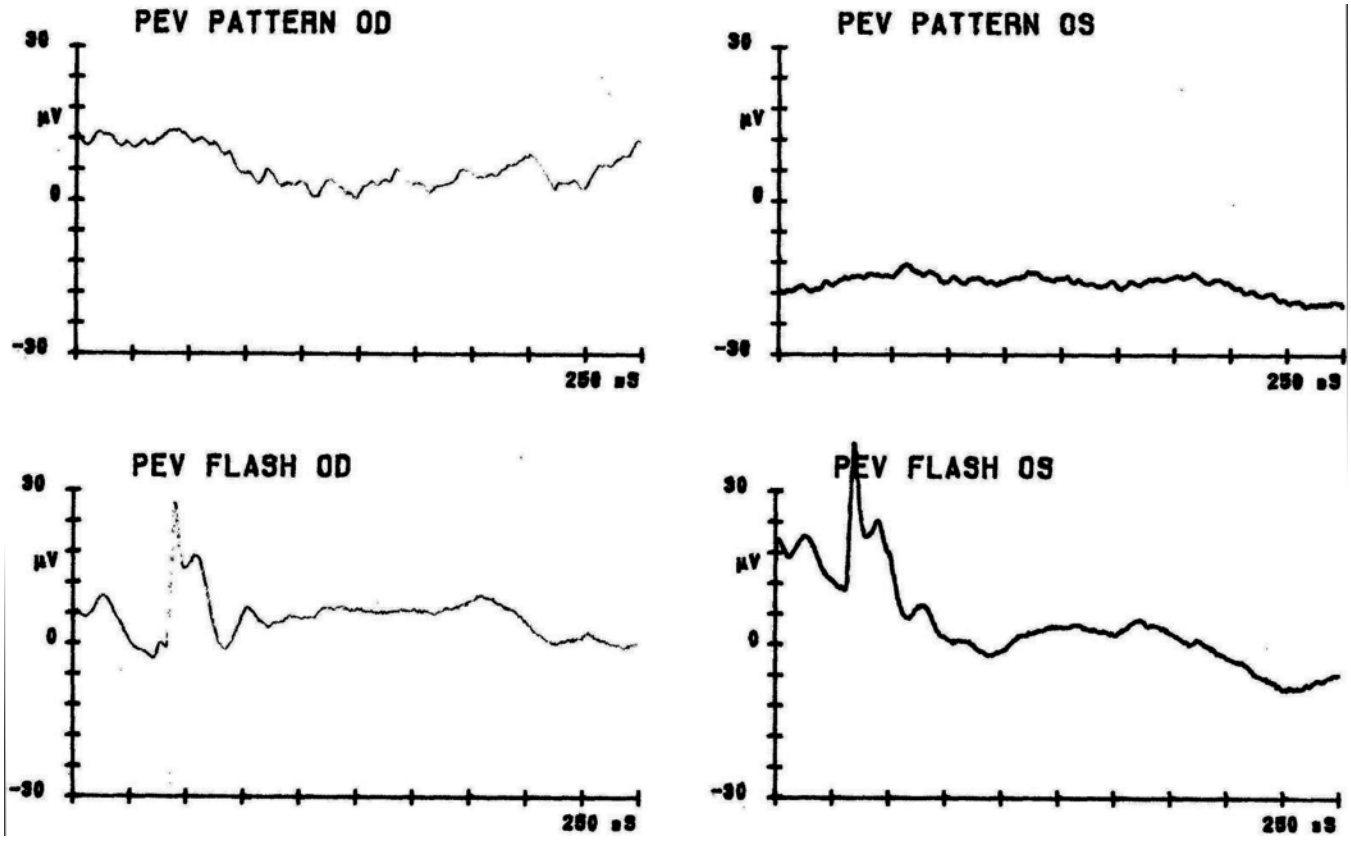

Fig. 3. Preoperative pattern and flash visual evoked potentials showing an almost complete absence of cortical signal. OS = left eye; OD = right eye; PEV = visual evoked potentials.

impairment of the optic pathways occurs more rapidly in children under 3 years of age.[1,13] It has been demonstrated that visual acuity deficits seldom improve even after surgical decompression of optic nerves;[13] in fact, the deficit often remains unchanged or continues to worsen.[2,6,7,28] For patients suffering from amaurosis, it is suggested that preoperative visual loss is strongly predictive of persistent postoperative visual deficits.[13]

Pediatric patients presenting with amaurosis and showing improvement in visual function after surgical treatment of craniopharyngioma are extremely rare.[4,18,25] The complete vision recovery in a 9-year-old girl reported by Stark et al.[28] should be considered exceptional. In fact, only a few cases of complete visual recovery after surgery have been reported in patients suffering from nontraumatic compression of the anterior visual pathway.[14,28,29] All other pediatric patients for whom clinical evaluation at follow-up is available showed uniformly persistent visual acuity deficits. Although pediatric craniopharyngioma patients presenting with amaurosis are often included in larger series and specific visual follow-up is only occasionally available, the outcome for unilateral amaurosis does not seem to be different than that for bilateral amaurosis.[3,5,10] No significant improvement should be expected when serious damage to one or both optic nerves is present.[10,21]

For these reasons, a well-timed diagnosis of visual impairments is vital to avoid irreparable deficits in children. Special attention to any behavioral change, usually reported by parents, is sometimes the most important way to reduce the diagnostic delay. Moreover, neuroradiological assessments like MR imaging should be taken into consideration in cases of long-lasting strabismus or papillary alterations on fundus oculi examination.

Although visual function only occasionally improves after surgery, especially in cases of amaurosis, every effort should be made to preserve the anatomical integrity of the optic nerve during the removal of the tumor. The surgical planning is important, as the pterional approach carries a not-negligible risk of postoperative visual worsening.[23] Instead, we chose the interhemispheric approach, which allows for minimal traction on the optic structures.

Due to the excellent survival rates of these patients in the modern era, long-term consequences of treatment and overall quality of life are of utmost importance, especially when deciding on a treatment strategy. In addition to the visual deficits, endocrine balance, neurological and hypothalamic function, school performance, and behavioral and emotional status are often impaired in patients with craniopharyngioma.[24] Therefore, these children may have a worse quality of life than patients who are blind for other causes. In the major pediatric series of surgically treated cases, the rates of diabetes insipidus and hypothalamic obesity vary between 33–100% and 15–94%, respectively, and the incidences of visual deficits and neurological morbidity vary between 0 and 41% and 0 and 29%,

TABLE 1: Review of amaurosis caused by craniopharyngioma in childhood*

Authors & Year	No. of Pts	No. of Pts w/ Amaurosis (%)		Outcome	FU
		Monolat	Bilat		
Kennedy & Smith, 1975	14	1 (7)			
Al-Mefty et al., 1985	20†	2 (10)	5 (25)	not impr	up to 3 yrs
Adeloye et al., 1988	20		4 (20)	not impr	
Ammirati et al., 1990		1		not impr	
al-Wahhabi et al., 1993	1		1	rt eye: impr; lt eye: not impr	2 wks
Abrams & Repka, 1997	20	2 (10)‡		8 pts‡	mean 6.5 yrs
Stark et al., 1999	1	1		impr	6 yrs
Duff et al., 2000		5		80% poor	
Van Effenterre & Boch, 2002	29		7 (24)		
Gonc et al., 2004	64	14 (22)	6 (9)		median 5.1 yrs
Erşahin et al., 2005	87	13 (15)			
Hukin et al., 2005	29	2 (7)	2 (7)	impr	median 84 mos
Lena et al., 2005	47	3 (6)	2 (4)	not impr	min 5 yrs
Mottolese et al., 2005	60		2 (3)		
Teo, 2005	36		5 (14)		
Sainte-Rose et al., 2005	66		7 (10)		mean 7 yrs
Zuccaro, 2005	153		13 (8.5)	not impr	
Hamid et al., 2007	12		4 (33)		
Puget et al., 2007	66 (retrosp)	10 (15)		not impr	
	22 (prosp)	4 (18)		3 impr	

* FU = follow-up; impr = improved; prosp = prospective; Pts = patients; retrosp = retrospective.
† Giant craniopharyngiomas.
‡ Visual acuity < 20/200.

respectively.[11,24] Moreover, several authors reported worse outcome and a higher chance of recurrence in younger children.[8,9,12,13] Age under 5 years has been reported to be a predictor of poor outcome at a long-term follow-up,[9] higher risk of tumor progression following Gamma Knife surgery,[20] and decreased resistance of the hypothalamus to surgical trauma.[17]

The case presented in this paper and those reviewed in the literature caution against underestimation of visual impairments in children, and demonstrate the importance of careful ophthalmological evaluation in pediatric patients who are often unable to identify and reliably report visual deficits. In order to arrive at the correct diagnosis, the physician often needs to know details of the child's daily behavior and changes of habits, as provided by the parents of the child in our case.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: A Feletti. Acquisition of data: A Feletti. Analysis and interpretation of data: A Feletti. Drafting the article: A Feletti. Critically revising the article: E Marton, GM Mazzucco, S Fang, P Longatti. Reviewed final version of the manuscript and approved it for submission: A Feletti, E Marton, GM Mazzucco, S Fang, P Longatti. Study supervision: P Longatti.

References

1. Abrams LS, Repka MX: Visual outcome of craniopharyngioma in children. **J Pediatr Ophthalmol Strabismus 34:**223–228, 1997
2. Adeloye A, Nottidge VA, Udi J: Craniopharyngioma in Nigerian children. **Childs Nerv Syst 4:**128–134, 1988
3. Al-Mefty O, Hassounah M, Weaver P, Sakati N, Jinkins JR, Fox JL: Microsurgery for giant craniopharyngiomas in children. **Neurosurgery 17:**585–595, 1985
4. al-Wahhabi B, Choudhury AR, al-Moutaery KR, Aabed M, Faqeeh A: Giant craniopharyngioma with blindness reversed by surgery. **Childs Nerv Syst 9:**292–294, 1993
5. Ammirati M, Samii M, Sephernia A: Surgery of large retrochiasmatic craniopharyngiomas in children. **Childs Nerv Syst 6:**13–17, 1990
6. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C: Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. **Childs Nerv Syst 21:**747–757, 2005
7. Chen C, Okera S, Davies PE, Selva D, Crompton JL: Craniopharyngioma: a review of long-term visual outcome. **Clin Experiment Ophthalmol 31:**220–228, 2003
8. Choux M, Lena G, Genitori L: Le craniopharyngiome de l'enfant. **Neurochirurgie 37 (1 Suppl):**1–174, 1991
9. De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, et al: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? **J Neurosurg 85:**73–81, 1996
10. Duff JM, Meyer FB, Ilstrup DM, Laws ER, Schleck CD, Scheithauer BW: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000

11. Elliott RE, Wisoff JH: Successful surgical treatment of craniopharyngioma in very young children. **J Neurosurg Pediatr 3:**397–406, 2009
12. Erşahin Y, Yurtseven T, Ozgiray E, Mutluer S: Craniopharyngiomas in children: Turkey experience. **Childs Nerv Syst 21:**766–772, 2005
13. Fisher PG, Jenab J, Gopldthwaite PT, Tihan T, Wharam MD, Foer DR, et al: Outcomes and failure patterns in childhood craniopharyngiomas. **Childs Nerv Syst 14:**558–563, 1988
14. Garrott HM, Wallace D, Wallace DJ: Ossifying fibroma of the jugum sphenoidale. **J Clin Neurosci 11:**544–546, 2004
15. Gonc EN, Yordam N, Ozon A, Alikasifoglu A, Kandemir N: Endocrinological outcome of different treatment options in children with craniopharyngioma: a retrospective analysis of 66 cases. **Pediatr Neurosurg 40:**112–119, 2004
16. Hamid R, Sarkar S, Hossain MA, Mazumder U, Akanda NI, Parvin R: Clinical picture of craniopharyngioma in childhood. **Mymensingh Med J 16:**123–126, 2007
17. Hayward R: The present and future management of childhood craniopharyngioma. **Childs Nerv Syst 15:**764–769, 1999
18. Hukin J, Visser J, Sargent M, Goddard K, Fryer C, Steinbok P: Childhood craniopharyngioma: Vancouver experience. **Childs Nerv Syst 21:**758–765, 2005
19. Kennedy HB, Smith RJ: Eye signs in craniopharyngioma. **Br J Ophthalmol 59:**689–695, 1975
20. Kobayashi T, Kida Y, Mori Y, Hasegawa T: Long-term results of gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. **J Neurosurg 103 (6 Suppl):**482–488, 2005
21. Lena G, Paz Paredes A, Scavarda D, Giusiano B: Craniopharyngioma in children: Marseille experience. **Childs Nerv Syst 21:**778–784, 2005
22. Mottolese C, Szathmari A, Berlier P, Hermier M: Craniopharyngiomas: our experience in Lyon. **Childs Nerv Syst 21:** 790–798, 2005
23. Pierre-Kahn A, Sainte-Rose C, Renier D: Surgical approach to children with craniopharyngiomas and severely impaired vision: special considerations. **Pediatr Neurosurg 21 (Suppl 1):**50–56, 1994
24. Poretti A, Grotzer MA, Ribi K, Schönle E, Boltshauser E: Outcome of craniopharyngioma in children: long-term complications and quality of life. **Dev Med Child Neurol 46:**220–229, 2004
25. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106 (1 Suppl):**3–12, 2007
26. Rushing EJ, Giangaspero F, Paulus W, Burger PC: Craniopharyngioma, in Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds): **WHO Classification of Tumours of the Central Nervous System.** Lyon: IARC Press, 2007, pp 238–240
27. Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, et al: Craniopharyngioma: the pendulum of surgical management. **Childs Nerv Syst 21:**691–695, 2005
28. Stark KL, Kaufman B, Lee BC, Primack J, Tychsen L: Visual recovery after a year of craniopharyngioma-related amaurosis: report of a nine-year-old child and a review of pathophysiologic mechanisms. **J AAPOS 3:**366–371, 1999
29. Taşdemiroğlu E, Zuccarello M, Tew JM Jr: Recovery of vision after transcranial decompression of pituitary apoplexy characterized by third ventricular hemorrhage. **Neurosurgery 32:**121–124, 1993
30. Teo C: Application of endoscopy to the surgical management of craniopharyngiomas. **Childs Nerv Syst 21:**696–700, 2005
31. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
32. Zuccaro G: Radical resection of craniopharyngioma. **Childs Nerv Syst 21:**679–690, 2005

Manuscript submitted November 10, 2009.
Accepted January 19, 2010.

Address correspondence to: Alberto Feletti, M.D., Department of Neurosurgery, Treviso Regional Hospital–University of Padova, 31100, Treviso, Italy. email: alberto.feletti@unipd.it.

See the corresponding editorial, **DOI:** 10.3171/2010.2.FOCUS104.

Endocrinological and ophthalmological consequences of an initial endonasal endoscopic approach for resection of craniopharyngiomas

Peter G. Campbell, M.D.,[1] Brian McGettigan, M.D.,[2] Adam Luginbuhl, M.D.,[2] Sanjay Yadla, M.D.,[1] Marc Rosen, M.D.,[2] and James J. Evans, M.D.[1]

Departments of [1]Neurosurgery and [2]Otolaryngology, Thomas Jefferson University, Philadelphia, Pennsylvania

Object. The expanded endoscopic approach to craniopharyngiomas has recently been described in several small case series. The authors present their experience with this technique and review the available literature.

Methods. Between September 2006 and September 2009, 14 patients underwent a purely endoscopic, endonasal approach for resection of newly diagnosed craniopharyngiomas. These procedures represent index surgeries; no patient had undergone previous tumor resection. A retrospective review of endocrinological and ophthalmological outcomes, extent of resection, and complication prevalence was completed. Additionally, a review of the English literature was performed to evaluate outcomes of similar endoscopic techniques for resection of craniopharyngiomas.

Results. Four patients (28.6%) underwent gross-total resection; near total resection or better was achieved in 9 patients (64.3%). All patients presented with some form of visual field or acuity deficit. Postoperatively, 12 patients (85.7%) experienced visual improvement, with 6 patients (42.9%) having complete visual recovery. One patient experienced worsening of her visual deficit. Visual acuity improved in 8 patients ((57.1%), while visual field defects improved in 11 (78.6%). The pituitary stalk was preserved in all cases. Eight (57.1%) of 14 patients experienced some form of anterior pituitary dysfunction postoperatively. Although 9 patients (64.3%) were documented to have either transient or permanent new diabetes insipidus immediately after surgery, at 1-month follow-up only 1 patient met clinical criteria. Five patients (35.7%) developed CSF leaks that were successfully treated by subsequent endoscopic revision. All CSF leaks occurred early in the series. Two patients (14.2%) were treated for presumed meningitis postoperatively.

Conclusions. The endoscopic endonasal approach is a minimally invasive alternative to open transcranial approaches for select craniopharyngiomas. Similar to previous transcranial series, rates of endocrinopathy and gross-total resection were dependent upon the adherence of the tumor capsule to the hypothalamus, pituitary stalk, and associated vasculature. A review of the literature suggests that the results of the current series are similar to other published series on this topic. *(DOI: 10.3171/2010.1.FOCUS09292)*

Key Words • **craniopharyngioma** • **endonasal resection** • **endoscopic resection** • **endocrinology** • **ophthalmology** • **outcome**

Craniopharyngiomas are rare tumors that originate from squamous epithelial remnants of the Rathke pouch. Craniopharyngiomas are designated as a WHO Grade I tumor, comprising 2 to 5% of all CNS tumors.[43,57] Adamantinomatous and papillary histological subtypes of craniopharyngiomas have been described. The adamantinomatous type may be encountered at any age, but predominantly in the first 2 decades of life.[54] The papillary variety has been primarily reported in adults.[1,54] Some authors report a lower recurrence rate with the papillary variety, while others have found no difference in surgical outcome or recurrence between the 2 subtypes.[1,17,54] Despite a benign histological classification, craniopharyngiomas are often associated with a poor prognosis and their optimal treatment remains controversial.[31]

Secondary to mass effect, these tumors commonly lead to neurological, endocrinological, or visual symptoms. Patients with these tumors often present with impaired pituitary function.[33] Reported rates for anterior pituitary hormone deficits prior to any operative intervention vary from 35 to 95% for growth hormone, 38 to 82% for follicle-stimulating hormone/luteinizing hormone, 21 to 62% for corticotrophin, and 21 to 42% for thyroid-stimulating hormone.[32] Authors of large patient series have reported that between 6 and 38% of patients present with insufficient secretion of antidiuretic hormone.[32] Because of the proximity of these tumors to the optic chiasm, bitemporal hemianopia has been reported

Abbreviations used in this paper: DI = diabetes insipidus; GTR = gross-total resection; NTR = near total resection; STR = subtotal resection; VP = ventriculoperitoneal.

TABLE 1: Patient and tumor characteristics*

Case No.	Age (yrs), Sex	Presenting Complaint/Hx (duration)	Tumor Consistency	Tumor Size (cm)/Extension
1	44, M	blurry vision (1 mo)	cystic/solid	5.7 × 4.0 × 5.1/suprasellar extending to 3rd ventricle, subfrontal area
2	29, F	bitemporal visual field loss, HA	solid	1.5 × 1.1 × 1.5/sellar-suprasellar
3	56, M	OD blindness, OS field deficits (2 wks)	cystic/solid	2.8 × 2.9 × 2.6/suprasellar compressing 3rd ventricle
4	58, F	progressive visual loss, cognitive deficits, lt hemiparesis	solid	2.6 × 4.1 × 3.8/sellar-suprasellar compressing 3rd ventricle, hypothalamus
5	24, M	progressive visual loss OD > OS, HA (1 mo)	cystic/solid	3.6 × 2.1 × 2.9/sellar-suprasellar compressing hypothalamus
6	18, M	hydrocephalus, progressive visual loss, endocrinopathy (3 yrs)	cystic/solid	5.8 × 6.4 × 8.1/sellar-suprasellar e×tending to subfrontal area, corpus callosum
7	34, M	progressive visual loss, OS > OD (2 mos)	cystic/solid	3.5 × 2.7 × 3.1/sellar-suprasellar compressing 3rd ventricle
8	65, F	OD blindness, HA (3 mos)	cystic	1.7 × 2.6 × 2.2/sellar-suprasellar
9	38, M	progressive visual loss, HA	cystic/solid	1.5 × 2.9 × 2.2/sellar-suprasellar compressing 3rd ventricle/hypothalamus
10	56, M	progressive visual loss	cystic/solid	2.0 × 1.5 × 1.9/suprasellar tumor w/ 1.3 × 2.5 × 1.2 cystic compression of the 3rd ventricle
11	64, F	bitemporal hemianopsia, HA	solid	1.5 × 1.9 × 1.8/suprasellar
12	49, M	progressive visual loss, HA	cystic/solid	2.0 × 2.0 × 1.7/suprasellar compressing 3rd ventricle
13	51, M	hydrocephalus, progressive visual loss, HA (2 mos)	solid	3.9 × 2.9 × 3.8/suprasellar involving 3rd ventricle
14	55, F	blurry vision, HA, lt face/arm pain (1 yr)	cystic/solid	3.2 × 4.3 × 3.6/suprasellar compressing 3rd ventricle, hypothalamus, thalamus

* All measurements are given in superior/inferior × anteroposterior × transverse dimensions. Abbreviations: HA = headache; OD = oculus dexter (right eye); OS = oculus sinister (left eye).

in as many as 49% of cases.[3,17] In children and adolescents, some authors have reported that presenting signs or symptoms are more typically related to increased intracranial pressure or sexual immaturity.[2,50]

Craniopharyngiomas remain one of the most difficult tumors to treat effectively. Adherence to the pituitary stalk, hypothalamus, and anterior cerebral vessels often makes complete resection unattainable.[49] Involvement of surrounding critical structures, diminutive intraoperative visualization, distorted anatomical relationships, and limited sharp dissection often hinders complete resection regardless of approach.[49] These tumors have traditionally been surgically removed via a microscopic transcranial approach, whereas the transsphenoidal approach, either microsurgical or endoscopic, has been recently used to access intrasellar or subdiaphragmatic tumors.[28,39] With the increasing use of endoscopic techniques and the improved illumination and expansive view they provide, endonasal approaches have shown efficacy and safety in treating certain midline lesions of the cranial base beyond the sellar region.[15,19,29] These approaches provide direct access to pathology, reduce brain retraction and manipulation of the optic chiasm, and may decrease hospital stay and morbidity.[4,8]

The endoscopic endonasal approach is emerging as a credible surgical alternative for removal of select suprasellar craniopharyngiomas.[9,13,15,24] We present a series of 14 cases in which a purely endoscopic, endonasal approach was chosen for the initial resection of craniopharyngiomas. This case series consisted of tumors that advanced superiorly and laterally to the sella, posteriorly to the optic chiasm, and (in some) extended into the third ventricle. Short-term ophthalmological and endocrinological outcomes as well as the extent of resection are reported. A literature review of previously published case series and outcomes after endoscopic endonasal resection is presented.

Methods

Study Population

After obtaining the approval of the Thomas Jefferson University institutional review board to conduct the study, we retrospectively reviewed the medical records of 20 patients who presented to our institution with pathologically confirmed craniopharyngioma between September 2006 and September 2009. Only index surgeries were reviewed; patients with any previous operative interventions or radiotherapy were excluded. Fourteen adult patients ultimately comprised the study population. All patients underwent full preoperative endocrine laboratory evaluations, which were repeated 1 month postoperatively. All patients underwent formal visual field and visual acuity evaluation pre- and postoperatively. Neuroradiological evaluation included skull base protocol MR imaging, with and without intravenous contrast enhancement, as well as high-resolution CT scanning of the craniofacial bones and sella. Postoperative MR imaging was performed within 24 hours of surgery and repeated at 3

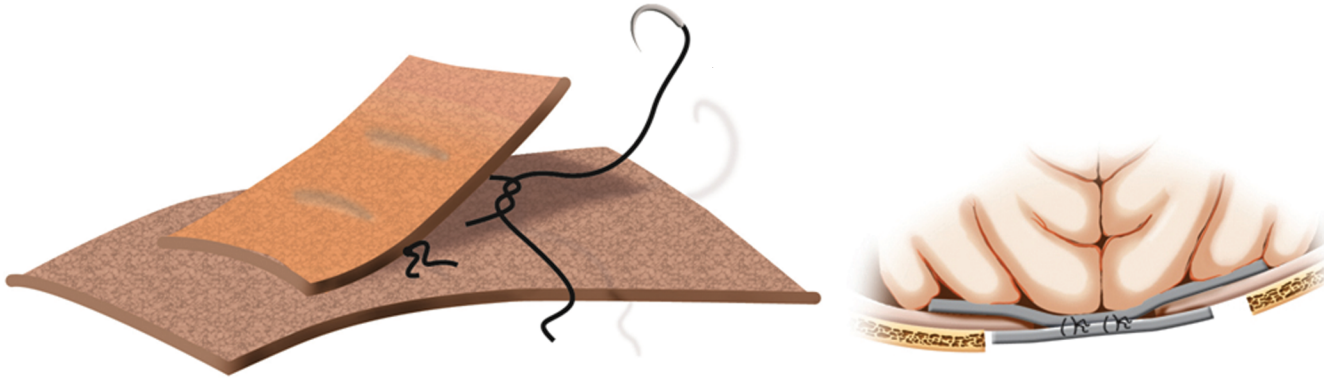

Fig. 1. Illustration of the creation of a "button" graft. **Left:** Two pieces of fascia lata are yoked together using a suture. **Right:** After placement in the skull base dural defect; note that the inlay graft is larger than the onlay portion.

months to confirm the extent of tumor removal. Interpretation of the 3-month MR imaging results was independently performed by a neuroradiologist.

Patients ranged in age from 18 to 65 years, with a mean age of 45 years. The series consisted of 9 men and 5 women (Table 1). Tumors ranged from 1.5 to 5.8 cm at their largest dimension. All tumors extended beyond the sella and 7 compressed the third ventricle. All patients demonstrated some objective visual abnormalities at presentation. One patient (7.1%) presented to the emergency department with DI and the tumor was discovered as a causative factor during further investigation. Seven (50%) of the 14 patients presented with some form of anterior pituitary dysfunction. Length of stay and perioperative complications were recorded and analyzed using logistic regression analysis.

Operative Technique

The initial operative technique for endonasal endoscopic resection of midline skull base lesions has been previously reported in detail in other case series; the approach used in the current series does not differ significantly from that described in the literature.[10,13,34,49] However, reconstruction represents one of the most challenging steps of the expanded approach and the current authors have developed a multilayered closure using a 2-layer fascia lata "button" graft to seal the dural defect. The "button" is constructed of 2 pieces of fascia lata attached to one another by suture (Fig. 1). One layer of the button is inserted inside the defect as an inlay while the other layer lies over the dura as an onlay. The position of the inlay may be manipulated by moving the onlay, since the two are anchored. A nasoseptal flap is then placed against the skull base over the button graft. The graft is secured with synthetic glue (DuraSeal, Confluent Surgical). The middle turbinates are medialized, both to restore normal sinus function and to protect the exposed resection bed. Sheets of Gelfilm (Pfizer) are then placed between the septum and middle turbinate, and in the ostiomeatal complex. No catheters, stents, or balloons are used in this reconstruction.

Literature Review

A literature review of the MEDLINE bibliographic database was performed. Using the key words "craniopharyngioma," "endoscopic," "endonasal," "transsphenoidal," and "surgery," 7 case series devoted to endoscopic endonasal resections of craniopharyngiomas were identified. By searching the bibliographic contents of this series, 1 additional report was found. Case reports were not included in this analysis.

Results

Evaluation of Tumor Resection

The extent of tumor resection was recorded as a GTR when 3 criteria were met: the senior author (J.J.E.) believed no residual disease was present postoperatively, and the immediate postoperative and 3-month follow-up MR imaging findings documented no evidence of residual disease on either scan. In the current series, 4 (28.6%) of 14 patients met these criteria (Table 2; Fig. 2). An NTR was achieved in 5 (35.7%) of 14 patients, indicating removal of at least 95% of the tumor burden. In this group, total resection was limited by residual adherence to neurovascular structures in 2 patients, hypothalamic involvement in 2 patients, and the fifth patient expressed a strong preference for minimal resection favoring the preservation of pituitary function. A statistical ANOVA was performed on the extent of resection as it related to tumor volume. In this analysis, the extent of resection was significantly more likely to be greater in tumors of smaller volume ($p = 0.033$). The pituitary stalk was preserved in all 14 patients.

Ophthalmological Results

All 14 patients underwent ophthalmological evaluation before and after surgical intervention (Table 3). Patients were referred to a neuroophthalmologist for visual acuity as well as formal perimetry and visual field testing. All patients showed evidence of visual defects preoperatively. Bitemporal hemianopsia was the most frequent ophthalmological finding, noted in 7 (50%) of 14 patients. Postoperatively, 12 (85.7%) of 14 patients experienced some visual improvement, with normal vision attained in 6 (42.9%) of 14 patients after tumor resection. Postoperatively, 11 patients (78.6%) showed an improvement in visual fields upon testing, while 8 (57.1%) demonstrated

TABLE 2: Summary of extent of resection, evaluation of residual disease, and pathological subtype of craniopharyngioma*

Case No.	Initial Postop Evaluation of Tumor Resection	Radiographic FU at 3 mos	Radiographic Residual Disease at 3 mos	Ultimate Result	Final Pathology (type)
1	STR, residual adherent to neurovascular structures	crescent-shaped residual tumor enhancement	yes	STR	adamantinomatous
2	NTR, residual where adherent to pituitary stalk	residual sellar tissue enhancement	yes	NTR	adamantinomatous
3	NTR, residual where adherent to medial hypothalamus	partially enhancing suprasellar mass	yes	NTR	papillary
4	STR, residual adherent to infundibulum	residual enhancement	yes	STR	papillary
5	GTR	GTR	no	GTR	adamantinomatous
6	STR, residual adherent to neurovascular structures	large residual sellar-suprasellar mass	yes	STR	adamantinomatous
7	STR, residual adherent to neurovascular structures	peripheral rim/nodular enhancement	yes	STR	adamantinomatous
8	GTR	enhancement of chiasm, likely residual tumor	yes	NTR	adamantinomatous
9	GTR	GTR	no	GTR	adamantinomatous
10	GTR	GTR	no	GTR	adamantinomatous
11	NTR, residual adherent to hypothalamus	minimal residual tissue in suprasellar region	yes	NTR	papillary
12	GTR	GTR	no	GTR	adamantinomatous
13	STR, residual adherent to optic chiasm	large residual sellar-suprasellar mass	yes	STR	adamantinomatous
14	NTR, residual adherent to hypothalamus	residual cystic suprasellar mass	yes	NTR	adamantinomatous

* GTR indicates no radiographic evidence of residual tumor; NTR indicates ≥ 95% removal; STR indicates < 95% removal. Abbreviation: FU = follow-up.

an improvement in acuity. One patient was found to have worsened visual acuity postoperatively.

Endocrinological Results

All patients underwent endocrinological evaluation both preoperatively and 1-month postoperatively with complete serum endocrine panels (Table 4). One patient presented with panhypopituitarism. Seven patients showed no preoperative deficits in anterior pituitary function. Postoperatively, 1 patient experienced new adrenal

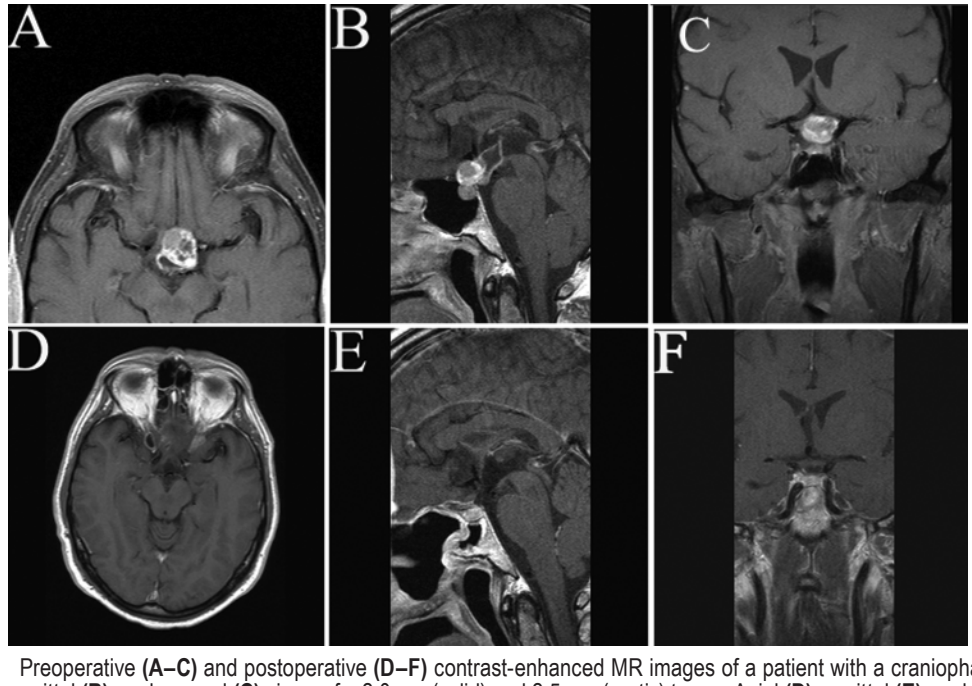

Fig. 2. Preoperative **(A–C)** and postoperative **(D–F)** contrast-enhanced MR images of a patient with a craniopharyngioma. Axial **(A)**, sagittal **(B)**, and coronal **(C)** views of a 2.0-cm (solid) and 2.5-cm (cystic) tumor. Axial **(D)**, sagittal **(E)**, and coronal **(F)** views obtained at the 3-month follow-up showing a GTR of the lesion.

TABLE 3: Ophthalmological results*

Case No.	Presenting Ophthalmological Sx (duration)	Preop Evaluation	Postop Evaluation	Final Assessment
1	blurry vision (1 mo)	OD temporal hemianopsia 20/200, OS NLP	OD temporal hemionopsia 20/70, OS NLP	improved
2	bitemporal visual field loss	OD temporal hemianopsia 20/25, OS temporal hemianopsia 20/15	OD full visual fields 20/25, OS full visual fields 20/15	improved, normalized
3	OD blindness, OS field deficits (2 wks)	OD temporal hemianopsia 20/800, OS temporal hemianopsia 20/200	minimal bitemporal hemianopsia	improved
4	progressive visual loss	OD temporal hemianopsia 20/40, OS temporal hemianopsia 20/70	OD temporal hemianopsia 20/200, OS temporal hemianopsia 20/100	declined
5	progressive visual loss OD > OS (1 mo)	OD 20/400, OS superior temporal quadrantanopsia 20/20	OD 20/25, OS improved superior temporal quadrantanopsia 20/20	improved
6	progressive visual loss (3 yrs)	OD central vertical deficit, restricted upward gaze, able to count fingers; OS NLP	OD full visual fields, weak lateral gaze; OS NLP	improved
7	progressive visual loss OS > OD (2 mos)	OD inferior temporal quadrantanopsia 20/400, OS 20/400	OD 20/50, full visual fields; OS 20/20, full visual fields	improved
8	OD blindness (3 mos)	OD temporal hemianopsia, OS NLP	OD inferior temporal quadrantanopsia 20/100, OS full visual fields 20/25	improved
9	progressive visual loss	OD diminished peripherally all quadrants, OS full visual fields	OD full visual fields, OS full visual fields	improved, normalized
10	progressive visual loss	OD superior/inferior temporal hemianopsia, OS superior/inferior nasal hemianopsia	OD full visual fields, OS full visual fields	improved, normalized
11	bitemporal hemianopsia	OD temporal hemianopsia, OS temporal hemianopsia	OD full visual fields, OS full visual fields	improved, normalized
12	progressive visual loss	OD temporal hemianopsia 20/50, OS superior temporal quadtrantopia 20/100	OD full visual fields, OS full visual fields	improved, normalized
13	progressive visual loss	OD partial temporal field deficit, OS partial temporal field deficit	OD full visual fields, OS full visual fields	improved, normalized
14	blurry vision	OD full visual fields 20/200, OS full visual fields 20/70	OD full visual fields, OS full visual fields	no change

* NLP = no light perception.

insufficiency requiring steroid replacement at 1-month follow-up and 1 patient experienced resolution of adrenal insufficiency. Seven patients demonstrated preoperative deficits in 1 or more hormones secreted by the anterior pituitary axis. Three of these 7 patients experienced a new, single-axis, low serum cortisol requiring hormone replacement. Overall, 9 patients (64.3%) showed no change in their anterior pituitary function, 4 (28.6%) experienced a worsening of preoperative anterior pituitary function in at least 1 axis, and 1 (7.1%) showed an improvement.

Diabetes insipidus was present preoperatively in 1 (7.1%) of 14 patients (Table 4). Postoperatively, 9 patients (64.3%) experienced new DI, according to serum sodium, urine osmolality, and urinary output requiring desmopressin. In 4 patients the DI was transient, resolving after 1 to 5 doses of desmopressin (average of 2 doses). Five (35.7%) of 14 patients had DI at the time of discharge requiring continued administration of desmopressin. However, at the 1-month follow-up evaluation, only 1 patient (7.1%) met clinical criteria for DI requiring continued treatment with desmopressin (considered permanent DI).

Postoperative Complications

Complications related to surgical intervention are listed in Table 5. One patient experienced a decrease in visual acuity postoperatively (Table 3). Although there was a preoperative visual deficit with reported recent deterioration, postoperatively there was further worsening in the patient's acuity. No patient died during or as a direct result of endoscopic surgery or during the 30-day postoperative period. However, 1 patient who underwent a partial endoscopic resection followed by an open transcranial approach ultimately developed hydrocephalus followed by multiple shunt failures and revisions. This patient died after a withdrawal of support order was initiated 6 months after the initial procedure. No other patient experienced new permanent neurological deficits. Two (14.3%) of 14 patients in this series were treated for meningitis; one for *Haemophilus influenzae* infection and another for presumed meningitis secondary to an elevated CSF white blood cell count at the recommendation of the infectious disease service, although no infectious organism was ever identified.

In the current case series, the most common complication was CSF leak, occurring in 5 patients (35.7%). Lumbar drains were used preoperatively in 5 patients. All patients with CSF leaks underwent a successful primary endoscopic repair. Two patients (14.3%) required long-

TABLE 4: Endocrinology results*

Case No.	Anterior Pituitary Function		Posterior Pituitary Function			
	Preop Deficit	Postop Deficit	Preop DI	Post-op DI	Postop DI at Discharge	New Permanent DI
1	none	none	no	yes	yes	yes
2	hypogonadism, hyperprolactinemia	hypogonadism, hyperprolactinemia	no	no	no	no
3	hypothyroidism, hypogonadism, hyperprolactinemia	AI, hypothyroidism, hypogonadism, hyperprolactinemia	no	yes	no	no
4	hypothyroidism, hypogonadism, hyperprolactinemia	AI, hypothyroidism, hypogonadism, hyperprolactinemia	no	yes	yes	no
5	hypogonadism	AI, hypothyroidism, hypogonadism	no	yes	no	no
6	panhypopituitarism	panhypopituitarism	no	yes	no	no
7	none	none	no	yes	no	no
8	none	none	no	no	no	no
9	hyperprolactinemia	none	no	yes	yes	no
10	none	none	no	yes	no	no
11	AI, hypothyroidism	hypothyroidism	no	no	no	no
12	none	AI	yes	yes	yes	no
13	none	none	no	no	no	no
14	AI, hypogonadism, hyperprolactinemia	AI, hypogonadism, hyperprolactinemia	no	yes	yes	no

* AI = adrenal insufficiency.

term CSF diversion for treatment of hydrocephalus. One patient experienced a leak 1-month postoperatively, which ultimately required long-term CSF diversion; a VP shunt was also required in another patient after lumbar puncture demonstrated elevation of intracranial pressure. Logistic regression analysis of the date of surgery and the time of the CSF leaks showed a statistically significant decrease in the CSF leak rate as the endoscopic experience progressed ($p = 0.0481$; OR 0.97, 95% CI 0.94–0.99).

Length of Hospital Stay

The duration of hospital stay varied from 3 to 14 days (median 9 days). No significant relationship between CSF leak and length of stay was found. However, 2 of the 5 patients with postoperative CSF leaks were discharged home and subsequently required readmission from the emergency department for treatment of CSF rhinorrhea.

Discussion

Complete resection for craniopharyngiomas has been shown to provide a survival benefit, but often at the expense of neurological, ophthalmological, and endocrinological function.[42,53] Authors have reported GTR rates ranging from 5 to 90%.[3,5,7,9,14,20,26,37,40,42,47,51–53,56] Yaşargil et al.[56] was able to achieve a 90% GTR rate, but reported a 9.0% rate of intraoperative and early postoperative mortality and a 16.7% overall mortality rate. Given the morbidity and mortality associated with GTRs, some investigators have advocated STR combined with postoperative radiation as an alternative when the risk of a GTR would likely be associated with formidable morbidity.[36] Several authors have reported similar disease control rates after partial resection and postoperative radiotherapy as compared with GTR, with decreased perioperative complication rates.[14,22,36,41,45,55]

When compared with the more traditional microscopic transsphenoidal approaches, the use of the endoscope provides the surgeon with a more expansive volumetric exposure of the skull base, theoretically enhancing the extent of resection, while providing a safety profile not available with microscopy alone. Accordingly, several authors have reported on the addition of an endoscope to augment visualization of remaining tumor during microscopic resections.[12,18] In a series of 800 patients, Fatemi et al.[21] examined the benefits and limitations of the microscopic endonasal approach to the sella and reported little difficulty with removal of standard microadenomas, but encountered formidable challenges when attempting to remove larger suprasellar nonadenomatous lesions. Studies report rates of GTR after microscopic transsphenoidal surgery that range from 6.9 to 90%.[11,37,40] Chakrabarti et al.[11] presented 5-year outcome data on 68 patients undergoing standard and expanded transnasal craniopharyngioma resection; in this study, 34 new cases of anterior pituitary dysfunction occurred postoperatively, along with 41 new cases of DI (67%). Tumor size was not available for consideration, introducing a possible selection bias, because patients harboring larger tumors may have been assigned to an open craniotomy. Endoscopic endonasal series in the literature to date have reported greater preservation and recovery of endocrinological and ophthalmological outcomes, with possibly a lesser extent of resection (Table 6).

In the current series, although insufficiently powered to allow for a direct comparison with these larger series, the rates of resection are comparable to historical

TABLE 5: Postoperative complications*

Case No.	LOS (days)	Complication	Treatment	Result
1	12	fevers, culture negative lumbar puncture, high CSF white blood cell count	intravenous antibiotics	resolution
2	2	none	NA	NA
3	8	CSF leak, pneumocephalus, hydrocephalus	endoscopic repair, ventriculostomy	resolution
4	6	CSF leak, pneumocephalus, hydrocephalus	endoscopic repair, VP shunt	resolution
5	11	CSF leak, pneumocephalus	endoscopic repair, lumbar drain	resolution
6	10	none	NA	NA
7	3	none	NA	NA
8	14	CSF leak, hematoma at abdominal donor site	endoscopic repair, lumbar drain, hematoma evacuation	resolution
9	10	meningitis	antibiotics	resolution
10	6	none	NA	NA
11	11	none	NA	NA
12	10	none	NA	NA
13	5	CSF leak and hydrocephalus 1-mo postop, multiple cystic recurrences	endoscopic repair, lumbar drain, VP shunt	death from shunt failure
14	6	none	NA	NA

* LOS = length of stay; NA = not applicable.

case series. Within endonasal endoscopic series for craniopharyngioma, reported rates of GTR range from 16.7 to 100%[6,9,13,15,23,24,38,49] (Table 6). In the present series, the initial goal of the procedure in most cases was complete resection and cure, but when a considerable potential for decrement in the patient's preoperative function was realized, resection was often suspended in favor of an STR followed by postoperative radiosurgery. Five of the 10 patients (50%) who experienced an STR or NTR have been treated with fractionated linear accelerator-based radiosurgery. Four of the remaining 5 are undergoing follow-up using serial MR imaging scans, and 1 foreign-born patient is receiving follow-up care by an oncologist in his country of origin.

The initial visual complications of craniopharyngioma are often progressive visual field defects, which may result in permanent visual loss if the tumor compression is not relieved.[30] In this series, all patients presented with some degree of objective visual loss (Table 3). Visual improvement after transnasal resection of craniopharyngiomas has been reported in 50 to 93% of patients.[3,6,9,11,13,15,20,23,24,37,38,49,53] In the present series, visual acuity and field deficits had either improved (85.7%) or resolved (42.9%) in most patients at 1 month follow-up. In series including radical resections, the rate of visual deterioration is approximately 15%.[20,46,53] In the current series, 1 patient did experience a decrease in visual acuity postoperatively, which was believed to be caused by increased intraoperative manipulation of the optic chiasm, secondary to tumor invasion.

Upon presentation, craniopharyngiomas often demonstrate laboratory evidence of hypogonadism (75–80%) and growth hormone deficiency (80–100%). A more moderate degree of adrenal insufficiency (30–60%) and hypothyroidism (20–40%) is frequently noted, while the rate of DI (10–20%) is less common.[27,31] Abundant rates of postoperative pituitary deficiency have been reported in multiple surgical series.[14,30,44,48] Yaşargil et al.[56] reported permanent DI in 98.7% of patients. Jung et al.[30] reported that preservation of the pituitary stalk could result in a protection of pituitary function, with 58.3% of the patients in their series requiring complete hormone replacement therapy. Other series of endonasal endoscopic craniopharyngioma resections have reported a prevalence of postoperative anterior pituitary dysfunction between 57.1 and 100%, and rates of DI ranging from 56.3 to 100% based on the aggressivity of the resection[6,9,13,15,23,24,38,49] (Table 6). In the present series, the authors report a rate of hypopituitarism of any axis of 57.1% at 1-month follow-up. Temporary or permanent DI was noted in of 64.3% of patients, while at 1-month follow-up only 1 patient (7.1%) was noted to have DI (considered permanent) after tumor resection. The extent of resection showed a nonsignificant trend toward more patients with GTRs experiencing temporary DI ($p = 0.12$). Throughout the literature, preoperative endocrinological defects rarely recovered after surgery, regardless of the operative approach.[11,16,27,28,31] In the present series, 1 patient's adrenal insufficiency resolved, but continued to require treatment for hypothyroidism with hormone replacement at 1-month follow-up (Table 4).

In performing a purely endoscopic resection, the main complications are primarily related to control of intracranial vessels (should they be lacerated), and skull base reconstruction with its associated risk of CSF leak, tension pneumocephalus, and meningitis.[10] In the present series no patient experienced damage to a neurovas-

TABLE 6: Literature review of outcomes after endoscopic endonasal approach to craniopharyngioma resections*

Authors & Year	No. of Patients	Tumor Size > 2 cm (%)	Postop Endocrinology DI (%)/HP (%)	Postop Ophthalmology		GTR (%)	CSF Leak (%)
				No Deficit (%)	Improved (%)		
Cappabianca et al., 2002	4	NR	NR	NR	NR	100	NR
Frank et al., 2006	10	80	60/100	40	70	70	30
Laufer et al., 2007	4	75	100/100	NR	NR	100	0
de Divitiis et al., 2007	10	NR	60/60	30	50	70	20
Stamm et al., 2008	7	NR	85.7%/NR	57.1	67	57	29
Gardner et al., 2008	16	81.3	56.3/88.3	50	75	50	58
Cavallo et al., 2009†	22	91.0	72.7/91.0	36.4	68.1	40.9	13.6
Dehdashti et al., 2009	6	NR	50/NR	16.7	80	16.7	33.3
current study	14	85.7	64.3/57.1	42.9	85.7	28.6	35.7

* HP = partial or complete hypopituitarism; NR = not reported.
† Series of recurrent and revision cases only.

cular structure. The reported rates of CSF leakage after endoscopic craniopharyngioma resection range from 0 to 58%.[6,9,13,15,23,24,38,49] Most series report a decline in the rates of CSF leakage as the authors became more proficient in skull base reconstruction.[9,24] The introduction of a septal-mucosal flap described by Hadad et al.[25,35] has shown clinical utility in reducing CSF leaks in the setting of high flow fistulas. In the current series, the authors report an overall CSF leak rate of 35.7%. However, the leak rate has significantly fallen over time as the authors have adopted the nasoseptal flap as well as a fascial "button" for reconstruction of the skull base in the setting of high flow leaks. Nine (64.3%) of 14 patients underwent a button-augmented closure, with CSF leaks occurring in 2 of these 9 patients. When comparing the duration since the beginning of this series, logistic regression analysis proved the authors achieved a statistically significant ($p = 0.0481$) reduction in CSF leak rates by the end of the study period (Fig. 3).

All patients underwent primary endoscopic repair as the procedure of choice to repair postoperative CSF leaks without additional morbidity. Two (14.2%) of 14 patients required VP shunt placement secondary to hydrocephalus. Two patients (14.2%) were treated for meningitis postoperatively. Neither patient received a lumbar drain at any time during their hospitalization, nor did they experience a CSF fistula. Both were treated with an intravenous antibiotic regimen based on the recommendation of infectious disease consultants.

There was 1 death in this series. This patient was a 51-year-old man who presented initially with visual loss, headaches, and hydrocephalus. He underwent an attempted endoscopic resection of a solid adamantinomatous craniopharyngioma with a sizable residual secondary to rigorous adherence to neurovascular structures. One month later, this patient presented with recurrent hydrocephalus and a cystic recurrence, at which time an open craniotomy was performed and an NTR was achieved.

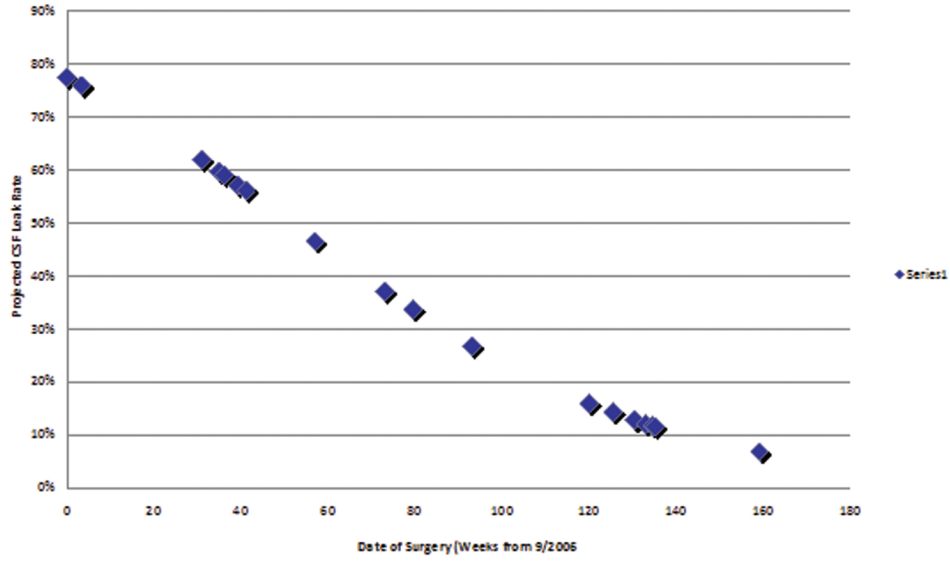

Fig. 3. Graph of the logistic regression analysis of the CSF leak rate over time showing a decrease in the leak rate.

However, the patient's hydrocephalus did not resolve and he subsequently underwent shunt placement. Over the next 5 months, the patient's hydrocephalus was treated with multiple ventriculostomy catheters, VP shunt placements, and revisions. Pathological evaluation of the viscous output from the external ventricular drains revealed a dense cellular and proteinaceous fluid believed to be produced by the tumor. It was postulated that this viscous fluid was responsible for the multiple shunt failures. Ultimately, the patient's family was unwilling to continue surgical intervention and the patient died secondary to hydrocephalus.

Conclusions

The extent of resection, along with the choice of surgical approach, has a significant effect on the rate of ophthalmological and endocrinological dysfunction after craniopharyngioma resection. Although not all tumors are amenable to an endonasal endoscopic approach, this small case series appears to support its use to provide a high rate of endocrine function preservation and visual recovery, while simultaneously attaining substantial resections. Other small case series in the literature demonstrate reasonable resection rates corresponding to favorable ophthalmological and endocrinological outcomes. A purely endoscopic technique, in appropriately selected patients, can substitute for classic transcranial approaches and allow safe and effective management of craniopharyngiomas with comparable outcomes.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: PG Campbell, B McGettigan, A Luginbuhl, JJ Evans. Acquisition of data: PG Campbell, B McGettigan, A Luginbuhl, S Yadla. Analysis and interpretation of data: PG Campbell, B McGettigan, A Luginbuhl, JJ Evans. Drafting the article: PG Campbell, JJ Evans. Critically revising the article: PG Campbell, B McGettigan, S Yadla, M Rosen, JJ Evans. Reviewed final version of the manuscript and approved it for submission: PG Campbell, B McGettigan, A Luginbuhl, S Yadla, M Rosen, JJ Evans. Statistical analysis: PG Campbell. Administrative/technical/material support: B McGettigan.

References

1. Adamson TE, Wiestler OD, Kleihues P, Yaşargil MG: Correlation of clinical and pathological features in surgically treated craniopharyngiomas. **J Neurosurg 73:**12–17, 1990
2. Banna M, Hoare RD, Stanley P, Till K: Craniopharyngioma in children. **J Pediatr 83:**781–785, 1973
3. Baskin DS, Wilson CB: Surgical management of craniopharyngiomas. A review of 74 cases. **J Neurosurg 65:**22–27, 1986
4. Batra PS, Citardi MJ, Lanza DC: Isolated sphenoid sinusitis after transsphenoidal hypophysectomy. **Am J Rhinol 19:**185–189, 2005
5. Cabezudo JM, Vaquero J, Areitio E, Martinez R, de Sola RG, Bravo G: Craniopharyngiomas: a critical approach to treatment. **J Neurosurg 55:**371–375, 1981
6. Cappabianca P, Cavallo LM, Colao A, Del Basso De Caro M, Esposito F, Cirillo S, et al: Endoscopic endonasal transsphenoidal approach: outcome analysis of 100 consecutive procedures. **Minim Invasive Neurosurg 45:**193–200, 2002
7. Carmel PW, Antunes JL, Chang CH: Craniopharyngiomas in children. **Neurosurgery 11:**382–389, 1982
8. Casler JD, Doolittle AM, Mair EA: Endoscopic surgery of the anterior skull base. **Laryngoscope 115:**16–24, 2005
9. Cavallo LM, Prevedello DM, Solari D, Gardner PA, Esposito F, Snyderman CH, et al: Extended endoscopic endonasal transsphenoidal approach for residual or recurrent craniopharyngiomas. **J Neurosurg 111:**578–589, 2009
10. Ceylan S, Koc K, Anik I: Extended endoscopic approaches for midline skull-base lesions. **Neurosurg Rev 32:**309–319, 2009
11. Chakrabarti I, Amar AP, Couldwell W, Weiss MH: Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. **J Neurosurg 102:**650–657, 2005
12. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T: Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. **Neurosurgery 55:**539–550, 2004
13. de Divitiis E, Cappabianca P, Cavallo LM, Esposito F, de Divitiis O, Messina A: Extended endoscopic transsphenoidal approach for extrasellar craniopharyngiomas. **Neurosurgery 61 (5 Suppl 2):**219–228, 2007
14. De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, et al: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? **J Neurosurg 85:**73–81, 1996
15. Dehdashti AR, Ganna A, Witterick I, Gentili F: Expanded endoscopic endonasal approach for anterior cranial base and suprasellar lesions: indications and limitations. **Neurosurgery 64:**677–689, 2009
16. Di Rocco C, Caldarelli M, Tamburrini G, Massimi L: Surgical management of craniopharyngiomas—experience with a pediatric series. **J Pediatr Endocrinol Metab 19 (Suppl 1):**355–366, 2006
17. Duff J, Meyer F, Ilstrup D, Laws E, Schleck C, Scheithauer B: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000
18. Dusick JR, Esposito F, Mattozo CA, Chaloner C, McArthur DL, Kelly DF: Endonasal transsphenoidal surgery: the patient's perspective-survey results from 259 patients. **Surg Neurol 65:**332–342, 2006
19. Esposito F, Cappabianca P, Del Basso De Caro M, Cavallo LM, Rinaldi C, De Divitiis E: Endoscopic endonasal transsphenoidal removal of an intra-suprasellar schwannoma mimicking a pituitary adenoma. **Minim Invasive Neurosurg 47:**230–234, 2004
20. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
21. Fatemi N, Dusick JR, de Paiva Neto MA, Kelly DF: The endonasal microscopic approach for pituitary adenomas and other parasellar tumors: a 10-year experience. **Neurosurgery 63 (4 Suppl 2):**244–256, 2008
22. 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
23. Frank G, Pasquini E, Doglietto F, Mazzatenta D, Sciarretta V, Farneti G, et al: The endoscopic extended transsphenoidal approach for craniopharyngiomas. **Neurosurgery 59 (1 Suppl):**ONS75–ONS83, 2006
24. Gardner PA, Kassam AB, Snyderman CH, Carrau RL, Mintz AH, Grahovac S, et al: Outcomes following endoscopic, ex-

panded endonasal resection of suprasellar craniopharyngiomas: a case series. **J Neurosurg 109:**6–16, 2008
25. Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, et al: A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. **Laryngoscope 116:**1882–1886, 2006
26. Hoffman HJ: Surgical management of craniopharyngioma. **Pediatr Neurosurg 21 (Suppl 1):**44–49, 1994
27. Honegger J, Buchfelder M, Fahlbusch R: Surgical treatment of craniopharyngiomas: endocrinological results. **J Neurosurg 90:**251–257, 1999
28. Honegger J, Buchfelder M, Fahlbusch R, Däubler B, Dörr HG: Transsphenoidal microsurgery for craniopharyngioma. **Surg Neurol 37:**189–196, 1992
29. Jho HD, Carrau RL: Endoscopic endonasal transsphenoidal surgery: experience with 50 patients. **J Neurosurg 87:**44–51, 1997
30. Jung TY, Jung S, Choi JE, Moon KS, Kim IY, Kang SS: Adult craniopharyngiomas: surgical results with a special focus on endocrinological outcomes and recurrence according to pituitary stalk preservation. **J Neurosurg 111:**572–577, 2009
31. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, et al: Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. **Clin Endocrinol (Oxf) 62:**397–409, 2005
32. Karavitaki N, Cudlip S, Adams CB, Wass JA: Craniopharyngiomas. **Endocr Rev 27:**371–397, 2006
33. Karavitaki N, Wass JA: Craniopharyngiomas. **Endocrinol Metab Clin North Am 37:**173–193, 2008
34. Kassam AB, Gardner PA, Snyderman CH, Carrau RL, Mintz AH, Prevedello DM: Expanded endonasal approach, a fully endoscopic transnasal approach for the resection of midline suprasellar craniopharyngiomas: a new classification based on the infundibulum. **J Neurosurg 108:**715–728, 2008
35. Kassam AB, Thomas A, Carrau RL, Snyderman CH, Vescan A, Prevedello D, et al: Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. **Neurosurgery 63 (Suppl 1):**ONS44–ONS 53, 2008
36. Komotar RJ, Roguski M, Bruce JN: Surgical management of craniopharyngiomas. **J Neurooncol 92:**283–296, 2009
37. König A, Lüdecke DK, Herrmann HD: Transnasal surgery in the treatment of craniopharyngiomas. **Acta Neurochir (Wien) 83:**1–7, 1986
38. Laufer I, Anand VK, Schwartz TH: Endoscopic, endonasal extended transsphenoidal, transplanum transtuberculum approach for resection of suprasellar lesions. **J Neurosurg 106:**400–406, 2007
39. Laws ER Jr: Transsphenoidal microsurgery in the management of craniopharyngioma. **J Neurosurg 52:**661–666, 1980
40. Maira G, Anile C, Rossi GF, Colosimo C: Surgical treatment of craniopharyngiomas: an evaluation of the transsphenoidal and pterional approaches. **Neurosurgery 36:**715–724, 1995
41. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
42. Minamida Y, Mikami T, Hashi K, Houkin K: Surgical management of the recurrence and regrowth of craniopharyngiomas. **J Neurosurg 103:**224–232, 2005
43. Nelson JS (ed): **Principles and Practice of Neuropathology, ed 2.** Oxford; New York: Oxford University Press, 2003
44. Paja M, Lucas T, García-Uría J, Salamé F, Barceló B, Estrada J: Hypothalamic-pituitary dysfunction in patients with craniopharyngioma. **Clin Endocrinol (Oxf) 42:**467–473, 1995
45. Scott RM, Hetelekidis S, Barnes PD, Goumnerova L, Tarbell NJ: Surgery, radiation, and combination therapy in the treatment of childhood craniopharyngioma—a 20-year experience. **Pediatr Neurosurg 21 (Suppl 1):**75–81, 1994
46. Shi XE, Wu B, Zhou ZQ, Fan T, Zhang YL: Microsurgical treatment of craniopharyngiomas: report of 284 patients. **Chin Med J (Engl) 119:**1653–1663, 2006
47. Shirane R, Ching-Chan S, Kusaka Y, Jokura H, Yoshimoto T: Surgical outcomes in 31 patients with craniopharyngiomas extending outside the suprasellar cistern: an evaluation of the frontobasal interhemispheric approach. **J Neurosurg 96:**704–712, 2002
48. Sorva R, Heiskanen O, Perheentupa J: Craniopharyngioma surgery in children: endocrine and visual outcome. **Childs Nerv Syst 4:**97–99, 1988
49. Stamm AC, Vellutini E, Harvey RJ, Nogeira JF Jr, Herman DR: Endoscopic transnasal craniotomy and the resection of craniopharyngioma. **Laryngoscope 118:**1142–1148, 2008
50. Sung DI: Suprasellar tumors in children: a review of clinical manifestations and managements. **Cancer 50:**1420–1425, 1982
51. Symon L, Sprich W: Radical excision of craniopharyngioma. Results in 20 patients. **J Neurosurg 62:**174–181, 1985
52. 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
53. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
54. 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:**1001–1010, 1994
55. 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
56. 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
57. Zülch KJ: **Histological Typing of Tumours of the Central Nervous System.** Geneva: World Health Organization, 1979

Manuscript submitted November 22, 2009.
Accepted January 5, 2010.
Part of these results were presented as an oral presentation at the North American Skull Base Society meeting on October 18, 2009, in New Orleans, Louisiana.

Address correspondence to: Peter G. Campbell, M.D., Department of Neurosurgery, 909 Walnut St, 3rd Floor, Philadelphia, Pennsylvania 19107. email: peter.campbell@jeffersonhospital.org.

See the corresponding article, **DOI:** 10.3171/2010.1.FOCUS09292.

Neurosurg Focus 28 (4):E8a, 2010

Editorial

Transnasal endoscopic surgery for craniopharyngiomas

Edward H. Oldfield, M.D.

University of Virginia, Charlottesville, Virginia

Dr. Campbell and colleagues[1] report on a series of 14 adults who underwent transnasal endoscopic surgery for craniopharyngiomas, in which one of the goals was to preserve the pituitary stalk while removing as much tumor as could be safely removed without causing new neurological or endocrinological deficits. In 4 patients (29%) a gross-total resection of the tumor was performed, while in 10 (71%) tumor removal was incomplete. In 5 of these 10 patients at least 95% tumor removal (near-total resection) was achieved, and in the other 5 subtotal resection was attained. The pituitary stalk was preserved in all 14 patients, including 9 patients who had some anterior pituitary function before surgery, most of whom retained this pituitary function after surgery. As the authors indicate, these are commendable results and they compare favorably with the results of previous reports of endonasal endoscopic surgery for craniopharyngiomas. It is unclear why they limit their discussion only to endoscopic surgery, rather than transsphenoidal surgery in general, because excellent results have been reported with transsphenoidal microscopic surgery for craniopharyngioma. For instance, Chakrabarti et al.[2] achieved complete tumor removal in 61 (90%) of 68 patients using transsphenoidal microscopic surgery, and found overall endocrine results comparable to those achieved in the current report, with the exception of diabetes insipidus, which occurred in 71% of their patients. It should be emphasized that finding only 7% of patients (1 of 14) with diabetes insipidus undergoing surgical removal of craniopharyngiomas may be linked to the relatively small fraction of patients in whom complete removal was performed, as similar experience has been observed in patients with limited surgery combined with radiation therapy.[3]

These authors emphasize the minimally invasive aspects of the endoscopic transsphenoidal approach, although considering the degree of removal of the posterior aspect of the midline nasal structures (see Fig. 2E), few today would agree that this approach is as minimally invasive as any of the mucosal sparing approaches used with the operating microscope.

Although it is becoming widely accepted, particularly in children, that incomplete tumor removal followed by modern irradiation techniques is associated with acceptable tumor control and side effects (when complete tumor removal cannot be performed without producing neurological deficits or risking hyperphagia), the most effective prevention of tumor recurrence is complete surgical removal. Modern endocrine replacement of pituitary function is easily accomplished today. Thus, if the difference in complete and incomplete tumor removal is based on anatomical preservation of the pituitary stalk, the preservation of which does not always retain pituitary function, in my view it is best to choose complete tumor resection and accept pituitary replacement therapy.

There are many important unanswered issues in the treatment of adults and children with craniopharyngiomas, several of which are raised by the current report. What is the clinical difference between near-complete removal (at least 95%) and subtotal removal of a craniopharyngioma? Are the rates, or timing, of recurrences likely to be different between these groups? What thresholds of percentage tumor removal influence rates and timing of recurrence, with or without irradiation after surgery? Will use of the endoscope or the operating microscope, or a combination (endoscopic-assisted surgery) for the surgery yield superior results? Is the optimal management of craniopharyngiomas the same for children (> 7 years old) and adults? We will address these issues in the years ahead only if we carefully document, analyze, and report our results, as Dr. Campbell and colleagues[1] have done in this report.
(DOI: 10.3171/2010.2.FOCUS104)

References

1. Campbell PG, McGettigan B, Luginbuhl A, Yadla S, Rosen M, Evans JJ: Endocrinological and ophthalmological consequences of an initial endonasal endoscopic approach for resection of craniopharyngiomas. **Neurosurg Focus 28(4):**E8, 2010
2. Chakrabarti I, Amar AP, Couldwell W, Weiss MH: Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. **J Neurosurg 102:**650–657, 2005
3. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002

See the corresponding article, **DOI:** 10.3171/2010.1.FOCUS09292.

Neurosurg Focus 28 (4):E8b, 2010

Response

Peter G. Campbell, M.D.
James J. Evans, M.D.

Thomas Jefferson University, Philadelphia, Pennsylvania

We would like to thank Dr. Oldfield for his thoughtful review and critique of our paper. Dr. Oldfield has astutely described some of the clinical controversies surrounding craniopharyngioma management. The ideal surgical treatment of craniopharyngiomas remains a significant challenge for neurosurgeons. In the literature, reported case series attracting attention for their radical resection rates also report permanent diabetes insipidus in 98.7%, as well as a 16.7% perioperative mortality rate.[7] Other authors have advocated a somewhat less-aggressive surgical approach and described good disease control rates after postoperative radiotherapy with fewer perioperative complications.[4]

We agree with Dr. Oldfield that the endoscopic approach should not be described as less invasive when compared with the microscopic approach. However, having had previous experience with open transcranial, microscopic transnasal, as well as endoscopic transnasal approaches, we posit that the endoscopic approach provides superior visualization of the tumor and surrounding neurovascular structures. We believe several aspects of the endoscopic approach add additional advantages. First, we take special care to preserve the middle and inferior turbinates bilaterally with no disruption of the anterior nasal septum. Also, we create a small posterior septectomy that improves surgical access and facilitates dissection by allowing entrance via the contralateral naris, thus allowing 2 surgeons to work simultaneously and expanding the angular range of the endoscope. Finally, at the conclusion of the procedure, we medialize the middle turbinates. We believe this technique allows for improved drainage from the middle meatus, closes the posterior nasal septal perforation, and protects future inadvertent insertion of nasogastric or nasotracheal tubes into the cranial vault.

In our case series of consecutive patients, the surgical goal was excision of as much of the tumor as possible without incurring serious endocrinological, neurological, or neuropsychological complications. Even with attempted hormone replacement therapy, many previous studies have demonstrated an association between premature death and hypopituitarism.[1–3,5,6] In a large prospective study, Tomlinson et al.[6] described a median survival of 11.3 years in men and 10.1 years in women after diagnosis of hypopituitarism. Furthermore, patients with craniopharyngiomas in this study had mortality rates that were nearly 10-fold greater than with other underlying diagnoses; the causes of death (respiratory and cardiovascular) were not different from the overall study population. While long-term follow-up will ultimately be required to adjudicate our results, we believe a purely endoscopic technique provides a viable option for the management of select craniopharyngiomas. *(DOI: 10.3171/2010.3.FOCUS1069)*

References

1. Bates AS, Bullivant B, Sheppard MC, Stewart PM: Life expectancy following surgery for pituitary tumours. **Clin Endocrinol (Oxf)** 50:315–319, 1999
2. Bates AS, Van't Hoff W, Jones PJ, Clayton RN: The effect of hypopituitarism on life expectancy. **J Clin Endocrinol Metab 81:**1169–1172, 1996
3. Bülow B, Hagmar L, Mikoczy Z, Nordström CH, Erfurth EM: Increased cerebrovascular mortality in patients with hypopituitarism. **Clin Endocrinol (Oxf) 46:**75–81, 1997
4. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
5. Rosén T, Bengtsson BA: Premature mortality due to cardiovascular disease in hypopituitarism. **Lancet 336:**285–288, 1990
6. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, et al: Association between premature mortality and hypopituitarism. **Lancet 357:**425–431, 2001
7. 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

Early outcomes of endoscopic transsphenoidal surgery for adult craniopharyngiomas

John A. Jane Jr., M.D.,[1] Erin Kiehna, M.D.,[1] Spencer C. Payne, M.D.,[2] Stephen V. Early, M.D.,[2] and Edward R. Laws Jr., M.D.[3]

[1]Department of Neurosurgery and [2]Department of Otolaryngology–Head and Neck Surgery, University of Virginia Health System, Charlottesville, Virginia; and [3]Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts

Object. Although the transsphenoidal approach for subdiaphragmatic craniopharyngiomas has been performed for many years, there are few reports describing the role of the endoscopic transsphenoidal technique for suprasellar craniopharyngiomas. The purpose of this study was to report the outcomes of the endoscopic transsphenoidal approach for adults with craniopharyngiomas in whom the goal was gross-total resection.

Methods. Twelve patients were identified who were older than 18 years at the time of their pure endoscopic transsphenoidal surgery. Their medical records and imaging studies were retrospectively reviewed.

Results. Gross-total resection was achieved in 42% of cases when assessed by intraoperative impression alone and in 75% when assessed by the first postoperative MR imaging study. However, 83% of patients achieved at least a 95% resection when assessed by both intraoperative impression and the first postoperative MR imaging study. Permanent diabetes insipidus occurred postoperatively in 44% of patients. Six (67%) of 9 patients who had a functioning hypothalamic-pituitary axis preoperatively developed panhypopituitarism after surgery. Visual improvement or normalization occurred in 78% of patients with preoperative visual deficits. Although no patient experienced a postoperative CSF leak, 1 patient was treated for meningitis.

Conclusions. The authors have achieved a high rate of radical resection and symptomatic improvement with the endoscopic transsphenoidal technique for both subdiaphragmatic (sellar/suprasellar) and supradiaphragmatic (suprasellar) craniopharyngiomas. However, this is also associated with a high incidence of new endocrinopathy. Endoscopic assessment of tumor resection may be more sensitive for residual tumor than the first postoperative MR imaging study. *(DOI: 10.3171/2010.1.FOCUS09319)*

Key Words • **transsphenoidal** • **craniopharyngioma** • **adult** • **endoscopic**

Craniopharyngiomas are highly variable and complex benign tumors. They present in any age group with a variety of neurological, visual, and endocrinological symptoms. The tumors vary regarding the degree and character of calcification and may be cystic, solid, or a combination. Although many are limited to the sellar and suprasellar space, they can present either entirely within the sella or third ventricle. Such a protean tumor requires diverse treatment methods for its proper management. Although radical resection is possible for many tumors, others may require a more conservative approach consisting of limited resection followed by radiation therapy or intracavitary therapies.

A subset of tumors may also be managed using a transsphenoidal approach. The transsphenoidal approach for craniopharyngiomas is widely accepted for intrasellar craniopharyngiomas. Select centers have also advocated the transsphenoidal route for tumors with subdiaphragmatic origin and subsequent suprasellar extension.[1,19,20] These subdiaphragmatic craniopharyngiomas are thought to be more easily removed by a transsphenoidal approach because the expanded sella provides a widened aperture to the suprasellar compartment and also diaphragmatic protection from pial invasion.[11,19] Although there is limited experience using the transsphenoidal approach for suprasellar tumors,[1,2,5,6] endoscopic transsphenoidal approaches introduced over the past decade are being increasingly used.[3,4,8–10,23] We describe our experience using the endoscopic transsphenoidal technique for adults with craniopharyngiomas and describe the neurological, endocrinological, and visual outcomes.

Abbreviations used in this paper: DI = diabetes insipidus; GTR = gross-total resection; IGF-I = insulin-like growth factor–I.

Methods

Inclusion criteria for the retrospective study included adult patients with craniopharyngiomas who underwent pure endoscopic transsphenoidal surgery. Between March 2005 and July 2009, 31 patients underwent transsphenoidal surgery for the treatment of a craniopharyngioma. Nineteen patients were excluded from the analysis. Nine patients were younger than 18 years of age, 6 adult patients underwent endoscopic-assisted microscopic resections, and 2 adults underwent purely microscopic

TABLE 1: Presenting signs and symptoms in 12 patients who underwent endoscopic transsphenoidal surgery for a craniopharyngioma*

Case No.	Age (yrs), Sex	Previous Op	Anterior Pituitary Dysfunction	Permanent DI	Visual Deficit	Tumor Characteristics		
						Size (mm)	Type	Location
1	31.9, F	none	no†	no	no	17	cystic	sellar/suprasellar
2	52.1, M	none	panhypopit	no	yes	42.9	mixed	sellar/suprasellar
3	29.5, M	none	partial	yes	no	17.9	mixed	suprasellar
4	61.7, F	none	no	no	yes	16	cystic	sellar/suprasellar
5	53.3, M	craniotomy	partial	no	yes	17.6	solid	suprasellar
6	53.4, M	none	partial	no	no	23.1	mixed	suprasellar
7	76.6, F	none	panhypopit	no	yes	29.2	mixed	suprasellar
8	48.2, F	none	partial	yes	yes	24	mixed	sellar/suprasellar
9	54.2, F	none	partial	no	yes	26.8	cystic	suprasellar
10	60.9, F	transsphenoidal	partial	no	yes	32.6	mixed	sellar/suprasellar
11	43.0, M	none	partial	no	yes	21	mixed	suprasellar
12	45.6, F	transsphenoidal	panhypopit	yes	yes	16.5	mixed	suprasellar

* panhypopit = panhypopituitarism.

† This patient was taking oral contraceptives.

procedures. Of the 14 adult patients who underwent pure endoscopic transsphenoidal resections, 2 were excluded. One patient was lost to follow-up and another had mixed pathology (adrenocorticotropic hormone adenoma and craniopharyngioma). With approval from our local institutional review board, the medical records and imaging studies were reviewed.

All patients underwent neurological and endocrinological evaluations prior to and after surgery. Those patients with visual signs or symptoms also underwent pre- and postoperative ophthalmological examinations including formal visual field testing. Women who were taking oral contraceptives, who were postmenopausal, or who had undergone a hysterectomy were excluded from analysis of postoperative gonadal function.

Maximal tumor diameter was measured on preoperative imaging studies and was measured as the largest diameter in the coronal, axial, or sagittal planes. Tumors were categorized as cystic, solid, or mixed based on their predominant features. If a tumor was primarily cystic but had a small solid nodule, the tumor was considered cystic. By contrast, a primarily solid tumor that had a small cystic component was considered mixed. Tumors were also categorized according to location. Tumors were considered subdiaphragmatic in origin if the tumor expanded the sellar bone. If the tumor had a small component within the sella but had not expanded the bony confines of the sella, the tumor was considered suprasellar.

The degree of resection was determined by a combination of the intraoperative assessment and the 2- or 3-month postoperative MR imaging studies. Resections were considered gross total only if the surgical impression and MR imaging assessment revealed no residual tumor. Resections were categorized as radical if both the surgical impression and the postoperative MR imaging study indicated that at least 95% of the tumor was resected. A subtotal resection was considered one in which at least 50% of the tumor was removed, and a partial resection indicated that more than 50% of the tumor remained.

Results

Study Population and Clinical Presentation

Of the 12 patients who underwent pure endoscopic surgery, there were 7 women and 5 men with a mean age of 50.77 years (range 29–76 years) (Table 1). The mean age of the women (54 years) was older than that of the men (46 years). The mean follow-up was 13.29 months with a range of 1.8–44.67 months. Three patients had undergone previous surgical treatment, 2 of whom had undergone previous transsphenoidal surgery for presumed pituitary adenomas at outside facilities and 1 had undergone a previous craniotomy. No patient had received radiation therapy prior to endoscopic transsphenoidal surgery.

Nine (75%) of 12 patients reported visual deficits as the presenting symptom (Table 1). A bitemporal hemianopia was the most common visual field deficit encountered. One patient was diagnosed on evaluation for DI, and 2 patients were diagnosed incidentally. One of these 2 patients was diagnosed on evaluation for a syncopal episode and another during workup of a left-sided thalamic stroke. Headache was a common symptom and was present in 10 (83%) of the 12 patients.

Diabetes insipidus was present in 3 patients (25%) prior to surgery (Table 1). By contrast, at least partial anterior pituitary dysfunction was common preoperatively, being present in 10 (83%) of 12 patients. Three patients developed panhypopituitarism preoperatively. All men were found to have low testosterone levels. Two of the women were taking oral contraceptives, and therefore, their gonadal function was not evaluable. Of the 5 women who could be evaluated, 3 were postmenopausal and 1 had had

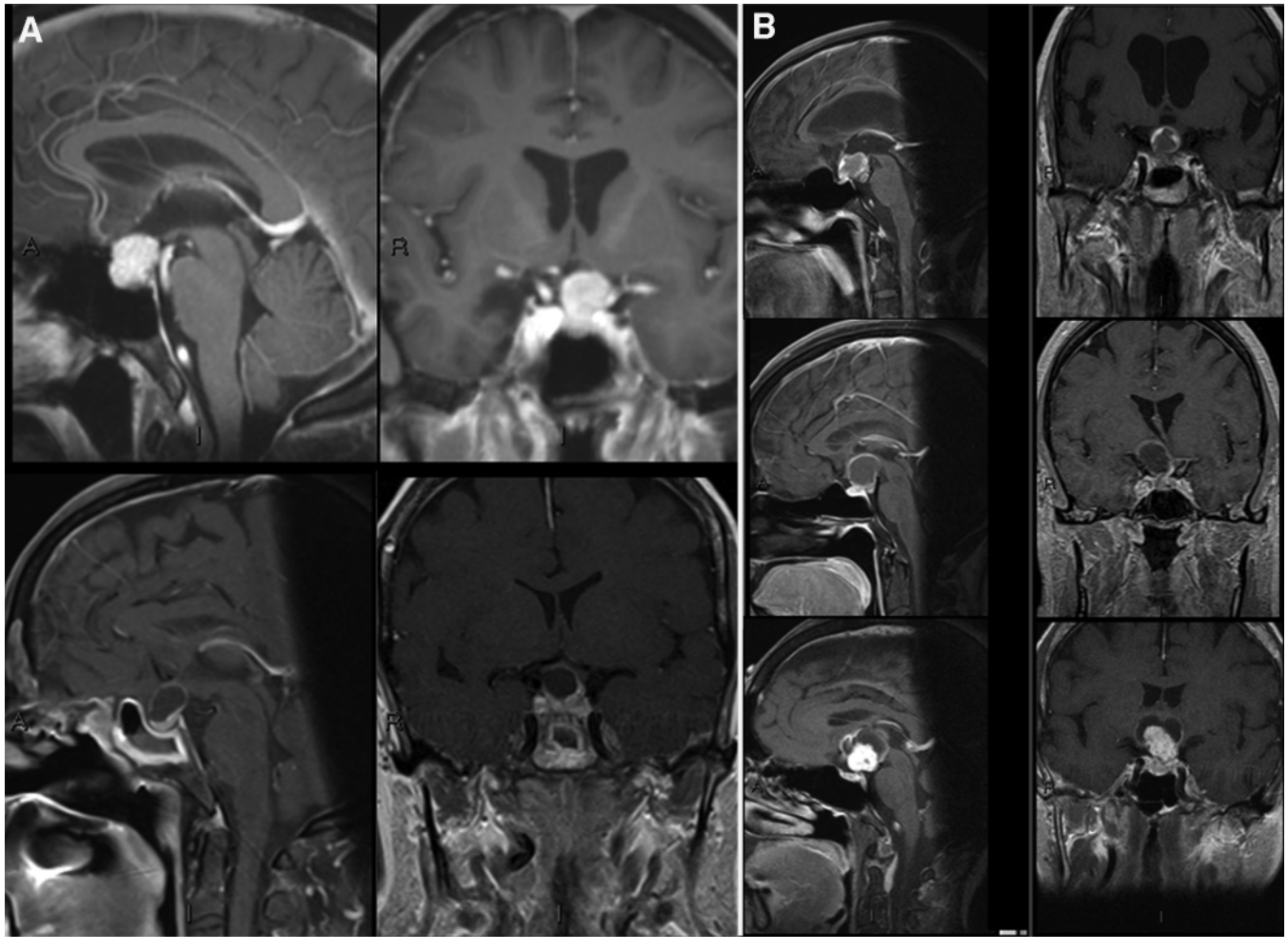

Fig. 1. Sagittal and coronal T1-weighted MR imaging with Gd of subdiaphragmatic **(A)** and supradiaphragmatic **(B)** tumors.

a hysterectomy. Gonadotroph deficiency (inappropriately low luteinizing hormone and follicle-stimulating hormone levels) was present in 3 of the 5 evaluable women. Somatotroph deficiency (low IGF-I levels) was found in 7 (58%) of 12 patients, thyrotroph deficiency was present in 6 (50%), and corticotroph deficiency was seen in 3 (25%).

Imaging Features

No tumor was confined to the sella (Table 1). Five tumors had suprasellar extension that presented with an expanded sella, and the tumors were considered to have a subdiaphragmatic origin (Fig. 1A). Two of these tumors extended into the third ventricle. Among the 7 supradiaphragmatic craniopharyngiomas, 2 extended into the third ventricle (Fig. 1B). The mean maximal diameter was 23.7 mm (range 16–43 mm). The subdiaphragmatic tumors were larger on average (mean 26.5 mm, range 16–43 mm) than the suprasellar tumors (mean 21.73 mm, range 16.5–29 mm). One tumor was solid, 3 were primarily cystic, and the remaining 9 tumors were mixed.

Surgical Approach

All patients underwent a purely endoscopic transsphenoidal approach that included a binarial 3-hand technique with wide anterior sphenoidotomy and partial posterior septectomy. In 9 operations (6 of 7 supradiaphragmatic suprasellar tumors and 3 of 5 subdiaphragmatic tumors), the opening was extended across the tuberculum sellae to include the planum sphenoidale to provide greater access to the suprasellar space. Neuronavigation was used in 10 of 12 cases. None of our patients required lumbar drainage intraoperatively or postoperatively. We encountered a CSF leak in all 12 patients. In 1 patient with a subdiaphragmatic sellar/suprasellar tumor, the leak was closed with a thin layer of dural substitute over the diaphragm. In another case, the defect was closed using a vascularized nasoseptal flap.[17] In the remaining 11 operations a large CSF leak was encountered, which was most often closed using abdominal fat (in 11 patients) held in place using a rigid buttress (in 10).[21] This closure was bolstered in 9 cases by also filling the sphenoid sinus with fat, while in 1 the sphenoid sinus was filled with DuraSeal.

Surgical Outcome

The average length of stay following surgery was 3.3 days (range 2–6 days). A GTR was achieved in 5 patients (41.67%), 5 (41.67%) were assessed as having a radical re-

TABLE 2: Surgical outcomes*

Case No.	Tumor Size (mm)	Location	Pathological Subtype	Resection by MRI	Resection by Endoscopic Inspection	Visual Outcome
1	17	sellar/suprasellar	adamantinomatous	GTR	radical	remained normal
2	42.9	sellar/suprasellar	adamantinomatous	GTR	radical	improved to VFF
3	17.9	suprasellar	not specified	GTR	GTR	remained normal
4	16	sellar/suprasellar	adamantinomatous	GTR	GTR	improved to VFF
5	17.6	suprasellar	papillary	subtotal	radical	no improvement†
6	23.1	suprasellar	adamantinomatous	GTR	radical	remained normal
7	29.2	suprasellar	papillary	GTR	radical	improved to VFF
8	24	sellar/suprasellar	papillary	GTR	GTR	improved to VFF
9	26.8	suprasellar	adamantinomatous	radical	radical	normalized
10	32.6	sellar/suprasellar	adamantinomatous	subtotal	subtotal	no improvement†
11	21	suprasellar	papillary	GTR	GTR	improved to VFF
12	16.5	suprasellar	adamantinomatous	GTR	GTR	normalized

* VFF = visual fields full to confrontation.

† Objective improvement by formal visual field testing but not dramatic. Deficits remain on confrontation testing.

section (> 95% removal), and 2 (16.67%) had partial removals (Table 2). Therefore, 83% of patients (10 of 12) experienced at least a 95% removal of their tumors. Both patients with subtotal resections had undergone previous surgery. Interestingly, postoperative MR imaging at 2–3 months was less sensitive at discerning small residual tumors than the intraoperative endoscopic inspection. Whereas the initial MR imaging indicated that at GTR had been achieved in 9 patients (75%), our intraoperative endoscopic impression was that a GTR had only been achieved in 5 (41.67%) (Figs. 2 and 3, Videos 1 and 2). The follow-up is too short (mean 13.29 months, range 1.8–44.67 months) to draw conclusions as to whether intraoperative endoscopic impression or postoperative MR imaging will be more predictive of recurrence.

Video 1. Incomplete resection. Intraoperative endoscopic views using the 0° and then the 45° endoscopes. The remaining tumor is progressively removed. A portion of the cyst wall is densely adherent to the optic chiasm and could not be removed. Using the 45° endoscope, the residual wall is seen adherent to the optic chiasm but confirms removal from the third ventricle wall. Both Monro foramina are visible.

Video 2. Complete removal. Intraoperative endoscopic views using the 0° and then the 45° endoscopes. After separating the tumor from the posterior aspect of the optic chiasm, its attachment to the third ventricle is sharply divided. Using the 45° endoscope, the tumor bed is inspected and no residual tumor is evident. Both Monro foramina and the cerebral aqueduct as well as the anterior cerebral arteries are visible.

Patients in whom GTR was achieved as assessed by both intraoperative impression and first postoperative MR imaging had smaller tumors than those in whom GTR was not achieved (19.08 vs 27.03 mm). However, when the degree of resection was assessed by initial postoperative MR imaging alone, the mean tumor size in patients who underwent GTR was only marginally smaller than all other resections (23.07 vs 25.67 mm). There was no difference in the rate of resection for subdiaphragmatic sellar/suprasellar (GTRs in 2 of 5, GTRs as noted on MR imaging in 4 of 5) versus suprasellar tumors (GTRs in 3 of 7, GTRs as noted on MR imaging in 5 of 7.

Review of the pathological findings in 11 of our 12 cases revealed 7 adamantinomatous and 4 papillary tumors (Table 2). The remaining case was not characterized by neuropathology. There did not appear to be a difference in the rate of resection according to subtype. We achieved at least a 95% resection of 6 of the 7 adamantinomatous craniopharyngiomas based on intraoperative assessment and first postoperative MR imaging (2 GTRs and 4 radical resections). Similarly, there was at least a 95% resection in 3 of the 4 papillary variants (2 GTRs and 1 radical resection).

All patients with at least 95% resection are undergoing follow-up with serial imaging and without adjuvant therapy. One of the 2 patients who underwent a subtotal resection received postoperative fractionated radiotherapy and experienced subsequent reduction in tumor volume (Fig. 4). Craniotomy was recommended for the other patient. However, this patient preferred serial imaging and has experienced visual deterioration and progressive tumor growth during follow-up (Fig. 5).

Endocrine Outcomes

Three of our patients had preoperative DI. Of the remaining 9 patients, 4 (44%) experienced new persistent DI following surgery (Table 3). Another patient experienced transient DI, which resolved by the first follow-up visit at 2 months. None of our patients experienced normalization of an anterior pituitary deficiency after surgery. All 3 patients who had panhypopituitarism still suffered from the condition postoperatively. Six (67%) of 9 patients who did not have panhypopituitarism preoperatively developed the condition. Two patients without preoperative anterior pituitary dysfunction appear to have maintained

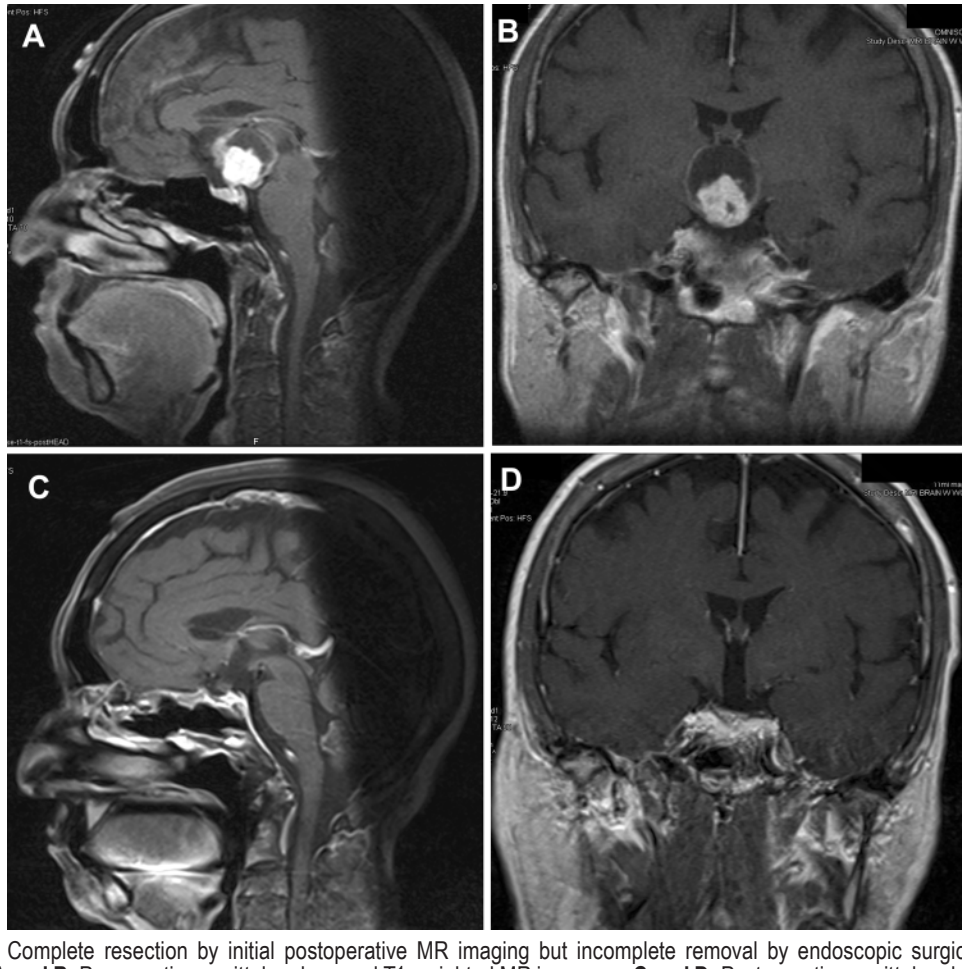

Fig. 2. Complete resection by initial postoperative MR imaging but incomplete removal by endoscopic surgical assessment. **A and B:** Preoperative sagittal and coronal T1-weighted MR images. **C and D:** Postoperative sagittal and coronal T1-weighted MR imaging showing apparent complete resection. However, intraoperative endoscopic inspection indicated residual tumor (see Video 1).

normal function postoperatively (one was taking oral contraceptive and could not be assessed, and the other did not have a postoperative IGF-I level to confirm somatotroph function). One patient with partial anterior pituitary dysfunction did not experience new deficits postoperatively. Overall, the incidence of new thyrotroph deficiency was 67% (4 of 6), and new adrenal insufficiency was 67% (6 of 9) (Table 4). All male patients continued to have gonadal dysfunction and were placed on replacement therapy. Of the 5 patients with normal preoperative IGF-I levels, 1 became deficient and 2 remained normal. Two others did not have postoperative IGF-I levels assessed. If these patients were assumed to have become deficient, then the incidence of new somatotroph deficiency would be 60% (3 of 5).

Visual Outcomes

None of the 3 patients with normal vision preoperatively experienced visual deterioration (Table 2). Of the 9 patients with preoperative visual deficits, in 2 patients there was normalization of their vision and in 5 patients the examination improved to full visual fields to confrontation with subtle persistent deficits on formal visual field testing. Two patients reported improvement, but on formal visual field testing the improvements were minimal and these patients were categorized as unchanged. One of these patients, who had undergone a subtotal resection, experienced subsequent tumor regrowth and recurrent visual deficits. Therefore, although all patients objectively experienced visual improvement at initial follow-up, 78% (7 of 9) experienced either substantial improvement or normalization.

Perioperative Complications

Perioperative complications occurred in one-third of the patients. Although no patient experienced a postoperative CSF leak, 1 patient experienced meningitis within 48 hours of surgery, which was confirmed by lumbar puncture and required antibiotics. Two patients who had been sent home on a regimen of desmopressin were readmitted for treatment of hyponatremia 3 weeks after surgery. One of these patients was also treated with antibiotics for sinusitis, which resolved by the 2-month follow-up. Two patients reported memory difficulties. One of these patients had undergone prior craniotomy and had neuropsychological testing prior to transsphenoidal surgery,

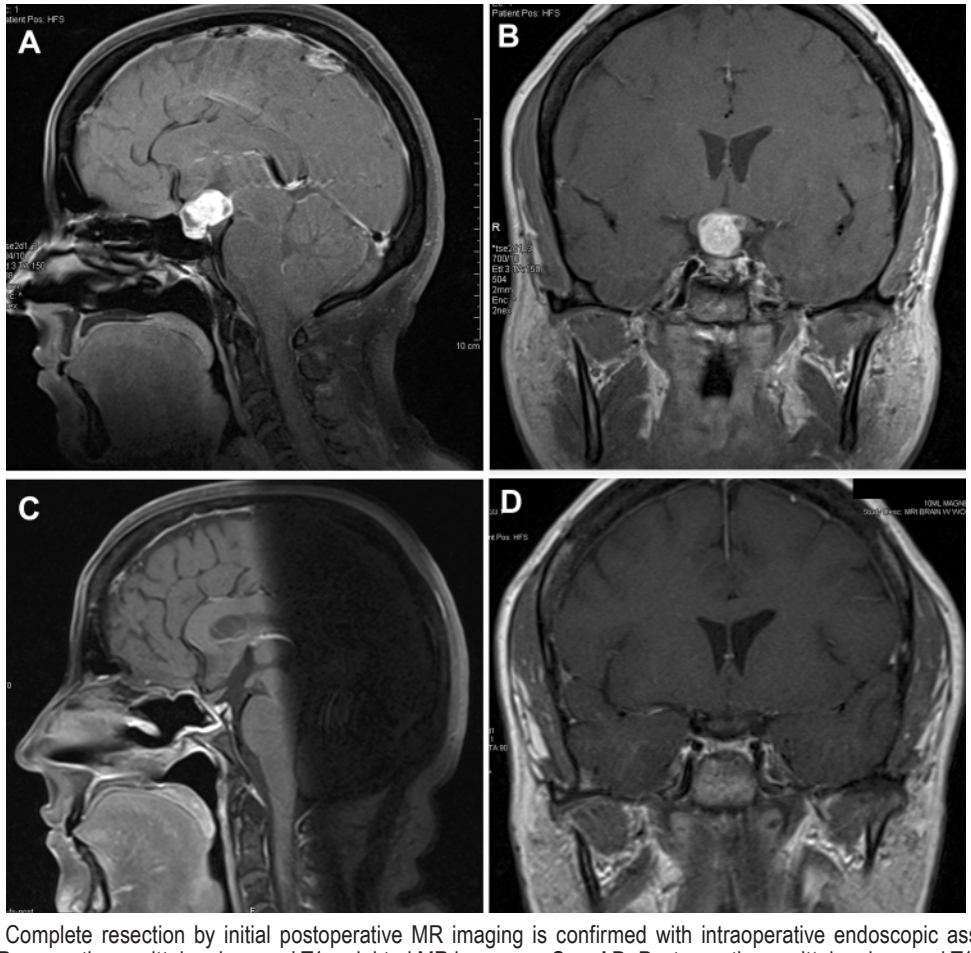

Fig. 3. Complete resection by initial postoperative MR imaging is confirmed with intraoperative endoscopic assessment. **A and B:** Preoperative sagittal and coronal T1-weighted MR images. **C and D:** Postoperative sagittal and coronal T1-weighted MR images showing complete resection. Intraoperative endoscopic inspection indicated complete resection (see Video 2).

confirming that the deficits predated the transsphenoidal operation. The other patient had experienced a thalamic stroke prior to transsphenoidal surgery. We did not perform preoperative cognitive testing, and therefore, some of the deficits could be related to the surgery.

Discussion

Although the transsphenoidal approach for the resection of craniopharyngiomas is not new, its application has traditionally been restricted to either intrasellar tumors or those with subdiaphragmatic origin because of the expanded sellar corridor and the protection from pial invasion from the diaphragmatic cuff.[1,7,20,22] Following the introduction of the extended transsphenoidal transplanum approach by Martin Weiss in the late 1980s, centers have begun to approach select suprasellar craniopharyngiomas through a transsphenoidal approach.[2–6,8,9,16,25] Our early results would suggest that in adults, the approach provides good outcomes for both subdiaphragmatic sellar/suprasellar and suprasellar craniopharyngiomas. No difference in the rate of resection was appreciated between these 2 groups in our series.

Previous studies have suggested that intraoperative assessment of the degree of resection underestimates the amount of residual tumor and that postoperative MR imaging is more accurate. This has been evidenced by the rate of recurrence after apparent GTR.[12,13,24,26] In this se-

TABLE 3: Preoperative and postoperative DI and panhypopituitarism

Case No.	Preop DI	Postop DI	Preop Panhypopit	Postop Panhypopit
1	no	no	no	no
2	no	no	yes	yes
3	yes	yes	no	yes
4	no	no	no	no
5	no	yes	no	yes
6	no	yes	no	yes
7	no	yes	yes	yes
8	yes	yes	no	yes
9	no	yes, transient	no	no
10	no	no	no	yes
11	no	yes	no	yes
12	yes	yes	yes	yes
total	3	7 persistent	3	9

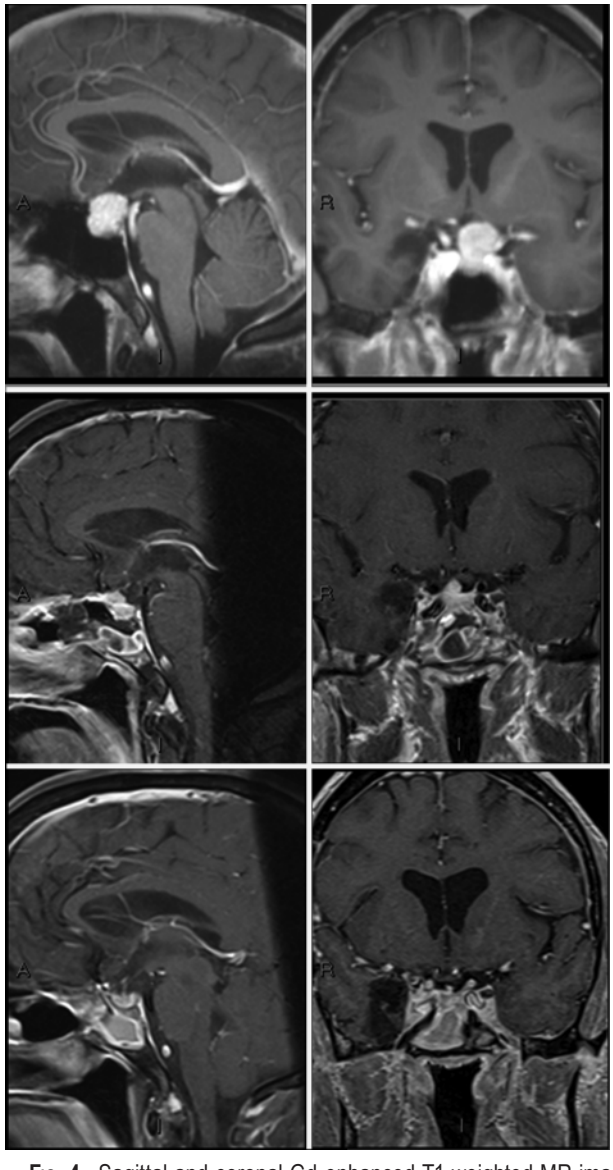

Fig. 4. Sagittal and coronal Gd-enhanced T1-weighted MR images showing the preoperative **(upper)** and postoperative **(center)** tumor volumes and after radiotherapy **(lower)**.

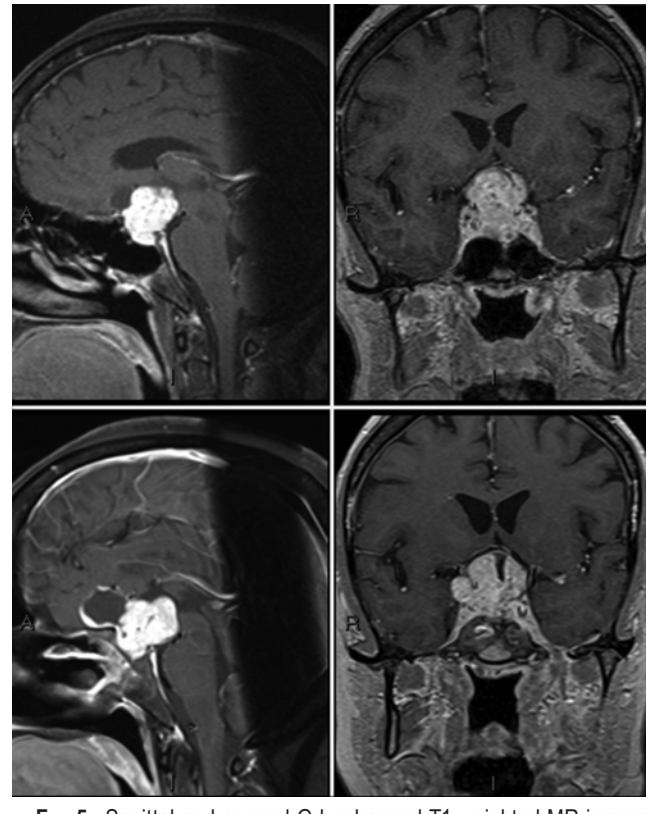

Fig. 5. Sagittal and coronal Gd-enhanced T1-weighted MR images obtained in a patient who presented with a large cystic and solid tumor **(upper)** and experienced progressive growth **(lower)** for which she declined further treatment.

ries, the surgeon's intraoperative endoscopic assessment was a more sensitive indicator of a small residual tumor than the initial postoperative MR imaging findings. Whereas by endoscopic assessment 5 patients had undergone GTR and 6 had undergone a radical resection, the first postoperative MR imaging study indicated that GTR had been achieved in 9 and radical resection had been achieved in 1. The short follow-up of this series does not allow conclusions to be drawn as to which (intraoperative endoscopic assessment or postoperative MR imaging) will be more clinically relevant regarding recurrence.

If the initial postoperative MR image is considered alone, our results are comparable to previous rates of resection of craniopharyngiomas by the microscopic transsphenoidal approach. Gross-total resection as determined by postoperative MR imaging was achieved in 83% of patients in this series. This compares favorably to previous reports that have indicated a GTR rate between 47 and 90% when performed using the microscope.[1,2,15,20,22] As has been noted in previous studies, transsphenoidal surgery does appear less effective for tumors that have been previously treated.[7,15,20] In our series, both patients who experienced subtotal resections had been treated previously (one by craniotomy and the other by transsphenoidal surgery).

For select tumors, the transsphenoidal approach effectively decompresses the optic chiasm and restores function. In our series, 78% of patients experienced either normalization or improvement to full fields by confrontation testing. These results are consistent with previous microscopic transsphenoidal series in which visual improvement occurred in 60–100%.[1,7,9,15,18]

The transsphenoidal approach does cause pituitary dysfunction in a large number of patients. New DI occurred in 44% of our patients, and 67% experienced new panhypopituitarism. None of our patients experienced a gain in pituitary function. Most centers have reported results consistent with this series. New DI has been reported to occur in 39–67% of patients who have undergone microscopic transsphenoidal resections.[1,6,14,15] Anterior pituitary dysfunction has been reported in 22–75%.[1,14,15,18]

The design of this study does not allow a definitive assessment of the comparative efficacy of the endoscopic and microscopic transsphenoidal approaches. The poten-

TABLE 4: Preoperative and postoperative anterior pituitary deficiencies*

		ACTH		TSH		Gonadal		IGF-I	
Case No.	Sex	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
1	F	0	0	0	0	OCP	OCP	0	0
2	M	1	1	1	1	1	1	0	0
3	M	0	1	0	1	1	1	0	1
4	F	0	0	0	0	0	NT	0	NT
5	M	0	1	1	1	1	1	1	1
6	M	0	1	1	1	1	1	0	NT
7	F	1	1	0	1	1	NT	1	1
8	F	0	1	1	1	1	1	1	1
9	F	0	0	0	1	0	NT	1	1
10	F	0	1	1	1	1	1	1	1
11	M	0	1	1	1	1	1	1	NT
12	F	1	1	0	1	OCP	OCP	1	1
total		3	9	6	10			7	

* ACTH = adrenocorticotropic hormone; TSH = thyroid-stimulating hormone; 0 = no deficiency in function; 1 = deficiency; OCP = oral contraceptives; NT = not tested.

tial advantages of the endoscope center on the panoramic view of the operative field. Unlike the microscope, which is limited by line of sight, the endoscope provides angled views that allow a more precise visualization of the suprasellar space and the relation of the tumor to critical neurovascular structures. This appeared to translate to a more critical assessment of the degree of resection. Despite these apparent advantages, the endoscopic rate of resection and its visual and endocrine outcomes are not definitively superior to those of the results of previously published microscopic transsphenoidal series. Although this may relate to selection bias, it may also be that although the endoscope provides a wider view of the operative field, it also is limited by a lack of true 3D views, instruments that can access what is visualized by the angled endoscopes, and a more cramped operative corridor because of the lack of a nasal speculum.

Conclusions

The endoscopic transsphenoidal approach for adult craniopharyngiomas allows for a high rate of radical resection with reliable visual improvement. New pituitary deficits do occur in the majority of patients with a low rate of major complications. The improved visualization with the endoscope may provide a more sensitive indicator of postoperative residual tumor than the initial postoperative MR imaging.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: JA Jane Jr. Acquisition of data: JA Jane Jr., E Kiehna, SC Payne, SV Early. Analysis and interpretation of data: JA Jane Jr. Drafting the article: JA Jane Jr., ER Laws. Critically revising the article: JA Jane Jr., E Kiehna, ER Laws. Reviewed final version of the manuscript and approved it for submission: JA Jane Jr., E Kiehna, ER Laws. Administrative/technical/material support: JA Jane Jr.

References

1. Chakrabarti I, Amar AP, Couldwell W, Weiss MH: Long-term neurological, visual, and endocrine outcomes following transnasal resection of craniopharyngioma. **J Neurosurg 102:**650–657, 2005
2. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T: Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. **Neurosurgery 55:**539–550, 2004
3. de Divitiis E, Cappabianca P, Cavallo LM, Esposito F, de Divitiis O, Messina A: Extended endoscopic transsphenoidal approach for extrasellar craniopharyngiomas. **Neurosurgery 61 (5 Suppl 2):**219–228, 2007
4. de Divitiis E, Cavallo LM, Cappabianca P, Esposito F: Extended endoscopic endonasal transsphenoidal approach for the removal of suprasellar tumors: part 2. **Neurosurgery 60:**46–59, 2007
5. Dusick JR, Esposito F, Kelly DF, Cohan P, DeSalles A, Becker DP, et al: The extended direct endonasal transsphenoidal approach for nonadenomatous suprasellar tumors. **J Neurosurg 102:**832–841, 2005
6. Dusick JR, Fatemi N, Mattozo C, McArthur D, Cohan P, Wang C, et al: Pituitary function after endonasal surgery for nonadenomatous parasellar tumors: Rathke's cleft cysts, craniopharyngiomas, and meningiomas. **Surg Neurol 70:**482–491, 2008
7. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
8. Frank G, Pasquini E, Doglietto F, Mazzatenta D, Sciarretta V, Farneti G, et al: The endoscopic extended transsphenoidal approach for craniopharyngiomas. **Neurosurgery 59 (1 Suppl 1):**ONS75–ONS83, 2006
9. Gardner PA, Kassam AB, Snyderman CH, Carrau RL, Mintz AH, Grahovac S, et al: Outcomes following endoscopic, expanded endonasal resection of suprasellar craniopharyngiomas: a case series. **J Neurosurg 109:**6–16, 2008

10. Gardner PA, Prevedello DM, Kassam AB, Snyderman CH, Carrau RL, Mintz AH: The evolution of the endonasal approach for craniopharyngiomas. **J Neurosurg 108:**1043–1047, 2008
11. Hardy J: Transsphenoidal hypophysectomy. **J Neurosurg 34:**582–594, 1971
12. Hoffman HJ: Surgical management of craniopharyngioma. **Pediatr Neurosurg 21 (Suppl 1):**44–49, 1994
13. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI: Aggressive surgical management of craniopharyngiomas in children. **J Neurosurg 76:**47–52, 1992
14. Honegger J, Buchfelder M, Fahlbusch R: Surgical treatment of craniopharyngiomas: endocrinological results. **J Neurosurg 90:**251–257, 1999
15. Honegger J, Buchfelder M, Fahlbusch R, Däubler B, Dörr HG: Transsphenoidal microsurgery for craniopharyngioma. **Surg Neurol 37:**189–196, 1992
16. Kaptain GJ, Vincent DA, Sheehan JP, Laws ER Jr: Transsphenoidal approaches for the extracapsular resection of midline suprasellar and anterior cranial base lesions. **Neurosurgery 49:**94–101, 2001
17. Kassam AB, Thomas A, Carrau RL, Snyderman CH, Vescan A, Prevedello D, et al: Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. **Neurosurgery 63 (1 Suppl 1):**ONS44–ONS53, 2008
18. Kitano M, Taneda M: Extended transsphenoidal surgery for suprasellar craniopharyngiomas: infrachiasmatic radical resection combined with or without a suprachiasmatic translamina terminalis approach. **Surg Neurol 71:**290–298, 2009
19. Laws ER Jr: Transsphenoidal microsurgery in the management of craniopharyngioma. **J Neurosurg 52:**661–666, 1980
20. Laws ER Jr: Transsphenoidal removal of craniopharyngioma. **Pediatr Neurosurg 21 (Suppl 1):**57–63, 1994
21. Leng LZ, Brown S, Anand VK, Schwartz TH: "Gasket-seal" watertight closure in minimal-access endoscopic cranial base surgery. **Neurosurgery 62 (5 Suppl 2):**ONSE342–ONSE343, 2008
22. Maira G, Anile C, Rossi GF, Colosimo C: Surgical treatment of craniopharyngiomas: an evaluation of the transsphenoidal and pterional approaches. **Neurosurgery 36:**715–724, 1995
23. Schwartz TH, Anand VK: The endoscopic endonasal transsphenoidal approach to the suprasellar cistern. **Clin Neurosurg 54:**226–235, 2007
24. Villani RM, Tomei G, Bello L, Sganzerla E, Ambrosi B, Re T, et al: Long-term results of treatment for craniopharyngioma in children. **Childs Nerv Syst 13:**397–405, 1997
25. Weiss MH: The transnasal transsphenoidal approach, in Apuzzo MLJ (ed): **Surgery of the Third Ventricle.** Baltimore: Williams and Wilkins, 1987, pp 476–494
26. 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

Manuscript submitted December 15, 2009.
Accepted January 13, 2010.
Address correspondence to: John A. Jane Jr., M.D., Department of Neurosurgery, University of Virginia Health System, Charlottesville, Virginia 22908. email: johnjanejr@virginia.edu.

Neurosurg Focus 28 (4):E10, 2010

Radiation therapy for pediatric craniopharyngioma

Erin N. Kiehna, M.D.,[1] and Thomas E. Merchant, D.O., Ph.D.[2]

[1]Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia; and [2]Division of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee

Object. The treatment of craniopharyngioma is highly controversial. Continued advances in limited surgery and radiation therapy have maintained excellent local disease control while minimizing treatment-related sequelae. Further analyses of outcomes are necessary to characterize the long-term effects of radiation therapy.

Methods. An extensive literature review was performed for all studies including radiation therapy, with or without surgery, for pediatric craniopharyngioma.

Results. The authors identified 32 papers describing radiation therapy for treatment of pediatric craniopharyngioma, with disease control ranging from 44 to 100%. Modern studies report at least 90% disease control with 5-year follow-up. Fifteen studies reported outcomes, demonstrating that more than two-thirds of patients treated with surgery and radiation therapy have favorable outcomes, and this rate is more than 85% in the modern era.

Conclusions. Conservative surgery and radiation therapy results in long-term disease control in pediatric patients with craniopharyngioma that is comparable to results obtained with radical surgery alone. However, children with craniopharyngioma remain vulnerable to late treatment failures and side effects from radiation therapy, including endocrinopathies, vasculopathies, and secondary tumors, which may be detrimental to the quality of life. Long-term follow-up beyond 5–10 years is necessary to assess tumor control relative to functional outcomes. *(DOI: 10.3171/2010.1.FOCUS09297)*

Key Words • **conformal radiation therapy** • **craniopharyngioma**

In 1932, Harvey Cushing described craniopharyngioma as "the most baffling problem which confronts the neuro-surgeon."[6] In 2 detailed accounts, he described performing frontal craniotomies for cystic fenestration of these lesions, only to have to return for subsequent fenestration and cystic resection due to symptomatic cystic recurrence.[21,40] The treatment of craniopharyngioma remains equally challenging and controversial in 2010. Although craniopharyngioma is pathologically benign in children, and should be curable by complete surgical removal, the morbidity and mortality associated with such attempts may be avoided by using a multimodality approach.

In 1961, Kramer et al.[18] at the Royal Marsden Hospital became the first group to publish a report on limited surgery and radiation therapy for pediatric craniopharyngioma. They recognized that with fenestration alone, symptomatic regrowth of the cystic portion of the tumor could be expected within 3–6 months.[14] By combining bur-hole aspiration with external-beam radiation therapy to 5000–6550 R, disease control was achieved in all 6 children who were reported to be "alive and well" at follow-up. Long-term disease control and outcomes in this group of patients were updated by Rajan et al.[32] in 1993, in an expanded cohort of 77 children also treated with planned limited surgery and radiation. The 10-year progression-free survival rate was 80% and overall survival was 77%. These results were comparable to major surgical series at that time.

Over the past decade, advances in image guidance and conformal radiation therapy have allowed for precise tumor localization and smaller treatment margins to limit the radiation dose to normal brain. Our preliminary experience with conformal radiation therapy for children with craniopharyngioma, both newly diagnosed and recurrent after prior surgery, showed that the volume of irradiation could be reduced without affecting the expected rate of tumor control. With a median follow-up period of 36.6 months (range 24.4–80 months), the 3-year estimate of progression-free survival was 90.3 ± 7.3%.[25] Longitudinal evaluation of IQ in these patients showed a negative correlation between IQ and the volume of normal brain receiving doses in excess of 45 Gy as well as a variety of surgical factors, most notably extent of resection. In this preliminary experience in which conformal radiation therapy was used, the clinical target volume margin surrounding the cystic solid tumor complex was relatively large (10 mm) for a tumor known to lack invasive properties. The clinical target volume margin was subsequently reduced to 5 mm, and with additional follow-up, disease control outcomes parallel those achieved in earlier reports in which conventional radiation therapy was used. Despite these advances in reducing dose to normal tissue, we recognize that these children are vulnerable to

Abbreviation used in this paper: DI = diabetes insipidus.

radiation sequelae that may be delayed in presentation. We have evaluated these patients for other measures, including behavior, to show that good functional outcomes may be achieved, and to show the contribution of factors other than radiation therapy to late effects.[8]

In this review we compare results of combined surgery and radiation therapy for pediatric craniopharyngioma, distinguishing outcomes for pediatric patients separately from adults to account for differences in natural history, which may lead to bias in selecting treatment, reporting tumor- and treatment-related complications, and outcome measures including quality of life.

Radiation Therapy for Pediatric Craniopharyngioma

We searched the literature for all published reports of radiation therapy for craniopharyngioma. Articles were excluded if specific results for children were not listed in the text. Table 1 summarizes the results of our review, based on series grouped by institution, number of patients, age, and follow-up and disease control, as reported in the original articles. Studies using statistical methods to estimate survival have been identified.

The earliest reports of radiation therapy for pediatric craniopharyngioma are from the Royal Marsden Hospital. Between 1952 and 1954 at that institution, 6 children underwent attempted stereotactic aspiration of cyst contents, followed by radiotherapy consisting of 2 arcs of 180°, delivering 5500 R over 6 weeks. Without the advantages of modern imaging, radiation was aimed at either the sella turcica for uncalcified tumors or at calcifications beyond the sella and presumed to be tumor. All 6 children were alive and free from disease recurrence over a follow-up period of 6 years.[18] During the ensuing decades, 188 patients received conservative surgery followed by external-beam radiation therapy at the Royal Marsden Hospital, 72 of whom were younger than 16 years of age. This represents experiences with one of the largest and most mature patient groups. During this time period, the linear accelerator replaced ^{60}Co radiation, allowing for a more predictable and precise method of delivering radiation therapy. Only 8 of these children experienced disease progression, resulting in an estimated progression-free survival rate of 84% when measured beyond 10 years.[1,33]

In addition to advances in the delivery of radiation with the linear accelerator, CT scans became readily available in the 1970s, as did the operating microscope. Many centers began retrospectively stratifying children into treatment groups for analysis of outcomes. At the University of California, San Francisco, patients who underwent biopsy sampling or cyst resection and radiation had 100% disease control, whereas in more than half of the children undergoing subtotal resection and radiation, the treatment failed.[19,36,44] Similarly, children treated with conservative surgery and radiation in Boston experienced 95–100% disease control, whereas patients treated with subtotal resection and radiation only achieved 67–83% disease control.[9,38] Sung[42] reported 87% disease control with minimal surgery and radiation therapy, and 72% disease control for patients undergoing subtotal surgery at Columbia. Overall, despite advances in neuroimaging and surgical technique, these results suggested that extensive resection does not improve disease control rates when adjuvant radiation therapy is used.

More modern studies conducted between 1980 and 2000 confirmed that conventional radiation therapy resulted in disease control rates ranging from 79 to 84% at 10 years.[28,30,41] These series also analyzed many treatment-related factors involving the delivery of radiation therapy. Moon et al.[28] analyzed the timing of radiation therapy following surgery and found no significant difference between early and late treatment. Radiation therapy was also found to be highly effective as salvage therapy for patients in whom initial surgery failed.[25,30,41]

Since 1998, in an effort to reduce the side effects, we have prospectively used conformal and intensity-modulated radiation therapy for the treatment of craniopharyngioma instead of conventional radiation therapy, which in the past included large, parallel, opposed beams. Modern radiation therapy treatment planning involves the use of CT imaging to define the frame of reference and calculate radiation dose. Registration of MR imaging data has further refined target delineation, which is based on the gross tumor volume that includes the entire residual solid and cystic tumor. Relative to the start of treatment, the timing of imaging and the acquired sequences ensures delineation of the proper target and reduces error associated with changes in the tumor over time. Imaging during therapy is critical, because these tumors are known to demonstrate cyst enlargement in response to irradiation. The target for treatment planning comprises the gross tumor volume, defined above, which is then surrounded by the clinical target volume margin to account for subclinical tumor infiltration and uncertainty in interpretation. Our current clinical target volume margin is 5 mm, and may be anatomically constrained at interfaces (for example, bone) where invasion is unlikely. Others have reported applying smaller margins with increasing requirements for stereotactic localization. Finally, the clinical target volume margin is surrounded by a geometrical margin called the planning target volume margin. This margin has been reduced to approximately 3 mm for daily clinical radiotherapy with the advent of linear accelerator on-board imaging systems, which are capable of daily cone-beam CT imaging. As the margins continue to shrink while practitioners gain more experience, it is critical that the images used to define the target have compatible resolution. In our experience, 3D MR imaging using postcontrast T1-weighted, T2-weighted, and postcontrast T2-weighted FLAIR imaging appear to be most useful. The T2-weighted imaging is critical at interfaces involving normal brain, whereas the postcontrast T2-weighted FLAIR imaging is key to defining tumor that interfaces with CSF. Our disease control for patients treated with surgery and radiation therapy is 90 and 85% at 3 and 5 years, respectively.[25] Puget et al.[31] have reported no treatment failures with this approach at a 14-month follow-up.

Patients treated with focused radiation require imaging during treatment to monitor for cyst progression, which may occur early or late during the treatment

TABLE 1: Literature review of radiation therapy for pediatric craniopharyngioma*

Authors & Year	Pts' Median Age in Yrs (range)	No. of Pts	FU (yrs)	% Disease Control
Kramer et al., 1961	10 (6–14)	6	6	100
Bloom et al., 1990		27	10	96
Rajan & coll, 1993, 1997	<16	72	10	87†
McMurry et al., 1977	<18	6	10	77
Lichter et al., 1977	10 (4–17)	7	6	71
Thomsett et al., 1980	9.2 (1.8–17.2)	7	4.5	82
Richmond et al., 1980	<20			
STR + RT		12	5	44
bx + RT		8	5	100
Onoyama et al., 1977	<25	12	10	77
Thompson et al., 1978	10 (5–18)	5	3.5	60
Shapiro et al., 1979				
STR + RT	7.10	7	9.4	50†
bx + RT	7.93	22	3.3	100†
Cabezudo et al., 1981	<15	9	3	100†
Sung, 1982	<15	14	10	
STR + RT				72
bx + RT				87
Calvo et al., 1983	10 (3–19)	11	6	100
Hoogenhout et al., 1984	<15	12	10	86†
Manaka et al., 1985	<14	21	10	63†
Clayton et al., 1988	9.5 (1–16)	10	6.3	100
Sorva et al., 1988	11 (1–18)	22		
STR + RT			5	100
bx + RT			5	100
Wen et al., 1989	<18	8	5	100
Shillito, 1986		10		
STR + RT	3.45 (11 mos–15 yrs)	6	10	67
bx + RT	11.4 (6–13)	4	10	100
Fischer et al., 1990		27	10	
STR + RT	7.4	4	11	83
bx + RT	9.6	16	10	95
Danoff et al., 1983	8 (3–19)	19		
STR + RT			10	50
bx + RT			10	83
Weiss et al., 1989	10 (3–14)	5	7	80
Regine & coll, 1992, 1993	<16	19	10	75
Hetelekidis et al., 1993		37	4	86
Stripp et al., 2004	8.5 (1.5–24)	18	10	84†
Moon et al., 2005	<20	15	10	80†
Pemberton et al., 2005	<15	28	10	79†
Habrand et al., 1999	7.4 (2–15)	37	10	56†
Puget et al., 2007		22		100
STR + RT (retrospective)	7.5 (4–16)	8	10	100
STR + RT (prospective)	7.9 (2–14)	10	1	100
Lin et al., 2008	9 (2–14)	11	10	100†

(continued)

TABLE 1: Literature review of radiation therapy for pediatric craniopharyngioma* *(continued)*

Authors & Year	Pts' Median Age in Yrs (range)	No. of Pts	FU (yrs)	% Disease Control
Merchant et al., 2002	7.3 (3–18)	15	6	94
Merchant et al., 2006	7.3 (3–18)	28	3	90†

* The median radiation doses ranged from 50 to 55 Gy. Articles from the same institution are grouped together and designated by shading. Abbreviations: bx = biopsy; coll = colleagues; FU = follow-up; Pts = patients; RT = radiation therapy; STR = subtotal resection.

† Studies that include statistically based survival estimates.

course.[33] Our current protocol includes weekly MR imaging, rapid assessment of changes in the target volume through imaging registration, and development of a new (adaptive) treatment plan when the gross tumor volume intersects with the clinical target volume at any point. Although there is no consensus in the literature on the treatment dose and fractionation schedule, the majority of series limited radiation dose to 50–55.8 Gy in children, delivered in 1.5- to 2.0-cGy fractions, 5 days per week for a period of 6 weeks. Concerns about the maximum dose to the optic chiasm and optic nerves precludes treatment to higher doses.

Side Effects After Radiation Therapy

Treatment-related side effects of radiation therapy have been well described in the literature, and include endocrine, visual, and cognitive sequelae as well as vasculopathy and secondary malignancies. Side effects may occur acutely, but are generally considered to be insidious. Regardless of their timing, they have the ability to affect the quality of life of these children.[16]

Visual Outcomes

Visual deterioration occurring during radiation therapy has been well documented, and is usually attributed to cystic progression and/or hydrocephalus.[33] Craniotomy and tumor decompression is sometimes required, but more often cyst aspiration alone reverses vision loss when performed in a timely manner. Aspiration may need to be performed repeatedly. The historical incidence is approximately 14%.[33] In our series, up to 46% of patients required cyst aspiration in the time period immediately before, during, or after radiation therapy.[25] Optic neuropathies and/or necrosis may also occur secondary to radiation therapy, and appear to be dose dependent.[11,13,25,30,32,34,35,41,46] Flickinger et al.[10] reported on 3 children in whom optic neuropathy developed at a radiation dose in excess of 60 Gy. We have not experienced any occurrences of optic neuritis or necrosis when the optic apparatus is treated to 54–55.8 Gy in 1.8-Gy fractions, a consensus dose in the literature.[27] We recently reviewed a cohort of 62 children, and found that 38 (61%) had normal vision, 14 (23%) had mildly to moderately impaired vision, and 10 (16%) had severely impaired vision at the start of irradiation. With extended follow-up, none of the patients had clinically significant changes in their vision that were not attributed to tumor progression. Only 5% required craniotomy for decompression when cystic change affected vision early after radiation therapy, and placement of an Ommaya reservoir was considered not to be feasible.

Endocrine Outcomes

Hypothalamic-pituitary dysfunction may result from the tumor burden alone; however, progressive pituitary dysfunction develops in the months to years following radiation therapy and must be closely monitored.[11,12,25] With long-term follow-up we have found that up to 70% of children require growth hormone supplementation, 90% require thyroid replacement, 40% require replacement for hypogonadism, and 75% require cortisol supplementation. The incidence of DI after radiotherapy is strictly related to changes in the tumor complex that mechanically impact the pituitary. In general, DI is not considered a common complication of irradiation. The incidence of the more common endocrine deficiencies appears to be dose dependent. At levels higher than 60 Gy it may be as high as 80%, versus 36% incidence at lower doses.[34]

Cognitive Outcomes

Early attempts to quantify the effects of surgery and adjuvant therapy on cognitive outcomes demonstrated that patients treated with primary radiation for craniopharyngioma had less frontal lobe dysfunction than patients who underwent radical excision.[4] As radiation treatment has become more conformal, with a reduction in dose to the normal brain, children are tolerating radiation therapy without treatment-related decline.[9,25,26,28,30,32,35,41] Our results with serial neuropsychometric testing show that overall IQ remains stable through 5 years of follow-up; however, there are factors that predispose some patients to worse outcomes. These characteristics include younger patients (age < 7 years) and those with hydrocephalus treated with shunt insertion, large cystic tumors requiring multiple aspirations, extensive surgery, and DI.[25] Jalali et al.[15] also demonstrated that IQ remains stable over a 2-year period, and that age < 15 years was a significant cause of decline, as was dose to the temporal lobe.

Functional Outcomes and Quality of Life

Fifteen articles published during the past 50 years have reported on functional and neurological outcomes following radiation therapy. The first children treated in a combined-modality approach were reported to have a 6% disability rate, with a median follow-up of 12 years.[32] With the use of more standardized scales of quality of life and performance status, including the Wen classification

index, Wechsler IQ and achievement tests, and Health Utility Index, 42–86% of patients treated with surgery and conventional radiation therapy have experienced a favorable functional outcome, defined as limited disability and functional independence, with improved scores in the more modern treatment era (Table 2). With a conversion to conformal radiation therapy, at least 85% of patients have a favorable outcome, as determined by cognitive testing.[26]

Cerebrovascular Disease

Radiation therapy targeted at the sellar/suprasellar region will unfortunately also include the intracranial carotid arteries and the circle of Willis. Liu et al.[22] reported on 6 patients in a series of 20 who developed a vasculopathy on neuroimaging after receiving radiation therapy for craniopharyngioma. Retrospective studies of radiation therapy directed at the sellar/suprasellar region have demonstrated an incidence as high as 21% for cerebrovascular events.[17] The treatment of vasculopathy and moyamoya disease should be approached systematically and cautiously by experienced caregivers, because the risks associated with treatment have been considerable. The relative risk of developing moyamoya has been estimated to increase by 7% for every 100 cGy increase in radiation dose above 5000 cGy. The delay to occurrence is approximately 5–12 years.[12,45]

Secondary Malignancies

The risk of a radiation-induced secondary malignancy is estimated to be 1.9% at 10 years, and remains a primary concern when managing craniopharyngioma in these children.[16] In the largest single-institution study of 173 patients who were treated with conservative surgery and radiation therapy, no secondary malignancies were reported at a median follow-up of 12 years.[32] Of the 626 patients in our literature review, the majority of whom received conventional radiation, there are only 4 reports of secondary malignancies. These were all high-grade glioma, of which the patients subsequently died.[9,11,38] In the modern treatment era, in which radiation is delivered in a conformal fashion, minimizing the dose to normal tissue, the rate of secondary malignancy may decline. The development of malignant craniopharyngioma after radiation therapy is considered a secondary malignancy by transformation, and it is rare.

TABLE 2: Literature review of neurological outcomes after radiation therapy for pediatric craniopharyngioma

Authors & Year	% Favorable Functional Outcomes
Kramer et al., 1961	83
Rajan & coll, 1993, 1997	94
Lichter et al., 1977	57
Thomsett et al., 1980	89
Sung, 1982	54
Shillito, 1986	
STR + RT	50
bx + RT	75
Fischer et al., 1990	
STR + RT	67
bx + RT	86
Danoff et al., 1983	79
Weiss et al., 1989	80
Regine & coll, 1992, 1993	42
Pemberton et al., 2005	75
Habrand et al., 1999	66
Puget et al., 2007	
STR + RT (retrospective)	76–80
STR + RT (prospective)	95
Lin et al., 2008	91
Merchant et al., 2002	85

Conclusions

We have reviewed the role of radiation therapy in the treatment of pediatric craniopharyngioma at more than 20 major medical centers worldwide over the course of nearly 50 years. When craniopharyngioma is treated using a multidisciplinary approach involving neurosurgeons, neurooncologists, and radiation oncologists, conservative surgery and radiation therapy results in long-term disease control in pediatric craniopharyngioma, and the control is comparable to results obtained with radical surgery alone. However, our results at present are limited to studies with only 5- to 10-year reported outcomes. At present children with this disease have an average life span of 75 years. Children with craniopharyngioma remain vulnerable to late treatment failures and side effects from radiation therapy including endocrinopathy and vasculopathy, which may have a detrimental impact on quality of life. Long-term follow-up beyond 5–10 years is necessary to assess tumor control relative to functional outcomes.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: TE Merchant. Acquisition of data: TE Merchant, EN Kiehna. Analysis and interpretation of data: TE Merchant, EN Kiehna. Drafting the article: TE Merchant, EN Kiehna. Critically revising the article: TE Merchant, EN Kiehna. Reviewed final version of the manuscript and approved it for submission: TE Merchant, EN Kiehna. Statistical analysis: TE Merchant, EN Kiehna. Administrative/technical/material support: TE Merchant. Study supervision: TE Merchant.

References

1. Bloom HJ, Glees J, Bell J, Ashley SE, Gorman C: The treatment and long-term prognosis of children with intracranial tumors: a study of 610 cases, 1950-1981. **Int J Radiat Oncol Biol Phys 18:**723–745, 1990
2. Cabezudo JM, Vaquero J, Areitio E, Martinez R, de Sola RG, Bravo G: Craniopharyngiomas: a critical approach to treatment. **J Neurosurg 55:**371–375, 1981

3. Calvo FA, Hornedo J, Arellano A, Sachetti A, de la Torre A, Aragon G, et al: Radiation therapy in craniopharyngiomas. **Int J Radiat Oncol Biol Phys 9:**493–496, 1983
4. Cavazzuti V, Fischer EG, Welch K, Belli JA, Winston KR: Neurological and psychophysiological sequelae following different treatments of craniopharyngioma in children. **J Neurosurg 59:**409–417, 1983
5. Clayton PE, Price DA, Shalet SM, Gattemaneni HR: Craniopharyngioma recurrence and growth hormone therapy. **Lancet 1:**642, 1988
6. Cushing H: **Intracranial Tumours. Notes Upon a Series of Two Thousand Verified Cases With Surgical-Mortality Percentages Pertaining Thereto.** Springfield, IL: Charles C Thomas, 1932, pp 93, 102
7. Danoff BF, Cowchock FS, Kramer S: Childhood craniopharyngioma: survival, local control, endocrine and neurologic function following radiotherapy. **Int J Radiat Oncol Biol Phys 9:**171–175, 1983
8. Dolson EP, Conklin HM, Li C, Xiong X, Merchant TE: Predicting behavioral problems in craniopharyngioma survivors after conformal radiation therapy. **Pediatr Blood Cancer 52:**860–864, 2009
9. 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
10. Flickinger JC, Lunsford LD, Singer J, Cano ER, Deutsch M: Megavoltage external beam irradiation of craniopharyngiomas: analysis of tumor control and morbidity. **Int J Radiat Oncol Biol Phys 19:**117–122, 1990
11. Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, et al: The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. **Int J Radiat Oncol Biol Phys 44:** 255–263, 1999
12. 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
13. Hoogenhout J, Otten BJ, Kazem I, Stoelinga GB, Walder AH: Surgery and radiation therapy in the management of craniopharyngiomas. **Int J Radiat Oncol Biol Phys 10:**2293–2297, 1984
14. Ingraham FD, Scott HW Jr: Craniopharyngiomas in children. **J Pediatr 29:**95–116, 1946
15. Jalali R, Mallick I, Dutta D, Goswami S, Gupta T, Munshi A, et al: Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. **Int J Radiat Oncol Biol Phys 26** [epub ahead of print], 2009
16. Kalapurakal JA: Radiation therapy in the management of pediatric craniopharyngiomas—a review. **Childs Nerv Syst 21:**808–816, 2005
17. Keene DL, Johnston DL, Grimard L, Michaud J, Vassilyadi M, Ventureyra E: Vascular complications of cranial radiation. **Childs Nerv Syst 22:**547–555, 2006
18. Kramer S, McKissock W, Concannon JP: Craniopharyngiomas. Treatment by combined surgery and radiation therapy. **J Neurosurg 18:**217–226, 1961
19. Lichter AS, Wara WM, Sheline GE, Townsend JJ, Wilson CB: The treatment of craniopharyngiomas. **Int J Radiat Oncol Biol Phys 2:**675–683, 1977
20. Lin LL, El Naqa I, Leonard JR, Park TS, Hollander AS, Michalski JM, et al: Long-term outcome in children treated for craniopharyngioma with and without radiotherapy. **J Neurosurg Ped 1:**126–130, 2008
21. Lindholm J, Nielsen EH: Craniopharyngioma: historical notes. **Pituitary 12:**352–359, 2009
22. Liu AK, Bagrosky B, Fenton LZ, Gaspar LE, Handler MH, McNatt SA, et al: Vascular abnormalities in pediatric craniopharyngioma patients treated with radiation therapy. **Pediatr Blood Cancer 52:**227–230, 2009
23. Manaka S, Teramoto A, Takakura K: The efficacy of radiotherapy for craniopharyngioma. **J Neurosurg 62:**648–656, 1985
24. McMurry FG, Hardy RW Jr, Dohn DF, Sadar E, Gardner WJ: Long term results in the management of craniopharyngiomas. **Neurosurgery 1:**238–241, 1977
25. Merchant TE, Kiehna EN, Kun LE, Mulhern RK, Li CH, Xiong X, et al: Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. **J Neurosurg 104 (2 Suppl):**94–102, 2006
26. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
27. Minniti G, Esposito V, Amichetti M, Enrici RM: The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngioma. **Neurosurg Rev 32:**125–132, 2009
28. Moon SH, Kim IH, Park SW, Kim I, Hong S, Park CI, et al: Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas—a study in single institute. **Childs Nerv Syst 21:**799–807, 2005
29. Onoyama Y, Ono K, Yabumoto E, Takeuchi J: Radiation therapy of craniopharyngioma. **Radiology 125:**799–803, 1977
30. Pemberton LS, Dougal M, Magee B, Gattamaneni HR: Experience of external beam radiotherapy given adjuvantly or at relapse following surgery for craniopharyngioma. **Radiother Oncol 77:**99–104, 1005, 2005
31. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106 (1 Suppl):**3–12, 2007
32. Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJ, et al: Craniopharyngioma—a long-term results following limited surgery and radiotherapy. **Radiother Oncol 26:**1–10, 1993
33. Rajan B, Ashley S, Thomas DG, Marsh H, Britton J, Brada M: Craniopharyngioma: improving outcome by early recognition and treatment of acute complications. **Int J Radiat Oncol Biol Phys 37:**517–521, 1997
34. Regine WF, Kramer S: Pediatric craniopharyngiomas: long term results of combined treatment with surgery and radiation. **Int J Radiat Oncol Biol Phys 24:**611–617, 1992
35. Regine WF, Mohiuddin M, Kramer S: Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. **Radiother Oncol 27:**13–21, 1993
36. Richmond IL, Wara WM, Wilson CB: Role of radiation therapy in the management of craniopharyngiomas in children. **Neurosurgery 6:**513–517, 1980
37. Shapiro K, Till K, Grant DN: Craniopharyngiomas in childhood. A rational approach to treatment. **J Neurosurg 50:**617–623, 1979
38. Shillito J Jr: Treatment of craniopharyngioma. **Clin Neurosurg 33:**533–546, 1986
39. Sorva R, Heiskanen O, Perheentupa J: Craniopharyngioma surgery in children: endocrine and visual outcome. **Childs Nerv Syst 4:**97–99, 1988
40. Spencer DD: Cohen-Gadol: **The Legacy of Harvey Cushing: Profiles of Patient Care.** New York: Thieme, 2007, pp 34–43, 60–65
41. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, et al: Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. **Int J Radiat Oncol Biol Phys 58:**714–720, 2004
42. Sung DI: Suprasellar tumors in children: a review of clini-

cal manifestations and managements. **Cancer 50:**1420–1425, 1982
43. Thompson IL, Griffin TW, Parker RG, Blasko JC: Craniopharyngioma: the role of radiation therapy. **Int J Radiat Oncol Biol Phys 4:**1059–1063, 1978
44. 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
45. Ullrich NJ, Robertson R, Kinnamon DD, Scott RM, Kieran MW, Turner CD, et al: Moyamoya following cranial irradiation for primary brain tumors in children. **Neurology 68:**932–938, 2007
46. 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
47. Wen BC, Hussey DH, Staples J, Hitchon PW, Jani SK, Vigliotti AP, et al: A comparison of the roles of surgery and radiation therapy in the management of craniopharyngiomas. **Int J Radiat Oncol Biol Phys 16:**17–24, 1989

Manuscript submitted December 15, 2009.
Accepted January 18, 2010.
Portions of this work were presented as proceedings at the International Society of Pediatric Neurosurgery meeting, Capetown, South Africa, in October of 2008, and at the Congress of Neurological Surgeons, New Orleans, Louisiana, in October of 2009.

Address correspondence to: Thomas E. Merchant, D.O., Ph.D., Division of Radiation Oncology, Mail Stop 220, St. Jude Children's Research Hospital, 332 North Lauderdale, Memphis, Tennessee 38105-2794. email: thomas.merchant@stjude.org.

Neurosurg Focus 28 (4):E11, 2010

The role of radiosurgery in the treatment of craniopharyngiomas

Anand Veeravagu, M.D.,[1] Marco Lee, M.D., Ph.D., F.R.C.S.,[1,2] Bowen Jiang, B.S.,[3] and Steven D. Chang, M.D.[1]

[1]Department of Neurosurgery, Stanford University School of Medicine, Stanford, California;
[2]Department of Neurosurgery, Santa Clara Valley Medical Center, San Jose, California;
[3]Stanford University School of Medicine, Stanford, California

The treatment of craniopharyngiomas is composed of an intricate balance of multiple modalities. Resection and radiotherapy have been combined to synergistically control tumor growth while preventing undue harm to crucial neurovascular structures. Although a craniopharyngioma is a benign lesion pathologically, it may induce severe neurological injury due to its location and rate of growth. More recently, the advent of targeted, fractionated radiotherapy has allowed for more aggressive tumor control while reducing the necessity for large resections. Initial studies have demonstrated significant tumor control in patients who are treated with resection combined with radiation therapy, versus surgery alone, with a lower rate of treatment-associated neurological deficits. In this review, a detailed account of the current studies evaluating the role of stereotactic radiosurgery in the management of craniopharyngiomas is presented. The authors also provide a short account of their experience to aid in defining the role of CyberKnife radiosurgery. *(DOI: 10.3171/2010.2.FOCUS09311)*

Key Words • craniopharyngioma • radiosurgery • CyberKnife • Gamma Knife

Craniopharyngiomas are benign extraaxial epithelial tumors that arise from squamous epithelial remnants of the Rathke pouch, near the pituitary gland.[46] These cells may extend from the nasopharynx to the tuber cinereum and may arise within the sphenoid bone, the sella, or the suprasellar region. Although craniopharyngiomas are rare, they are the most common suprasellar tumor in the pediatric age group, accounting for as many as 5% of all intracranial tumors or up to 10% of pediatric brain tumors.[72] The incidence of craniopharyngioma has been estimated to be approximately 1.5 per million people per year,[7,31] but may be considerably higher in specific ethnic groups, such as Japanese children (5.25 per million).[50] Craniopharyngiomas have a bimodal age distribution, generally appearing in young patients between the ages of 5 and 14 years and in adults between 50 and 74 years.

Although they are histologically benign, craniopharyngiomas can cause severe and often permanent damage to nearby hypothalamic, visual, and endocrine apparatus. The presentation of these tumors may include symptoms related to endocrine derangement of the hypothalamic-pituitary axis, with severity dependent upon location, size, and rate of growth. Mass effect from hypothalamic-pituitary axis dysfunction may result in increased intracranial pressure presenting as headache, nausea, and vomiting. Cases with large mass lesions may also present with hydrocephalus (noted more commonly in children than in adults) as a result of the obstruction of the cerebral aqueduct or the interventricular foramina.[25,39] Compression of the nearby optic chiasm typically results in VFDs such as hemianopia and papilledema. Endocrine disruption often manifests as amenorrhea, hypothyroidism, and diabetes insipidus.[24,28]

The structural composition of these tumors may include solid, cystic, mixed solid and cystic, or calcified components. Traditionally, craniopharyngiomas have been separated into either the adamantinomatous or papillary variety. More commonly observed in the pediatric population, the adamantinomatous type is characterized as calcified with mixed composition. Papillary craniopharyngiomas observed in adults are often more solid.

Current treatment strategies for craniopharyngiomas include cystic drainage, intracavity chemotherapy, limited resection or GTR, and radiation therapy. These strategies are often combined into a patient-specific treatment plan based on age at presentation, tumor size, relation to optic chiasm and third ventricle, presence of hydrocepha-

Abbreviations used in this paper: BED = biologically equivalent dose; CGE = cobalt Gy equivalent; GK = Gamma Knife; GTR = gross-total resection; PFS = progression-free survival; SRS = stereotactic radiosurgery; STR = subtotal resection; VFD = visual field deficit.

lus, and degree of pituitary endocrinopathy. If total excision can be safely performed with minimal risk to these structures, then surgery remains the treatment of choice because it allows rapid decompression, minimizes recurrence, and provides a histological diagnosis. However, judgment of minimal risk is often unclear as some favor STR coupled with adjunctive therapy to achieve similar outcomes.[9,18,34,35,38,43,80,82,92] Although surgical approaches are often curative, they can produce high treatment-related morbidity and even death due to the close proximity of crucial neurovascular structures. Recurrent craniopharyngiomas must be considered separately, because secondary surgery is associated with a higher risk of complications and a lower cure rate.[8,18,21,29,57,87] More recently, SRS techniques have become increasingly used as either a primary or secondary treatment for patients with craniopharyngioma.

Surgical Outcomes

Complete resection of craniopharyngiomas is a primary objective and has curative potential. In a recent patient series studied by Shi et al.,[77] 284 patients (58 children) were treated surgically with no adjunctive therapy between 1996 and 2006. Gross-total resection, STR, and partial removal of the tumors was achieved in 237 (83.5%), 34 (12.0%), and 13 patients (4.5%), respectively. Upon follow-up, 23 patients (14.1%) experienced recurrence 1.0 to 3.5 years after GTR, and 24 (64.9%) tumors recurred 0.25–1.5 years after STR or partial resection. In this series, the early mortality rate was 4.2%. In another 25-year retrospective study by Van Effenterre and Boch,[85] 122 patients underwent either GTR (59%), STR (29%), or partial resection (12%). During the follow-up period, 29 patients (24%) experienced 1 or more recurrences. The delay to recurrence ranged from 1 to 180 months (mean 42 months, median 12 months). In this study, 13% of patients in whom a GTR was achieved experienced tumor recurrence; 33% with STR experienced recurrence; and 69% with partial removal suffered a recurrence of tumor. Radiotherapy was not systematically administered and was only reserved for cases of recurrence. The surgical mortality rate was 2.5%, and overall patient survival was 95% at 2 years, 91% at 5 years, and 83% at 10 years.

The comparison of surgical complications for craniopharyngiomas across various patient series produces a variable picture. Most of the recent large patient series report a GTR rate of 59 to 90%.[18,33,85,89] The 10-year recurrence-free survival rates have been reported as 74 to 81% for GTR,[1,19,87] 41 to 42% after partial removal,[32,69] and 83 to 90% after a combination of surgery and radiotherapy.[32,69] Surgical mortality rates in these series vary between 1.1 and 4.2%.[18,76,85,89] It is well documented that recurrent tumors are associated with significantly higher risk and poorer outcome, with overall mortality rates reported to be between 10.5 and 40.6%.[18,89] Pituitary dysfunction may occur in 50 to 100% of patients, with diabetes insipidus as the most common dysfunction. Visual deterioration may occur in up to 50% of patients undergoing GTR for craniopharyngiomas.[45]

Radiation Therapy

Although surgical drainage or resection of craniopharyngiomas may be the initial step in management, the rate of complete obliteration is low using only 1 modality. The fine balance between further neurological deficit and complete tumor resection has led to the use of various noninvasive forms of therapy. Radiation therapy is often applied during the postoperative course in the event of STR or tumor recurrence. Frequently, external radiation therapy is the preferred strategy, but in recent years endocavitary/intracavitary radiation and SRS have also demonstrated efficacy in tumor control.

Proton Beam Radiotherapy

Proton beam radiotherapy, a specific form of conformal external beam therapy, is used as an adjuvant and/or salvage treatment modality for craniopharyngiomas, particularly those in the pediatric population. In a retrospective study by Luu and colleagues,[53] 16 patients (ages 7–34 years) were treated with proton beam radiation. A daily dose of 1.8 CGE was used for a total CGE of 50.4 to 59.4. Local tumor control was achieved in 14 patients with few acute side effects. The authors reasoned that if the dose to the optic pathway was kept below 55 CGE, the rate of complication would be < 10% with minimal damage to the optic apparatus. In a similar study by Fitzek et al.,[22] 15 patients with craniopharyngioma were treated with combined proton-photon irradiation at a median dose of 56.9 CGE. The actuarial 10-year survival rate was 72% and the 10-year local control rate was 85%. Two patients suffered visual defects (hemianopia and total loss of vision) after receiving doses of 64 and 55.3 CGE, respectively, to their optic chiasm.

Endocavitary Radiation Therapy

Endocavitary/intracavitary irradiation with a beta-emitter (^{186}Re, ^{32}P, ^{198}Au, or ^{90}Y) or an antitumoral antibiotic (bleomycin) can be used to treat purely cystic, or cystic components, of craniopharyngiomas.[15] This treatment modality requires the use of stereotactic technique to achieve intracystic instillation of radioactive agents. In a recent retrospective study of endocavitary irradiation (^{186}Re) treatment by Derrey et al.,[15] complete cystic resolution was achieved in 17 (44%) of 48 patients treated and partial resolution in another 17 patients (44%). Visual function improved in 12 patients while baseline endocrine function was preserved. Similarly, Julow and colleagues[42] observed an 80% reduction in 47 patients and complete disappearance of the cyst in 27 patients within 1 year after treatment with intracystic colloidal ^{90}Y. Across several studies, the response rate of tumors to endocavitary/intracavitary irradiation is 71 to 88%.[67,88] However, because intracavitary irradiation is limited to cystic tumors, recurrence and survival rates using only this type of therapy are considered inferior to those of surgery or external radiotherapy.[36,88] Additionally, the risk of visual deterioration is considerable, possibly due to unpredictable radiation dose to the optic pathway and radiation damage from leakage. In a review by Cáceres,[7] the numbers of patients experiencing no change or improvement in visual acuity

after intracavitary irradiation ranged from 42 to 99% of the different series, whereas 31 to 58% experienced deterioration in visual function.

External Radiation Therapy

Fractionated radiation therapy improves craniopharyngioma control and survival[23,49,56,65,69,74] and is the standard treatment for residual or recurrent tumor. Most patient series demonstrate that when combined with STR, adjuvant radiotherapy allows for greater tumor control and survival than surgery alone.[30,32,70,71,79,86] In a study by Varlotto et al.,[86] an 89% tumor control rate was noted in patients who received both STR and external beam irradiation. Stripp and colleagues[79] compared 57 patients treated only with surgery to 18 patients treated with STR combined with radiation therapy, and demonstrated a 10-year tumor control rate of 42 and 84%, respectively. The case for using primary radiation therapy for recurrent craniopharyngioma is even stronger, showing a lower risk of recurrence (30%) and better outcome (90%, 10-year PFS).[41,43,44,62] Finally, Karavitaki and colleagues[45] examined the records of 121 patients and subdivided the patients into 4 treatment categories: GTR, GTR with radiotherapy, partial removal, and partial removal with radiotherapy. The recurrence-free survival rate was 100% at 10 years in the GTR only and GTR with radiotherapy groups, 38% in the partial removal group, and 77% in the partial removal with radiotherapy group.

When using radiotherapy, the risk of neurotoxicity from radiation injury should be considered alongside gains in potential tumor control. Doses of 50–60 Gy are most commonly used.[86] Conventionally fractionated focal radiation therapy around the sellar-suprasellar region is also associated with risks similar to surgery. Disruption of the hypothalamic-pituitary axis may result in diabetes insipidus, panhypopituitarism, hypogonadism, hypothalamic obesity, or sleep disturbance.[2,14,54] The normal optic apparatus is particularly sensitive to radiation; optimized dose and fractionation regimes carry a 3% risk of optic neuropathy.[20,55,63] There is also considerable discussion about the effect of radiation on cognitive function, an issue particularly pertinent in the pediatric population. Additionally, radiation itself carries the risk of secondary malignancies,[5,73,83] radiation necrosis,[37,83] and vasculopathy, which also have secondary neurodegenerative effects.

Typically, craniopharyngiomas are treated with radiation doses between 45 and 55 Gy in 1.8 to 2 Gy fractions to prevent growth of tumor and minimize injury to the visual pathways. Long-term (10-year) local control ranges from 31 to 42% with surgery alone compared with 57 to 89% with surgery and radiotherapy.[30,32,69,71,79,86] However, there are limitations, as the wide treatment field includes irradiating many structures, such as the optic apparatus, pituitary gland, hypothalamus, and medial temporal lobe. The risk may only manifest itself after a long delay, but this issue is particularly important because benign conditions such as craniopharyngiomas confer favorable long-term survival and have a predilection for the pediatric population. Another limitation of radiation therapy is that when conventional radiotherapy fails, it almost inevitably precludes further radiotherapy treatment to the recurrent tumor. Finally, although of minor importance, conventional fractionated radiotherapy usually takes place over a 6-week course, which is less attractive to patients when compared with other shorter treatment courses. For these reasons, radiosurgery (particularly multisession radiosurgery) may present a more practical option, especially for treating those tumors surrounding the optic apparatus.

Stereotactic Radiosurgery

Stereotactic radiosurgery is a relatively recent therapeutic option for craniopharyngioma that has significantly improved the effectiveness of, and morbidity associated with, radiation therapy. With SRS, 1 to 5 radiation treatments are used to treat residual or recurrent lesions. The application of stereotaxis for target localization, treatment planning, and daily treatment immobilization allows for a more precise delivery of radiation dose, with a steeper dose gradient between tumor and parenchymal tissue to prevent further neurological deficit. The radiation dose can be delivered using either a multiple cobalt-60 gamma radiation-emitting source such as the GK or a modified linear accelerator (CyberKnife). Most stereotactic systems can deliver a radiation beam to within approximately 1 mm of the lesion. Historically, SRS for craniopharyngiomas was limited to tumors 3 cm or less in size that were 3 to 5 mm away from the optic chiasm and nerves. In the case of single-session SRS, the optic chiasm becomes a limiting anatomical structure capable of only receiving 8 to 10 Gy per session before the incidence of optic neuropathy increases.[27,51] More recent multisession SRS using image-guided radiosurgical techniques has allowed for treatment of craniopharyngiomas immediately adjacent to the anterior visual pathways.[1]

In the current literature, several studies have reported safe and effective long-term results with the application of SRS using the GK for the treatment of craniopharyngiomas.[10,48,75,84] Kobayashi et al.[47] published the largest treatment and outcomes series, involving 98 cases. At a mean marginal dose of 11.5 Gy and a mean tumor size of 3.5 cm^3, these authors observed a tumor control rate of 79.6%, with a complete response in 19.4% and partial response in 67.4% of the cases. The actuarial 5- and 10-year survival rates were 94.1 and 91%, respectively, with respective PFS rates of 60.8 and 53.8%. Also within the last year, Yomo and colleagues[90] demonstrated the outcomes in 18 patients with residual or recurrent craniopharyngioma who were treated using the Leksell GK Model C. Tumor growth was controlled in 17 cases (94%), and volume reduction was attained in 13 cases (72%). Mean tumor volume was 1.8 cm^3 and the mean marginal radiation dose was 11.6 Gy. No new endocrinopathy was observed and 3 patients experienced substantial improvement of visual functions following shrinkage of the neoplasm. In another study by Chung et al.,[11] tumor control was achieved in 87% of the 31 patients in the study, and 84% demonstrated fair to excellent clinical outcomes. Minniti et al.[58] completed a large meta-analysis of 8 published studies that included 252 patients who underwent either unfractionated radiosurgery or GK therapy, demonstrating a tumor control rate of 69%. Taken together (Table 1), the published studies on GK therapy for craniopharyngiomas

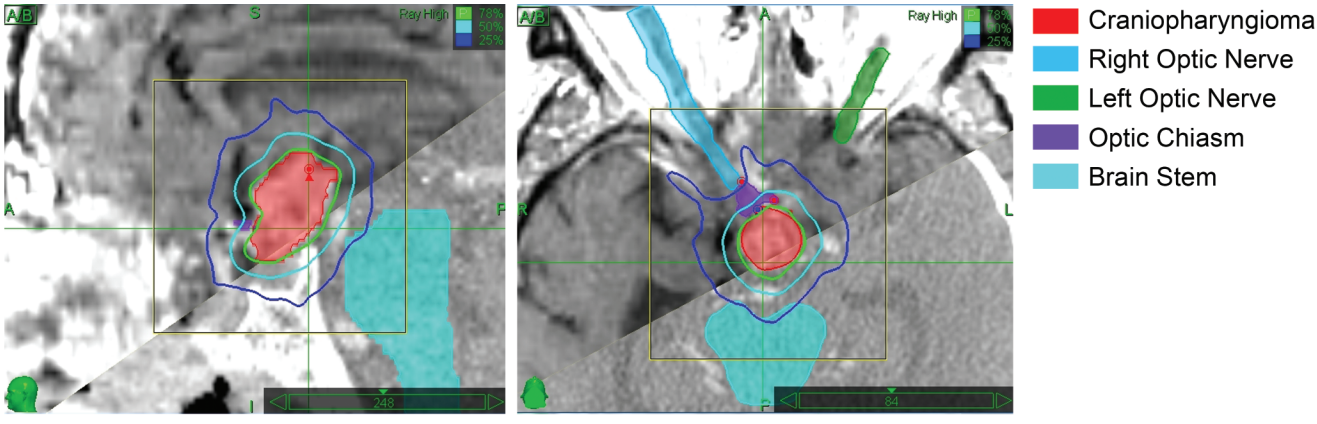

Fig. 1. Sagittal **(left)** and axial **(right)** CT/MR fusion planning images. **Left:** Area of targeted therapy and isodose lines are demonstrated. **Right:** Area of suspected tumor with regions of anatomical importance, including right optic nerves and brainstem, are shown.

demonstrate an average control rate of 90% for solid tumors, 88% for cystic tumors, and 60% for mixed tumors. Tumor control was achieved with a mean marginal dose of 12 Gy and recurrence of tumor was observed in 85% of cases that received a marginal dose < 6 Gy.

Given the current advances in image-guided radiosurgical technology, the principle of multisession delivery of SRS can be incorporated with the anatomical precision and conformality of radiosurgery. This incorporation allows for the precise delivery of potentially safer radiation doses than encountered in single session radiosurgery, while exploiting the volume effect by applying higher and more effective doses than was possible using conventional radiation therapy. The multisession delivery approach is particularly pertinent in treating craniopharyngiomas, which are often located near delicate neurovascular structures. The tolerance of these critical structures to radiation depends on the amount of radiation received, volume of tissue irradiated, previous insult, and prior radiotherapy. Due to the proximity of the tumors to the optic apparatus, only a single dose of 8 to 10 Gy is tolerable to avoid damage to the nearby structures.[36] Higher doses to optic nerves are associated with increasing rates of deficit. Leber et al.[51] reported that optic neuropathy occurred in 22 patients (26.7%) who received 10 to 15 Gy and 13 patients (78%) who received > 15 Gy, whereas 31 patients who received < 10 Gy were without optic insult. Likewise, Stafford and colleagues[78] observed radiation optic neuropathy in 1.7% of patients who received < 8 Gy, in 1.8% of patients who received 8–10 Gy, and in 6.9% of patients who received > 12 Gy after treatment with the GK for benign tumors of the sellar or parasellar region.

Cyberknife SRS: Our Experience

The CyberKnife (Accuray, Inc.) consists of a miniature lightweight linear accelerator mounted on a robotic arm with 6° of freedom of movement. This configuration allows unobstructed access to the entire body and a photon beam can be targeted with submillimeter accuracy[64] (Fig. 1). The CyberKnife employs an image-guided control loop with target tracking capabilities, thus it can adjust for patient movement and obviates the use of invasive frames to stabilize the patient. Patients do wear a thermoplastic mask that can be used for multisession SRS (hypofractionation) in patients with tumors near eloquent structures, allowing higher doses of radiation to be delivered over a longer period of time.

In a study by Lee et al.,[52] 11 patients with residual craniopharyngiomas within 2 mm of the optic apparatus or pituitary gland were treated using the CyberKnife SRS system. The clinical presentation, surgical history, radiation received, and outcome of these 5 male and 6 female patients with an average age of 34.5 years are documented in Table 2. A mean marginal dose of 21.6 Gy prescribed to a mean isodose line of 75% was applied over multiple sessions. The mean maximum dose was 29.9 Gy and the mean target volume was 6 cm^3 (Table 3). Patient outcomes were quantified using MR imaging and formal Goldman visual field assessments at 6-month intervals for 2 years, then once every year (Table 4). Prior to CyberKnife therapy, 10 patients suffered from a degree of visual loss, while 5 had endocrine abnormalities requiring hormonal replacement. Ten patients had operative reports documenting an STR with radiological confirmation, and 1 underwent a complete resection with follow-up MR imaging demonstrating recurrence 1 year after surgery. Residual tumor was most often located in the suprasellar region, and in 10 cases was found to be against or displacing the optic nerve or chiasm. The pituitary stalk only was compressed in 1 patient.

The mean follow-up time was 15.4 months (range 4–64 months). All 10 patients with visual field or acuity problems either improved or remained stable after CyberKnife radiosurgery. In this series, treatment plans were designed to keep the dose experienced by the optic apparatus to < 5 Gy during any single session. The volume of the optic apparatus that received 80% of the prescribed dose was < 0.05 cm^3, whereas the volume that received 50% of the dose was < 0.5 cm^3. Therefore, the actual volume of the optic segment that received 5 Gy would be small relative to the total volume of the optic apparatus. Preservation of baseline visual function is supported by our previous work, which showed that the risk

TABLE 1: Summary of published series of patients who underwent SRS for craniopharyngioma*

Authors & Year	Study Country	Intervention	No. of Patients	Mean Marginal Dose (Gy)	Mean Tumor Size (cm^3)	Outcome
Miyazaki et al., 2009	Japan	CyberKnife	13	22.7	NA	tumor shrinkage achieved in 6 of 13 patients, tumor control in another 5; 2 patients had cystic enlargement of the residual tumor followed by microsurgical resection
Yomo et al., 2009	Japan	GK	18	11.6	1.8	tumor growth controlled in 17 cases (94%), & volume reduction attained in 13 cases (72%); in 3 patients significant shrinkage of the neoplasm after radiosurgery was accompanied by improvement of the visual functions
Kobayashi, 2009	Japan	GK	98	11.5	3.5	complete response 19.4%, partial response 67.4%, tumor control rate 79.6%, & progression rate 20.4%; patient outcome excellent in 45 cases, good in 23, fair in 4, poor in 3; 16 patients died & deterioration of visual & endocrinological functions were found as side effects in 6 patients (6.1%)
Lee et al., 2008	US	CyberKnife	11	21.6	5.9	tumor shrinkage achieved in 7 of 11 patients, tumor control in another 3; 1 patient had cystic enlargement of the residual tumor; overall, control or shrinkage of tumor was achieved in 91% of patients, w/ no visual or neuroendocrine complications
Minniti et al., 2007	UK	SCRT	39	50	10.2	3- & 5-year PFS was 97 & 92%, respectively, & 3- & 5-year survival was 100%; 2 patients required further debulking surgery, 12 (30%) had acute clinical deterioration due to cystic enlargement of craniopharyngioma following SCRT & required cyst aspiration, 1 w/ severe visual impairment prior to radiotherapy had visual deterioration following SCRT; 7 of 10 patients w/ a normal pituitary function before SCRT had no endocrine deficits following treatment
Combs et al., 2007	Germany	FSRT	40	52.2	13.3	local control 100% at both 5 & 10 years; overall survival rates at 5 & 10 years were 97% & 89%, respectively; complete response observed in 4 patients & partial responses noted in 25 patients; 11 presented w/ stable disease during follow-up
Giller et al., 2005	US	CyberKnife	3	42	1.14	tumor regression w/o visual changes achieved in all 3 patients at 29, 39, & 40 months after treatment; dose to the optic apparatus was <8 Gy for all patients treated w/ a single dose or w/ hypofractionation (3–5 doses); dose to the brain stem <10 Gy in all single dose & hypofractionation treatments
Albright et al., 2005	US	GK	5	NA	6.5	no morbidity or mortality from GKS, which achieved tumor stabilization or shrinkage in 4 of 5 cases
Amendola et al., 2003	US	GK	14	14	3.7	all patients alive & w/o evidence of recurrent disease 6–86 mos after treatment; only 2 patients required retreatment
Selch et al., 2002	US	FSRT	16	55	7.7	3-year actuarial overall survival = 93%, rate of survival free of any imaging evidence of progressive disease = 75%; 3-year actuarial survival rates free of solid tumor growth or cyst enlargement = 94 & 81%, respectively
Ulfarsson et al., 2002	Sweden	GK	21	3–25	7.8	5 of 22 tumors were reduced in size, 3 unchanged, 14 increased; 11 (85%) of 13 tumors that received a dose <6 Gy to the margin increased in size, whereas only 3 (33%) of 9 tumors that received 6 Gy increased; in 5 of 6 tumors that became smaller after GKS, there were no recurrences w/in a mean follow-up period of 12 years; 9 (82%) of 11 tumors in children ultimately increased after GKS, compared with 5 (50%) of 10 in adults; in 8 patients there was a deterioration of visual function, 4 patients developed pituitary deficiencies
Chiou et al., 2001	USA	GK	10	16	1.7	7 of 12 tumors became smaller or vanished within a median of 8.5 mos; prior visual defects objectively improved in 6 patients; 1 patient w/ prior visual defect deteriorated further & lost vision 9 months after radiosurgery
Yu et al., 2000	China	GK	46	8–18	13.5	tumor control rate = 90% in solid tumors, 85.7% in mixed tumors, 92.1% in the solid segment, 89.5% in total

(continued)

TABLE 1: Summary of published series of patients who underwent SRS for craniopharyngioma* *(continued)*

Authors & Year	Study Country	Inter-vention	No. of Patients	Mean Marginal Dose (Gy)	Mean Tumor Size (cm^3)	Outcome
Chung et al., 2000	Taiwan	GK	31	12	8.9	tumor control achieved in 87% of patients & 84% had fair to excellent clinical outcome in an average follow-up period of 36 mos; treatment failure due to uncontrolled tumor progression noted in 4 patients; only 1 patient found to have a mildly restricted visual field; no additional endocrinological impairment or neurological deterioration could be attributed to the treatment; no treatment-related mortality
Mokry, 1999	Austria	GK	23	10.8	7.0	volume reduction of the residual tumor in 74% of the cases; smaller tumors & targets more likely to shrink; 5 patients with large multicystic residual or recurrent tumors showed further progression
Prasad et al., 1995	USA	GK	9	13	10	decrease in the solid component of tumor noted in 5 patients & no change in 2; 1 patient had increase in solid tumor component; clinical improvement noted in 6 of 8 cases

* FSRT = fractionated stereotactic radiotherapy; GKS = Gamma Knife surgery; NA = not available; SCRT = stereotactically guided conformational radiotherapy

of visual loss with multisession radiosurgery appears to be low for perioptic tumors.[1,66] Radiation-induced optic neuropathy is a known entity that tends to present over the course of several years, but the short follow-up duration of our study prevents making definitive conclusions regarding the effect of multisession therapy.

There were no new neuroendocrine problems and the 5 patients with endocrine derangement remained stable, with no new deterioration after CyberKnife treatment. Tumor shrinkage was observed in 7 patients, with 3 of these tumors remaining the same at 2 years after treatment, resulting in a 91% tumor control rate. One patient developed a cystic enlargement of the residual tumor without any worsening symptoms or signs. Irradiation of cystic craniopharyngiomas may result in cystic enlargement, which does not represent tumor recurrence and may later regress.[13] In our series, the patient's symptoms remained stable, but rigorous clinical and radiological assessment is critical, including visual and neuroendocrine assessment. We believe that multisession treatment regimens minimize the risk to the optic apparatus and pituitary gland while delivering an appropriate amount of radiation for disease control.

There are several assumptions that contributed to dosimetry calculations for stereotactic radiation delivery. In a review by Timmerman et al.,[81] the authors outlined 3 requirements necessary for a successful treatment: 1) the ability to describe the location of the target; 2) the ability to shape the prescription isodose surface to the surface of the target volume; and 3) the ability to construct radiation dose distributions with very rapid fall-off dose to spare surrounding healthy tissue. In calculating dosimetry, the best approach is to have multiple beam directions, which allows for attenuation of the primary beam outside of the targeted areas using multileaf collimators.

Radiosurgical Dosing

Several factors influence the choice of radiosurgical dose, including the pathology of the lesion, the nature of the adjacent tissues, and the volume of both of these structures. Much of what we know about the tolerance of normal brain structures came from studies using conventional radiation therapy and single fraction radiosurgery. As discussed, the CyberKnife, with its frameless platform, allows for multisession schedules. Multisession radiation allows sublethal injury to normal tissue, which can repopulate between fractions; other advantages include achieving higher tumor cell death by reoxygenation of hypoxic cells, and reassortment of cells into sensitive phases of the cell cycle.

To estimate the BED of different fractionation schemes, the linear quadratic model of cell survival from radiation is used.[40] Multifraction treatments were converted to a single-fraction BED using the linear quadratic model:

$$BED = nd[1+d/(\alpha/\beta)]$$

where n represents the number of fractions, d represents dose per fraction, and α/β represents the alpha/beta ratio.[16] The ratio of α/β reflects the radiosensitivity of the cell

TABLE 2: Summary of characteristics of patients who underwent CyberKnife SRS for residual craniopharyngiomas, 2000–2007*

Case No.	Age (yrs), Sex	Presentation	No. of Ops	Post-op RT	Pre-SRS Visual Problems	Pre-SRS Endocrine Problems	No. of Fractions	Treatment Dose (Gy)	Mean Isodose Line (%)	Max Dose (Gy)	Target Volume (cm^3)
1	32, F	HA & VFD	3	no	yes	no	3	18	75	22.5	1.4
2	16, F	HA & VFD	2	yes	yes	no	3	19.5	80	24.3	12.7
3	71, M	N&V & VFD	1	no	yes	no	3	20	74	26.6	0.7
4	45, F	hypopit & VFD	2	no	yes	yes	5	20	77	26	1.1
5†	43, M	hypopit & VFD	2	no	yes	yes	10	38	72	42.1	26.3
6	17, F	HA, VFD	1	no	yes	no	4	20	77	24.1	1.2
7	13, F	WG & hypopit	3	no	no	yes	5	27.5	71	36.7	10.1
8	20, M	VFD & hypopit	1	no	yes	yes	5	25	76	30.5	0.3
9	39, F	HA & VFD	2	no	yes	no	5	25	67	33.3	6.3
10	37, M	HA & VFD	3	no	yes	no	5	25	73	31.7	3.8
11	46, M	hypopit & VFD	1	no	yes	yes	5	25	80	31.3	1.3

* HA = headache; hypopit = hypopituitarism; N & V = nausea and vomiting; RT = radiation therapy; WG = weight gain.

† Patient underwent stereotactic radiotherapy.

TABLE 3: Summary of 11 patients and treatment planning characteristics included in analysis

Characteristic	Value
sex	
male	5
female	6
mean age in yrs (range)	34.5 (13–71)
no. of previous surgeries	
1	4
2	4
3	3
no. of previous radiotherapies	1
extent of last resection	
complete	1
subtotal	10
site of residual or recurrent tumor	
intrasellar	1
suprasellar	9
both	1
no. against optic apparatus	8
no. against pituitary stalk or gland	1
no. against both	2
no. of CyberKnife sessions	
3	3
4	1
5	6
10	1
mean target volume in cm^3 (range)	6 (0.3–26.3)
mean marginal dose in Gy (range)	21.6 (18–38)
mean maximal dose in Gy (range)	29.9 (24.1–42.1)

being exposed; the higher the α/β ratio, the more radiosensitive the cell. Various studies have shown that cranial nerve neuropathies occurred in 1 to 3% of cases when the brainstem was irradiated to 12 to 13 Gy. We have chosen to use a fractionation scheme when the single fraction dose exceeds 13 Gy to more than 20% of the brainstem, as is often encountered in craniopharyngiomas. In addition, we limit the single fraction dose to the optic apparatus to < 10 Gy by utilizing a fractionation scheme of 2 to 5 fractions and limiting the exposure to the optic apparatus to < 5 Gy per fraction. Using these parameters, we have been able to preserve preradiation visual function in 94% of cases involving perioptic lesions.[1]

The exact α/β ratio of craniopharyngiomas is unknown, but others have used a ratio of 2.[86] By assuming an α/β ratio of 2, we can calculate that a radiation schedule of 25 Gy in 5 sessions estimates a single-dose equivalent of 12.3 Gy, a dose that approaches our intended target.

Conclusions

Optimal management of craniopharyngiomas remains controversial. The often peculiar location of a

TABLE 4: Clinical and radiological outcome after CyberKnife treatment of residual tumor

Variable	Value
mean follow-up in mos (range)	15.4 (4–64)
tumor size	
decreased	7
stable	3
increased	1 (cyst enlargement)
no. w/ visual field deterioration	0
no. w/ endocrine deterioration	0

craniopharyngioma implicates vital structures that may be subjected to undue harm after radiotherapy. Thus, a custom multimodality treatment strategy is employed to optimize outcome. Radiotherapy has a definitive role in the treatment of craniopharyngiomas, both as an adjuvant therapy following primary STR and also as a primary treatment for recurrent disease. Our experience demonstrates that multisession therapy may prevent unintended consequences to surrounding optic structures and provide significant disease control. Although further long-term studies are required to fully evaluate clinical outcome, current evidence suggests beneficial results of radiotherapy for craniopharyngiomas.

Disclosure

Dr. Chang is a shareholder of Accuray, Inc., and is supported in part by a research gift from Robert C. and Jeannette Powell.

Author contributions to the study and manuscript preparation include the following. Conception and design: A Veeravagu, M Lee, SD Chang. Acquisition of data: A Veeravagu, M Lee, SD Chang. Analysis and interpretation of data: A Veeravagu, M Lee, B Jiang, SD Chang. Drafting the article: A Veeravagu, M Lee, B Jiang, SD Chang. Critically revising the article: A Veeravagu, B Jiang, SD Chang. Reviewed final version of the manuscript and approved it for submission: A Veeravagu, SD Chang. Statistical analysis: A Veeravagu, SD Chang. Administrative/technical/material support: A Veeravagu, SD Chang. Study supervision: A Veeravagu, SD Chang.

References

1. Adler JR Jr, Gibbs IC, Puataweepong P, Chang SD: Visual field preservation after multisession cyberknife radiosurgery for perioptic lesions. **Neurosurgery 59:**244–254, 2006
2. Agha A, Sherlock M, Brennan S, O'Connor SA, O'Sullivan E, Rogers B, et al: Hypothalamic-pituitary dysfunction after irradiation of nonpituitary brain tumors in adults. **J Clin Endocrinol Metab 90:**6355–6360, 2005
3. Albright AL, Hadjipanayis CG, Lunsford LD, Kondziolka D, Pollack IF, Adelson PD: Individualized treatment of pediatric craniopharyngiomas. **Childs Nerv Syst 21:**649–654, 2005
4. Amendola BE, Wolf A, Coy SR, Amendola MA: Role of radiosurgery in craniopharyngiomas: a preliminary report. **Med Pediatr Oncol 41:**123–127, 2003
5. Brada M, Ford D, Ashley S, Bliss JM, Crowley S, Mason M, et al: Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. **BMJ 304:**1343–1346, 1992
6. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM: The descriptive epidemiology of craniopharyngioma. **J Neurosurg 89:**547–551, 1998
7. Cáceres A: Intracavitary therapeutic options in the management of cystic craniopharyngioma. **Childs Nerv Syst 21:**705–718, 2005
8. Caldarelli M, di Rocco C, Papacci F, Colosimo C Jr: Management of recurrent craniopharyngioma. **Acta Neurochir (Wien) 140:**447–454, 1998
9. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C: Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. **Childs Nerv Syst 21:**747–757, 2005
10. Chiou SM, Lunsford LD, Niranjan A, Kondziolka D, Flickinger JC: Stereotactic radiosurgery of residual or recurrent craniopharyngioma, after surgery, with or without radiation therapy. **Neuro-oncol 3:**159–166, 2001
11. Chung WY, Pan DH, Shiau CY, Guo WY, Wang LW: Gamma knife radiosurgery for craniopharyngiomas. **J Neurosurg 93 (Suppl 3):**47–56, 2000
12. Combs SE, Thilmann C, Huber PE, Hoess A, Debus J, Schulz-Ertner D: Achievement of long-term local control in patients with craniopharyngiomas using high precision stereotactic radiotherapy. **Cancer 109:**2308–2314, 2007
13. Constine LS, Randall SH, Rubin P, McDonald J: Craniopharyngiomas: fluctuation in cyst size following surgery and radiation therapy. **Neurosurgery 24:**53–59, 1989
14. Darzy KH, Shalet SM: Hypopituitarism after cranial irradiation. **J Endocrinol Invest 28 (5 Suppl):**78–87, 2005
15. Derrey S, Blond S, Reyns N, Touzet G, Carpentier P, Gauthier H, et al: Management of cystic craniopharyngiomas with stereotactic endocavitary irradiation using colloidal 186Re: a retrospective study of 48 consecutive patients. **Neurosurgery 63:**1045–1053, 2008
16. Douglas BG, Fowler JF: The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation. **Radiat Res 66:**401–426, 1976
17. Duff JM, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck C, Scheithauer BW: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000
18. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
19. 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
20. Fisher BJ, Gaspar LE, Noone B: Radiation therapy of pituitary adenoma: delayed sequelae. **Radiology 187:**843–846, 1993
21. Fisher PG, Jenab J, Goplđthwaite PT, Tihan T, Wharam MD, Foer DR, et al: Outcomes and failure patterns in childhood craniopharyngiomas. **Childs Nerv Syst 14:**558–563, 1998
22. Fitzek MM, Linggood RM, Adams J, Munzenrider JE: Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. **Int J Radiat Oncol Biol Phys 64:**1348–1354, 2006
23. Flickinger JC, Lunsford LD, Singer J, Cano ER, Deutsch M: Megavoltage external beam irradiation of craniopharyngiomas: analysis of tumor control and morbidity. **Int J Radiat Oncol Biol Phys 19:**117–122, 1990
24. Garnett MR, Puget S, Grill J, Sainte-Rose C: Craniopharyngioma. **Orphanet J Rare Dis 2:**18, 2007
25. Garrè ML, Cama A: Craniopharyngioma: modern concepts in pathogenesis and treatment. **Curr Opin Pediatr 19:**471–479, 2007
26. Giller CA, Berger BD, Pistenmaa DA, Sklar F, Weprin B, Shapiro K, et al: Robotically guided radiosurgery for children. **Pediatr Blood Cancer 45:**304–310, 2005
27. Girkin CA, Comey CH, Lunsford LD, Goodman ML, Kline LB: Radiation optic neuropathy after stereotactic radiosurgery. **Ophthalmology 104:**1634–1643, 1997
28. Gopalan R, Dassoulas K, Rainey J, Sherman JH, Sheehan JP: Evaluation of the role of Gamma Knife surgery in the treatment of craniopharyngiomas. **Neurosurg Focus 24(5):**E5, 2008
29. 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
30. Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, et al: The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. **Int J Radiat Oncol Biol Phys 44:**255–263, 1999
31. Haupt R, Magnani C, Pavanello M, Caruso S, Dama E, Garrè

ML: Epidemiological aspects of craniopharyngioma. **J Pediatr Endocrinol Metab 19 (Suppl 1):**289–293, 2006
32. 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
33. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI: Aggressive surgical management of craniopharyngiomas in children. **J Neurosurg 76:**47–52, 1992
34. Honegger J, Barocka A, Sadri B, Fahlbusch R: Neuropsychological results of craniopharyngioma surgery in adults: a prospective study. **Surg Neurol 50:**19–29, 1998
35. Honegger J, Buchfelder M, Fahlbusch R: Surgical treatment of craniopharyngiomas: endocrinological results. **J Neurosurg 90:**251–257, 1999
36. Honegger J, Tatagiba M: Craniopharyngioma surgery. **Pituitary 11:**361–373, 2008
37. Hoshi M, Hayashi T, Kagami H, Murase I, Nakatsukasa M: Late bilateral temporal lobe necrosis after conventional radiotherapy. **Neurol Med Chir (Tokyo) 43:**213–216, 2003
38. Isaac MA, Hahn SS, Kim JA, Bogart JA, Chung CT: Management of craniopharyngioma. **Cancer J 7:**516–520, 2001
39. Jane JA Jr, Laws ER: Craniopharyngioma. **Pituitary 9:**323–326, 2006
40. Jones B, Dale RG, Finst P, Khaksar SJ: Biological equivalent dose assessment of the consequences of hypofractionated radiotherapy. **Int J Radiat Oncol Biol Phys 47:**1379–1384, 2000
41. Jose CC, Rajan B, Ashley S, Marsh H, Brada M: Radiotherapy for the treatment of recurrent craniopharyngioma. **Clin Oncol (R Coll Radiol) 4:**287–289, 1992
42. Julow J, Backlund EO, Lányi F, Hajda M, Bálint K, Nyáry I, et al: Long-term results and late complications after intracavitary yttrium-90 colloid irradiation of recurrent cystic craniopharyngiomas. **Neurosurgery 61:**288–296, 2007
43. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH: Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. **Med Pediatr Oncol 40:**214–218, 2003
44. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH: Clinical outcome in children with recurrent craniopharyngioma after primary surgery. **Cancer J 6:**388–393, 2000
45. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, et al: Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. **Clin Endocrinol (Oxf) 62:**397–409, 2005
46. Karavitaki N, Cudlip S, Adams CB, Wass JA: Craniopharyngiomas. **Endocr Rev 27:**371–397, 2006
47. Kobayashi T: Long-term results of gamma knife radiosurgery for 100 consecutive cases of craniopharyngioma and a treatment strategy. **Prog Neurol Surg 22:**63–76, 2009
48. Kobayashi T, Kida Y, Mori Y, Hasegawa T: Long-term results of gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. **J Neurosurg 103 (6 Suppl):** 482–488, 2005
49. Kramer S, Southard M, Mansfield CM: Radiotherapy in the management of craniopharyngiomas: further experiences and late results. **Am J Roentgenol Radium Ther Nucl Med 103:**44–52, 1968
50. Kuratsu J, Ushio Y: Epidemiological study of primary intracranial tumors in childhood. A population-based survey in Kumamoto Prefecture, Japan. **Pediatr Neurosurg 25:**240–247, 1996
51. Leber KA, Berglöff J, Pendl G: Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. **J Neurosurg 88:**43–50, 1998
52. Lee M, Kalani MY, Cheshier S, Gibbs IC, Adler JR, Chang SD: Radiation therapy and CyberKnife radiosurgery in the management of craniopharyngiomas. **Neurosurg Focus 24(5):**E4, 2008
53. Luu QT, Loredo LN, Archambeau JO, Yonemoto LT, Slater JM, Slater JD: Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. **Cancer J 12:**155–159, 2006
54. McCollough WM, Marcus RB Jr, Rhoton AL Jr, Ballinger WE, Million RR: Long-term follow-up of radiotherapy for pituitary adenoma: the absence of late recurrence after greater than or equal to 4500 cGy. **Int J Radiat Oncol Biol Phys 21:**607–614, 1991
55. McCord MW, Buatti JM, Fennell EM, Mendenhall WM, Marcus RB Jr, Rhoton AL, et al: Radiotherapy for pituitary adenoma: long-term outcome and sequelae. **Int J Radiat Oncol Biol Phys 39:**437–444, 1997
56. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
57. Minamida Y, Mikami T, Hashi K, Houkin K: Surgical management of the recurrence and regrowth of craniopharyngiomas. **J Neurosurg 103:**224–232, 2005
58. Minniti G, Esposito V, Amichetti M, Enrici RM: The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngioma. **Neurosurg Rev 32:**125–132, 2009
59. Minniti G, Saran F, Traish D, Soomal R, Sardell S, Gonsalves A, et al: Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. **Radiother Oncol 82:**90–95, 2007
60. Miyazaki ST, TakusagawaY, Fukushima T: Multisession cyberknife radiosurgery in the management of craniopharyngioma. Presented at the Eighth Annual CyberKnife Users' Meeting, Hollywood, Florida, Saturday, February 7, 2009 (Abstract). **www.cksociety.org/CKSociety/document/docdownload.aspx?docid=65.** [Accessed February 26, 2010]
61. Mokry M: Craniopharyngiomas: a six year experience with Gamma Knife radiosurgery. **Stereotact Funct Neurosurg 72 (Suppl 1):**140–149, 1999
62. Moon SH, Kim IH, Park SW, Kim I, Hong S, Park CI, et al: Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas—a study in single institute. **Childs Nerv Syst 21:**799–807, 2005
63. Movsas B, Movsas TZ, Steinberg SM, Okunieff P: Long-term visual changes following pituitary irradiation. **Int J Radiat Oncol Biol Phys 33:**599–605, 1995
64. Murphy MJ, Chang SD, Gibbs IC, Le QT, Hai J, Kim D, et al: Patterns of patient movement during frameless image-guided radiosurgery. **Int J Radiat Oncol Biol Phys 55:**1400–1408, 2003
65. Pemberton LS, Dougal M, Magee B, Gattamaneni HR: Experience of external beam radiotherapy given adjuvantly or at relapse following surgery for craniopharyngioma. **Radiother Oncol 77:**99–104, 2005
66. Pham CJ, Chang SD, Gibbs IC, Jones P, Heilbrun MP, Adler JR Jr: Preliminary visual field preservation after staged CyberKnife radiosurgery for perioptic lesions. **Neurosurgery 54:**799–812, 2004
67. Pollock BE, Lunsford LD, Kondziolka D, Levine G, Flickinger JC: Phosphorus-32 intracavitary irradiation of cystic craniopharyngiomas: current technique and long-term results. **Int J Radiat Oncol Biol Phys 33:**437–446, 1995
68. Prasad D, Steiner M, Steiner L: Gamma knife surgery for craniopharyngioma. **Acta Neurochir (Wien) 134:**167–176, 1995
69. Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJ, et al: Craniopharyngioma—a long-term results following limited surgery and radiotherapy. **Radiother Oncol 26:**1–10, 1993
70. Rajan B, Ashley S, Thomas DG, Marsh H, Britton J, Brada M: Craniopharyngioma: improving outcome by early recognition

and treatment of acute complications. **Int J Radiat Oncol Biol Phys 37:**517–521, 1997
71. Regine WF, Mohiuddin M, Kramer S: Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. **Radiother Oncol 27:**13–21, 1993
72. Rickert CH, Paulus W: Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. **Childs Nerv Syst 17:**503–511, 2001
73. Sachs RK, Brenner DJ: Solid tumor risks after high doses of ionizing radiation. **Proc Natl Acad Sci U S A 102:**13040–13045, 2005
74. Schubert T, Trippel M, Tacke U, van Velthoven V, Gumpp V, Bartelt S, et al: Neurosurgical treatment strategies in childhood craniopharyngiomas: is less more? **Childs Nerv Syst 25:**1419–1427, 2009
75. Selch MT, DeSalles AA, Wade M, Lee SP, Solberg TD, Wallace RE, et al: Initial clinical results of stereotactic radiotherapy for the treatment of craniopharyngiomas. **Technol Cancer Res Treat 1:**51–59, 2002
76. Shi XE, Wu B, Fan T, Zhou ZQ, Zhang YL: Craniopharyngioma: surgical experience of 309 cases in China. **Clin Neurol Neurosurg 110:**151–159, 2008
77. Shi XE, Wu B, Zhou ZQ, Fan T, Zhang YL: Microsurgical treatment of craniopharyngiomas: report of 284 patients. **Chin Med J (Engl) 119:**1653–1663, 2006
78. Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ, et al: A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. **Int J Radiat Oncol Biol Phys 55:**1177–1181, 2003
79. Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, et al: Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. **Int J Radiat Oncol Biol Phys 58:**714–720, 2004
80. Thompson D, Phipps K, Hayward R: Craniopharyngioma in childhood: our evidence-based approach to management. **Childs Nerv Syst 21:**660–668, 2005
81. Timmerman R, Papiez L, Suntharalingam M: Extracranial stereotactic radiation delivery: expansion of technology beyond the brain. **Technol Cancer Res Treat 2:**153–160, 2003
82. Tomita T, Bowman RM: Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. **Childs Nerv Syst 21:**729–746, 2005
83. Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ: Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. **Int J Radiat Oncol Biol Phys 30:**557–565, 1994
84. Ulfarsson E, Lindquist C, Roberts M, Rähn T, Lindquist M, Thorén M, et al: Gamma knife radiosurgery for craniopharyngiomas: long-term results in the first Swedish patients. **J Neurosurg 97 (5 Suppl):**613–622, 2002
85. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
86. Varlotto JM, Flickinger JC, Kondziolka D, Lunsford LD, Deutsch M: External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. **Int J Radiat Oncol Biol Phys 54:**492–499, 2002
87. Vinchon M, Dhellemmes P: Craniopharyngiomas in children: recurrence, reoperation and outcome. **Childs Nerv Syst 24:**211–217, 2008
88. Voges J, Sturm V, Lehrke R, Treuer H, Gauss C, Berthold F: Cystic craniopharyngioma: long-term results after intracavitary irradiation with stereotactically applied colloidal beta-emitting radioactive sources. **Neurosurgery 40:**263–270, 1997
89. 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
90. Yomo S, Hayashi M, Chernov M, Tamura N, Izawa M, Okada Y, et al: Stereotactic radiosurgery of residual or recurrent craniopharyngioma: new treatment concept using Leksell gamma knife model C with automatic positioning system. **Stereotact Funct Neurosurg 87:**360–367, 2009
91. Yu X, Liu Z, Li S: Combined treatment with stereotactic intracavitary irradiation and gamma knife surgery for craniopharyngiomas. **Stereotact Funct Neurosurg 75:**117–122, 2000
92. Zuccaro G: Radical resection of craniopharyngioma. **Childs Nerv Syst 21:**679–690, 2005

Manuscript submitted December 15, 2009.
Accepted February 3, 2010.
Address correspondence to: Steven D. Chang, M.D., Stanford University Hospital, 300 Pasteur Drive, Stanford, California 94305. email: sdchang@stanford.edu.

Neurosurg Focus 28 (4):E12, 2010

Craniopharyngiomas: intratumoral chemotherapy with interferon-α: a multicenter preliminary study with 60 cases

Sergio Cavalheiro, Ph.D.,[1] Concezzio Di Rocco, Ph.D.,[3] Sergio Valenzuela, Ph.D.,[4] Patricia A. Dastoli, M.D.,[1] Gianpiero Tamburrini, M.D.,[3] Lucca Massimi, M.D.,[3] Jardel M. Nicacio, M.D.,[1] Igor V. Faquini, M.D.,[1] Daniela F. Ierardi, M.D.,[1] Nasjla S. Silva, M.D.,[1] Benedetta Ludovica Pettorini, M.D.,[5] and Silvia R. C. Toledo, M.D.[2]

[1]Department of Neurosurgery and [2]Section of Pediatric Neurosurgery, Federal University of São Paulo, Brazil; [3]Department of Neurosurgery, Catholic University of Rome, Italy; [4]Department of Neurosurgery, Neurosurgery Institute of Santiago, Santiago, Chile; and [5]Section of Pediatric Neurosurgery, Department of Neurosurgery, Policlinico Gemelli, Rome, Italy

Object. The authors assessed the efficacy of intratumoral interferon-α (IFNα)–based chemotherapy in pediatric patients with cystic craniopharyngiomas.

Methods. In a prospective multicenter study of 60 pediatric patients, the authors assessed the efficacy of intratumoral INFα2A-based chemotherapy. The study was conducted between 2000 and 2009 at 3 locations: the Medical School of the Federal University of São Paulo, Catholic University of Rome, and the Neurosurgery Institute of Santiago, Chile. The assessment included clinical and radiological control examinations, side effects observed, and total dose used.

Results. Sixty cases of cystic craniopharyngioma were analyzed. The cohort consisted of 35 male and 25 female children (mean age 11 years). Clinical and radiological improvement was achieved in 76% of the cases. New endocrinological deficits were observed in 13% of the cases. In approximately 30% of the patients, the evolution included some light side effects, the most common being headache (33%) and eyelid edema (28%). The number of cycles varied from 1 to 9 (mean 5 cycles), and the total dose applied per cycle was 36,000,000 IU.

Conclusions. This has been the largest documented series of intratumoral chemotherapy using INFα for the control of cystic craniopharyngiomas. The treatment has proved efficacious; there was no mortality, and morbidity rates were low. *(DOI: 10.3171/2010.1.FOCUS09310)*

Key Words • **craniopharyngioma** • **interferon-α** • **hypothalamus** • **obesity** • **diabetes insipidus**

Craniopharyngiomas are benign slow-growing lesions that challenge every neurosurgeon, even since the advent of major technological developments, with important refinements, such as microscopic techniques, ultrasonic aspirators, neuroendoscopes, and hormone replacement therapy. In major centers of pediatric neurosurgery with excellent endocrinological support, is not uncommon to see patients with CPs suffer deterioration with the onset of obesity, panhypopituitarism, hypercholesterolemia, and psychological disorders.[9] If on the one hand a complete resection of these lesions is tremendously satisfying to neurosurgeons, on the other hand this feeling is temporary because the lesion and the effects of hypothalamic dysfunction will recur. The use of intratumoral chemotherapy with the cytokine INFα is a simple method, with a very low cost, that allows the control of these tumors.

Abbreviations used in this paper: CP = craniopharyngioma; IFNα = interferon-α.

Methods

We prospectively analyzed 60 patients with predominantly cystic CPs (> 60% of the tumor volume). The patients underwent treatment at the Pediatric Oncology Institute of the Federal University of Sao Paulo (37 cases), Catholic University of Rome (9 cases) and University of Chile (14 cases). Intratumoral chemotherapy involved INFα2A and the same protocol was used at each institution after the approval of the respective ethics committee. Thirty-five patients were male (58.3%) and 25 female (41.7%). Patients ranged in age from 20 months to 18 years (mean age 11 years). Twenty-five patients (41.7%) presented with initial symptoms such as intracranial hypertension, 6 presented endocrinological disturbances (10%), and only 4 (6.7%) had initial symptoms of isolated visual disturbances. The association of intracranial hypertension with visual impairment was found in 8 cases and with endocrinological disorders in 14 cases; the association of intracranial hypertension with visual impair-

ment and endocrine disorders was observed in 3 cases. Eleven patients presented only with diabetes insipidus and 8 patients with isolated growth hormone dysfunction. Eleven patients had more than 3 hormonal deficits. Of 60 patients, only 39 (65%) were treatment naïve, and the other 21 patients had received other therapies for control of the disease. Eighteen patients had undergone surgery, and 3 patients had undergone intratumoral bleomycin-based chemotherapy.

Nineteen patients had hydrocephalus at presentation and 13 needed shunt implantation.

In 37 patients it was possible to analyze and compare the pre- and posttreatment tumor volume using the modified ellipsoid volume equation: $A \times B \times C \times 0.52$, where A, B, and C are the major diameters measured in the 3 special plans.

The treatment protocol begins with the implantation of a catheter into the cystic tumor cavity; the catheter is connected to a subcutaneous Ommaya reservoir. In 40 cases the catheter was implanted via craniotomy, in 13 cases using the neuroendoscope, in 4 guided by neuronavigation, in 2 by free-hand puncture, and in 1 case by neuroendoscopy coupled with neuronavigation (Fig. 1). In 52 cases (86.6%) only 1 catheter was implanted, but 7 patients required 2 catheters, and in 1 case 3 catheters were implanted. Five days after implantation of the catheter, a contrast agent was injected into the cyst to determine if there was any leakage. The presence of leakage was not considered a contraindication for the treatment because the interferon alpha had no related neurotoxicity.

After checking that the catheter was well positioned, we injected, every other day, 3,000,000 IU of INFα2A. Prior to the injections of INF the liquid of the CP was aspirated.

The amount of fluid removed depended on the symptoms of patients and the size of the cyst. We interrupted suction when more than 20 ml was removed or when the patient complained of headache. Thirty minutes before the puncture of the reservoir, anesthetic ointment was placed over the skin at the puncture site. The volume of injected liquid did not exceeded 2 ml, and to avoid a high concentration of INF in the reservoir after the injection, we aspirated more liquid, with the same syringe, and reinjected it another 2–3 times.

Interferon was applied in cycles of 36,000,000 IU, divided into 12 applications of 3,000,000 IU each. The cycles were repeated as often as necessary, according to the reduction in tumor volume or change in the signal on MR imaging. One characteristic is that the often hyperintense cysts on T1-weighted sequences usually become hypointense on T1-weighted images after treatment; whenever control MR imaging revealed that the cyst had become hyperintense again, a new cycle of INF was prescribed.

The number of cycles ranged from 1 to 9 (average 5 cycles) per patient (Figs. 2 and 3). The follow-up duration ranged from 4 to 84 months (average 44 months). All the patients were treated in an ambulatory regimen.

Results

In 47 patients (78.3%) tumor control was possible.

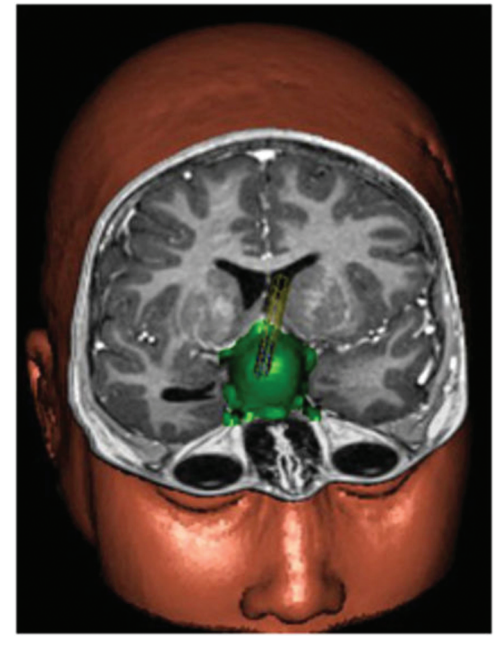

Fig. 1. Neuronavigational image showing the catheter trajectory and the cystic CP.

However, in 13 patients the tumor continued to grow and excision was necessary. The pretreatment tumor volume in 37 patients ranged from 3.3 to 134.5 ml (mean 27.7 ml). The posttreatment tumor volume ranged from 0.14 to 70.7 ml (mean 9.6 ml).

We considered disease to be controlled when a tumor decreased more than 50%. In 1 patient, although there was a reduction in the tumor, there was no improvement in visual symptoms, and surgery was required for optic chiasm decompression. Eight patients (13.3%) exhibited new endocrinological dysfunctions after treatment. In 3 patients a thyroidal hormonal deficit developed, in 2 of whom the deficit was associated with corticosteroid deficit and in 1 with testosterone deficit. One patient had only a new testosterone deficit.

Eighteen patients (30%) had some kind of side effect due to INFα2A therapy, which did not prevent the continuation of treatment. Six patients complained of headache, 5 of palpebral edema, 5 had fever, 1 had chronic fatigue syndrome, and 1 had arthritis. These effects were easily controlled with simple medication and disappeared after treatment. We observed no difference with respect to disease course based on whether the patient had undergone previous treatment or not. Among the 37 cases in which tumor volume measurement was performed, 81.8% of the previously treated patients had a cyst reduction greater than 50%. In 85.5% of the patients who had not undergone a previous treatment, cyst reduction was also greater than 50%. In 3 patients who had been treated with bleomycin, the tumors were controlled with INF.

Discussion

Interferon-alpha is the first cytokine produced by a DNA recombinant technique that is effective against can-

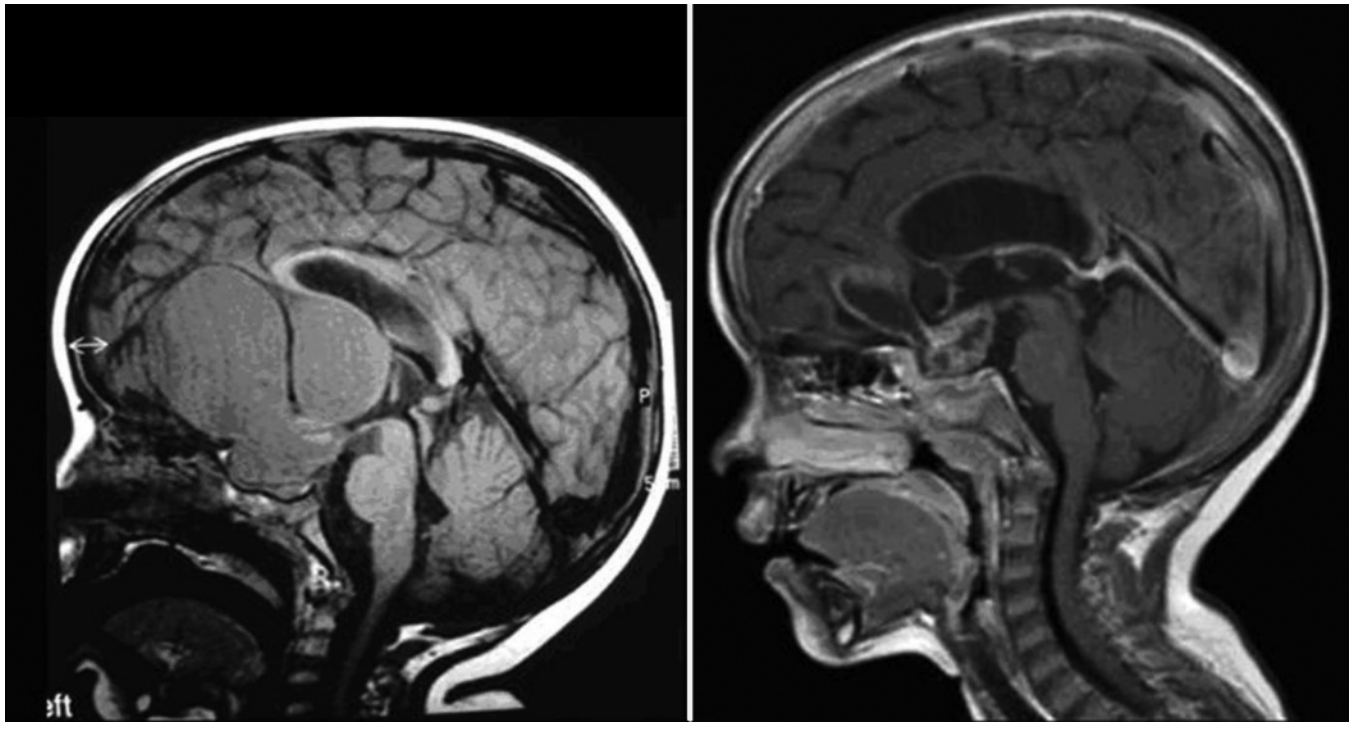

Fig. 2. Left and Right: Sagittal T1-weighted enhanced MR images obtained before treatment of a cystic CP and the 4 years after the IFNα2A treatment (5 cycles).

cer.[8] It is classified as a helical cytokine and is included in an evolutionary conserved family of secreted proteins. It is used therapeutically for its properties of inducing an "antiviral" state in cells, inhibiting cellular proliferation, and creating immunomodulation.[22] The effects of IFNα are mediated by the interaction with its receptor, which activates the JAK proteins, resulting in the activation by phosphorylation of the STAT proteins, which finally activate the transcription of the *ISGs*.[21] The first use of IFN for control of CP was by Jakacki et al.[16] with good results in 3 of 12 patients treated with subcutaneous injections of interferon in predominantly cystic CP. The first use of intratumoral interferon to control CP was by Cavalheiro et al.[6] Craniopharyngioma is a benign, slow-growing tumor that causes severe disturbances due to involvement of the hypothalamic-pituitary axis and requires a multidisciplinary team for its control. Several therapies have been proposed for patients with CPs, which allows the surgeon to choose the best way to treat each individual patient.[2]

The best treatment for this type of tumor is complete removal with preservation of all endocrine and visual functions, which is achieved in a small number of cases.[11,12]

Curtis et al.[10] reported a low mortality rate after total resection, but almost all patients needed hormone replacement therapy and 50% of the patients were obese, presumably caused by damage to the hypothalamic satiety center. Sanford[18] demonstrated that in 95% of the cases of radical surgery the patients needed hormone replacement.

In 2005 Tomita and McLone[23] report achieving total resection in 76.7% of 54 children with CPs, 27.3% of whom presented with recurrence in the first 2 years of follow-up. Additionally, in 92.5% of these patients panhypopituitarism developed, and in 9.2% severe obesity developed.[23] The same result was described by Zuccaro,[26] who demonstrated a 77% rate of total resection, with 87% of 153 patients having a hormone deficit. According to the literature, the condition in the vast majority of patients will progress to visual and endocrine dysfunction, hypothalamic dysfunction, disorders of hunger, psychiatric disorders, and a poor quality of life.[14]

Reviewing the data, 50–80% of patients undergoing resection of a CP will present later with hyperphagia and obesity.[3,4,20] All the aforementioned recent results emphasized the thinking of Epstein,[13] who stated, "surgical removal of these tumors is only appropriate for patients living in countries with ready access to appropriate endocrinological follow-up. Those returning to undeveloped countries or even to rural areas in this nation are at great risk of morbidity and even death."

To begin the treatment of CPs with IFN, we sought to use an easy, inexpensive, nonneurotoxic drug without adverse side effects. We decided to combine 2 previously reported concepts: the treatment of CPs with intratumoral injection of bleomycin (our experience)[7] and the use of subcutaneous injections of IFN for the same purpose (the experience of Jakacki et al.[16]).

We treated 60 patients in a multicenter study, and disease control was achieved in 78% of these patients; only 13% developed a worsening of endocrinological function, and there were few side effects, and the mortality rate was 0%.

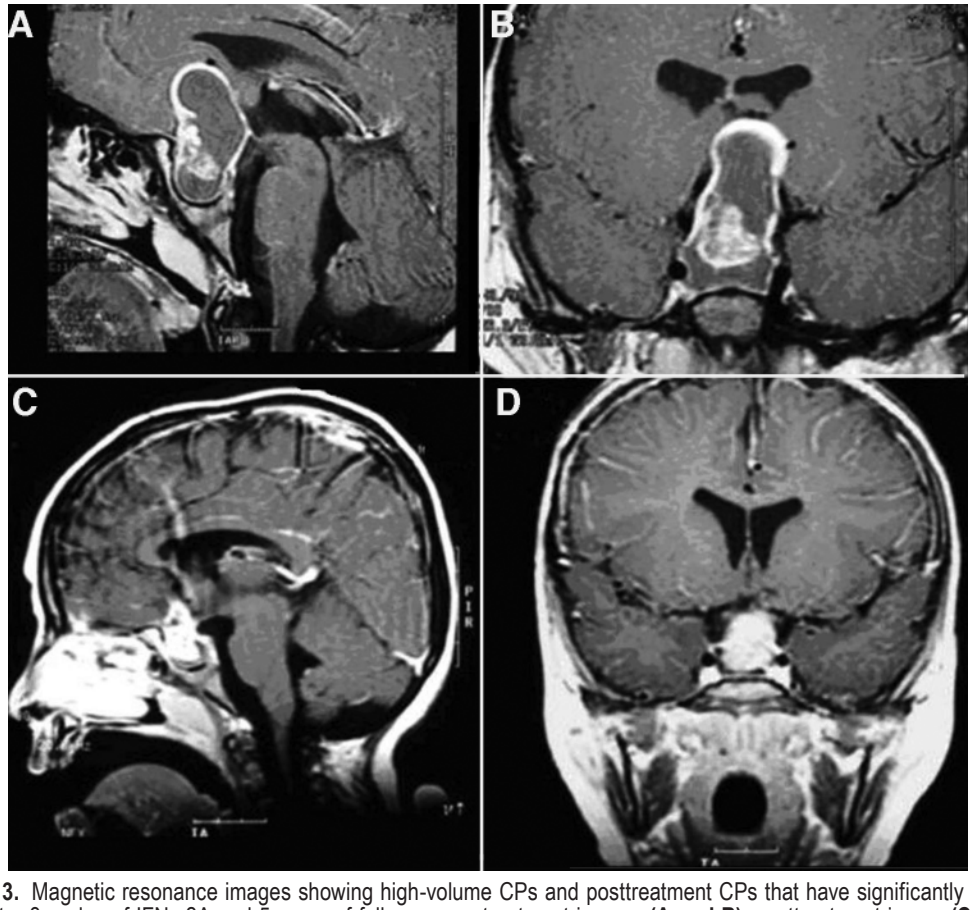

Fig. 3. Magnetic resonance images showing high-volume CPs and posttreatment CPs that have significantly decreased in size after 3 cycles of IFNα2A and 5 years of follow-up: pretreatment images **(A and B)**, posttreatment image **(C)**, and 5-year follow-up image **(D)**.

In the cases involving a good response to therapy, the reduction in the size of the cystic component was more evident than a reduction in the size of the solid portion of the tumor, as already demonstrated by Jakacki et al.[16]

The main difference between radical surgery and our approach is that no patient in our series developed, during the treatment, hunger disorders, had severe hypothalamic disturbances, or became obese. The results of our therapy proved to be better than those presented in the majority of series that advocate other intratumoral chemotherapy involving radioisotopes or bleomycin.[1,5,19,25]

We emphasized that the medical literature considers a predominantly cystic CP to be one in which greater than 60% of the tumor volume is cystic.[18] It is important keep in mind that 90% of pediatric CPs have this characteristic.[17]

The CP is a slow-growing tumor that demands a chronic management. As we noted in our results, up to 9 cycles of intratumoral INFα2A injections are needed to control the disease; in light of this, IFN therapy appears to be a chronic treatment.

During the early stages of this treatment protocol we thought that the decrease in tumor volume might be due to the mechanical action of withdrawing the intratumoral liquid, but Ierardi et al.[15] have shown an increase in the rates of apoptosis when CP fluid was analyzed in different stages of treatment. New research has yet to be carried out to isolate a "magic" drug, able to control CPs. Perhaps CPs are not tumors themselves, but embryonic immune defects. Indeed, few genetic changes are found in CPs.[24] The balance between the aggressiveness of the tumor and the patient's immune response will determine the winner of this battle.

There are cases in which even after 9 cycles of treatment there was no tumor control, and there are cases in which a single application could control them. We had more surgical difficulties when we had to surgically treat a patient undergoing bleomycin chemotherapy than when we had to do so after IFN treatment. Perhaps the delivery of intratumoral IFN coated with slow-release capsules may increase the rates of control of CPs, reducing the number of applications per patient.

Conclusions

Despite tremendous neurosurgical advances and refinements, which make it possible to achieve higher rates of complete CP resection, endocrinological deterioration seems inevitable, especially after invasion of the hypothalamus. In the pursuit of a better quality of life, the quest for other CP-controlling techniques should be encouraged, with the purpose of preserving metabolic functions.

The use of INFα for the treatment of cystic forms of

CP has been efficacious, easy to handle, and available at a low cost; it is also associated with a low morbidity rate and few side effects. Further studies are still necessary for better definition of the proper dose, number of cycles, and time of evolution.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: S Cavalheiro, C Di Rocco. Acquisition of data: S Cavalheiro, S Valenzuela, C Di Rocco, PA Dastoli, G Tamburrini, L Massimi, JM Nicacio, IV Faquini, Nasjla Saba da Silva. Analysis and interpretation of data: S Cavalheiro, S Valenzuela, PA Dastoli, G Tamburrini, JM Nicacio, IV Faquini, DF Ierardi. Drafting the article: S Cavalheiro. Critically revising the article: S Cavalheiro, IV Faquini, DF Ierardi. Reviewed final version of the manuscript and approved it for submission: S Cavalheiro, IV Faquini, BL Pettorini, SRC Toledo. Statistical analysis: S Cavalheiro, JM Nicacio, IV Faquini, DF Ierardi. Administrative/technical/material support: S Cavalheiro, JM Nicacio, IV Faquini, DF Ierardi. Study supervision: S Cavalheiro, PA Dastoli, L Massimi, JM Nicacio, IV Faquini.

References

1. Albright AL, Hadjipanayis CG, Lunsford LD, Kondziolka D, Pollack IF, Adelson PD: Individualized treatment of pediatric craniopharyngiomas. **Childs Nerv Syst 21:**649–654, 2005
2. Backlund EO: Treatment of craniopharyngiomas: the multimodality approach. **Pediatr Neurosurg 21 (Suppl 1):**82–89, 1994
3. Blethen SL, Weldon VV: Outcome in children with normal growth following removal of a craniopharyngioma. **Am J Med Sci 292:**21–24, 1986
4. Bucher H, Zapf J, Torresani T, Prader A, Froesch ER, Illig R: Insulin-like growth factors I and II, prolactin, and insulin in 19 growth hormone-deficient children with excessive, normal, or decreased longitudinal growth after operation for craniopharyngioma. **N Engl J Med 309:**1142–1146, 1983
5. Cáceres A: Intracavitary therapeutic options in the management of cystic craniopharyngioma. **Childs Nerv Syst 21:**705–718, 2005
6. Cavalheiro S, Dastoli PA, Silva NS, Toledo S, Lederman H, da Silva MC: Use of interferon alpha in intratumoral chemotherapy for cystic craniopharyngioma. **Childs Nerv Syst 21:**719–724, 2005
7. Cavalheiro S, Sparapani FV, Franco JO, da Silva MC, Braga FM: Use of bleomycin in intratumoral chemotherapy for cystic craniopharyngioma. Case report. **J Neurosurg 84:**124–126, 1996
8. Chawla-Sarkar M, Lindner DJ, Liu YF, Williams BR, Sen GC, Silverman RH, et al: Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. **Apoptosis 8:**237–249, 2003
9. Choux M, Lena G, Genitori L: Le craniopharyngiome de l'enfant. **Neurochirurgia (Stuttg) 37 (Suppl 1):**1–174, 1991
10. Curtis J, Daneman D, Hoffman HJ, Ehrlich RM: The endocrine outcome after surgical removal of craniopharyngiomas. **Pediatr Neurosurg 21 (Suppl 1):**24–27, 1994
11. Elliott RE, Moshel YA, Wisoff JH: Minimal residual calcification and recurrence after gross-total resection of craniopharyngioma in children. **J Neurosurg Pediatr 3:**276–283, 2009
12. Elliott RE, Wisoff JH: Successful surgical treatment of craniopharyngioma in very young children. **J Neurosurg Pediatr 3:**397–406, 2009
13. Epstein FJ: Meeting summary. **Pediatr Neurosurg 21:**129–130, 1994
14. Halac I, Zimmerman D: Endocrine manifestations of craniopharyngioma. **Childs Nerv Syst 21:**640–648, 2005
15. Ierardi DF, Fernandes MJ, Silva IR, Thomazini-Gouveia J, Silva NS, Dastoli P, et al: Apoptosis in alpha interferon (IFN-alpha) intratumoral chemotherapy for cystic craniopharyngiomas. **Childs Nerv Syst 23:**1041–1046, 2007
16. Jakacki RI, Cohen BH, Jamison C, Mathews VP, Arenson E, Longee DC, et al: Phase II evaluation of interferon-alpha-2a for progressive or recurrent craniopharyngiomas. **J Neurosurg 92:**255–260, 2000
17. Marchal JC, Klein O, Thouvenot P, Bernier V, Moret C, Chastagner P: Individualized treatment of craniopharyngioma in children: ways and means. **Childs Nerv Syst 21:**655–659, 2005
18. Sanford RA: Craniopharyngioma: results of survey of the American Society of Pediatric Neurosurgery. **Pediatr Neurosurg 21 (Suppl 1):**39–43, 1994
19. Savas A, Erdem A, Tun K, Kanpolat Y: Fatal toxic effect of bleomycin on brain tissue after intracystic chemotherapy for a craniopharyngioma: case report. **Neurosurgery 46:**213–217, 2000
20. Sklar CA: Craniopharyngioma: endocrine abnormalities at presentation. **Pediatr Neurosurg 21 (Suppl 1):**18–20, 1994
21. Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD: How cells respond to interferons. **Annu Rev Biochem 67:**227–264, 1998
22. Stubgen JP: Effects of recombinant type I interferon therapy on human muscle diseases. **Muscle Nerve** [epub ahead of print], 2009
23. Tomita T, McLone DG: Radical resections of childhood craniopharyngiomas. **Pediatr Neurosurg 19:**6–14, 1993
24. Yoshimoto M, de Toledo SR, da Silva NS, Bayani J, Bertozzi AP, Stavale JN, et al: Comparative genomic hybridization analysis of pediatric adamantinomatous craniopharyngiomas and a review of the literature. **J Neurosurg 101 (1 Suppl):**85–90, 2004
25. Zanon N, Cavalheiro S, da Silva MC: Does the choice of surgical approach to insert an intratumoral catheter influence the results of intratumoral cystic treatment? **Surg Neurol 70:**66–69, 2008
26. Zuccaro G: Radical resection of craniopharyngioma. **Childs Nerv Syst 21:**679–690, 2005

Manuscript submitted December 17, 2009.
Accepted January 19, 2010.

Address correspondence to: Sergio Cavalheiro, Ph.D., Rua Botucatu 591/42, São Paulo, Brazil 04023-061. email: iscava@uol.com.br.

Neurosurg Focus 28 (4):E13, 2010

Intracystic treatments for craniopharyngioma

Paul Steinbok, B.Sc., M.B.B.S., F.R.C.S.C.,[1] and Juliette Hukin, M.B.B.S., F.R.C.P.C.[2]

[1]Division of Pediatric Neurosurgery, Department of Surgery; and [2]Division of Neurology, Department of Pediatrics, University of British Columbia, and British Columbia's Children's Hospital, Vancouver, British Columbia, Canada

Craniopharyngioma is a benign tumor histopathologically and in theory should be curable by radical resection. In practice, this tumor behaves like a chronic disease, with many issues related to the effect of the tumor itself and the various treatments on the adjacent structures, such as the pituitary stalk and gland, hypothalamus, visual apparatus, and suprasellar arteries. A multimodality approach to the management of these tumors may produce the optimal outcome, balancing disease control and quality of life. In this paper, the role of intracystic therapies is reviewed, with the major focus on intracystic bleomycin and interferon-α. *(DOI: 10.3171/2010.1.FOCUS09315)*

Key Words • craniopharyngioma • intracystic therapy • radiotherapy • bleomycin • interferon

Craniopharyngiomas are histologically benign tumors, extrinsic to the brain parenchyma. As such, the ideal treatment of craniopharyngiomas should be complete resection, which might be expected to result in a cure with preservation of patient function. Unfortunately, the tumor may present with irreversible loss of visual, hormonal, and/or hypothalamic functions, and all treatments have the potential to produce additional deficits. As a result, children with these tumors suffer from a chronic disease process. The goal of treatment is tumor control and improved length of survival, while maintaining quality of life. To achieve this goal, one needs to consider the multiple potential interventions that exist for management of craniopharyngiomas, including surgery, radiotherapy, and intracystic treatments. One then needs to choose the intervention or interventions that are most appropriate for the individual, based on the anatomy of the tumor, patient age, and clinical picture (medical history and examination findings).

The location of the tumor, with variable involvement of the pituitary stalk and gland, the optic nerves and chiasm, the carotid and anterior cerebral arteries, and the hypothalamus, makes radical resection difficult, risky, and often technically impossible. In most recent patient series, gross-total resection of craniopharyngiomas was achieved in only 50 to 80% of attempted radical resections,[7,40,45,46,51] although there are rare reports of much higher success rates.[12] Furthermore, even when total resection of the tumor has been achieved, and confirmed by CT scans and MR imaging, recurrences occur in 10 to 30%,[11,13,47] with more recurrences revealed the longer one follows these patients.

Radical resection usually results in loss of anterior pituitary hormonal function and diabetes insipidus, and may also be complicated by visual deterioration. Most devastating is the complication of hypothalamic injury, with development of life-long morbid obesity and neurocognitive changes.[36,40] Using the standard intracranial approaches for resection, tumors that, on MR imaging, appear to be anterior to the hypothalamus or are simply pushing the floor of the third ventricle upwards are those most amenable to complete resection without loss of hypothalamic function.[37] It may be that, in this group of patients, attempted radical resection should be the first line of treatment. For the tumors that appear to invade the hypothalamus on MR imaging scans, especially if children with these tumors already have clinical evidence of hypothalamic dysfunction, the risks of radical resection are higher and thus there is a role for considering alternative approaches to treatment.

The most commonly used alternative treatments for craniopharyngiomas have been a biopsy procedure, cyst drainage, or planned partial resection, followed by EBRT. Based on studies of patients treated mainly in the 1960s and 1970s, 10- and 20-year progression-free survival rates of approximately 80% have been achieved using conventional fractionated radiotherapy.[24,38,39,45] This approach

Abbreviations used in this paper: EBRT = external beam radiation therapy; IFN = interferon.

has resulted in less early morbidity, but there have been significant problems that occurred later, including visual loss, hormonal deficiencies, decreased memory and intellect, moyamoya disease, strokes, and rarely, a secondary neoplasm. More modern techniques of radiotherapy, including proton beam therapy, conformal radiotherapy, intensity modulated radiotherapy, and stereotactic radiotherapy and radiosurgery might be expected to reduce the long-term complications while preserving the positive results of radiotherapy.[15,24,31,32] For any type of radiotherapy, the potential for complications is higher the younger the child, so that any management protocol that delays the use of radiotherapy may be beneficial.[31]

One of the typical characteristics of craniopharyngiomas is the presence of a cyst within the tumor. Such cysts occur in more than 90% of tumors and often the cyst comprises the major component of the tumor.[2] This characteristic has led to another line of therapy, specifically instillation of antineoplastic agents into the tumor, including beta-emitting radionuclides, bleomycin, and IFNα into the cyst. In this review, the focus will be on the use of bleomycin and IFNα.

Intracystic Beta-Emitting Radionuclides

The first intracystic therapy comprised the use of radioactive beta-emitting radionuclides, such as phosphorus[32], yttrium[90], rhenium[186], and aurum[198], and this treatment is reviewed here only briefly. The beta-emitting radionuclides are instilled after stereotactic puncture of the cyst and the appropriate dose is calculated on the basis of the size of the cyst. The goals of intracavitary radiotherapy are reduction of the cyst and long-term control of the tumor, in many respects similar to the goals of EBRT. Regardless of the beta-emitting radionuclide used, intracavitary radiotherapy reduces the size of the cyst in 50 to 100% of cases, according to different case series.[6,23] Patient survival at 10 years after this treatment is also good, ranging from 45 to 80%.[6] However, in the longest followed series of patients reported, survival continued to decline over time, falling to < 20% after 20 years and 0% by 30 years.[23] New endocrinopathy is very unusual after intracystic radiotherapy, but visual loss and radionecrosis of the hypothalamic or pontomesencephalic regions have been noted in approximately 5% of patients, and vascular involvement with moyamoya disease or subarachnoid hemorrhage more rarely.[6,23] One of the negatives of intracavitary radiotherapy is the small number of facilities with access to the radioisotopes and the complexity of the process for instillation of such materials into the cyst.

Intracystic Bleomycin

More recently, bleomycin has been used for intracystic treatment of craniopharyngiomas, both initially and at the time of recurrence. At one center, bleomycin has been proposed as a treatment that can provide durable control of the tumor.[34] However, in general, bleomycin has been used for temporary tumor control with the expectation that other therapies, such as resection or radiotherapy, will be required for longer term tumor control. In that respect, the goals of treatment are different from those of intracavitary radiotherapy.

TABLE 1: Case series of 10 or more patients in which intracystic bleomycin monotherapy was used without concomitant radiotherapy*

Authors & Year	No. of Patients	% Patients w/ Cyst Shrinkage	Mean Follow-Up (yrs)	% Progression-Free at Last Follow-Up
Mottolese et al., 2005	24	100	5	71
Broggi & Franzini, 1996	14	100	3.6	NA
Hukin et al., 2007	17	94	2.5	59
Park et al., 2002	10	100	2.8	60
Takahashi et al., 1985, 2005	15	100	NA	80
Zanon, 1998	20	62	NA	85

* NA = not available.

Takahashi et al.[43] first reported the use of intracavitary bleomycin after partial excision of craniopharyngiomas. Subsequently, there have been a number of single-center case series[5,14,16,22,25,27,33,35] and case reports[1,3,9,17,26,41,42] published on the use of intracystic bleomycin for craniopharyngioma, both as de novo treatment and as treatment for recurrences. In addition, the experience of intratumoral bleomycin use across multiple centers in Canada has been reviewed.[19] In a detailed review of all reports of intracystic bleomycin for brain tumors up to 2007, Linnert et al.[28] identified 189 cases, of which 130 were craniopharyngiomas. In the craniopharyngioma group, 1 series of 9 patients[16] was part of a later report,[19] and 1 report is misquoted and should include 3 rather than 8 patients,[25] so that, in fact, there were no more than 116 patients treated, some of whom underwent concomitant radiotherapy. The response to bleomycin therapy was not reported. We have reviewed the published data and have identified 100 patients included in series of 10 or more patients who were treated with intracystic bleomycin for craniopharyngioma. The outcomes of these patients are summarized in Table 1.

Bleomycin is usually injected into the craniopharyngioma cyst via a subgaleal Ommaya reservoir attached to a catheter, with its tip located in the craniopharyngioma cyst. Many approaches have been used to insert the catheter into the cyst. These approaches include an open subfrontal or pterional approach with direct visualization of the tumor, a transcortical approach, and a transcortical transventricular approach, often supplemented by intraoperative ultrasonography, endoscopy, and/or stereotaxy. One of the concerns with the transventricular route is that there may be toxic effects from spillage of the cyst contents into the ventricular system.[5] However, such spillage has not caused any ill effects in our experience.[16] Real-time ultrasonography or endoscopy is helpful in directing the catheter into the cyst, especially when the cyst wall is tough. It is important to avoid leakage of the bleomycin

outside the cyst into the subarachnoid space, because this may be toxic. Thus, it is important to position all the holes at the tip of the catheter within the cyst.

The standard ventricular catheters typically have holes starting 3 mm behind the tip, and continuing as far back as 1.8 cm from the tip, so that the cyst needs to be at least 2 cm in diameter to allow all the holes to be within the cyst. We have used a modified catheter containing holes that go back only 8 mm from the tip to make the margin of safety greater. Furthermore, to minimize leakage around the catheter, we try to insert the catheter using a push technique with a stylet in place or a minimal incision, if one is using an open approach to visualize the cyst directly.[16] Intraoperative ultrasonography also allows the surgeon to place the catheter tip deeply in the cyst and to know exactly where the tip is located. Postoperatively, prior to instilling bleomycin, contrast material is injected into the Ommaya reservoir, the head of the child is shaken around vigorously, and a CT scan is performed to confirm that there is no leakage of contrast material outside the cyst. If there is leakage, a CT scan with intracystic contrast enhancement may be repeated in 1 or 2 weeks, by which time the leakage is usually no longer present. If there is no leakage, the first dose of bleomycin is instilled. Some of the fluid in the cyst is aspirated from the Ommaya reservoir and is replaced with a smaller volume of bleomycin, followed by a 1-ml flush of normal saline. The intent is to keep the volume of the cyst stable during the injection, with no attempt made to collapse the cyst by excessive aspiration, because that could cause the holes in the catheter to be outside the wall of the cyst.

The appropriate dose and frequency of intracystic bleomycin use have not been defined in a scientific manner. The usual dose per instillation has been between 2 and 5 mg, with the larger dose used for larger cysts. Generally, bleomycin has been used 3 times per week, but some centers have used it daily. The treatment is continued for up to 5 weeks, or until the fluid in the cyst becomes fairly clear. Lactate dehydrogenase levels in the cyst fluid gradually decrease with treatment and have been used by some investigators to determine when to discontinue treatment, but we have not found that useful. When the tumor did not respond to the first course of bleomycin, additional courses of the drug have been used.[19] In the Canadian experience,[19] the median total dose administered during the first course was 36 mg (range 8–75 mg) and the median total dose of bleomycin was 55 mg (range 15–115 mg). The median dose/kg/week was 0.43 (range 0.17–1 dose/kg/week). The median dose of a single injection, in terms of concentration within the cyst, was 0.09 mg/ml/dose (range 0.01–2 mg/ml/dose).

Intracystic bleomycin is effective in inducing at least more than 25% shrinkage of the craniopharyngioma cyst in up to 90% of patients, with a more than 90% reduction in cyst size in approximately 25% of patients.[19] At a mean follow-up of 2 to 7 years (the range of means for the studies), 43 to 70% of patients required no treatment in addition to bleomycin,[5,16,19,33,43] but there is no information about the durability of the bleomycin effect at 10 years or longer. In the Canadian experience,[19] which is similar to the other reported series, 94% responded to intracystic bleomycin, but the duration of response was < 1 year in 47%. Sustained benefit was noted in 53% for a median of 34 months (range 15–107 months). However, in our experience, progression of the tumor inevitably occurs with longer follow-up, and we have noted tumor progression in 2 patients as long as 8 and 10 years after excellent responses to bleomycin. Importantly, in the Canadian series, radiation therapy was delayed by a median of 43 months (range 2–112 months), which is particularly important in the youngest children, in whom there is the most concern about adverse effects from radiotherapy.

The acute morbidity of intracystic bleomycin includes transient mild fever, nausea, vomiting, or headache, which occur in as many as 70% of patients, typically 24 hours after each instillation, and are self-limiting.[19] More importantly, there are delayed complications, which are rare, but serious. In a review of the complications of intracystic bleomycin in 189 patients with brain tumors, Linnert et al.[28] identified 5 patients (3%) with severe adverse effects and 6 patients (3%) with moderate adverse effects. Reported delayed complications include sensorineural hearing loss,[5,14] peritumoral edema,[19] visual loss,[33,35] hypothalamic dysfunction resulting in transient hypersomnolence, personality changes, poor memory,[17,35] cerebral ischemia,[5] hemiparesis,[22,35] progressive panhypopituitarism,[19] precocious puberty,[19] and death possibly related to a high individual and cumulative dose.[42] There have been a number of reported cases of moyamoya disease after intracystic bleomycin treatment for craniopharyngioma in patients who have also received radiotherapy, and it may be that radiotherapy sensitizes the vessels to bleomycin or vice versa.[19,29]

The effects of intratumoral bleomycin on future resection, if required, are not clear. Some neurosurgeons have stated anecdotally that there appeared to be more adhesions around the tumor and others have indicated that they believed that tumor resection was easier after bleomycin use. In cases in which the pathology was examined after bleomycin use, there were no unusual features to the tumor or its vasculature following recurrence and subsequent resection.[19]

In summary, intratumoral bleomycin has a limited role in the management of predominantly cystic craniopharyngiomas, in which an attempt at total resection is believed to be inappropriate or in which delay of other treatment such as EBRT is desirable. This therapy may result in control of the cyst for a variable period of time and may allow delay of radiotherapy or radical resection, which may be beneficial, especially in very young children. In the occasional case of what is believed to be an unresectable tumor, reduction of the cyst may change the assessment of the resectability of the tumor and allow an attempt at complete resection. The use of intracystic bleomycin does have some potentially serious complications and it may be possible that a similar effect can be achieved more safely with the use of IFNα, as described below.

Intracystic IFNα

As an alternative to bleomycin, intracystic IFNα has been used for patients with craniopharyngiomas.[8,20] The

mechanism of action of IFNα in tumor control is not definitively known, but preliminary studies have suggested that it may be tumoricidal by activating Fas-mediated apoptosis.[20]

Prior to the intracystic use of IFNα in craniopharyngiomas, data were available that suggested that IFNα could be given safely in this manner, could enter the subarachnoid space without significant morbidity (unlike bleomycin), and would potentially have an antitumoral effect. Postoperative intracavitary IFNα, given daily in a dose of 5×10^6 IU/ml for 14 days and then weekly for 10 weeks, was well tolerated with intracavitary concentrations of 4×10^5 IU/ml in patients with malignant glioma.[30] Systemic IFNα has induced objective responses in children with recurrent craniopharyngioma, anaplastic astrocytoma, brainstem glioma, and cerebral primitive neuroectodermal tumor, and in adults with newly diagnosed low-grade astrocytoma. Dose limiting toxicities of IFNα included hematological, hepatic, and neurological complications.[21,49] Systemic IFNα has also been used successfully without side effects in the treatment of viral encephalitis.[18,48] Furthermore, IFNα was used intrathecally in 22 patients with neoplastic meningitis with a response in 10 of these patients.[10] The only side effects reported in this study were transient chemical arachnoiditis and chronic fatigue, which occurred in the majority of patients but was not severe enough to require hospitalization.

In 2005, Cavalheiro et al.[8] first reported on the successful use of intracystic IFNα in 9 children with cystic craniopharyngiomas and expanded his series to 21 children in a further report in 2007.[20] These are the only reports in the literature at this time concerning this treatment. All patients underwent insertion of a catheter into the cyst, which was then attached to a subgaleal Ommaya reservoir. Five days later, after withdrawing as much cyst fluid as possible, 3 MIU of IFNα was injected into the cyst via the reservoir. This process was repeated on alternate days for a total of 12 injections (total 36 MIU). Up to 3 additional similar courses of IFNα were used in some patients, but the indications for the repeated treatment and the time between courses were not described. Cavalheiro has indicated that a second cycle of IFNα was started after 30 days if the cyst did not decrease or if the cyst appeared white on the T1 sequence of MR imaging (personal communication, December 2009). Further cycles of intracystic IFNα were administered after many months or years, if the cyst enlarged, or if the cyst became white on T1-weighted MR imaging. Of the 21 children, in all of whom the cyst comprised > 60% of the tumor, there were 11 complete responses (> 90% reduction), 7 partial responses (> 70% reduction), and 3 minor responses (< 70% reduction). In 2 patients the tumor progressed and resection was performed. It was noted in this study that, at minimum, the tumor was less adherent than a typical craniopharyngioma after IFNα treatment, making resection easier. There were minor complications related to the use of IFNα, such as transient fatigue, weight loss, loss of appetite, and behavioral changes.[20] Cavalheiro has treated 29 patients, and the results, including complications, have not changed from those reported by his group previously (personal communication, December 2009). Di Rocco and colleagues in Rome, Italy, have used IFNα in 8 patients (personal communication, December 2009). The complications noted in this study were similar to those observed by Cavalheiro's group,[20] but the efficacy in reducing cysts has not been as good as reported by Cavalheiro, with 2 patients exhibiting a rapid increase in the size of the cyst after use of IFNα. At the Hospital for Sick Children in Toronto, 2 children have been treated with IFNα and both have been followed for < 1 year. One had a complete response after 2 courses with IFNα, and the other, with a giant cystic tumor, had a partial response after 4 courses (Ute Bartels, personal communication, December 2009). There were no significant side effects from the treatment.

In summary, intracystic IFNα, like intracystic bleomycin, may provide short-term control of a predominantly cystic tumor and delay more definitive treatment aimed at longer term control. Unlike bleomycin, IFNα has similar advantages to intracystic bleomycin, but does not appear to have any significant major toxicity, even if it spills into the subarachnoid space. As such, use of IFNα would appear preferable to bleomycin as an intracystic treatment for craniopharyngiomas, but further reported series would allow a stronger recommendation in this regard as the experience with this treatment remains small and long-term follow-up is not well documented at this stage.

Conclusions

Craniopharyngioma is a benign tumor pathologically and in theory should be curable by radical resection. In reality, this tumor behaves like a chronic disease, with many issues related to the impact of the tumor itself and the various treatments on the adjacent structures, such as the pituitary gland and stalk, hypothalamus, visual apparatus, and suprasellar arteries. A multimodality approach to the management of these tumors may provide the optimal outcome, balancing disease (tumor) control and quality of life, which is the goal of managing any chronic disease. As part of the multimodality armamentarium, intracystic therapies with bleomycin and most recently IFNα have a role, particularly in the predominantly cystic craniopharyngiomas. Currently, of these 2 intracystic modalities, IFNα appears to have fewer side effects, but experience is limited and further studies are awaited.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: P Steinbok. Acquisition of data: P Steinbok, J Hukin. Analysis and interpretation of data: P Steinbok, J Hukin. Drafting the article: P Steinbok. Critically revising the article: P Steinbok, J Hukin. Reviewed final version of the manuscript and approved it for submission: P Steinbok, J Hukin.

References

1. Alén JF, Boto GR, Lagares A, de la Lama A, Gómez PA, Lobato RD: Intratumoural bleomycin as a treatment for recur-

rent cystic craniopharyngioma. Case report and review of the literature. **Neurocirugia (Astur) 13:**479–485, 2002
2. Backlund EO: Treatment of craniopharyngiomas: the multimodality approach. **Pediatr Neurosurg 21 (Suppl 1):**82–89, 1994
3. Belen D, Er U, Yigitkanli K, Bolay H: Delayed neurotoxic complication of intracavitary bleomycin therapy for craniopharyngioma in a child who had previously undergone radiosurgery. Case report. **J Neurosurg 106 (5 Suppl):**391–393, 2007
4. Broggi G, Franzini A: Bleomycin for cystic craniopharyngioma. **J Neurosurg 84:**1080–1081, 1996
5. Broggi G, Giorgi C, Franzini A, Leocata F, Riva D: Therapeutic role of intracavitary bleomycin administration in cystic craniopharyngioma, in Broggi G (ed): **Craniopharyngioma. Surgical Treatment.** Milan: Springer-Verlag, 1995, pp 113–119
6. Cáceres A: Intracavitary therapeutic options in the management of cystic craniopharyngioma. **Childs Nerv Syst 21:**705–718, 2005
7. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C: Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. **Childs Nerv Syst 21:**747–757, 2005
8. Cavalheiro S, Dastoli PA, Silva NS, Toledo S, Lederman H, da Silva MC: Use of interferon alpha in intratumoral chemotherapy for cystic craniopharyngioma. **Childs Nerv Syst 21:**719–724, 2005
9. Cavalheiro S, Sparapani FV, Franco JO, da Silva MC, Braga FM: Use of bleomycin in intratumoral chemotherapy for cystic craniopharyngioma. Case report. **J Neurosurg 84:**124–126, 1996
10. Chamberlain MC: A phase II trial of intra-cerebrospinal fluid alpha interferon in the treatment of neoplastic meningitis. **Cancer 94:**2675–2680, 2002
11. Duff M, Meyer F, Ilstrup D, Laws E, Schleck C, Scheitauer B: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000
12. Elliott RE, Wisoff JH: Successful surgical treatment of craniopharyngioma in very young children. **J Neurosurg Pediatr 3:**397–406, 2009
13. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
14. Frank F, Fabrizi AP, Frank G, Fioravanti A: Stereotactic management of craniopharyngiomas. **Stereotact Funct Neurosurg 65:**176–183, 1995
15. Gopalan R, Dassoulas K, Rainey J, Sherman JH, Sheehan JP: Evaluation of the role of Gamma Knife surgery in the treatment of craniopharyngiomas. **Neurosurg Focus 24(5):**E5, 2008
16. Hader WJ, Steinbok P, Hukin J, Fryer C: Intratumoral therapy with bleomycin for cystic craniopharyngiomas in children. **Pediatr Neurosurg 33:**211–218, 2000
17. Haisa T, Ueki K, Yoshida S: Toxic effects of bleomycin on the hypothalamus following its administration into a cystic craniopharyngioma. **Br J Neurosurg 8:**747–750, 1994
18. Horiguchi Y, Ohya T: [Successful treatment of subacute sclerosing panencephalitis with long-term intrathecal large dose of alpha-interferon—a case report.] **No To Hattatsu 27:**231–237, 1995 (Jpn)
19. Hukin J, Steinbok P, Lafay-Cousin L, Hendson G, Strother D, Mercier C, et al: Intracystic bleomycin therapy for craniopharyngioma in children: the Canadian experience. **Cancer 109:**2124–2131, 2007
20. Ierardi DF, Fernandes MJ, Silva IR, Thomazini-Gouveia J, Silva NS, Dastoli P, et al: Apoptosis in alpha interferon (IFN-alpha) intratumoral chemotherapy for cystic craniopharyngiomas. **Childs Nerv Syst 23:**1041–1046, 2007
21. Jakacki RI, Cohen BH, Jamison C, Mathews VP, Arenson E, Longee DC, et al: Phase II evaluation of interferon-alpha-2a for progressive or recurrent craniopharyngiomas. **J Neurosurg 92:**255–260, 2000
22. Jiang R, Liu Z, Zhu C: Preliminary exploration of the clinical effect of bleomycin on craniopharyngiomas. **Stereotact Funct Neurosurg 78:**84–94, 2002
23. Julow J, Backlund EO, Lányi F, Hajda M, Bálint K, Nyáry I, et al: Long-term results and late complications after intracavitary yttrium-90 colloid irradiation of recurrent cystic craniopharyngiomas. **Neurosurgery 61:**288–296, 2007
24. Kalapurakal JA: Radiation therapy in the management of pediatric craniopharyngiomas—a review. **Childs Nerv Syst 21:**808–816, 2005
25. Kim SD, Park JY, Park J, Lee JB, Kim SH, Lim DJ: Radiological findings following postsurgical intratumoral bleomycin injection for cystic craniopharyngioma. **Clin Neurol Neurosurg 109:**236–241, 2007
26. Lafay-Cousin L, Bartels U, Raybaud C, Kulkarni AV, Guger S, Huang A, et al: Neuroradiological findings of bleomycin leakage in cystic craniopharyngioma. Report of three cases. **J Neurosurg 107 (4 Suppl):**318–323, 2007
27. Lena G, Paz Paredes A, Scavarda D, Giusiano B: Craniopharyngioma in children: Marseille experience. **Childs Nerv Syst 21:**778–784, 2005
28. Linnert M, Gehl J: Bleomycin treatment of brain tumors: an evaluation. **Anticancer Drugs 20:**157–164, 2009
29. Liu AK, Bagrosky B, Fenton LZ, Gaspar LE, Handler MH, McNatt SA, et al: Vascular abnormalities in pediatric craniopharyngioma patients treated with radiation therapy. **Pediatr Blood Cancer 52:**227–230, 2009
30. Maleci A, Antonelli G, Guidetti B, Dianzani F: Pharmacokinetics of recombinant interferon-alpha 2 following intralesional administration in malignant glioma patients. **J Interferon Res 7:**107–109, 1987
31. Merchant TE, Kiehna EN, Kun LE, Mulhern RK, Li C, Xiong X, et al: Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. **J Neurosurg 104 (2 Suppl):**94–102, 2006
32. Minniti G, Esposito V, Amichetti M, Enrici RM: The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngioma. **Neurosurg Rev 32:**125–132, 2009
33. Mottolese C, Stan H, Hermier M, Berlier P, Convert J, Frappaz D, et al: Intracystic chemotherapy with bleomycin in the treatment of craniopharyngiomas. **Childs Nerv Syst 17:**724–730, 2001
34. Mottolese C, Szathmari A, Berlier P, Hermier M: Craniopharyngiomas: our experience in Lyon. **Childs Nerv Syst 21:**790–798, 2005
35. Park DH, Park JY, Kim JH, Chung YG, Lee HK, Lee KC, et al: Outcome of postoperative intratumoral bleomycin injection for cystic craniopharyngioma. **J Korean Med Sci 17:**254–259, 2002
36. Pierre-Kahn A, Recassens C, Pinto G, Thalassinos C, Chokron S, Soubervielle JC, et al: Social and psycho-intellectual outcome following radical removal of craniopharyngiomas in childhood. A prospective series. **Childs Nerv Syst 21:**817–824, 2005
37. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106 (1 Suppl):**3–12, 2007
38. Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJ, et al: Craniopharyngioma—a long-term results following limited surgery and radiotherapy. **Radiother Oncol 26:**1–10, 1993
39. Rajan B, Ashley S, Thomas DG, Marsh H, Britton J, Brada M: Craniopharyngioma: improving outcome by early recognition

and treatment of acute complications. **Int J Radiat Oncol Biol Phys 37:**517–521, 1997
40. Sainte-Rose C, Puget S, Wray A, Zerah M, Grill J, Brauner R, et al: Craniopharyngioma: the pendulum of surgical management. **Childs Nerv Syst 21:**691–695, 2005
41. Savas A, Arasil E, Batay F, Selcuki M, Kanpolat Y: Intracavitary chemotherapy of polycystic craniopharyngioma with bleomycin. **Acta Neurochir (Wien) 141:**547–549, 1999
42. Savas A, Erdem A, Tun K, Kanpolat Y: Fatal toxic effect of bleomycin on brain tissue after intracystic chemotherapy for a craniopharyngioma: case report. **Neurosurgery 46:**213–217, 2000
43. Takahashi H, Nakazawa S, Shimura T: Evaluation of postoperative intratumoral injection of bleomycin for craniopharyngioma in children. **J Neurosurg 62:**120–127, 1985
44. Takahashi H, Yamaguchi F, Teramoto A: Long-term outcome and reconsideration of intracystic chemotherapy with bleomycin for craniopharyngioma in children. **Childs Nerv Syst 21:**701–704, 2005
45. Thompson D, Phipps K, Hayward R: Craniopharyngioma in childhood: our evidence-based approach to management. **Childs Nerv Syst 21:**660–668, 2005
46. Tomita T, Bowman RM: Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. **Childs Nerv Syst 21:**729–746, 2005
47. Villani RM, Tomei G, Bello L, Sganzerla E, Ambrosi B, Re T, et al: Long-term results of treatment for craniopharyngioma in children. **Childs Nerv Syst 13:**397–405, 1997
48. von der Wense A, Herrmann B, Deppermann R, Harms F, Wehinger H: Intrathecal interferon therapy in chronic echovirus meningoencephalitis in Bruton type agammaglobulinemia. **Klin Padiatr 210:**51–55, 1998
49. Watanabe T, Katayama Y, Yoshino A, Komine C, Yokoyama T, Fukushima T: Treatment of low-grade diffuse astrocytomas by surgery and human fibroblast interferon without radiation therapy. **J Neurooncol 61:**171–176, 2003
50. Zanon N: Craniopharyngiomas: intratumoral chemotherapy with bleomycin in children and adolescents. Thesis, Sao Paulo 1997. **Arq Neuropsiquiatr 56:**859–864, 1998
51. Zuccaro G: Radical resection of craniopharyngioma. **Childs Nerv Syst 21:**679–690, 2005

Manuscript submitted December 15, 2009.
Accepted January 19, 2010.

Address correspondence to: Paul Steinbok, B.Sc., M.B.B.S., F.R.C.S.C., Division of Pediatric Neurosurgery, 4480 Oak Street, #K3-159, Vancouver, British Columbia, Canada V6H 3V4. email: psteinbok@cw.bc.ca.

Neurosurg Focus 28 (4):E14, 2010

Fusiform dilation of the carotid artery following radical resection of pediatric craniopharyngiomas: natural history and management

Robert E. Elliott, M.D.,[1] and Jeffrey H. Wisoff, M.D.[1,2]

Departments of [1]Neurosurgery and Pediatrics, New York University School of Medicine, New York, New York

Object. Fusiform dilation of the supraclinoid internal carotid artery (FDCA) is a reported occurrence following surgery for suprasellar tumors, in particular craniopharyngiomas. We report our experience of the incidence and natural history of FDCA following aggressive surgical resection of craniopharyngiomas in children.

Methods. Between 1986 and 2006, 86 patients under the age of 21 underwent radical resection of craniopharyngiomas at our institution. Ten cases with < 1 year of follow-up imaging (6), perioperative death (3), or nonsuprasellar tumors (1) were excluded. Data were retrospectively collected on the remaining 76 patients (43 male, 33 female; mean age 9.5 years; mean tumor size 3.3 cm) to determine the risk factors for and the rate and clinical significance of FDCA.

Results. Fifty patients had primary tumors and 26 patients received treatment before referral to our center. Sixty-six children (87%) had gross-total resection. At a mean follow-up time of 9.9 years, FDCA had developed in 7 patients (9.2%), all of whom had primary tumors and gross-total resection. The mean time to onset of FDCA was 6.8 months (range 3–11 months) with stabilization occurring at mean of 17.7 months (range 9–29.5 months). The mean size of the aneurysms was 9.1 mm (range 7.1–12 mm). After arrest, no lesions showed continued growth on serial imaging or produced symptoms or required treatment. There were no significant differences in age, sex, tumor size, pre- or retrochiasmatic location, extent of resection, or surgical approach ($p > 0.05$) between patients with and without FDCA.

Conclusions. Fusiform dilation of the supraclinoid internal carotid artery occurred in almost 10% of children following radical resection of craniopharyngiomas. In agreement with other reports, the authors concluded that FDCA probably occurs as a result of surgical manipulation of the supraclinoid carotid artery and should be managed conservatively because very few patients exhibit continued symptoms or experience growth or rupture of the lesion. *(10.3171/2010.1.FOCUS09296)*

Key Words • pediatric neurosurgery • radical resection • craniopharyngioma • aneurysm • carotid artery

Craniopharyngiomas are the most common nonglial brain tumors of childhood, constituting 6–8% of pediatric brain tumors.[2,6,38] They are benign neoplasms thought to arise from embryological remnants of squamous epithelium of the craniopharyngeal duct.[46,54] They most commonly arise in the suprasellar region and have intimate relationships with the hypothalamus, optic pathways, pituitary stalk, and, importantly, the circle of Willis.

In addition to the chronic and severe debilitation caused by hypothalamic injury, the risks of ICA injury during surgery can result in immediate injury or death from stroke or uncontrollable hemorrhage. This complication has been reported by a number of centers with large series of craniopharyngiomas treated both transcranially and transsphenoidally.[5,8,12,24,30,32,33,59] Originally reported by Sutton and colleagues in 1991,[51] a more subacute and subclinical manifestation of vascular injury can also occur and result in fusiform aneurysmal dilation of the carotid artery (FDCA). More common than intraoperative ICA laceration, FDCA has been reported to occur in 11–29% of cases after radical resection.[3,50,51]

Our treatment paradigm centers on radical resection for curative intent of craniopharyngiomas in patients of all age groups regardless of lesion size, predominantly via a pterional approach. We sought to determine the risk of FDCA with our aggressive surgical treatment strategy, identify risk factors that may predict the development of FDCA, and determine the clinical significance and natural history of FDCA in children with craniopharyngiomas.

Methods

Between 1986 and 2008, a total of 86 consecutive patients under the age of 21 underwent 104 operations for

Abbreviations used in this paper: DI = diabetes insipidus; FDCA = fusiform dilation of the supraclinoid internal carotid artery; GTR = gross-total resection; ICA = internal carotid artery; NYU = New York University; RT = radiation therapy; STR = subtotal resection; VP = ventriculoperitoneal.

excision of craniopharyngiomas performed by the senior author (J.H.W.) at NYU Langone Medical Center. Following study approval by the NYU institutional review board, data were retrospectively collected through review of clinic/office and inpatient records, pre- and postoperative and last follow-up CT and/or MR imaging studies, and operative and pathology reports. Patient characteristics, prior treatments, imaging features, extent of resection, and other oncological treatments were recorded. Long-term follow-up information was obtained between 2006 and 2009 by contacting patients, families, and referring physicians, and from records of the last follow-up office visit. Current follow-up data were not available in 2 patients and their follow-up duration was censored at time of last visit (131 and 180 months). Primary tumors were those treated at NYU at time of initial presentation; recurrent tumors were those referred to NYU for surgery after failure of prior treatment at other hospitals. Of note, some patients in this series were included in other reports on various aspects of the management of craniopharyngiomas in children.[14–17,48,55–57]

Ten cases were excluded for the following reasons: less than 1 year of follow-up imaging (6), perioperative death (3), and nonsuprasellar tumors (1). Data were retrospectively collected on the remaining 76 cases to determine the risk factors for and the rate and clinical significance of FDCA.

Gross-total resection was the primary aim of treatment in all cases. Our preferred approach is a modified pterional craniotomy with removal of the superior orbital rim. Details of our operative approach have been described elsewhere.[48,56] Gross-total resection was defined as lack of residual tumor on intraoperative visual inspection and lack of residual soft-tissue mass or enhancement suspicious for tumor on postoperative images as determined by an independent neuroradiologist. If these criteria were not met, the resection was deemed subtotal. Postoperative imaging was performed as follows: every 3 months for the first year, every 4 months for the second year, every 6 months for the next 3 years, and then every 1 year for the next 5 years. If FDCA was discovered, MR angiography was performed at the time of each follow-up MR imaging study.

All times are recorded from time of surgery at NYU. Averages are reported as means ± SDs. The Mann-Whitney U-test (Wilcoxon rank sum test) was used to compare nonparametric variables between groups. The Fisher exact and chi-square tests were used to compare proportions of 2 or more groups, respectively. All statistics were calculated with SSPS software (SSPS 17.0 for Mac; SSPS, Inc.). A 2-tailed p value < 0.05 was considered statistically significant.

Results

Patient Demographics and Preoperative Imaging

The study group consisted of 33 female (43%) and 43 male (57%) patients. Their mean age was 9.54 ± 4.95 years at time of surgery (median 9.5, range 9 months–20.5 years). Fifty patients (66%) had primary tumors and 26 (34%) had received prior treatment (recurrent). Thirty-nine tumors (51.3%) were prechiasmatic, 32 (42.1%) were retrochiasmatic, and 5 (6.6%) had both pre- and retrochiasmatic components. The mean maximum tumor diameter was 4.06 ± 1.59 cm (median 4, range 1.2–8 cm). Twenty-nine patients (38%) had hydrocephalus on preoperative imaging and 19 patients (25%) had VP shunts before or required a VP shunt after surgery at NYU.

TABLE 1: Comparison of demographic, clinical, and imaging characteristics in patients who did and did not develop FDCA after craniopharyngioma resection

Variable	FDCA	no FDCA	p Value
no. of pts	7	69	
pt sex			NS
M	4	39	
F	3	30	
mean pt age in yrs	10.3 ± 5.4	9.5 ± 4.9	NS
mean tumor size in cm	3.3 ± 1.6	4.13 ± 1.6	NS
primary tumors	7 (100)	43 (62)	NS
tumor location			NS
prechiasmatic	2	37	
retrochiasmatic	4	28	
complex (both)	1	4	
hydrocephalus	2 (29)	27 (39)	NS
VPS	1 (14)	18 (26)	NS
mean FU duration in yrs	10.5 ± 8.3	9.8 ± 6.3	NS
GTR	7 (100)	59 (86)	NS

* Values represent numbers of patients (%) unless otherwise indicated.
Abbreviations: FU = follow-up; pt = patient; VPS = VP shunt.

Surgical Outcomes and Follow-Up

The modified pterional approach with removal of the superior orbital rim was used in all 76 patients. It was combined with another approach in 5 patients (contralateral pterional, transsphenoidal, transcallosal [2] or subtemporal). Sixty-six patients (87%) had GTR and 10 patients (13%) had STR.

The mean follow-up duration was 9.86 ± 6.4 years (median 9.12, range 1.25–23.8 years). Nine patients died during the study period, yielding a crude overall survival rate of 88%.

Incidence and Disease Course of FDCA

Seven patients (9.2%) developed unilateral FDCA during the follow-up period. All 7 had primary tumors and GTR. No instances of FDCA occurred in patients with recurrent tumors, after any reoperations for recurrences in the primary tumor group, or after RT. The mean time to diagnosis of FDCA on postoperative imaging was 6.8 ± 3.0 months (median 6 months, range 3–11 months). The mean preoperative ICA diameter ipsilateral to the eventual FDCA was 4.5 ± 0.4 mm (median 4.6 mm, range 4–5 mm). The mean maximum diameter at time of FDCA stabilization was 9.1 ± 1.6 mm (median 9 mm, range 7.1–12 mm). Stabilization of FDCA occurred in all 7 cases. The mean

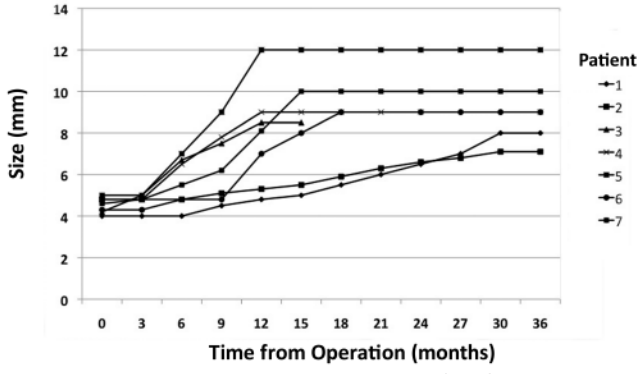

Fig. 1. Line graph demonstrating evolution of FDCA diameter over time. The ICA dilation eventually ceased in all patients.

time from surgery at our hospital to stabilization of FDCA was 17.7 ± 8.2 months (median 15.4 months, range 9–29.5 months). Figure 1 illustrates the evolution of FDCA over time in all 7 patients. No patient exhibited progressive dilation of the ICA as evidenced by the eventual flattening of the curves in all cases. All patients remained asymptomatic from FDCA and no patient required treatment.

Risk Factors for FDCA

Table 1 compares the demographic, clinical, and imaging data between patients who developed and those who did not develop FDCA. No patients received RT prior to the development of FDCA. There were no between-group differences in age, sex distribution, tumor location, presence of hydrocephalus or VP shunt, or surgical approach, technique, or extent of resection. There were statistically insignificant trends toward patients with FDCA having smaller tumors than those who did not develop FDCA ($p = 0.11$) and toward a higher proportion of patients with primary compared with recurrent tumors in the FDCA group ($p = 0.09$). Otherwise, no risk factors could be identified that were associated with the onset of FDCA.

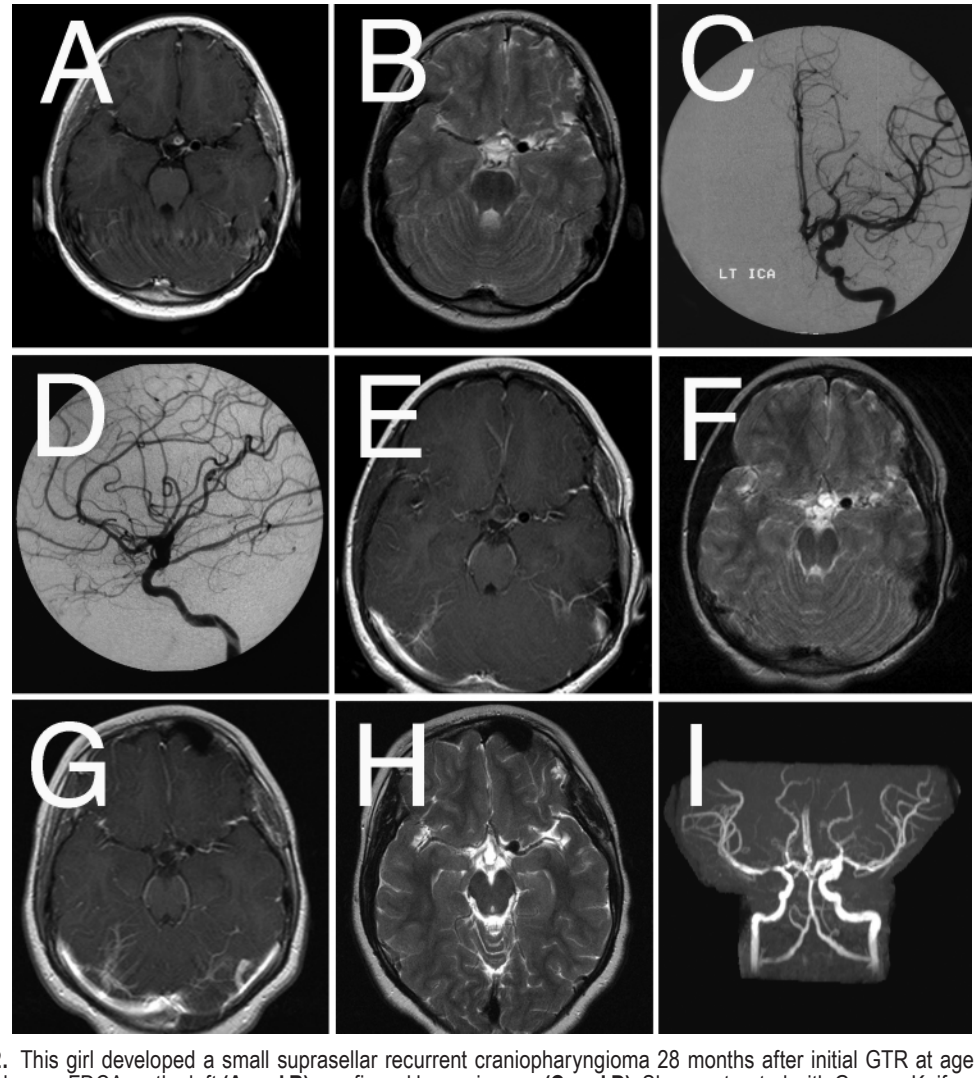

Fig. 2. This girl developed a small suprasellar recurrent craniopharyngioma 28 months after initial GTR at age 6 and was noted to have a FDCA on the left **(A and B)**, confirmed by angiogram **(C and D)**. She was treated with Gamma Knife surgery, with a progressive decrease in tumor size **(E–H)** and stable FDCA **(I)**. She remains disease free 68 months after the last treatment.

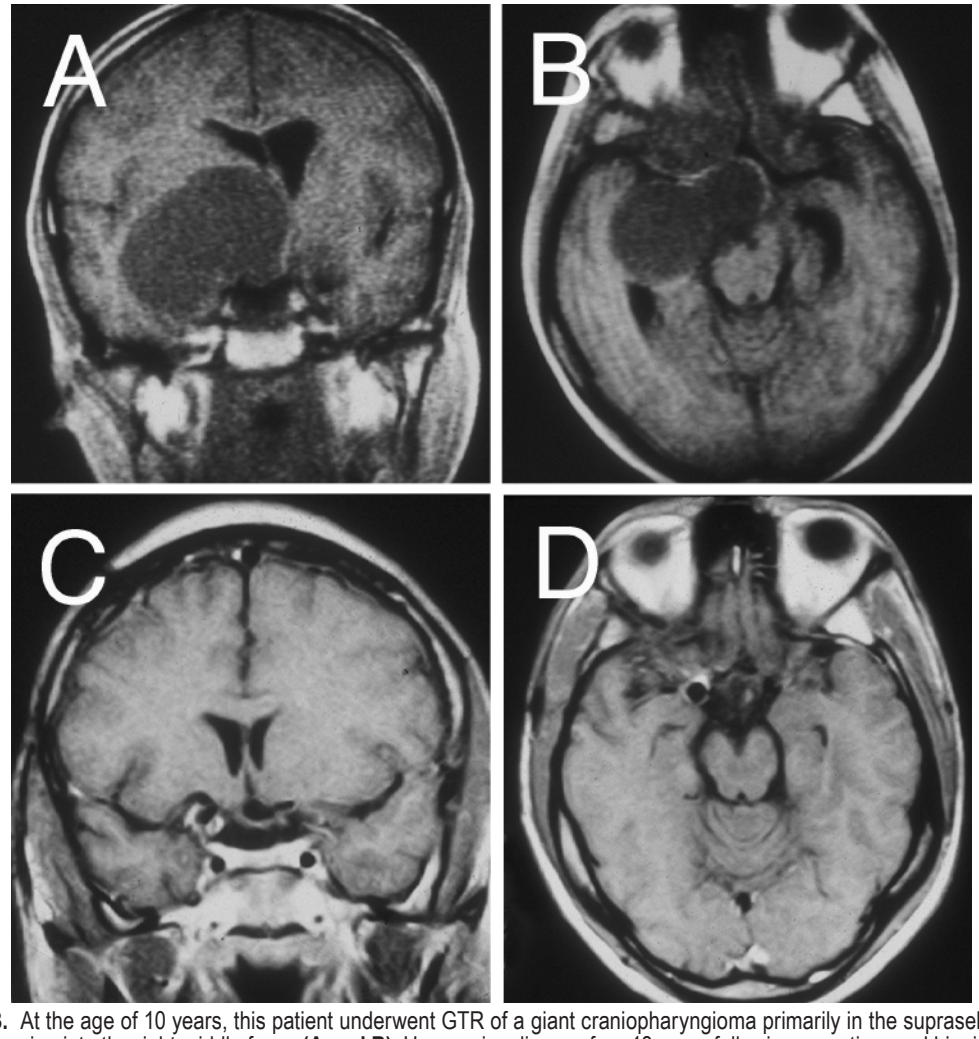

Fig. 3. At the age of 10 years, this patient underwent GTR of a giant craniopharyngioma primarily in the suprasellar region with extension into the right middle fossa **(A and B)**. He remains disease free 18 years following resection, and his right FDCA stabilized at 9 mm in diameter 12 months following resection **(C and D)**. Panel A is reproduced with permission from Wisoff JH et al.: Craniopharyngiomas, in Albright AL et al. (eds): **Principles and Practice of Pediatric Neurosurgery, ed 2.** Stuttgart: Thieme Medical Publishers, 2008.

Illustrative Cases

Case 1: Left FDCA and Recurrent Craniopharyngioma

This 4-year-old girl presented with headache and was diagnosed with a 3-cm retrochiasmatic craniopharyngioma. She underwent GTR of this lesion via a left pterional craniotomy with resultant DI and hypopituitarism. She developed slight dilation of the left ICA 9 months following surgery—from a baseline diameter of 4 mm to a maximum of 8 mm. Stabilization was documented at 28 months but she was noted to have a small, asymptomatic suprasellar recurrence of the tumor (Fig. 2A and B). Digital subtraction angiography prior to consideration of a second resection better illustrated her FDCA (Fig. 2C and D). Given the perceived increased risk of additional surgery, the child was treated with Gamma Knife surgery, with a progressive decrease in tumor size (Fig. 2E–H) and stable FDCA (Fig. 2I). She remains disease free 6 years after her last treatment, has remained without symptoms from her FDCA, and has required no further treatment.

Case 2: Right FDCA After Removal of Giant Craniopharyngioma

This 10-year-old boy presented with headache and lethargy. On examination, he had a moderate left hemiparesis and left homonymous hemianopsia. A MR imaging study revealed a 5-cm multicystic tumor arising in the suprasellar region with extension into the right middle fossa with significant mass effect and deformation of the insula, hypothalamus, and thalamus (Fig. 3A and B). Via pterional craniotomy, he had an uncomplicated GTR of this tumor with resolution of his lethargy and hemiparesis and improvement in his visual field status (residual left superior quadrantanopsia). He had no hypothalamic disturbance pre- or postoperatively despite significant mass effect on the hypothalamus. On 6-month follow-up MR imaging, however, there was increase in the caliber of the right ICA from the 4.8-mm baseline to 6.5 mm. On the 9-month study the lesion was found to have increased again, to 7.8 mm, but it stabilized at 9 mm at 12 months (Fig. 3C and D). The patient has had no further growth in

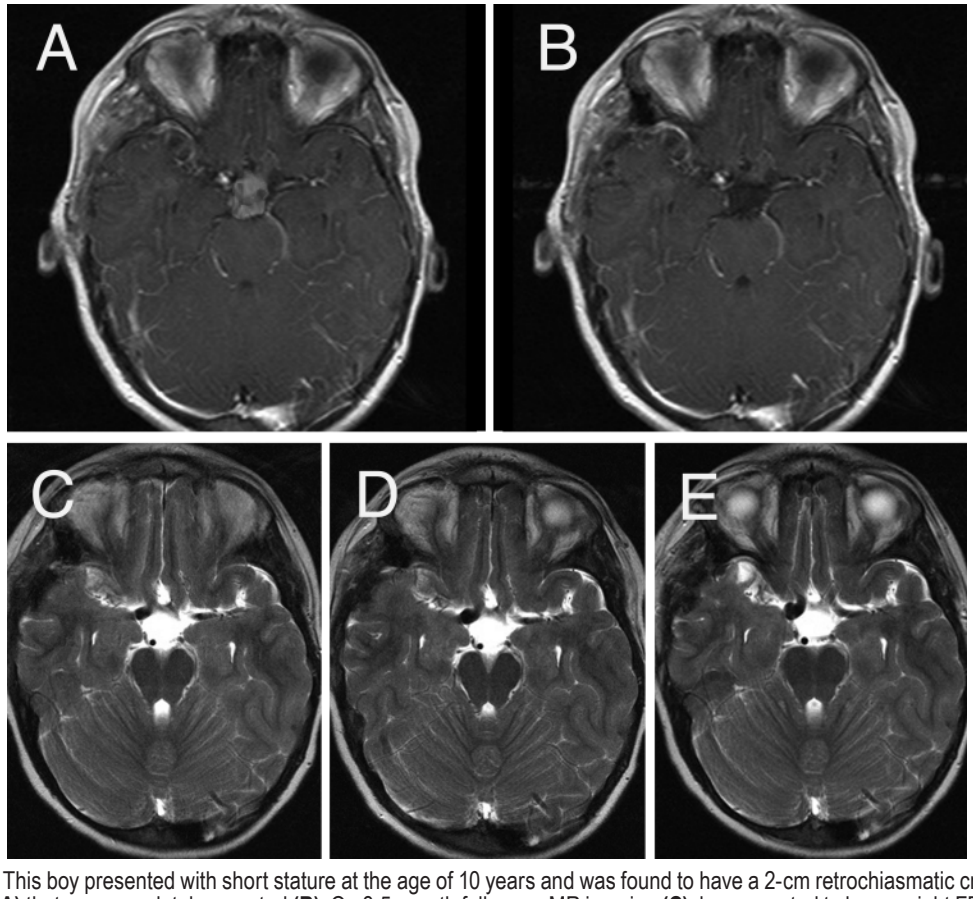

Fig. 4. This boy presented with short stature at the age of 10 years and was found to have a 2-cm retrochiasmatic craniopharyngioma **(A)** that was completely resected **(B)**. On 3.5-month follow-up MR imaging **(C)**, he was noted to have a right FDCA (from a baseline of 4.2 mm to 5 mm). Imaging at 9 months **(D)** showed further increase in size; 12-month follow-up imaging **(E)** showed that the lesion had stabilized at 9 mm.

the size of the lesion or symptoms referable to his FDCA. He required no adjuvant therapy and has remained disease free for 18 years following resection.

Case 3: Right FDCA With Onset 3 Months Following Resection

This 10-year-old boy presented with short stature and was found to have a 2-cm retrochiasmatic craniopharyngioma (Fig. 4A). He underwent GTR via pterional craniotomy (Fig. 4B) with subsequent DI and hypopituitarism and visual improvement. On his 3.5-month follow-up MR images, he was noted to have right FDCA, with an increase from his baseline of 4.2 mm (Fig. 3C) to 5 mm. Serial imaging at 6 and 9 months showed further increase in size (Fig. 4D and E) with eventual stabilization at 9 mm on his 12- and 15-month studies.

Discussion

In our review of 76 consecutive patients under the age of 21 who were treated with aggressive microsurgical resection of craniopharyngiomas with complete follow-up imaging, we found that almost 10% experienced postoperative FDCA. In all cases, however, the aneurysm size stabilized on serial imaging and none of the patients experienced symptoms due to the FDCA or required treatment for it. Our results corroborate work by other authors[3,50,51] showing that FDCA may be a relatively frequent but clinically benign complication following craniopharyngioma resection.

Given the predominantly suprasellar location of craniopharyngiomas, treatment can be fraught with side effects—both major and minor—that are detrimental to patients' quality of life. The most commonly reported complications include DI, hypopituitarism, vision deterioration, hypothalamic dysfunction, and obesity.[5,10,11,13,14,18,21,23,24,26,31,39,40,47,53,59,60] Acute vascular injury, however, can be one of the most devastating and deadly complications of craniopharyngioma resection, occurring after both transcranial and transsphenoidal approaches.[5,8,12,14,24,30,32,33,59] Both ICA laceration and severe vasospasm[14,24,50,51] have been reported as causes of severe strokes and death.

Fusiform dilation of the supraclinoid ICA is a subacute and subclinical vascular injury to the supraclinoid segment of the ICA, originally described in conjunction with craniopharyngioma resection by Sutton and colleagues.[51] In general, fusiform aneurysms are nonsacular dilations involving the entire circumference of a vessel wall for a short distance.[9,41,42,45] The proposed pathogenetic mechanisms of "spontaneous" fusiform aneurysms

include atherosclerosis and dissection and appears to involve disruption of the internal elastic lamina.[41–43]

The pathogenesis of FDCA remains uncertain. Damage to the ICA adventitia from surgical manipulation,[50,51] injury to the sympathetic plexus adherent to the adventitia of ICA[3,52] and injury to the vasa vasorum of the ICA have been hypothesized as possible causes of FDCA.[50,51] The condition, however, has not been reported in adults following resection of suprasellar tumors or is not routinely noted following arterial manipulation during aneurysm clipping. Whether this makes the causes proposed above less likely is unknown; the unique presence of FDCA in the pediatric population may be secondary to anatomical and biological differences between the more immature cerebral arteries of children and those of adults.[52] Histopathological examinations of the supraclinoid segment of the ICA have demonstrated the absence of vasa vasorum, making this hypothesis less likely.[58]

Sutton and colleagues[51] first reported FDCA in 9 of 31 (29%) children who had radical resection of craniopharyngiomas at a mean follow-up of 3.7 years. The mean tumor size in children who developed FDCA was 2.9 cm. All instances of FDCA occurred before 18 months following resection, all stabilized in size and none became symptomatic or required treatment. Clipping was performed in 1 patient at the time of surgery for recurrent tumor to aid in the exposure of the tumor. Sutton[50] went on to provide extended follow-up on these patients (mean: 6.2 years), which then comprised 15.7% (9 of 57) of resected craniopharyngiomas. No further changes were noted in the aneurysms.

Bendszus and colleagues[3] examined a single-surgeon series of 62 children who underwent frontotemporal resection of suprasellar tumors (49 of which were craniopharyngiomas) and noted FDCA in 7 children (11%) at a mean follow-up duration of 4 years. Five of these children had craniopharyngiomas (5 of 49 [10%]). All cases of FDCA developed within 15 months following surgery and all were ipsilateral to the side of approach. Fusiform dilation of the supraclinoid ICA regressed in 1 patient, stabilized in 3, and exhibited progressive enlargement in 3. None, however, required treatment for FDCA. They reported no instances of FDCA in 40 adults who underwent resection of suprasellar tumors by the same surgeon and frontotemporal approach (11 craniopharyngiomas, 29 pituitary adenomas).

Table 2 summaries the 26 reported cases of FDCA following craniopharyngioma resection in children and young adults.[3,29,35,36,50–52] Combining the 19 previously reported cases with 7 in this study, the mean age at time of surgery was 10.4 years. The mean tumor size was 3.3 cm and the mean interval from surgery to the diagnosis of FDCA was 12.5 months. Fusiform dilation of the supraclinoid ICA lesions stabilized in 20 of 24 cases (83%) over an average follow-up duration of 6.5 years (2 lesions were treated upon initial diagnosis without serial imaging[36,52]). Follow-up duration was in general shorter in patients reported to have growing lesions. All 15 lesions that have been observed for at least 5 years have stabilized in size. Only 2 (7.7%) cases became symptomatic (headache in 1 patient, vision loss from optic nerve compression in another patient) and 4 (15.4%) were treated surgically with clipping. No patients experienced rupture during the follow-up period.

While RT may have contributed to the onset or progression of FDCA in 3 reported cases, the majority of patients (88%) had not received RT prior to the onset of FDCA. The natural history of FDCA appears to run a dramatically difference disease course compared with radiation-induced aneurysms.[1,4,22,25,49] Sciubba et al.[49] reviewed 26 reported cases of RT-induced intracranial aneurysms—most of which were saccular in morphology, not fusiform. These aneurysms occurred at a mean time of 10 years following treatment and presented with subarachnoid hemorrhage in more than 60% of cases. The putative pathogenesis of RT-induced aneurysms is endothelial damage from the ionizing radiation and smaller vessels and capillaries are usually more affected than larger caliber vessels.[44]

Thus, the pathogenesis and natural history of radiation-induced aneurysms is markedly different from FDCA following craniopharyngioma surgery and these lesions should not be treated in a similar manner. Similarly, progressive growth of saccular aneurysms in both adults and children is a harbinger for rupture and would be an indication for intervention. We believe FDCA represents a benign entity that should be radiographically observed. Despite the anxiety provoked in patients, families, and practitioners by FDCA growth, a conservative approach may be wiser as long as the progressive dilation remains asymptomatic. We consider the following scenarios reasonable indications for treatment of FDCA: persistent or severe headache referable to the lesion location and side, neurological deficits from mass effect, thromboembolic events or focal change in morphological characteristics (development of a significant asymmetry along one wall or saccular component) that is worrisome for rupture. Treatment options include microsurgical clip reconstruction, or endovascular luminal reconstruction with a Neuroform stent (Boston Scientific)[19] or the Pipeline embolization device (PED; Chestnut Medical Technologies, Inc.).[20,37] The PED is a high-coverage but flexible stent that was specifically designed to achieve curative parent artery reconstruction of wide-necked and fusiform aneurysms.[20,37] Given the critical branches and perforators arising from the supraclinoid ICA, the PED may be a better endovascular treatment to maintain branch artery patency.

We agree with Sutton et al.[51] that a contralateral approach may be safer if additional surgery is necessary for the treatment of recurrence. We support this recommendation based on our experience of finding extensive scar tissue and tumor densely adherent to the circle of Willis that prevented complete resection at repeat surgery in 38% of patients—especially in children who were treated with RT.[14] In the presence of such scarring around a vessel already compromised, the risk for further injury may be significant. For small, recurrent craniopharyngiomas, stereotactic radiosurgery may be a useful and safe option, and it is associated with high rates of reported local control.[7,27,28,34]

Conclusions

Fusiform dilation of the supraclinoid ICA occurred

TABLE 2: Reported cases of FDCA following craniopharyngioma resection*

Authors & Year	Pt Age at Op (yrs)	Tumor Size (cm)	Extent of Resection	RT Before FDCA	FDCA Onset (mos)	FDCA Course	Max FDCA Size (cm)	Sx	FDCA Treatment	FU Duration (yrs)
Sutton et al., 1991	9	3	GTR	no	16	stable	NA	none	none	9
(Sutton, 1994)†	6	4	GTR	no	5	stable	NA	none	none	7
	12	4	GTR	no	15	stable	NA	none	clipping‡	6
	4	2	GTR	no	4	stable	NA	none	none	5
	19	1	GTR	no	17	stable	NA	none	none	7
	10	1.5	GTR	no	7	stable	NA	none	none	8
	8	2.5	GTR	no	13	stable	NA	none	none	6
	3	3	STR	yes	13	stable	NA	none	none	5
	7	5	STR	yes	8	stable	NA	none	none	6
Liu et al., 1991	24	large	GTR	no	4	increase	NA	none	clipping§	3
Lakhanpal et al., 1995	14	5	GTR	no	NA	increase	NA	vision loss	clipping	NA
	12	4	STR	yes	16	stable	NA	none	none	2.3
Bendszus et al., 1998	8	NA	NA	no	<15	increase	NA	none	none	4.3
	6	NA	NA	no	<15	stable	NA	none	none	6.5
	10	NA	NA	no	<15	stable	NA	none	none	5.9
	8	NA	NA	no	<15	increase	NA	none	none	1.8
	14	NA	NA	no	<15	stable	NA	none	none	2.4
Tirakotai et al., 2002	10	5	GTR	no	12	increase	NA	headache	clipping	2
Linfante et al., 2008	15	NA	GTR	no	60	stable	NA	none	none	1
present study	4	3	GTR	no	9	stable	8	none	none	8.6
	7	2.5	GTR	no	9	stable	7.1	none	none	4.8
	10	2	GTR	no	3.5	stable	8.5	none	none	1.4
	10	5	GTR	no	6	stable	9	none	none	18.7
	12	6	GTR	no	12	stable	12	none	none	2.2
	21	2	GTR	no	12	stable	9	none	none	16.7
	8	2.5	GTR	no	9	stable	10	none	none	21.4
mean values	10.4	3.3	—	3	12.5	—	9.1	—	—	6.5

* NA = data not available; — = not applicable.
† Study reported longer follow-up on the same group of patients.
‡ Asymptomatic aneurysm clipped at time of repeat surgery for tumor recurrence.
§ Asymptomatic aneurysm clipped for increase in size.

in almost 10% of children following radical resection of craniopharyngiomas in this series and is likely secondary to surgical manipulation of the supraclinoid carotid artery. Given the low incidence of symptoms, rupture, or continued growth at a mean follow-up of nearly 10 years, we believe FDCA should be managed conservatively and patients should be followed up with serial imaging. The risk of reoperation in a heavily scarred operative field to obtain clip reconstruction or wrapping does not appear to justify the benefits of treating this radiographic finding with apparently limited clinical significance.

Disclosure

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 to the study and manuscript preparation include the following.

Conception and design: RE Elliott. Acquisition of data: RE Elliott. Analysis and interpretation of data: RE Elliott, JH Wisoff. Drafting the article: RE Elliott, JH Wisoff. Critically revising the article: RE Elliott, JH Wisoff. Reviewed final version of the manuscript and approved it for submission: JH Wisoff. Statistical analysis: RE Elliott. Administrative/technical/material support: JH Wisoff.

References

1. Azzarelli B, Moore J, Gilmor R, Muller J, Edwards M, Mealey J: Multiple fusiform intracranial aneurysms following curative radiation therapy for suprasellar germinoma. Case report. **J Neurosurg 61:**1141–1145, 1984
2. Baskin DS, Wilson CB: Surgical management of craniopharyngiomas. A review of 74 cases. **J Neurosurg 65:**22–27, 1986
3. Bendszus M, Sörensen N, Hofmann E, Röll E, Solymosi L: Fusiform dilatations of the internal carotid artery following surgery for pediatric suprasellar tumors. **Pediatr Neurosurg 29:**304–308, 1998
4. Benson PJ, Sung JH: Cerebral aneurysms following radiotherapy for medulloblastoma. **J Neurosurg 70:**545–550, 1989

5. Caldarelli M, Massimi L, Tamburrini G, Cappa M, Di Rocco C: Long-term results of the surgical treatment of craniopharyngioma: the experience at the Policlinico Gemelli, Catholic University, Rome. **Childs Nerv Syst 21:**747–757, 2005
6. Carmel PW, Antunes JL, Chang CH: Craniopharyngiomas in children. **Neurosurgery 11:**382–389, 1982
7. Chiou SM, Lunsford LD, Niranjan A, Kondziolka D, Flickinger JC: Stereotactic radiosurgery of residual or recurrent craniopharyngioma, after surgery, with or without radiation therapy. **Neuro Oncol 3:**159–166, 2001
8. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T: Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. **Neurosurgery 55:**539–550, 2004
9. Day AL, Gaposchkin CG, Yu CJ, Rivet DJ, Dacey RG Jr: Spontaneous fusiform middle cerebral artery aneurysms: characteristics and a proposed mechanism of formation. **J Neurosurg 99:**228–240, 2003
10. De Vile CJ, Grant DB, Kendall BE, Neville BG, Stanhope R, Watkins KE, et al: Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? **J Neurosurg 85:**73–81, 1996
11. Dhellemmes P, Vinchon M: Radical resection for craniopharyngiomas in children: surgical technique and clinical results. **J Pediatr Endocrinol Metab 19 (Suppl 1):**329–335, 2006
12. Di Rocco C, Caldarelli M, Tamburrini G, Massimi L: Surgical management of craniopharyngiomas—experience with a pediatric series. **J Pediatr Endocrinol Metab 19 (Suppl 1):**355–366, 2006
13. Duff J, Meyer F, Ilstrup D, Laws ER Jr, Schleck C, Scheithauer B: Long-term outcomes for surgically resected craniopharyngiomas. **Neurosurgery 46:**291–305, 2000
14. Elliott RE, Hsieh K, Hochm T, Belitskaya-Levy I, Wisoff J, Wisoff JH: Efficacy and safety of radical resection of primary and recurrent craniopharyngiomas in 86 children. **J Neurosurg Pediatr 5:**30–48, 2010
15. Elliott RE, Moshel YA, Wisoff JH: Minimal residual calcification and recurrence after gross-total resection of craniopharyngioma in children. **J Neurosurg Pediatr 3:**276–283, 2009
16. Elliott RE, Moshel YA, Wisoff JH: Surgical treatment of ectopic recurrence of craniopharyngioma. Report of 4 cases. **J Neurosurg Pediatr 4:**105–112, 2009
17. Elliott RE, Wisoff JH: Successful surgical treatment of craniopharyngioma in very young children. **J Neurosurg Pediatr 3:**397–406, 2009
18. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M: Surgical treatment of craniopharyngiomas: experience with 168 patients. **J Neurosurg 90:**237–250, 1999
19. Fiorella D, Albuquerque FC, Deshmukh VR, McDougall CG: Usefulness of the Neuroform stent for the treatment of cerebral aneurysms: results at initial (3-6-mo) follow-up. **Neurosurgery 56:**1191–1202, 2005
20. Fiorella D, Woo HH, Albuquerque FC, Nelson PK: Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the pipeline embolization device. **Neurosurgery 62:**1115–1121, 2008
21. 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
22. Gonzales-Portillo GA, Valdivia JM: Uncommon presentation of pediatric ruptured intracranial aneurysm after radiotherapy for retinoblastoma. Case report. **Surg Neurol 65:**391–396, 2006
23. Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, et al: The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. **Int J Radiat Oncol Biol Phys 44:**255–263, 1999
24. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI: Aggressive surgical management of craniopharyngiomas in children. **J Neurosurg 76:**47–52, 1992
25. Jensen FK, Wagner A: Intracranial aneurysm following radiation therapy for medulloblastoma. A case report and review of the literature. **Acta Radiol 38:**37–42, 1997
26. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, et al: Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. **Clin Endocrinol (Oxf) 62:**397–409, 2005
27. Kobayashi T, Kida Y, Hasegawa T: Long-term results of gamma knife surgery for craniopharyngioma. **Neurosurg Focus 14(5):**e13, 2003
28. Kobayashi T, Kida Y, Mori Y, Hasegawa T: Long-term results of gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. **J Neurosurg 103 (6 Suppl):**482–488, 2005
29. Lakhanpal SK, Glasier CM, James CA, Angtuaco EJ: MR and CT diagnosis of carotid pseudoaneurysm in children following surgical resection of craniopharyngioma. **Pediatr Radiol 25:**249–251, 1995
30. Landolt AM, Zachmann M: Results of transsphenoidal extirpation of craniopharyngiomas and Rathke's cysts. **Neurosurgery 28:**410–415, 1991
31. Laws ER: Craniopharyngiomas in children and young adults. **Prog Exp Tumor Res 30:**335–340, 1987
32. Laws ER Jr: Transsphenoidal removal of craniopharyngioma. **Pediatr Neurosurg 21 (Suppl 1):**57–63, 1994
33. Laws ER Jr: Vascular complications of transsphenoidal surgery. **Pituitary 2:**163–170, 1999
34. Lee M, Kalani MY, Cheshier S, Gibbs IC, Adler JR, Chang SD: Radiation therapy and CyberKnife radiosurgery in the management of craniopharyngiomas. **Neurosurg Focus 24(5):**E4, 2008
35. Linfante I, Tucci C, Andreone V: Fusiform dilatation of the internal carotid artery after craniopharyngioma resection. **Pediatr Neurol 39:**139–140, 2008
36. Liu SS, Zabramski JM, Spetzler RF: Fusiform aneurysm after surgery for craniopharyngioma. **J Neurosurg 75:**670–672, 1991
37. Lylyk P, Miranda C, Ceratto R, Ferrario A, Scrivano E, Luna HR, et al: Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. **Neurosurgery 64:**632–633; quiz N636, 2009
38. Matson DD, Crigler JF Jr: Radical treatment of craniopharyngioma. **Ann Surg 152:**699–704, 1960
39. Merchant TE, Kiehna EN, Kun LE, Mulhern RK, Li C, Xiong X, et al: Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. **J Neurosurg 104 (2 Suppl):**94–102, 2006
40. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, et al: Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984-2001. **Int J Radiat Oncol Biol Phys 53:**533–542, 2002
41. Mizutani T, Kojima H: Clinicopathological features of nonatherosclerotic cerebral arterial trunk aneurysms. **Neuropathology 20:**91–97, 2000
42. Mizutani T, Miki Y, Kojima H, Suzuki H: Proposed classification of nonatherosclerotic cerebral fusiform and dissecting aneurysms. **Neurosurgery 45:**253–260, 1999
43. Nakatomi H, Segawa H, Kurata A, Shiokawa Y, Nagata K, Kamiyama H, et al: Clinicopathological study of intracranial fusiform and dolichoectatic aneurysms : insight on the mechanism of growth. **Stroke 31:**896–900, 2000
44. O'Connor MM, Mayberg MR: Effects of radiation on cerebral vasculature: a review. **Neurosurgery 46:**138–151, 2000

45. Park SH, Yim MB, Lee CY, Kim E, Son EI: Intracranial fusiform aneurysms: it's pathogenesis, clinical characteristics and managements. **J Korean Neurosurg Soc 44:**116–123, 2008
46. Prabhu VC, Brown HG: The pathogenesis of craniopharyngiomas. **Childs Nerv Syst 21:**622–627, 2005
47. Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, et al: Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. **J Neurosurg 106 (1 Suppl):**3–12, 2007
48. Sands SA, Milner JS, Goldberg J, Mukhi V, Moliterno JA, Maxfield C, et al: Quality of life and behavioral follow-up study of pediatric survivors of craniopharyngioma. **J Neurosurg 103 (4 Suppl):**302–311, 2005
49. Sciubba DM, Gallia GL, Recinos P, Garonzik IM, Clatterbuck RE: Intracranial aneurysm following radiation therapy during childhood for a brain tumor. Case report and review of the literature. **J Neurosurg 105 (2 Suppl):**134–139, 2006
50. Sutton LN: Vascular complications of surgery for craniopharyngioma and hypothalamic glioma. **Pediatr Neurosurg 21 (Suppl 1):**124–128, 1994
51. Sutton LN, Gusnard D, Bruce DA, Fried A, Packer RJ, Zimmerman RA: Fusiform dilatations of the carotid artery following radical surgery of childhood craniopharyngiomas. **J Neurosurg 74:**695–700, 1991
52. Tirakotai W, Sure U, Benes L, Aboul-Enein H, Schulte DM, Riegel T, et al: Successful management of a symptomatic fusiform dilatation of the internal carotid artery following surgery of childhood craniopharyngioma. **Childs Nerv Syst 18:**717–721, 2002
53. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. **J Neurosurg 97:**3–11, 2002
54. Wang KC, Hong SH, Kim SK, Cho BK: Origin of craniopharyngiomas: implication on the growth pattern. **Childs Nerv Syst 21:**628–634, 2005
55. 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
56. Wisoff JH, Donahue BR: Craniopharyngiomas, in Albright AL, Pollack IF, Adelson PD (eds): **Principles and Practice of Pediatric Neurosurgery, ed 2.** Stuttgart: Thieme Medical Publishers, 2008, pp 560–579
57. Wisoff JH: Surgical management of recurrent craniopharyngiomas. **Pediatr Neurosurg 21 (Suppl 1):**108–113, 1994
58. Yaşargil M: Craniopharyngiomas, in **Microneurosurgery, vol. IVB.** New York: Thieme Medical Publishers, 1995, pp 205–216
59. 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
60. Zuccaro G: Radical resection of craniopharyngioma. **Childs Nerv Syst 21:**679–690, 2005

Manuscript submitted December 6, 2009.
Accepted January 5, 2010.

Address correspondence to: Jeffrey H. Wisoff, M.D., Division of Pediatric Neurosurgery, NYU Langone Medical Center, 317 East 34th Street, Suite 1002, New York, New York 10016. email: jhw1@nyumc.org.