EDITORIAL

Endoscopic endonasal surgery for pediatric craniopharyngiomas**Davis G. Taylor, MD, and John A. Jane Jr., MD**

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WE congratulate Yamada et al. for their work, which chronicles a single center's experience over 25 years and includes 65 patients, a large case series for pediatric craniopharyngiomas.¹⁶ They report excellent results through the transsphenoidal approach, with a high rate of gross-total resection (GTR) and low incidence of postoperative obesity. Previous meta-analyses and other series have supported the notion that transsphenoidal resection (TSR) provides advantages over a transcranial approach with respect to GTR and recurrence.⁴ However, tumors amenable to TSR have traditionally been more likely to be smaller, be confined to the midline, and have a large sellar component, leading to selection bias that should be considered in the evaluation of these results, and some expert series have demonstrated comparable results using a transcranial approach.³

The authors note that they attempted GTR in all circumstances. In the setting of initial surgeries, there is a strong argument for this aggressive approach, as initial surgery seems to offer a superior opportunity for surgical cure of craniopharyngioma and may spare the child the negative risks associated with postoperative radiation.^{4,6,8,9,17} However, GTR is not without risk and often comes at the likely cost of diminished or complete absence of pituitary function, which may result in long-term medical dependence and worsened quality of life.¹⁵

In addition to resulting in pituitary deficits, resection of tumors involving the hypothalamus may place patients at risk for hypothalamic obesity when complete resection is attempted. Postoperative obesity in craniopharyngioma patients is quite morbid, also resulting in reduced quality of life as well as sedentary lifestyles, increased risk of cardiovascular complications, and cognitive deficits.^{2,9–12} In our own experience with 22 pediatric patients with craniopharyngioma treated through TSR, we observed postoperative obesity after 3 of 11 initial surgeries (an incidence of

27%),⁶ but the authors report an incidence of 9%, suggesting that low rates can be achieved despite hypothalamic involvement. Because of the risk of postoperative obesity in our own experience, our surgical strategy in the pediatric population has largely been determined by tumor origin in relation to the diaphragma sellae. Tumors that originate below the diaphragma sellae, which then expand the sella and grow intracranially, are generally considered amenable to GTR. However, if pituitary function is largely intact and the tumor is primarily cystic, a less aggressive resection is often pursued, with the patients being subsequently treated by radiotherapy. Those tumors that take origin above the diaphragma sellae and are wholly suprasellar without sellar involvement are most often treated with subtotal resection with planned radiotherapy.

Radiosurgery can result in excellent tumor control (72.7% at 5 years for solid tumors), but it increases the risk of later development of panhypopituitarism.⁷ Furthermore, and particular to the pediatric population, radiation therapy is associated with a decline in cognitive function in children younger than 8 years of age.⁸ It should be noted, however, that the decline may be further exacerbated by aggressive resection, particularly in association with hypothalamic involvement, leading some surgeons to advocate for observation following subtotal resection rather than prophylactic radiotherapy.^{5,9,15}

In support of this observational approach, recent advances in molecular medicine may prove to further limit the role of total resection due to the identification of unique mutations in *BRAF* and *CTNNB1* among papillary and adamantinomatous craniopharyngiomas, respectively, and the development of targeted therapy.¹ To this point, several reports suggest rapid and dramatic response to targeted therapy with *BRAF* inhibitors, which may provide surgeons with alternative modes of treatment for patients with these tumors.^{13,14}

ACCOMPANYING ARTICLE See pp 549–562. DOI: 10.3171/2017.10.PEDS17254.

INCLUDE WHEN CITING Published online March 30, 2018; DOI: 10.3171/2017.11.PEDS17568.

The study by Yamada et al. demonstrates excellent results with a very low incidence of postoperative obesity of 9%—considerably better than other reported results (average of 27%), including our own. These results are particularly remarkable for the relative control for possible selection bias as 93% of all patients with craniopharyngioma were treated with TSR within a 10-year period. The authors note particular attention to the dissection plane of reactive gliosis adjacent to the hypothalamus, and perhaps their experience with this technique has aided in achieving these excellent results and further supports the importance of surgeon experience to functional outcomes following surgery for craniopharyngioma.⁹

<https://thejns.org/doi/abs/10.3171/2017.11.PEDS17568>

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Disclosures

The authors report no conflict of interest.

Response

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We are very grateful to Drs. Davis G. Taylor and John A. Jane Jr. for their thoughtful and insightful comments on our recent study of surgical outcomes of transsphenoidal surgery in pediatric patients with craniopharyngiomas. Optimal treatment of primary and recurrent craniopharyngiomas remains controversial. The debate centers around treatment strategy—radical tumor resection versus limited resection plus adjuvant radiotherapy.

Drs. Taylor and Jane pointed out the potential for selection bias in comparing results of transsphenoidal surgery and transcranial surgery, because the targets of TSR have traditionally been more likely to be smaller, confined to the midline, and have a large sellar component. However, the primary aim of this study was not to compare the results of TSR and transcranial resection (TCR). In the last 10 years, 93% of all pediatric patients who underwent surgery at our institute for craniopharyngioma were treated with a transsphenoidal approach, regardless of tumor type or size (46% of the tumors in the study Drs. Taylor and Jane commented on were supradiaphragmatic). Moreover, all operations in our study were performed by a single experienced surgeon who attempted complete resection in all patients using the transsphenoidal approach (an extended one, in most cases), constituting one consistent aim across the series.

Our series provided further support for the efficacy of radical resection of pediatric craniopharyngioma, at both primary and repeat surgeries. Among 65 children with craniopharyngioma, GTR was achieved in 98% of patients at primary surgery and in 75% of patients at repeat surgery. We are aware that GTR does not preclude recurrence, which occurred in 7% of the patients in the pri-

mary surgery group and 27% of the patients in the repeat surgery who had undergone GTR. However, these data emphasize the importance of pursuing GTR at primary surgery, whenever feasible.

After reports emerged in the literature suggesting that GTR and limited resection plus radiotherapy yielded similar rates of disease control and overall survival,^{4,6} the focus in comparing treatment modalities shifted more toward functional outcome and quality-of-life (QoL) metrics.⁶ Müller advocated hypothalamus-sparing strategies followed by salvage radiotherapy for craniopharyngioma with hypothalamic involvement to prevent severe sequelae, primarily hypothalamic obesity.⁶ Similarly, Drs. Taylor and Jane state that tumors that originate above the diaphragma sellae and are wholly suprasellar without sellar involvement are most often treated with subtotal resection and planned radiotherapy. In keeping with the recommendation by Müller, we attempted complete resection (GTR) in all patients except in those in whom we could not remove the tumor without injury to the hypothalamus. However, such situations in this series were quite rare, and most tumors could be totally removed, especially in primary surgeries. Although detailed pre- and postoperative neuropsychological or QoL testing was not performed in our series, postoperative memory disturbance was noted in only 2 of 45 patients undergoing primary surgery (and both were able to graduate from university). Müller et al. also reported morbid obesity (BMI > +3 SDs) in 44% of children (n = 185) at long-term postoperative follow-up.⁷ Puget et al. used a 3-tiered MRI-based scale that graded preoperative hypothalamic involvement and reported correlations between increased hypothalamic disturbance with increasing grade.⁹ In our series, however, at the time of final follow-up, obesity was newly diagnosed in 9% and 21% of the primary and repeat surgery patients, respectively. In contrast, preoperative obesity was significantly higher in repeat (30%) than in primary (4%) surgery patients (p < 0.01). Therefore, prior hypothalamic damage was a frequent complication in repeat surgery patients, which may have been due to hypothalamic disturbance resulting from surgeries (mainly transcranial surgery) and/or radiotherapy performed at other institutes. Moreover, in this series most tumors, even those judged as having hypothalamic involvement based on preoperative MRI (suspected in 38% of patients in this series), could be totally removed without hypothalamic impairment in almost all of the primary surgery patients. In the context of primary tumors, radical resection is facilitated by the presence of intact arachnoid membranes separating the tumor from the surrounding vital structures. There is also a gliotic pseudocapsule that separates craniopharyngiomas from the floor of the third ventricle and hypothalamus. We believe such a meticulous microsurgical maneuver to the hypothalamus is more easily performed under direct vision via the extended transsphenoidal approach without dissection or retraction of surrounding structures.¹ However, this maneuver is more difficult in repeat surgery patients due to severe tumor adhesion resulting from prior treatments. Thus, in the interest of preventing the hypothalamic or optic damage that can occur with forcible dissection, the number of attempted GTR procedures was more

conservative in repeat surgery patients.³ Therefore, even in the absence of formal postoperative neuropsychological testing, there was little to suggest reduced QoL due to the GTR procedure in our observations of cognitive and endocrine outcomes.

Drs. Taylor and Jane also expressed the concern that GTR often comes at the cost of diminished or complete absence of pituitary function, which may result in long-term medical morbidity and reduced QoL. Regarding pituitary endocrine function, it is unnecessary to preserve the pituitary stalk in patients with preoperative panhypopituitarism and diabetes insipidus, given that pituitary dysfunction generally does not recover after surgery. In contrast, every effort should be made to preserve pituitary function when it is normal or only partially disturbed preoperatively. We believe TSR is superior to TCR in terms of pituitary function preservation, because identification of the pituitary stalk and assessment of its proximity to the tumor can be performed earlier and more easily during transsphenoidal surgery. Indeed, radical resection can cause high rates of iatrogenic pituitary dysfunction,¹ but irradiation can also lead to hypothalamic-pituitary axis dysfunction. Moreover, these effects are especially pronounced in young children and can be delayed and unpredictable.⁵ These effects must be considered when comparing risk-benefit profiles of GTR, especially given that modern endocrine support can adequately supplement pituitary dysfunction and GTR offers the attractive opportunity for surgical cure of craniopharyngioma without the negative risks associated with postoperative radiation. In this series, pituitary dysfunction was well controlled and did not seem to have an adverse impact on QoL based on our long-term observations. This may be due to the availability of exceptional medical resources and close follow-up by experienced multidisciplinary teams, including a team of pediatric endocrinologists at Toranomon Hospital. Nevertheless, the conclusions reached in this report may not be generalizable to all practices and patients. The success and safety of radical resection depend on surgical expertise and postoperative endocrinological support to manage the nearly universal postoperative endocrine deficiencies.

Future advances in radiotherapy technology will, undoubtedly, improve the rate of disease control and limit the toxicity to the surrounding brain.⁸ In addition, we eagerly anticipate a new era in which targeted therapy, like BRAF inhibitor treatment, will provide surgeons with less-invasive alternatives for these complicated and cumbersome tumors.²

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