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Treatment-related morbidity and the management of pediatric craniopharyngioma

A systematic review

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Object. Craniopharyngiomas are benign tumors but their close anatomical relationship with critical neurological, endocrine, and vascular structures makes gross-total resection (GTR) with minimal morbidity difficult to achieve. Currently, there is controversy regarding the extent, timing, and modality of treatment for pediatric craniopharyngioma.

Methods. The authors performed a systematic review of the published literature on pediatric craniopharyngioma to determine patterns of clinical practice and the reported outcomes of standard treatment strategies. This yielded 109 studies, which contained data describing extent of resection for a total of 531 patients. Differences in outcome were examined based upon extent of resection and choice of radiation treatment.

Results. Gross-total resection was associated with increased rates of new endocrine dysfunction (OR 5.4, $p < 0.001$), panhypopituitarism (OR 7.8, $p = 0.006$), and new neurological deficits (OR 9.9, $p = 0.03$) compared with biopsy procedures. Subtotal resection (STR) was not associated with an increased rate of new neurological deficits. Gross-total was associated with increased rates of diabetes insipidus (OR 7.7, $p = 0.05$) compared with the combination of STR and radiotherapy (RT). The addition of RT to STR was associated with increased rates of panhypopituitarism (OR 9.9, $p = 0.01$) but otherwise similar rates of morbidities.

Conclusions. Although subject to the limitations of a literature review, this report suggests that GTR is associated with increased rates of endocrinopathies compared with STR + RT, and this should be considered when planning goals of surgery.

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Key Words • **pediatric surgery** • **craniopharyngioma** • **morbidity** • **radiotherapy**

Craniopharyngiomas are rare tumors arising from remnants of the Rathke pouch. The peak incidence of these tumors is between 5 and 15 years of age, although another group is encountered between 45 and 60 years. Craniopharyngiomas account for 1%–3% of all pediatric brain tumors.[16] Although classified as indolent WHO Grade I tumors, they frequently recur and can cause significant morbidity due to their location or effects of treatment. Craniopharyngiomas typically arise in the suprasellar region and can involve the pituitary stalk, the hypothalamus, and the optic pathways. Preoperative and postoperative deficits can be of endocrinological, visual, or neurological origin.[31] Recurrence is influenced by extent of resection, with improved disease control in patients who undergo GTR[100,123,124] Aggressive resection, however, can be associated with significant treatment-related morbidity.[112]

Therefore, some have suggested that STR combined with RT as an adjunctive treatment may provide equal or

Abbreviations used in this paper: GTR = gross-total resection; RT = radiotherapy; STR = subtotal resection.

superior long-term results. Merchant et al.[83] reviewed a large single-institution series of cases involving pediatric patients with craniopharyngioma and stratified a cohort of 30 patients into 2 groups: those who had aggressive resection compared with those who had a limited resection combined with radiotherapy. The outcome measures examined were tumor control; endocrine dysfunction, including diabetes insipidus; neurological dysfunction, including vision changes; IQ; and quality of life. The 2 groups demonstrated a similar rate of tumor recurrence, but the patients who had aggressive surgery had a higher rate of diabetes insipidus and lower quality of life, as defined by standardized metrics. Based on these results, the authors advocated aggressive surgery only in the hands of experienced surgeons and only for tumors with anatomical features that suggest the possibility of safe complete removal. In contrast, Fahlbusch et al.[32] analyzed a series of 168 cases involving patients (including 30 pediatric patients) treated for craniopharyngioma with the goal of aggressive curative surgery. They were able to obtain complete tumor removal in 51% of cases. They report higher rates of tumor control in patients with completely removed tumors compared with incomplete tumor removal, with low rates of perioperative morbidity and mortality, although endocrine dysfunction was not examined. Of note, there were no reported morbidities or mortalities in the pediatric group. Surgery for recurrent tumors was associated with lower rates of complete resection, shorter survival, and increased rates of complications. The authors thus recommend that the initial treatment be surgery with the goal of GTR and that STR only be considered if intraoperative findings demonstrate that aggressive surgery would be dangerous.

There is no standard approach for the treatment of craniopharyngioma in children and no Class I data exists to guide management. Treatment-related morbidity should be a key consideration in the choice of modality. Therefore, we reviewed the published literature on pediatric craniopharyngioma to determine how extent of resection and choice of adjuvant therapy affect treatment-related morbidity.[1–15,17–27,30,33–81,84,85,87–93,96–99,102–111,113–120,122,125]

Methods

Article Selection

A comprehensive systematic review of the literature was conducted by pooling data from the existing English language literature on the subject of craniopharyngioma. Articles were identified via a PubMed search using the key words "craniopharyngioma" and "pediatric," in combination. After reviewing these articles, a review of all referenced sources was also performed. The initial search yielded 1451 publications. All references that contained disaggregated data specifically describing patients who had undergone surgery (biopsy or resection) of histologically confirmed craniopharyngioma were included in our analysis. Any paper that did not provide follow-up data on patients with follow-up imaging was excluded, as these studies did not allow for Kaplan-Meier analysis.

Data Extraction

Median largest dimension and median tumor volume were not reportable or analyzable in our analysis, as most studies did not consistently report either value. Data were first stratified into 3 groups (biopsy, STR, and GTR) irrespective of adjuvant therapies, based on the extent of resection presented in each report. Data from patients who had STR were then stratified depending on whether they received RT or had a biopsy followed by intracystic chemotherapy. The main comparison of interest was the morbidity difference between GTR compared with STR combined with RT (STR + RT). Subtotal resection was compared with STR + RT to evaluate differences in morbidity associated with the addition of RT. The combination of STR and RT was also compared with biopsy followed by intracystic chemotherapy, as these are 2 different treatment options when the preoperative decision is made that GTR is too risky. Morbidity analyses focused on pituitary dysfunction, hypothalamic dysfunction, and neurological deficits. Postoperative morbidity was divided into anterior lobe pituitary dysfunction, panhypopituitarism, postoperative diabetes insipidus, obesity, new postoperative visual deficits, and new postoperative nonvisual neurological deficits.

Statistical Analysis

The Pearson chi-square test was used to analyze for differences in preoperative categorical factors, including gender and preoperative endocrine and visual deficits. The Fisher exact test was used 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. Chi-square test was used to evaluate differences in postoperative outcomes between the different treatment groups. Logistic regression was used to determine odds ratios associated with each outcome measure. Analyses were carried out using SPSS version 16.0 (SPPS, Inc.).

Results

Clinical Features

Our search yielded a total of 109 studies that described surgical procedures for the treatment of craniopharyngioma, with a total of 531 pediatric patients. Of the included studies, the median number of patients per study was 10 (range 1–29 patients). The clinical characteristics of the study population are described in Table 1. There was no statistically significant difference between the surgical cohorts with respect to the demographic and clinical variables age, sex, preoperative endocrine, and visual dysfunction (data not shown).

Extent of Resection and Postoperative Outcomes

To determine if extent of resection was associated with increased postoperative deficits, we compared outcomes in all patients who underwent biopsy, STR, and GTR (Table 2). GTR was associated with increased rates of postoperative anterior lobe pituitary dysfunction ($p <$

TABLE 1: Clinical characteristics of the study population*

Variable	Value
sex (n = 531)	
male	243 (46)
female	288 (54)
age in yrs (n = 527)	
median	4
range	0–19
preop endo dysfxn (n = 145)	
yes	89 (61)
no	56 (39)
preop visual dysfxn (n = 161)	
yes	96 (60)
no	65 (40)
operation (n = 531)	
biopsy	165 (31)
STR	148 (28)
GTR	218 (41)
RT (n = 531)	
yes	156 (29)
fRT	110 (70)
SRS	47 (30)
no	375 (71)
intracystic chemo (n = 531)	
yes	76 (14)
no	455 (86)

* Values represent numbers of cases (%) unless otherwise indicated. Abbreviations: chemo = chemotherapy; dysfxn = dysfunction; endo = endocrine; fRT = fractionated RT; panhypopit = panhypopituitarism; SRS = stereotactic radiosurgery.

0.001; OR 5.4; 95% CI 3.0–9.7) and panhypopituitarism (p = 0.006; OR 7.8; 95% CI 1.8–33.5) compared with biopsy alone. The rate of postoperative diabetes insipidus was increased with GTR (p = 0.001; OR 5.4; 95% CI 2.1–14.2). Likewise, GTR was associated with increased rates of postoperative new neurological deficits (p = 0.03; OR 9.9; 95% CI 1.3–75.3). STR was also associated with increased rates of postoperative anterior lobe dysfunction (p < 0.001; OR 4.6, 95% CI 2.3–9.3) and panhypopituitarism (p = 0.015; OR 6.9; 95% CI 2.1–14.2) compared with biopsy. However, STR was not associated with increased rates of postoperative diabetes insipidus (p = 0.35) or new neurological deficits (p = 0.10).

The Effect of Adjunctive RT After STR

A major question is whether STR in conjunction with adjuvant RT, presumably associated with reduced morbidity, results in equivalent long-term tumor control when compared with GTR. Therefore, we next analyzed outcome differences between GTR alone and STR combined with adjunctive RT (STR + RT). The results are described in Table 3. Gross-total resection was associated with increased postoperative diabetes insipidus (p = 0.05; OR 7.7; 95% CI 1.0–58.5). Otherwise, there were no significant differences in postoperative outcomes between the two groups.

TABLE 2: Association between extent of resection (biopsy +/- adjuvant therapy vs STR +/- RT vs GTR +/- RT) and outcomes irrespective of adjuvant therapy*

Outcome	Biopsy	STR	GTR	p Value†
postop endo dysfxn				
yes	18 (21)	39 (55)	112 (59)	<0.001
no	68 (79)	32 (45)	79 (41)	
postop DI				
yes	5 (6)	7 (10)	48 (25)	<0.001
no	81 (94)	64 (90)	143 (75)	
postop obesity				
yes	2 (2)	1 (1)	11 (6)	0.18
no	84 (98)	70 (99)	180 (94)	
postop panhypopit				
yes	2 (2)	10 (14)	30 (16)	0.006
no	84 (98)	61 (81)	161 (84)	
postop visual dysfxn				
yes	12 (14)	3 (4)	11 (6)	0.03
no	74 (86)	69 (96)	180 (94)	
postop neuro dysfxn				
yes	1 (1)	5 (7)	20 (11)	0.02
no	85 (99)	66 (93)	171 (89)	

* DI = diabetes insipidus; neuro = neurological ; panhypopit = panhypopituitarism.
† Chi-square test.

The Effect of the Addition of RT to STR

In some situations, STR is not followed with RT. We then compared STR alone to STR + RT to evaluate the affect of adjunctive RT on outcomes. There is an increased rate of panhypopituitarism after STR + RT compared with STR (p = 0.01; OR 9.1; 95% CI 1.7–48.0). With that exception, there were no other significant differences in specific outcomes with the addition of adjunctive RT (Table 4).

Comparison of STR and Biopsy Procedures

Chemotherapy has had limited success in the treatment of craniopharyngioma. The most common form of chemotherapy has been the use of intracystic agents, particularly when monocystic lesions were encountered. Biopsy followed by intracystic chemotherapy was compared with STR + RT (Table 5). The combination of STR and RT was associated with significantly more postoperative anterior lobe pituitary dysfunction (p = 0.02; OR 4.2; 95% CI 1.4–13.3). Likewise, STR + RT was associated with significantly more panhypopituitarism (p = 0.01; OR 8.2; 95% CI 1.5–43.8). Otherwise, there were no significant differences in postoperative outcomes.

Discussion

Craniopharyngiomas are considered WHO Grade I

TABLE 3: Comparison of outcomes between GTR alone and STR + RT

Outcome	GTR	STR + RT	p Value
postop endo dysfxn			
yes	108 (59)	11 (46)	0.22
no	75 (41)	13 (54)	
postop DI			
yes	46 (25)	1 (4)	0.02
no	137 (75)	23 (96)	
postop obesity			
yes	10 (6)	1 (4)	1.0
no	173 (94)	23 (96)	
postop panhypopit			
yes	27 (15)	7 (29)	0.08
no	156 (85)	17 (71)	
postop visual dysfxn			
yes	9 (5)	1 (4)	1.0
no	174 (95)	23 (96)	
postop neuro dysfxn			
yes	20 (11)	0 (0)	0.14
no	163 (89)	24 (100)	

tumors, and GTR has been regarded as the primary treatment modality during the past several decades. Despite its classification as a "benign" tumor, the defining features of craniopharyngioma (involvement of eloquent structures, recurrence, associated mortality) suggest a more aggressive natural history.[94] The overall objective, however, remains tumor cure without causing intolerable patient disability. To achieve this objective, a variety of strategies have been attempted at many institutions over the past several decades, and strong positions have emerged based on certain viewpoints. For well-defined lesions in some patients, it is believed that GTR results in lower recurrence rates without the need for adjuvant therapy, such as RT, which carries its own associated morbidity.[28,32] However, there are also some patients who experience substantial morbidity related to either hypothalamic injury or panhypopituitarism—particularly with respect to diabetes insipidus. In comparison with GTR, durable long-term tumor control has also been reported in patients who have undergone STR and conformal external beam RT with care taken to avoid irradiation of critical structures.[82,83,122]

Attempting to examine outcomes in a rigorous manner was affected by several factors: the low incidence of these tumors, the lack of standardized clinical trials, and the heterogeneity of treatment approaches. Therefore, to better understand the results obtained with the current standard of care, we systematically reviewed and analyzed the published literature with an emphasis on treatment-related morbidity, extent of resection, and type of RT. There are clear limitations to this approach, which are detailed below. However, aggregation of published data does provide an impression of current standards of care and reported outcomes when those standards are applied to patient treatment.

TABLE 4: Outcomes after STR compared to STR + RT

Outcome	STR	STR + RT	p Value
postop endo dysfxn			
yes	27 (59)	11 (46)	0.31
no	19 (41)	13 (54)	
postop DI			
yes	6 (13)	1 (4)	0.41
no	40 (87)	23 (96)	
postop obesity			
yes	0 (0)	1 (4)	0.34
no	46 (100)	23 (96)	
postop panhypopit			
yes	2 (4)	7 (29)	0.006
no	44 (96)	17 (71)	
postop visual dysfxn			
yes	2 (4)	1 (4)	1.0
no	45 (96)	23 (96)	
postop neuro dysfxn			
yes	5 (11)	0 (0)	0.16
no	41 (89)	24 (100)	

Treatment-related morbidity is a key determinant of which modality should be preferred. In our analysis, postoperative endocrine function is the main morbidity outcome that varies with respect to extent of resection and adjuvant therapy in pediatric craniopharyngioma. Postoperative obesity, visual function, and nonvisual neurological function in general do not appear to vary with respect to extent of resection. However, GTR was associated with increased rates of new neurological dysfunc-

TABLE 5: Comparison of outcomes between STR + RT and biopsy + intracystic chemotherapy

Outcome	STR + RT	Biopsy + Chemo	p Value
postop endo dysfxn			
yes	11 (46)	7 (17)	0.02
no	13 (54)	35 (83)	
postop DI			
yes	1 (4)	5 (12)	0.40
no	23 (96)	37 (88)	
postop obesity			
yes	1 (4)	1 (2)	1.0
no	23 (96)	41 (98)	
postop panhypopit			
yes	7 (29)	2 (5)	0.009
no	17 (71)	40 (95)	
postop visual dysfxn			
yes	1 (4)	7 (17)	0.24
no	23 (96)	35 (83)	
postop neurol dysfxn			
yes	0 (0)	1 (2)	1.0
no	24 (100)	41 (98)	

tion compared with biopsy, while STR was not. Gross-total resection is also associated with increased rates of postoperative diabetes insipidus compared with STR and STR + RT—presumably resulting from damage to the pituitary stalk during surgical dissection. Evidence indicates that endocrine dysfunction can affect long-term outcomes in the pediatric population.[101,121] Although some argue that preservation of the pituitary stalk should not preclude an attempt at radical resection, children left with endocrinopathies, including diabetes insipidus, are at risk for both perioperative and delayed morbidity and mortality.[14,121] Therefore, the effect of aggressive resection on endocrine function should be considered and anticipated when planning surgery for craniopharyngioma. In general, if similar rates of tumor control can be obtained with GTR and STR + RT, then the less morbid procedure should be considered as an option. A smaller number of papers have reported the extent of resection as it relates to measures of tumor control. Our group is conducting an analysis of these data.

Expanded endoscopic endonasal approaches are being used to treat craniopharyngiomas in children. A recent meta-analysis comparing outcomes in children with craniopharyngioma treated with transsphenoidal surgery to those treated with conventional transcranial surgery reported that transcranial surgery was associated with increased rates of diabetes insipidus, postoperative worsening of vision, and postoperative nonvisual neurological deficits.[29] However, the authors noted significant baseline differences between the groups—specifically smaller and more predominantly intrasellar tumors in the transsphenoidal group—which preclude a direct comparison of outcomes. We would expect that primarily sellar tumors that did not invade the hypothalamus would have a better outcome. In our data set, the surgical approach and results of surgery were not consistently reported, and thus we were unable to generate comparisons with respect to extent of resection and outcomes.

A secondary outcome that we analyzed was the change in morbidity associated with the addition of RT to STR. The addition of RT to STR is associated with an overall postoperative morbidity similar to that of STR alone. Although RT in close proximity to the optic nerves theoretically carries the risk of visual deterioration, we note that the overall rate of new postoperative visual deficits was low. Furthermore, STR followed by RT was not associated with an increased rate of visual deterioration when compared with either GTR or STR alone. This suggests that surgery directed at tumor debulking and creating space around the optic apparatus can lead to safe application of adjuvant RT and protect visual function.

There are inherent limitations associated with a systematic review of the published literature. The major limitation is that because of differences in reporting, potentially important variables cannot be analyzed or controlled. As an example, tumor size was not consistently reported in a disaggregated fashion and could not be included in this analysis. This may explain the differences noted between biopsy procedures followed by intracystic chemotherapy and other more aggressive resections. We can assume that patients treated with intracystic chemotherapy probably harbored smaller monocystic tumors compared with patients who underwent open resection. Another limitation is that all included reports used retrospective methodologies, which are all affected by various selection biases. Finally, at present, there are no reporting standards for craniopharyngioma, so extent of resection, histology, and method of RT vary from study to study. Certainly a preliminary step in improved data collection in the future, in the absence of controlled clinical trials, will be a consensus on reporting standards for case series arising from different institutions.

An important outcome measure that we were not capable of including is quality of life. This is particularly important when considering treatment modalities in children who are often treated either before or during important stages of physical, social, and emotional development. Müller et al.[86] prospectively analyzed a large cohort of pediatric patients treated for craniopharyngioma and found that hypothalamic obesity was associated with lower quality of life. Likewise, hypothalamic obesity was related to tumor involvement of the posterior hypothalamus. As mentioned above, we did not have sufficient data in our systematic review to evaluate the association of tumor location. We did not observe a difference in hypothalamic obesity with respect to the different treatment modalities, but quality of life measures were not consistently reported in the reports we analyzed. Finally, the neuropsychological effects of treatment-related hypothalamic injury extend beyond hypothalamic obesity. Pierre-Kahn et al.[95] prospectively followed 14 children treated surgically with the goal of GTR and subsequently reported their results. Postoperatively, although cognitively normal, 12 children had varying degrees of psychosocial problems, including antisocial behavior, depression, and worse global functioning. Unfortunately, neuropsychological outcomes were reported infrequently and on the basis of a variety of outcome measures, such that it was not possible to include these data in our review.

Conclusions

Analysis of reported data for pediatric craniopharyngioma demonstrate that treatment-related morbidity is common and that planned STR followed by adjuvant fractionated RT results in reduced endocrine dysfunction compared with GTR.

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: Gupta, Clark, Aranda, Parsa. Acquisition of data: Clark, Aranda. Analysis and interpretation of data: Gupta, Clark, Cage, Aranda, Parsa. Drafting the article: Gupta, Clark, Cage, Parsa, Auguste. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Clark. Administrative/technical/material support: Gupta, Clark, Parsa. Study supervision: Gupta, Clark, Parsa.

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