Comparative effectiveness of treatment options for pediatric craniopharyngiomas

Clinical article

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Object. No clear treatment guidelines for pediatric craniopharyngiomas exist. The authors developed a decision analytical model to evaluate outcomes of 4 surgical approaches for craniopharyngiomas in children, including attempted gross-total resection (GTR), planned subtotal removal plus radiotherapy, biopsy plus radiotherapy, and endoscopic resections of all kinds.

Methods. Pooled data, including the authors’ own experience, were used to create evidence tables, from which incidence, relative risks, and summary outcomes in quality-adjusted life years (QALYs) were calculated for the 4 management strategies.

Results. Quality-adjusted life years at the 5-year follow-up were $2.3 \pm 0.1$ for attempted GTR, $2.9 \pm 0.2$ for planned subtotal removal plus radiotherapy, $3.9 \pm 0.2$ for biopsy plus radiotherapy, and $3.7 \pm 0.2$ for endoscopic resection ($F = 17,150, p < 0.001$). Similarly, QALYs at 10-year follow-up were $4.5 \pm 0.2$ for attempted GTR, $5.7 \pm 0.5$ for planned subtotal removal plus radiotherapy, and $7.8 \pm 0.5$ for biopsy plus radiotherapy ($F = 6,173, p < 0.001$). On post hoc pairwise comparisons, the differences between all pairs compared were also highly significant ($p < 0.001$). Since follow-up data at 10 years are lacking for endoscopic cases, this category was excluded from 10-year comparisons.

Conclusions. Biopsy with subsequent radiotherapy is the preferred approach with respect to improved overall quality of life. While endoscopic approaches also show promise in preserving quality of life at five-year follow-up, there are not sufficient data to draw conclusions about this comparison at 10 years.

Abbreviations used in this paper: BMISD = body mass index standard deviation; GTR = gross-total resection; QALY = quality-adjusted life year; QOL = quality of life; STR = subtotal resection.

Craniofacial structures, including the pituitary gland, optic chiasm and nerves, third ventricle, and hypothalamic nuclei, as well as multiple major intracranial vessels traversing this region. As a result, achieving gross-total resection (GTR) of these lesions without significant morbidity to the patient remains inherently challenging. Moreover, these tumors frequently recur, requiring additional treatment.

A variety of treatment paradigms exist, but no Class I data exist to guide management of pediatric craniopharyngiomas. Some advocate that, since lower recurrence rates are achieved with GTR, it is the preferred treatment modality. Indeed, adjuvant therapy, such as radiation therapy, is not without associated morbidity. However, others propose that durable tumor control is achieved with...
subtotal resection (STR) with conformal beam radiotherapy and confers limited risk of hypothalamic injury or panhypopituitarism in comparison with GTR. Still others advocate a minimally invasive approach via expanded endoscopic endonasal surgery.

A recent systematic review of the treatment of pediatric craniopharyngiomas by Clark et al. concluded that planned STR followed by adjuvant fractionated radiotherapy results in reduced endocrine dysfunction when compared with GTR.\(^1\)\(^7\) In their analysis, postoperative endocrine function was the main morbidity outcome that varied with respect to extent of resection and adjuvant therapy in pediatric craniopharyngiomas. Their review, however, lacks an analysis of quality of life (QOL). While a prospective, randomized trial evaluating the prognosis and QOL of pediatric patients with craniopharyngiomas who are undergoing current surgical treatment options is lacking, we created a decision analytical model to evaluate outcomes of different surgical approaches to these lesions in children.

**Methods**

We developed a decision analytical model to evaluate outcomes of 4 surgical approaches to craniopharyngiomas in children. These included aggressive tumor removal (attempt at GTR), planned STR plus radiotherapy, biopsy plus radiotherapy, and endoscopic resections of all kinds. The model projects quality-adjusted life years (QALYs) of different follow-up periods. We derived data for the model using a critical review of published reports.

The possible pathways and outcomes after surgery for craniopharyngioma are shown in Fig. 1. A patient may have an uneventful surgical recovery, suffer perioperative (within 30 days of surgery) complications, or even die in the perioperative period. The nature and frequency of these complications vary with the type of surgical procedure. During the follow-up period, the patient may have an uneventful course, suffer delayed complications due to tumor growth or radiation damage, or die of tumor-related causes. Each case also runs the risk of tumor recurrence (defined as the need for delayed surgical or radiation therapy).

**Data Collection**

We performed a MEDLINE search of articles published between 1990 and July 2011, using the following key words as medical subject headings or in the titles: “craniopharyngioma (craniopharyngiomas),” combined with “therapy (treatment), surgery (surgical),” or “radiotherapy (radiation).” We supplemented this search by repeating it in Embase and the Cochrane database, as well as using the “Related Citations” feature of PubMed and doing a manual review of the bibliographies of selected articles. The initial search yielded 801 abstracts. We also added 46 previously unreported cases treated at Children’s Hospital of Philadelphia between 1990 and 2007.

In general, our rules for study inclusion followed the practice of Elliott and associates.\(^2\) Like them, we excluded reports containing fewer than 10 operated cases, those not written in English, and those published before 1990. We also excluded reports that duplicated previously published data and review articles and reports that dealt only with cyst aspiration, intracavitary treatment, and shunt insertion. However, we specifically added studies that reported results of planned STRs and biopsies, followed by radiotherapy. We also included articles describing outcomes in a single domain, such as vision or endocrine function. If a report included both children and adults and did not separate the outcomes, we included the data only if at least 60% of the patients were 21 years of age or younger. Articles limited to microscopic transphenoidal removal were also omitted.

Our search yielded 801 articles. We excluded 166 publications for concentrating on adults, 334 that lacked original data, 102 that reported too few operated cases, 33 for reporting on radiation therapy only, 17 that dealt with intracavitary treatment, 20 that dealt with recurrent tumors, and 76 in which outcomes of different surgical approaches or different age groups could not be separated. We were left with 58 case series, 8 of which reported multiple surgical approaches.\(^1\)\(^,\)\(^2\)\(^,\)\(^5\)\(^,\)\(^1\)\(^1\)\(^,\)\(^2\)\(^1\)\(^,\)\(^2\)\(^1\)\(^2\)\(^,\)\(^3\)\(^1\)\(^,\)\(^3\)\(^2\)\(^,\)\(^4\)\(^4\)\(^,\)\(^4\)\(^5\)\(^,\)\(^4\)\(^6\)\(^,\)\(^4\)\(^7\)\(^,\)\(^4\)\(^8\)\(^,\)\(^4\)\(^9\)\(^,\)\(^5\)\(^0\)\(^,\)\(^5\)\(^1\)\(^,\)\(^5\)\(^2\)\(^,\)\(^5\)\(^3\)\(^,\)\(^5\)\(^4\)\(^,\)\(^5\)\(^5\)\(^,\)\(^5\)\(^6\)\(^,\)\(^5\)\(^7\)\(^,\)\(^5\)\(^8\)\(^,\)\(^5\)\(^9\)\(^,\)\(^6\)\(^0\)\(^,\)\(^6\)\(^1\)\(^,\)\(^6\)\(^2\)\(^,\)\(^6\)\(^3\)\(^,\)\(^6\)\(^4\)\(^,\)\(^6\)\(^5\)\(^,\)\(^6\)\(^6\)\(^,\)\(^6\)\(^7\)\(^,\)\(^6\)\(^8\)\(^,\)\(^6\)\(^9\)\(^,\)\(^7\)\(^0\)\(^,\)\(^7\)\(^1\)\(^,\)\(^7\)\(^2\)\(^,\)\(^7\)\(^3\)\(^,\)\(^7\)\(^4\)\(^,\)\(^7\)\(^5\)\(^,\)\(^7\)\(^6\)\(^,\)\(^7\)\(^7\)\(^,\)\(^7\)\(^8\)\(^,\)\(^7\)\(^9\)\(^,\)\(^8\)\(^0\)\(^,\)\(^8\)\(^1\)\(^,\)\(^8\)\(^2\)\(^,\)\(^8\)\(^3\)\(^,\)\(^8\)\(^4\)\(^,\)\(^8\)\(^5\)\(^,\)\(^8\)\(^6\)\(^,\)\(^8\)\(^7\)\(^,\)\(^8\)\(^8\)\(^,\)\(^8\)\(^9\)\(^,\)\(^9\)\(^0\)\(^,\)\(^9\)\(^1\)\(^,\)\(^9\)\(^2\)\(^,\)\(^9\)\(^3\)\(^,\)\(^9\)\(^4\)\(^,\)\(^9\)\(^5\)\(^,\)\(^9\)\(^6\)\(^,\)\(^9\)\(^7\)\(^,\)\(^9\)\(^8\)\(^,\)\(^9\)\(^9\)\(^,\)\(^10\)\(^0\)\(^,\)\(^10\)\(^1\) No studies were controlled trials of prospectively collected. Thus all represent Level 4 evidence.\(^14\)

**Data Management**

In calculating outcomes, we omitted transient postoperative complications, such as transient diabetes insipidus or hypoglycemia. We also omitted some long-term complications, such as short stature and shunt complications. It was impossible to calculate the number of cases at risk for the former complications and to confirm a relationship between surgery and the latter. To avoid attributing all endocrine abnormalities to surgery, perioperative anterior and posterior pituitary complications were calculated as the difference between pre- and postoperative incidences. Similarly, the incidence of late endocrine disturbances was calculated as the number of late occurrences divided by the number of cases at risk (cases surviving the perioperative period with intact function). This approach was also used for other complications.

Pooled data from more than 2300 cases in these reports were used to create evidence tables, from which we calculated incidence, relative risks, and summary outcomes for the management strategies. These probabilities report the likelihood that a hypothetical patient travels along a particular pathway pictured in Fig. 1. The reported point estimates of pooled data represent variance-weighted means and were tested to exclude heterogeneity.\(^2\)\(^0\) A supplementary literature search was performed as above to provide a measure for relative health-related QOL associated with each complication. Units used were expressed in utility, a measure of an individual’s preference for a given health state in the face of uncertainty.\(^1\)\(^0\)\(^2\) To factor in the effect of quantity of life, we reported outcomes at various follow-up durations as QALYs, a measure that combines both aspects: \(^2\)\(^3\)\(^9\) perfect health (QOL = 1) × 1 year of life = 1 QALY. We examined outcomes at the 5-year follow-up and, where data were available, 10-year follow-up.

To calculate their effect on QALYs, we assumed that
all late complications occurred 2.5 years after the original surgery and persisted for the duration of follow-up. Cognitive and psychosocial complications were assumed to be delayed complications, although it is rarely clear whether they result from surgery, radiation, or disease progression. Quality of life associated with treatment for recurrence was calculated as 75% of that calculated for patients without recurrence.

Analysis

A detailed methodology of our analysis can be found in the Appendix. Briefly, we evaluated the optimal operative strategy for a child with a craniopharyngioma that was not operated on or irradiated previously. Meta-analysis was used to calculate pooled values for probabilities and QOL. The tree illustrated in Fig. 1 was populated by using the values for the probabilities of various outcomes and the QALYs associated with each outcome. The sum of the probabilities of each branch multiplied by the QALYs associated with that branch (roll-back analysis) yields the expected outcome of a particular operative approach. The approach associated with the most QALYs is considered the superior one. The average impact of complications on QOL was calculated using a series of subtrees. Each subtree was specific for perioperative or chronic complications and different for each treatment strategy. We performed sensitivity analysis using Monte Carlo simulation, generating the expected value and variance of 100 trials, each of 1000 subjects. The 2D Monte Carlo simulation varied every parameter for every subject and every trial, using beta distributions. Statistical comparisons used ANOVA, with the Bonferroni correction for multiple comparisons. Meta-analytical pooling and statistical analyses were done using Stata (version 12, StataCorp LP). Analyses of the model used TreeAge Pro 2011 (Tree Age Software, Inc.).

Results

Table 1 reports the pooled incidences of perioperative and delayed complications associated with each of the 4 surgical strategies. The number at risk represents the total number of cases in which the presence (or absence) of a specific complication was noted. Table 2 lists the utilities of these complications and the source of each value. Recurrence rates after each surgical strategy were estimated by meta-regression and are illustrated in Fig. 2.

Using these values in a Monte Carlo simulation of a series of “virtual” randomized clinical trials yielded the results shown in Table 3 for 5-year and (where available) 10-year follow-up. At both follow-up times, biopsy with radiotherapy yielded the best results, followed by endoscopic excision and subtotal and total microsurgi-
TABLE 1: Complication rates of treatment*

<table>
<thead>
<tr>
<th>Treatment/Complication</th>
<th>GTR</th>
<th>STR</th>
<th>Biopsy</th>
<th>Endoscopic Excision</th>
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<tr>
<td></td>
<td>No. at Risk</td>
<td>Mean Incidence</td>
<td>SD</td>
<td>No. at Risk</td>
</tr>
<tr>
<td>periop complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>mortality</td>
<td>1775</td>
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<td>0.0050</td>
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<td>0.1026</td>
<td>0.0079</td>
<td>202</td>
</tr>
<tr>
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<td>0.1722</td>
<td>0.0098</td>
<td>202</td>
</tr>
<tr>
<td>DI</td>
<td>974</td>
<td>0.7038</td>
<td>0.0123</td>
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<td>0.0101</td>
<td>109</td>
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<tr>
<td>PVS</td>
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<td>0.0222</td>
<td>0.0045</td>
<td>220</td>
</tr>
<tr>
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<td>0.0086</td>
<td>80</td>
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<tr>
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<td>0.0021</td>
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<td>0</td>
<td>80</td>
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<td>0.0102</td>
<td>0.0031</td>
<td>80</td>
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<tr>
<td>facial palsy</td>
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<td>0.0009</td>
<td>80</td>
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<tr>
<td>late complications</td>
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<td>death†</td>
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<td>241</td>
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<td>0.00004</td>
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<td>0.0023</td>
<td>135</td>
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<td>0.1989</td>
<td>0.0111</td>
<td>120</td>
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<tr>
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<td>120</td>
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<td>0</td>
<td>0</td>
<td>120</td>
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<td>0.0645</td>
<td>0.0068</td>
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<tr>
<td>severe hypothalamic damage</td>
<td>1302</td>
<td>0.0092</td>
<td>0.0026</td>
<td>120</td>
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</table>

* ant = anterior; decr acuity = decreased visual acuity without blindness; DI = diabetes insipidus; PVS = persistent vegetative state due to hypothalamic or brainstem damage.
† Death due to effects of the tumor or its treatment.
At 5 years, patients treated with biopsy plus radiotherapy had overall significantly more QALYs (3.9 ± 0.2) than those treated with either open attempted GTR (2.3 ± 0.1), planned STR with radiotherapy (2.9 ± 0.2), or those who underwent endoscopic treatment (3.7 ± 0.2). These differences are statistically significant (F = 17,150, p < 0.001). The superiority of QALYs after biopsy plus radiotherapy was also demonstrated at 10 years (7.8 ± 0.5) compared with open attempted GTR (4.5 ± 0.2) or planned STR with radiotherapy (5.7 ± 0.5). These differences were highly significant (F = 6173, p < 0.001). On post hoc pairwise comparisons, the differences between all pairs compared were also highly significant (p < 0.001). Data for endoscopic resection were not available at 10 years and could not be compared with the other surgical treatment strategies at that time point.

![Fig. 2. Estimated tumor recurrence rate after each surgical strategy. In each figure, the x axis marks the length of follow-up in months; the y axis marks the recurrence rate. The fitted mean rate is marked by the line, and the gray area marks the 95% confidence intervals. The arrowheads mark the recurrence rates at the 5- and 10-year follow-up. A: Attempt at GTR. B: Planned subtotal removal. C: Biopsy. D: Endoscopic removal.](image-url)

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Complication</th>
<th>Mean Utility</th>
<th>SD</th>
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<td>0.7500</td>
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<td>0.1200</td>
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<td>Lau et al., 2008</td>
<td>DI</td>
<td>0.8710</td>
<td>0.1150</td>
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<td>0.8220</td>
<td>0.1370</td>
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<td>PVS</td>
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<td>0.1600</td>
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<td>0</td>
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<td>0.5640</td>
<td>0.1770</td>
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</table>
Decision analysis for pediatric craniopharyngioma

TABLE 3: Quality-adjusted life years after surgery*

<table>
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<tr>
<th>Treatment/Follow-Up</th>
<th>Total Removal</th>
<th>Subtotal</th>
<th>Biopsy, RT</th>
<th>Endoscopic Removal</th>
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<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>5-yr follow-up</td>
<td>2.3</td>
<td>0.1</td>
<td>2.9</td>
<td>0.2</td>
</tr>
<tr>
<td>10-yr follow-up</td>
<td>4.5</td>
<td>0.2</td>
<td>5.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* ND = no data; RT = radiotherapy.

Discussion

Advancements in supportive care, hormone replacement, and radiation treatment have resulted in improved survival for children with craniopharyngiomas. As a result, outcome assessments focusing on QOL, rather than mortality, become critical, especially in the pediatric population. This study is the first quantitative and comprehensive decision analysis for the treatment of pediatric craniopharyngiomas. Our decision analytical model evaluates QALYs of 4 surgical approaches to craniopharyngiomas in children including aggressive tumor removal (attempt at GTR), planned STR plus radiotherapy, biopsy plus radiotherapy, and endoscopic resections of all kinds. We identify highly significant differences between treatments, both on 5-year follow-up (F = 17.150, p < 0.001) and 10-year follow-up (F = 6.173, p < 0.001) and determine that patients treated with biopsy plus radiotherapy have overall significantly more QALYs, both at 5- and 10-year follow-up (3.9 ± 0.2 and 7.8 ± 0.5, respectively).

Historically, GTR of this pathologically benign tumor prevailed as the optimal treatment strategy for this disease.18,31,71,103 Furthermore, significant advances in image-guided surgical techniques and conformation radiation therapy have emerged, making aggressive resection coupled with radiation treatment an attractive management approach. However, despite this technological progress, the anatomical proximity of craniopharyngiomas to the optic chiasm, hypothalamus, and pituitary gland makes gross-total, and even subtotal, resection inherently challenging. Operative mortality, and postoperative morbidities, largely due to hypothalamic failure, and recurrences are not uncommonly observed after both radical and limited surgery plus radiotherapy. Postoperative morbidities include polyendocrinopathy and neurological dysfunction, including shunt dependence, seizures, and headaches.13,21,101,106 Endocrine disorders, including panhypopituitarism, associated with aggressive tumor resection was considered “incurable” and “acceptable.”76 Irreversible central diabetes insipidus and growth hormone deficiency after attempted GTR results in lifelong replacement therapy. Obesity, fatigue, and sleep disorders are the most notable manifestations of hypothalamic dysfunction, and treatment is extremely difficult.18,69 Psychological and educational limitations are also recognized in a significant number of individuals. Our study establishes the pooled incidences of these perioperative complications, including mortality, blindness, visual changes, hypothalamic dysfunction, motor deficits, and cerebrospinal fistula and infection, as well as delayed complications, including epilepsy, cognitive and psychosocial dysfunction, associated with each of the 4 surgical strategies (Table 1).

Due to these morbidities, the QOL of long-term survivors is substantially reduced in approximately 50% of patients.66 We identify a range of utilities for the various complications associated with craniopharyngioma surgery. One of the most notable morbidities is severe hypothalamic obesity, with a mean utility of 0.67 ± 0.1. With its associated physiological and psychological sequelae, this complication has a major negative impact on the QOL of long-term craniopharyngioma survivors. Müller et al. prospectively recruited 120 patients between 2001 and 2007 and evaluated the degree of obesity (body mass index standard deviation [BMISD]) and QOL at diagnosis and 36 months after diagnosis.67 They found that surgical lesions of both anterior and posterior hypothalamic areas were associated with a greater increase in BMI compared with patients without or only anterior lesions (+1.8 BMISD, p = 0.033; +2.1 BMISD, p = 0.011). They also found an association between patients with posterior hypothalamic lesions and negative impact on QOL, suggesting that radical surgical approaches leading to posterior hypothalamic lesions may contribute to exacerbating hypothalamic obesity and impairing QOL.

In an attempt to identify poor prognostic factors, Puget et al. recently retrospectively reviewed data from a cohort of 66 children who underwent craniopharyngioma resection between 1984 and 2001.77 They identified 3 factors that significantly predicted poor outcome, including preoperative MRI grade, clinically assessed hypothalamic function, and the surgeon’s operative experience (p = 0.007, p = 0.047, and p = 0.035, respectively). Preoperative hypothalamic grading was then used in a prospective cohort of 22 children treated between 2002 and 2004 to stratify patients according to whether they underwent attempted GTR (20%), complete resection avoiding the hypothalamus (40%), or STR (40%). The authors found that with preoperative stratification, no new cases of postoperative hyperphagia, morbid obesity, or behavioral dysfunction developed. They concluded that stratifying treatment preoperatively minimizes postoperative morbidity and improved QOL. As hypothalamic injury was considered the main source of morbidity after craniopharyngioma surgery, many groups similarly developed treatment strategies to avoid hypothalamic injury, most substantially by applying limited surgery, and instituting multimodal therapy.54,65,71,81,89 Our data suggest that to provide the most significant QOL in children with craniopharyngioma, the trend toward limited resection should be further defined to focus on simply surgical biopsy, coupled with radiation treatment.

These data are supported by recent advancements in radiation therapy, which offers at least 80% disease
control at 10 years and a favorable functional outcome in 42%–86% of cases.\textsuperscript{49} Along the same lines, preliminary experiences with proton-beam therapy applied to craniopharyngioma are promising, offering a less morbid radiological option for tumors localized in the vicinity of the optic nerve or chiasm, pituitary gland, or hypothalamus.\textsuperscript{5,32,64} Reported long-term consequences after limited craniopharyngioma surgery combined with irradiation include optic neuropathy and brainstem necrosis, but this is not as common in modern radiation therapy series as in more dated publications. There have also been reports of malignant transformation of craniopharyngioma, although this too is a rare event.\textsuperscript{7}

While craniopharyngiomas arising in childhood usually extend to the suprasellar area, transcranial approaches (pterional, subfrontal, and presigmoid) have traditionally been used. However, transsphenoidal neuroendoscopic techniques are becoming increasingly popular for accessing both intrasellar and suprasellar lesions.\textsuperscript{3,35} Our analysis demonstrates that the 5-year QALYs for biopsy plus radiotherapy (3.9 ± 0.2) and endoscopic resections of all kinds (3.7 ± 0.2) are comparable, despite a statistically significant difference. These data may reflect the limited morbidity offered by the endoscopic approach due to allowing for a more direct approach to the lesion, with less manipulation of surrounding neurovascular structures to access the tumor, early decompression of the optic tract, as well as improved reconstructive techniques limiting the incidence of postoperative CSF leaks.\textsuperscript{3,10,51,59,62} We cannot exclude that the positive QALYs identified may be subject to the selection bias of limiting this approach to those tumors that are primarily intrasellar and of small size. As optics, video equipment, and endoscopic surgical instrumentation all continue to improve, one can predict that transsphenoidal endoscopic approaches to craniopharyngiomas may facilitate a high rate of endocrine function preservation and visual improvement, while concurrently achieving comparable resections\textsuperscript{36} and, consequently, improving QALYs, even compared with biopsy and radiotherapy. While this is the case in our series at the 5-year follow-up, we do not have sufficient data to make firm conclusions about this comparison at 10 years due to limited data. As such, members of our group currently pursue transsphenoidal endoscopic approaches to craniopharyngioma resection with favorable results.\textsuperscript{3}

This study is not intended as a substitute for a well-planned, adequately powered, prospective randomized controlled trial; it merely provides an approximate estimate of the results of a trial if it were to occur. Multiple barriers to designing a randomized clinical trial to prospectively study the outcomes of different surgical approaches for the treatment of craniopharyngiomas exist, including lack of clinical equipoise. Our comparison applies only to craniopharyngiomas for which there is some clinical equipoise. Many tumor variants (size, composition, extension, and associated symptoms) exist, in which a particular approach has advantages over the others. We simply cannot address all of these variants. Consequently, our study relies on the accumulation and analysis of less rigorous trial designs to answer the question of which treatment strategy may be most effective. As such, our meta-analysis is inherently limited by aggregating the retrospective experience of multiple centers with different surgical experiences and reporting of complications. In addition, in our model, we made several simplifying assumptions, all of which may impact our results. There are differences in the preoperative characteristics of the subjects reported, which may have influenced the choice of surgical strategy and for which our model cannot account. Some data were not uniformly reported in the studies from which our data are drawn. For example, the timing of postoperative radiation is inconsistent and unclear in clinical practice.

As an example, many patients received postoperative radiotherapy. In some cases this was planned; in others radiotherapy was begun only after evidence of growth of residual tumor. Radiotherapy rates also varied with the type of surgery. Radiotherapy delivery, timing, and dosage may have important effects on outcome. Since we lacked access to individual case records, we were forced to omit this important variable. These shortcomings may have introduced bias into the calculation of complications and recurrences. However, we believe the sacrifice of some internal validity produced by pooling data from multiple sources is somewhat compensated by the improvement in external validity introduced by pooling. We accept the conclusion of Elliott and associates that a direct comparison between different surgical techniques may not be valid.\textsuperscript{28} However, we emphasize that a comparison of this sort may be instructive, especially if it uses a single global measure of utility, which encompasses all important outcomes.

**Conclusions**

We believe that this decision analysis provides guidance as to treatment choice for managing craniopharyngiomas in children, with the outcome focus centered on QOL. These data are critical to discuss with patients and their families when determining the optimal treatment strategy for these tumors in children. Pending the results of Kranioharyngiomet 2007, a prospective, multinational trial, that is currently evaluating prognoses in patients with craniopharyngiomas, including QOL, after defined therapeutic strategies, our study provides a reasonable approach to guiding treatment strategies, as dictated by patient QOL.

**Appendix**

**Decision Analysis**

This approach is predicated on the theory that one can anticipate and calculate the relative values of different approaches to a challenge,\textsuperscript{92} in this case a medical condition. Following the choice of a strategy, the probability of each possible outcome can be calculated, as can its effect on health-related QOL. Quantifying the latter enables the calculation of expected QOL with each management strategy and hence the quantitative comparison of different strategies.

Quantification of QOL commonly uses utility theory, in which QOL is expressed in terms of a patient's preference for a given health state in the presence of uncertainty. Utility is a parametric measure that represents this preference along a scale from
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0 (death) to 1 (perfect health). Utilities for a given health state can be obtained in a number of ways, including standard gamble,102 time tradeoff or generic questionnaires, such as the EuroQol and Health Utilities Index.41 In cases in which quantity of life is as important as its quality, we need a measure that reflects this. A QALY is commonly used to quantify both quality and quantity of life.43 Perfect health (QOL = 1) × 1 year of life = 1 QALY.

Multiplying a particular outcomes probability by its utility gives a measure known as “expected utility,” an indication of its likely impact on QOL.89 If one repeats this process for every possible outcome and every treatment strategy, a process known as “rollback analysis,” one can calculate the expected utility for each strategy. The strategy with the greatest expected utility is preferable and ordinarily should be recommended.

Meta-Analysis

In the absence of a single randomized controlled trial, which directly compares all the alternative management strategies, data must be obtained from multiple sources. These data are thus subject to heterogeneity, namely different patient populations, different selection criteria for treatment, different definitions of outcome, and variations of each treatment used. This heterogeneity from sampling variability may be great enough to invalidate pooled estimates, and excessive heterogeneity is usually excluded before further analysis.89 Data are then pooled using a random-effects model (accounts for between-group variance), in which a group's contribution is weighted inversely to its within-group variance.45

Sensitivity Analysis

In a typical randomized controlled trial, the question of how robust the differences between strategies can be resolved using standard statistical techniques. However, data for decision analyses are obtained from multiple sources and pooled, thus obviating this approach. Our approach for this study was to use Monte Carlo simulation.85 In this approach, the computer samples each parameter by randomly sampling values according to their distributions, recording the result for the individual virtual “patient,” repeating this as often as needed for a virtual “trial.” Two-dimensional Monte Carlo simulations, in which multiple such trials are run, are commonly used. The trial generates mean outcome values and measures of variance, thus allowing statistical comparison.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Dr. Lee reports owning stock in VisionSense and receiving clinical or research support from the study described from Storz.

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