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ORIGINAL PAPER

A systematic review of the results of surgery and radiotherapy on tumor control for pediatric craniopharyngioma

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Abstract
Objective Craniopharyngiomas are rare tumors with bimodal incidence in the pediatric and adult age groups. Treatment strategies range from aggressive resection to planned limited resection combined with adjuvant therapies. Currently there is no consensus for standard of care for pediatric craniopharyngioma.
Materials and methods We performed a systematic review of the published literature on pediatric craniopharyngioma. Patients were grouped based on extent of resection into gross total resection (GTR), subtotal resection (STR), and biopsy procedures. These groups were compared with respect to tumor control. Chi square was used to compare rates of recurrence. Kaplan–Meier was used to generate progression-free survival (PFS) estimates. Cox proportional hazard modeling was used to evaluate risk of progression. Each extent of resection group was also subdivided based on adjuvant therapy and compared.
Results A total of 109 studies described extent of resection resulting in a cohort of 531 patients. Recurrence data were available for 377 patients. There was no difference in 1- or 5-year PFS between the groups who underwent GTR and STR combined with radiation (XRT; log-rank; $p=0.76$; 1-year PFS 89 vs 84 %; 5-year PFS 77 vs 73 %, respectively). One-year PFS was 84 % for STR+XRT compared to 76 % for STR alone while 5-year PFS was 73 % for STR+XRT compared to 43 % for STR alone (log-rank; $p=0.003$).
Conclusion Although there are limitations of a systematic review of retrospective data, our results suggest that STR+XRT of pediatric craniopharyngioma is associated with similar rates of tumor control as GTR.

Keywords Pediatric · Craniopharyngioma · Surgery · Extent of resection · Tumor control · Radiotherapy

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Introduction

Craniopharyngiomas are rare tumors arising from Rathke's pouch, a remnant of the primitive pharynx. The incidence is bimodal with peaks occurring between 5 to 15 and 45 to 60 years. Craniopharyngiomas account for 1–3 % of all pediatric brain tumors [17]. The histopathology is typical and consists of stratified papillary epithelial tissue with either solid, cystic, or mixed components. Although classified as WHO grade I tumors, their clinical behavior is more aggressive with many patients experiencing frequent tumor recurrence and significant morbidity due to their location and/or treatment. A recent study suggests that the adamantinomatous variant which is common in children should be designated a grade II tumor due to high rates of recurrence and significant treatment-related morbidity [95].

Craniopharyngiomas typically arise in the suprasellar region but can involve the pituitary stalk, the hypothalamus, and the optic pathways. Although these tumors do not widely infiltrate the brain as do primary astrocytic tumors, they can be densely adherent to brain structures. Recurrence is influenced by extent of resection with improved disease control in patients who undergo gross total resection (GTR) [100, 120, 121]. Experienced surgeons have reported that

GTR can be achieved in 50–79 % of patients with craniopharyngiomas [32, 48, 84]. The factors that prevent GTR are hypothalamic involvement, significant calcification, and involvement of critical vessels [32]. Perioperative mortality is low, ranging from 0 to 3 % even in the setting of planned aggressive resection [31, 84]. Perioperative morbidity, however, ranges from 8 to 14 %, including CSF leaks, infections, and visual worsening [31, 48]. In a large series of adult and pediatric craniopharyngioma patients treated with the initial goal of GTR [32], when GTR was achieved, the 5-year progression (PFS)/recurrence-free survival was 87 % as compared to 49 % in the subtotal resection (STR) group. Elliott et al. in a large series of exclusively pediatric patients also noted significantly longer progression/recurrence free survival in GTR patients [31]. They also noted worse outcomes in patients being treated for a recurrent tumor, which led them to propose that aggressive resection at initial presentation is most important. In contrast, Mechant et al. reported similar rates of tumor control in patients undergoing planned attempted GTR and planned STR followed by radiotherapy (XRT) [84]. They noted decreased IQ and quality of life metrics in the aggressive surgical group. They also reported a 73 % rate of diabetes insipidus in the aggressive surgical group compared to 33 % in the conservative surgical group. Diabetes insipidus can have long-term negative effects on children and has been suggested to be a predictor of poor response to adjuvant XRT [85]. These data suggest that the treatment for craniopharyngioma should be planned STR followed by XRT. Still others recommend biopsy followed by intracystic chemotherapy for certain craniopharyngiomas [20].

The current literature that is focused on pediatric craniopharyngioma consists mainly of single institution or single surgeon case series. Due to the rarity of this tumor, some series combine adult and pediatric age groups [32, 95]. Currently, there is no consensus regarding standard treatment of craniopharyngioma in pediatric patients and it is unlikely that prospective randomized trials will be performed to definitively address this issue. In order to place the reported experience with craniopharyngioma into context, we reviewed the published literature on to in order to determine if tumor control was dependent on degree of resection [1–8, 10–16, 18, 19, 21–30, 33–47, 49–62, 64–83, 86–99, 101–119, 122].

Materials and methods

Article selection

In order to determine overall recurrence rates and progression-free survival after treatment of craniopharyngioma, data from the existing English language literature were systematically reviewed. Articles were identified using a PubMed search combining the key word "craniopharyngioma" with "pediatric." After reviewing these articles, all referenced sources were compiled and analyzed, yielding a total of 1,451 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. Disaggregated data are defined as individual patient information presented in a manner that allowed assignment of pre- and postoperative factors and outcomes to the individual patient described in the report. Any paper which did not provide follow-up data on these patients with follow-up imaging was excluded, as these would not facilitate Kaplan–Meier analysis.

Data extraction

Median largest dimension and median tumor volume were not reportable or analyzable in our analysis, as the identified studies did not consistently report either value. The data were stratified into three groups based on extent of resection data presented in each reference: biopsy, subtotal resection, and gross total resection. The data were then further stratified based on subtotal resection with or without radiotherapy, or biopsy followed by intracystic chemotherapy. Tumor control data were included if adequate radiographic follow-up data were presented and stated in the study, demonstrating evidence of recurrence or continued tumor control. Time to progression was defined as time from diagnosis to radiographic evidence of progression. PFS was calculated at the 1- and 5-year time points.

Statistical analysis

Pearson's χ^2 test was used to analyze for differences in preoperative categorical factors, including gender and preoperative endocrine and visual deficits. Fisher's exact test was used if there were less than five 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. Cox proportional hazard modeling was used to determine hazard ratios associated with each outcome measure. Kaplan–Meier estimates were used to generate progression curves. Differences in progression-free survival were analyzed by the log-rank test. Analyses were carried out using SPSS version 16.0 (SPSS, Inc.).

Results

Clinical characteristics

Our search yielded a total of 109 studies that described the surgical procedures performed for craniopharygioma in 531 pediatric patients. Of these, data on recurrence were available

for 377 patients and were included in the analysis. Of the included studies, the median number of patients per study was 11 (range 1–29, Table 1). There was no difference in age between the cohorts analyzed (data not shown). There were significantly fewer males in the biopsy group compared to GTR and STR (29 vs 52 vs 49 %, respectively; $p=0.002$; chi-square).

Extent of resection and postoperative outcomes

To evaluate if greater extent of resection irrespective of other adjuvant treatments was associated with differences in tumor control, we separated patients into three groups based on whether they underwent biopsy, STR, or GTR, and then compared their outcomes. We specifically evaluated the rate of reported recurrence after surgical procedures (Table 2). The GTR group included patients who underwent GTR alone and those who received adjuvant XRT. Likewise, the STR group included those who received surgery alone and those who received surgery and XRT. The biopsy group was comprised of patients who underwent biopsy alone or biopsy and delivery of intracystic chemotherapy. STR was associated with a small but highly statistically significant increased rate of tumor recurrence compared to GTR ($p=0.008$; HR 1.4; 95 % CI 1.1, 1.8).

Radiotherapy after STR

Although, when taken as a whole, STR appeared to be associated with worse tumor control, we were interested in evaluating if the addition of radiotherapy could result in improvement in tumor control rates. Therefore, we next analyzed outcome differences between GTR alone and STR combined with adjunctive radiotherapy (STR+XRT). The results are described in Table 3. There was no difference in 1- or 5-year PFS between the GTR and STR+XRT groups (Fig. 1, log-rank; $p=0.76$; 1-year PFS 89 vs 84 %; 5-year PFS 77 vs 73 %, respectively).

Table 1 Clinical characteristics of the study population

Variable (no. of cases)	Value (%)
Sex (377)	
Male	171 (45)
Female	206 (55)
Age in years (374)	
Median (range)	10 (0–18)
Operation (377)	
Biopsy	91 (24)
STR	134 (36)
GTR	152 (40)
Radiation therapy (377)	
Yes	131 (35)
fXRT	95 (72)
SRS	37 (28)
No	246 (65)
Intracystic chemotherapy (377)	
Yes	22 (6)
No	355 (94)

Table 2 The association between EOR (biopsy±adjuvant therapy vs STR±XRT vs GTR±XRT) and outcomes irrespective of adjuvant therapy

Outcome	Biopsy	STR	GTR	*p*
Recurrence				
Yes (%)	31 (34)	79 (59)	55 (36)	<0.001
No (%)	60 (66)	55 (41)	97 (64)	

Addition of XRT to STR

We then compared STR alone to STR+XRT to evaluate the effect of adjunctive XRT on outcomes (Table 3). The addition of XRT was associated with a significant increase in PFS. One-year PFS was 84 % for STR+XRT compared to 76 % for STR alone ,while 5-year PFS was 73 % for STR+XRT compared to 43 % for STR alone (Fig. 2; log-rank; $p=0.003$).

Comparison of STR and biopsy procedures

Biopsy followed by intracystic chemotherapy was compared with STR+XRT (Table 3). There was no difference in PFS between the two groups (log-rank; $p=0.31$).

Discussion

There is no consensus regarding a standard treatment for craniopharyngioma in children. Aggressive resection with the goal of GTR and planned conservative resection with subsequent adjuvant radiotherapy have both been reported

Table 3 Comparison of outcomes between the different surgical and adjuvant therapy subgroups

Subgroup	Recurrence (%)	No recurrence (%)
GTR alone	51 (35)*	94 (65)
STR alone	51 (65)**	28 (35)
STR+XRT	27 (50)*, **, ***	27 (50)
Bx+chemo	9 (41)***	13 (59)

Bx+chemo biopsy followed by chemotherapy

*$p=0.06$; **$p=0.11$; ***$p=0.63$

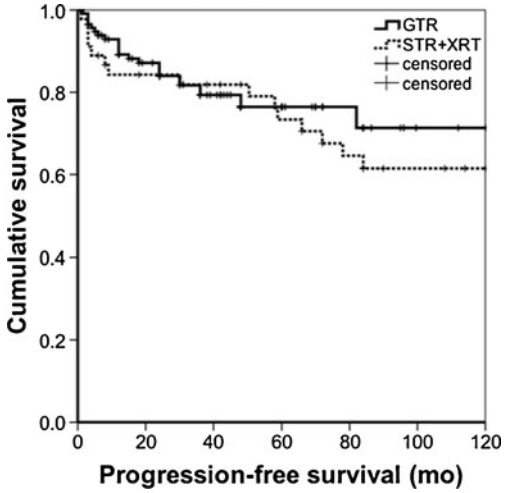

Fig. 1 Kaplan–Meier survival estimates comparing PFS between GTR and STR+XRT@@

to result in superior outcomes [32, 84]. Most reports, however, analyzed small patient cohorts undergoing heterogeneous treatments, which limits the relevance of the results. In order to exploit the advantages of a larger cohort of patients, we performed a systematic review of the literature to compare tumor control in patients treated with GTR, or STR combined with postoperative XRT.

Based on our results, GTR is not associated with significantly increased rate of tumor control or increased PFS compared to STR+XRT. It has been argued that successful GTR avoids the use of subsequent XRT its associated complications [32]. Conversely, some groups argue that aggressive resection can lead to increased postoperative neurologic and endocrine deficits [84]. We have recently reported in a systematic review of treatment-related morbidity that GTR

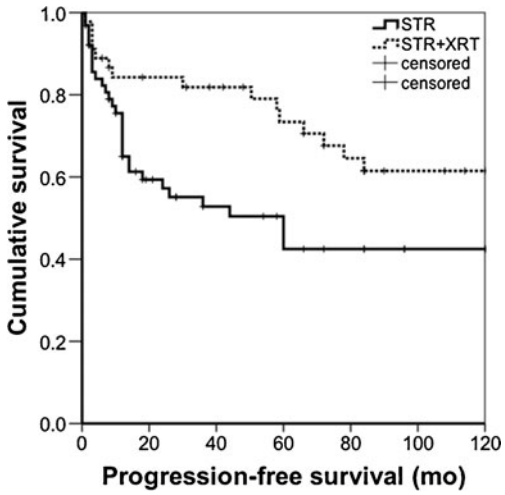

Fig. 2 Kaplan–Meier survival estimates comparing PFS between STR and STR+XRT

for pediatric craniopharyngioma is associated with increased rates of anterior lobe dysfunction and new neurologic deficits (Clark et al., in press). When compared specifically to STR+XRT, GTR was associated with significantly increased rates of diabetes insipidus. Taken together, our data reported here would suggest that in the setting of increased postoperative deficits related to GTR, STR+XRT may represent the optimal treatment in this patient population yielding similar rates of tumor control.

In this study, the addition of XRT to STR was associated with significant increases in PFS. STR is targeted at improving neurologic symptoms including vision by tumor debulking, restoring more normal CSF flow, and decreasing the tumor volume that will be targeted by XRT. However, radiotherapy in close proximity to the optic nerves carries the risk of visual deterioration as well as the risk of new or worsening of endocrinopathies and worse cognitive outcomes [63]. Tumor control benefits of XRT must be weighed against these risks. It is possible that future techniques for improved targeting of XRT will lead to decreased morbidity with preserved tumor control [85].

As a secondary comparison, we evaluated the difference between STR+XRT and biopsy followed by intracystic chemotherapy. A recent systematic review has described the current literature on intracystic chemotherapy [9]. Catheters are placed into the cyst either under direct visualization through an open craniotomy, stereotactically through a burr hole, or endoscopically. The catheter is then connected to a subcutaneous reservoir which is used to receive the agent. The goal of the agent is to destroy the secretory capacity of the epithelial cells lining the cyst to cause cyst shrinkage. The agents which have been used are radioisotopes, bleomycin, and interferon. We found similar effects on tumor control between STR+XRT and intracystic chemotherapy. Unfortunately, tumor size was not consistently reported in a disaggregated fashion and could not be included. This may partially explain the lack of difference in recurrence noted between biopsy procedures followed by intracystic chemotherapy and other more aggressive resections. We can assume that patients treated with intracystic chemotherapy likely harbored smaller monocystic tumors compared to patients who underwent open resection.

This report represents a systematic review of the published literature and therefore has inherent limitations. Currently there are no reporting standards for craniopharyngioma, so reports of extent of resection, histology, and method of radiotherapy likely vary from study to study and cannot be examined. It is entirely possible that there are features of those tumors that lend themselves to GTR are in fact important in determining overall outcome. Due to differences in reporting for each included study, potentially important variables could not be analyzed or controlled. Anatomic features that could affect extent of resection and outcomes including hypothalamic

involvement and vascular encasement were not routinely reported. Finally, all included studies were retrospective analyses and therefore are limited by potential selection biases.

Conclusions

Although subject to the limitations of a systematic review, our data support the conclusion that planned STR followed by adjuvant XRT is associated with similar rates of tumor control compared to planned GTR. Optimized multimodality treatment for craniopharygioma in the pediatric population may center around planned STR followed by adjuvant fractionated XRT.

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