Adult Craniopharyngioma: Case Series, Systematic Review, and Meta-Analysis

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BACKGROUND: The optimal therapeutic approach for adult craniopharyngioma remains controversial. Some advocate for gross total resection (GTR), while others advocate for subtotal resection followed by adjuvant radiotherapy (STR + XRT).

OBJECTIVE: To conduct a systematic review and meta-analysis assessing the rate of recurrence in the follow-up of 3 yr in adult craniopharyngioma stratified by extent of resection and presence of adjuvant radiotherapy.

METHODS: MEDLINE (1946-July 1, 2016) and EMBASE (1980-June 30, 2016) were systematically reviewed. From1975 to 2013, 33 patients were treated with initial surgical resection for adult onset craniopharyngioma at our center and were reviewed for inclusion in this study.

RESULTS: Data from 22 patients were available for inclusion as a case series in the systematic review. Eligible studies (n = 21) were identified from the literature in addition to a case series of our institutional experience. Three groups were available for analysis: GTR, STR + XRT, and STR. The rates of recurrence were 17%, 27%, and 45%, respectively. The risk of developing recurrence was significant for GTR vs STR (odds ratio [OR]: 0.24, 95% confidence interval [CI]: 0.15-0.38) and STR + XRT vs STR (OR: 0.20, 95% CI: 0.10-0.41). Risk of recurrence after GTR vs STR + XRT did not reach significance (OR: 0.63, 95% CI: 0.33-1.24, $P = .18$).

CONCLUSION: This is the first and largest systematic review focusing on the rate of recurrence in adult craniopharyngioma. Although the rates of recurrence are favoring GTR, difference in risk of recurrence did not reach significance. This study provides guidance to clinicians and directions for future research with the need to stratify outcomes per treatment modalities.

KEY WORDS: Craniopharyngioma, Recurrence, Recurrence rate, Meta-analysis, Neurosurgery

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Craniopharyngiomas are rare, slow growing, benign (WHO grade I) epithelial tumors, believed to be derived from cell remnants of Rathke's pouch.[1-5] They make up between 2% and 5% of all primary intracranial tumors[2,3,6] with an overall incidence rate of 0.5 to 2 cases per million per year.[5,7,8] Half of all cases occur in adulthood with a peak incidence between the ages of 40 and 44 and a second small peak in the sixth decade.[9,10] There are 2 distinct histopathological subtypes of craniopharyngioma: adamantinomatous and papillary. The papillary type occurs almost exclusively in adults. Recent reports show a difference in pathological behavior between the 2 subtypes.[10-12] Malignant behavior is often observed due to infiltration of, adherence to, and pressure on surrounding critical structures of the sellar region, notably the pituitary gland, hypothalamus, optic nerve, blood vessels, and third ventricle.[10] This may result in considerable morbidity and mortality due to the disease itself or its treatments.[1,3,7]

The optimal therapeutic approach remains controversial.[3,13,14] Some authors suggest that gross total resection (GTR) should be the primary goal if it can be achieved with limited associated morbidity.[3,7,15-17] Other authors advocate less aggressive subtotal resection followed by adjuvant radiotherapy (STR + XRT).[3,18,19] There are competing arguments to

ABBREVIATIONS: CI, confidence interval; **GTR,** gross total resection; **OR,** odds ratio; **STR,** subtotal resection; **UBC,** University of British Columbia

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support both treatment paradigms. It has been reported that STR + XRT may have similar outcomes as GTR in the pediatric and mixed-age population.[2,20,21] This has not been established for the adult population.

The risk of recurrence of craniopharyngioma post-treatment appears highest in the first 3 to 5 yr after surgery.[10,22] There is a wide range of reported recurrence rates in the literature: GTR (0%-26%), SRT + XRT (10%-63%), and STR (25%-100%).[4,6,7,10,23] Surgery for recurrences constitutes a challenge with higher associated mortality rates than primary surgery.[6] Limited studies with mid-term follow-ups for adult craniopharyngioma patients are available. As this disease is quite rare, many studies in the literature combine adult and childhood onset.[1,21]

Thus, this investigation aimed at reporting the rate of recurrence in mid-term follow-up of minimum 3 yr in adult craniopharyngioma by pooling the results of our institutional series and a large number of patients' data from the literature for factors affecting the rate of recurrence. This study aims at assessing the overall state of the literature on adult craniopharyngioma to provide benchmark numbers and guide future research. To this end, a systematic review of the literature and meta-analysis were performed.

METHODS

Case Series

All craniopharyngiomas treated at our institution were retrospectively reviewed using our prospectively collected database. Inclusion criteria were: (1) surgical resection for craniopharyngioma; (2) confirmed pathological diagnosis of craniopharyngioma; (3) minimum 3-yr radiological follow-up after treatment; and (4) over 18 yr of age at the time of diagnosis. Information including patient characteristics on admission, radiological characteristics, extent of resection, adjuvant radiotherapy, pathological subtypes, and time of recurrence were collected. Treatment decisions were made at the time of the initial evaluation by the treating surgeon. Extent of resection was collected based on intraoperative impression extracted from operative reports and evidence of residual on postoperative radiological imaging with magnetic resonance imaging (MRI). Postoperative imaging time points were recorded to identify time of recurrence. Recurrence was defined as radiological progression defined by radiologist regardless of the extent of resection.

Literature Review

Search Strategy

Preferred Reporting of Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P)[24,25] was used. Medical literature including MEDLINE (1946-July 1, 2016) and EMBASE (1980-June 30, 2016) database were searched without limiting for language. Keywords and MESH terms used in complete or partial combinations were: "craniopharyngioma", "resection", "removal", "radiotherapy", and "radiation." Our search was limited to adults and humans.

Study Selection

Two authors (C.D. and P.G.) reviewed titles and abstracts for selection criteria. We included studies that assessed surgical outcomes (rate of recurrence) with a minimum 3-yr follow-up stratified by treatment modalities. Exclusion criteria were: (1) articles that combined craniopharyngiomas with other type of tumors (unless a clear distinction was made, allowing separation of tumor types); (2) studies with a mean follow-up less than 3 yr (unless follow-up duration was specified for each patient and only those with over 3 yr follow-up were included); (3) studies with the rate and time of recurrence not stratified by extent of resection and adjuvant radiotherapy; (4) studies with pediatric population or childhood-onset craniopharyngiomas, unless we were able to extract data specifically for the adult patients; and (5) case reports, letters to the editors, and articles without an abstract. Any disagreement during article selection was resolved by a discussion with a senior author (R.A.). Review references were scrutinized for additional studies.[10]

Data Extraction and Quality Evaluation

Data were extracted from the included studies using a standardized collection form. We extracted study data including year of publication, geographic origin, and study design. Demographic data including sex distribution and mean age at operation were recorded. We extracted clinical presentation, pathological subtypes and maximal tumor diameter, extent of resection, adjuvant radiotherapy, follow-up period, time and rate of recurrence, morbidities (visual outcome, endocrinopathies, hypothalamic syndrome, and cognitive impairment), and mortality. The time to progression or recurrence was defined as progression regardless of the extent of resection seen on radiological follow-up. We accepted the author's statement that GTR or STR was achieved and radiologically confirmed. We accepted the author's statement that progression or recurrence was radiologically confirmed. We accepted any forms of radiation. Time and rate of recurrence were stratified into 4 treatment groups: GTR alone, GTR + XRT, STR + XRT, or STR alone. We assessed quality of evidence using Oxford Centre for Evidence-Based Medicine—Levels of Evidence and Grading of Recommendations, Assessment, Development, and Evaluation framework.[26,27]

Statistical Analysis

From each study, we retrieved number of total cases undergoing craniopharyngioma resection, and number of recurrences to allow calculation of the aggregate event rates (effect-sizes/point estimates) and odd-ratio (OR) with the 95% Confidence Interval (CI) using the Comprehensive Meta-Analysis software (Ver. 2.0, Biostat Inc, Englewood, New Jersey).[28] Additionally, data from the literature were aggregated with data emerging from our center. This allowed global analysis of the event rate; and subsequently stratification by treatment modalities (GTR, GTR + XRT, STR + XRT, and STR). For the meta-analysis, we pooled the results using the random-effects model set a priori to take into account data distribution. Results were aggregated only in the presence of 2 or more individual patient cases. At all levels of analysis, alpha level of significance was set to 0.05.

Between studies, heterogeneity was assessed using the Cochran's Q-statistics and the I^2 statistic. A significant Q-statistics value suggests rejection of the homogeneity hypothesis of the effect set, and an I^2 value greater than 50% as indicative of substantial heterogeneity (variation across studies that is due to heterogeneity rather than chance)[29] requiring further investigation. We have used the 1-study removed analysis to examine the effect of each study on the overall prevalence, and potential heterogeneity.

Sensitivity analyses were carried out based on study quality, sample size, publication year, and non-peer-reviewed series of cases, when applicable. Sensitivity analysis based on sample size was carried out by using 2 approaches, (A) using categorical variable, categorizing studies into 2 groups (>10 and ≤10 in sample size and then >25 and ≤25), and (B) using continuous variable, running single-variable meta-regression using sample size as variable of interest affecting the global prevalence estimate. Sensitivity analysis for the effect of publication-year was carried out using single-variable random effect models meta-regression. Sensitivity analysis to examine the effect of experimental bias (University of British Columbia [UBC] data)/non-peer-reviewed series of cases was carried out by removing our case series (Vancouver General Hospital [VGH]) from the overall analysis.

Publication bias was appraised using schematic representation (funnel plot) and quantitative analysis (Egger's test and Begg and Mazumdar tests).[30,31] Publication bias was further investigated by, (A) classic fail-safe N and (B) Duval and Tweedie's trim and fill. Under the random effects model, the Duval and Tweedie's trim and fill approach "firstly trims the asymmetric studies from the left-hand side to locate the unbiased effect (in an iterative procedure), and then fills the plot by re-inserting the trimmed studies on the left as well as their imputed counterparts to the right the mean effect."[28] Classic fail-safe N assessment was carried out using alpha 0.05 under 2-tailed condition.

In the presence of sufficient data (3 > studies), moderating demographic variables (age and sex), as well as average time to recurrence was investigated using DerSimonian mixed effect single-variable meta-regressions.[32] Posthoc exploratory analyses (based on categorical or continuous type variables) were carried out in the presence of sufficient data. Decision on selecting posthoc variables was carried out using evidence-based medicine as well as referral to an expert surgeon (P.G. and R.A.).

TABLE 1. Clinical and Surgical Characteristics of UBC Single-Center Series.

Variable	Number of cases*	(%)
Sex		
Male	12/22	54.5
Female	10/22	45.5
Age		
Mean (yr)	46.7/22**	
Clinical presentation		
Visual deficits	21/22	95.6
Headache/hydrocephalus	8/22	36.4
Endocrinopathies	5/22	22.7
Cognitive impairment	1/22	4.5
Tumor size		
Overall mean (cm)	3.1/11***	
Pathological subtype		
Adamantinomatous	5/9	55.6
Papillary	4/9	44.4
Extent of resection and XRT		
GTR	9/22	40.9
GTR + XRT	1/22	4.5
STR + XRT	1/22	4.5
STR	11/22	50.0
Approach		
Endonasal	3/22	13.6
Transcranial	19/22	86.4

*Except for age expressed in years and tumor size expressed in centimeters.
**SD = 15.2.
***1.9 (11 patients reported).

RESULTS

Case Series

From 1975 to 2013, 33 patients were treated with initial surgical resection for adult-onset craniopharyngioma at VGH. Twenty-two patients (Male 54.5%, mean age: 46.7 yr) were included in the present case series as they meet selection criteria (see Table 1 for details). Five patients were excluded due to follow-up less than 3 yr. Six patients were excluded due to incomplete chart data. The most common clinical presentation was visual deficit (95.6%), followed by headache and hydrocephalus (36.4%), endocrinopathies (22.7%), and cognitive impairment (4.5%). Tumors measured on average 3.1 cm at their largest diameter. The majority of patients underwent a transcranial resection compared to the endonasal approach (86.4% vs 13.6%; see Table 1 for details). Eleven patients underwent STR (50.0%); 9 underwent GTR (41.0%); 1 had GTR + XRT (4.5%); and 1 had STR + XRT (4.5%). Pathological subtypes were available in 9 patients. Papillary subtype occurred in 4 out of 9 patients (44.4%). Average length of follow-up was 68.9 mo.

Search Results

Our search of the literature rendered 1512 articles (Figure 1). After duplicate removal, 1044 articles remained for examination. The rate of agreement between authors (C.D. and P.G.) for classifying a study for inclusion was 87%. Two hundred forty-one records were screened, 42 studies were reviewed in entirety for eligibility, and 22 unique studies including our center's case series provided sufficient data for 759 nonduplicated patients to allow analysis.[1,33-52] The largest sample consisted of 146 patients.[45] The smallest sample (2 patients) was collected from a study where information for each patient was available and we screened each patient for inclusion and exclusion criteria.[39] Studies were almost equally distributed between Europe, North America, and Asia (32%, 32%, and 36%, respectively). All studies were retrospective case series. When using Oxford Centre for Evidence-Based Medicine—Levels of Evidence and all included studies were level 4 (case series). When using Grading of Recommendations, Assessment, Development, and Evaluation framework all studies were graded low or very low due to their noncomparative nature.

Clinical Characteristics

Overall, there was a slight male predominance at 55.3% and mean age was 38.1 yr (Table 2). The most commonly reported clinical presentation was visual impairment (67.2%), followed by symptoms of intracranial pressure (headache and hydrocephalus; 36.6%), endocrinopathies (26.6%), and cognitive impairment (15.1%). A total of 65.6% of tumors were classified as

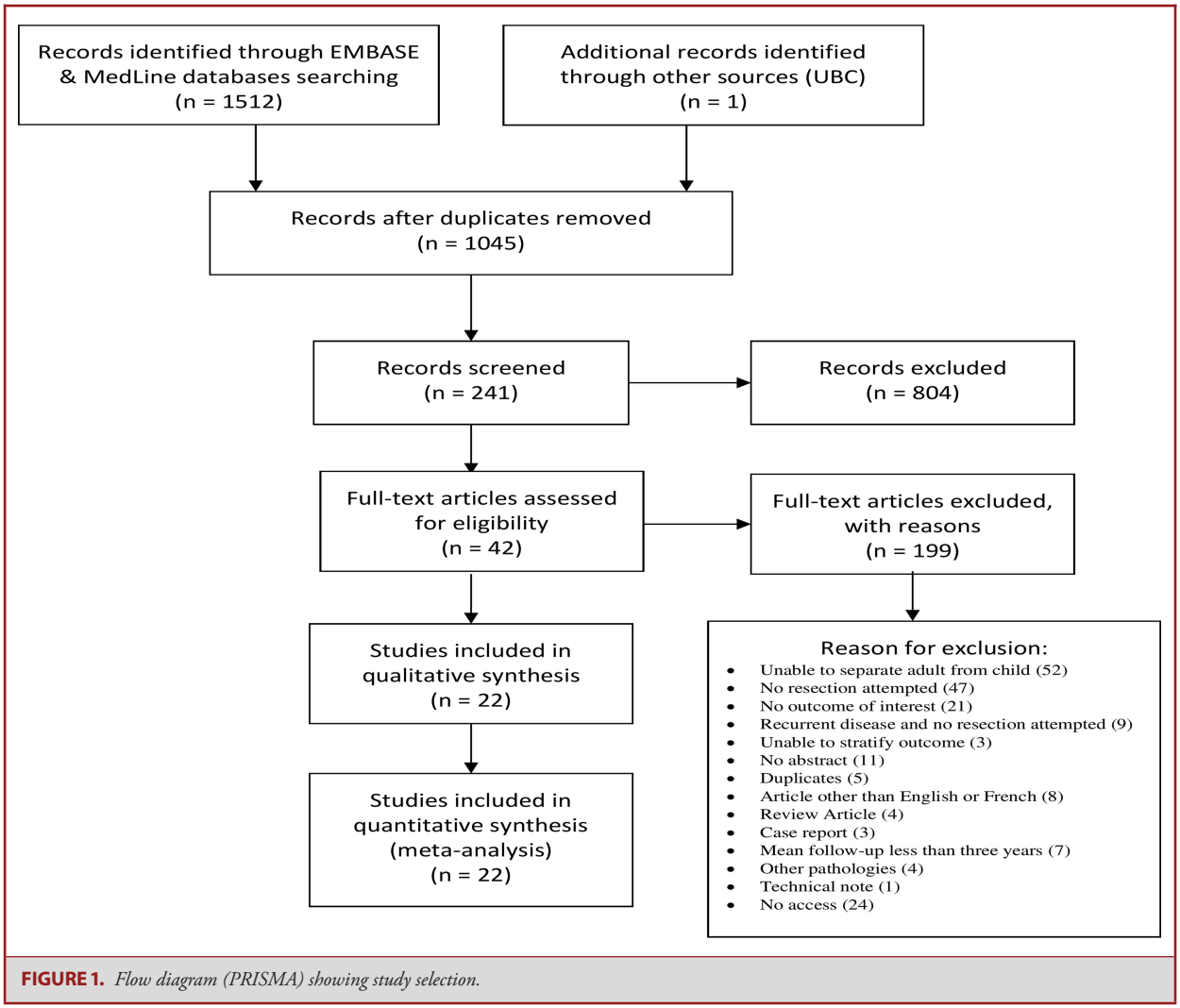

FIGURE 1. *Flow diagram (PRISMA) showing study selection.*

adamantinomatous; 34.3% were classified as papillary; and 1.5% were classified as mixed.

Recurrences were not stratified by pathological subtypes in the included series. Therefore, we were unable to determine if pathological subtypes had an effect on recurrences.

Extent of Resection and Treatment Paradigm

The majority of patients (57.4%) underwent GTR alone. GTR + XRT was undertaken in 6.6% of patients. STR + XRT was performed in 28.6% of patients and STR alone was performed in 13.0% of patients (Table 2). The number of patients in each extent of resection group per included studies is shown in Table 3.

Surgical Approach

In our case series, 2 out of 3 patients treated with endonasal approach had a recurrence (66.6%) and 9 out 19 patients treated with transcranial approach had a recurrence (47.4%). The majority of patients had an endonasal approach (73.3%), and 26.6% had a transcranial approach. To determine if surgical approach had an effect on the rate of recurrence, we analyzed the studies reporting exclusively surgically treated patients via the transcranial approach or endonasal approach. We were then able to attribute recurrences to a specific approach. Using meta-regressions, we determined that surgical approach did not have an effect on the rate of recurrence (Table 4). No statistical difference was observed between the 2 approaches.

Rate of Recurrence

The aggregate global rate of recurrence regardless of the extent of resection or presence of radiotherapy was 26.2% (Table 4 and Figure 2). We excluded single case reports and studies reporting 1 patient. Thus, we excluded GTR + XRT from analysis. Consequently, 3 groups were available for analysis: GTR, STR + XRT, and STR. The rates of recurrence were, respectively, 17%, 27%,

TABLE 2. Clinical and Surgical Characteristics of the Study Population.

Variable	Number of cases*	(%)
Sex		
Male	409/738	55.3
Female	331/738	44.7
Age		
Mean (yr)	38.14 (662 patients reported)	N/A
Clinical presentation		
Visual deficits	492/732	67.2
Headache/hydrocephalus	260/710	36.6
Endocrinopathies	192/721	26.6
Cognitive impairment	72/477	15.1
Tumor size		
Overall mean (cm)	3.00 (234 patients reported)	N/A
Pathological subtype		
Adamantinomatous	298/454	65.6
Papillary	156/454	34.3
Extent of resection and XRT		
GTR	436/759	57.4
GTR + XRT	6/759	0.8
STR + XRT	100/759	28.6
STR	217/759	13.2
Approach		
Endonasal	471/642	73.3
Transcranial	171/642	26.6

NA, not available.
*Except for age expressed in years and tumor size expressed in centimeters.

TABLE 3. Extent of Resection, Age, and Sex Per Included Study.

Study name	GTR	GTR+	STR	STR+	Average age	% male
Baldé et al[1]	31	0	4	0	44.7	34
Bosnjak et al[33]	6	0	2	0	63	50
Cabezudo et al[34]	8	0	9	0	–	–
Chakrabarti et al[35]	72	0	3	11	–	50
Crotty et al[36]	16	1	21	8	44.7	48
Eldevik et al[37]	0	0	4	4	38.6	38
Elwatidy et al[38]	3	0	5	3	33.7	45
Kim et al[44]	11	0	0	0	35.3	82
Lee et al[46]	71	0	8	2	42	65
Frank et al[39]	0	0	2	0	43	0
Gardner et al[40]	3	0	0	3	50.6	67
Hoogenhout et al[41]	0	0	9	4	37.6	69
Kawano et al[43]	8	0	0	2	35.5	80
Leng et al[48]	6	0	0	0	48	12.5
Lopez-Serna et al[52]	46	0	56	0	32.4	51.6
Lee et al[47]	61	4	15	10	43.3	55.5
Norris et al[49]	1	0	3	0	55.5	75
Present series	9	1	11	1	46.7	54.5
Jung et al[42]	30	0	9	0	45.8	63
Vyramuthu et al[50]	0	0	8	0	35.25	–
Wang et al[51]	1	0	10	0	36	45
Kim et al[45]	53	0	38	52	41.4	60

and 45%. Age and sex did not have an effect on the rate of recurrence as seen via single-variable meta-regressions. We examined for the presence of heterogeneity and publication bias. As per the *Q*-statistics and *I*-square tests, limited heterogeneity was observed only for the global rate (see Table 4). Using the 1-study removed approach to examine the effect of individual studies on the combined prevalence estimate showed that the removal of each study did not change the result of the meta-analysis substantially (prevalence ranged from 25.0% to 27.7%), suggesting that the heterogeneity we have observed among studies was negligible.

No publication bias was observed, as seen in the schematic presentation (Funnel plot-Figure 3) and quantitative measures ($P > .05$, 2-tailed). Fail-safe N, under the specified condition with the *Z*-value of 1.9599, and 22 included studies, the number of missing studies with equal characteristics that would bring *P*-value to over .05 was 604, which demonstrate the robustness of our finding.

The Duval and Tweedie's trim and fill approach showed no studies on the left of the mean, but 3 on the right side of the mean. The adjusted value using the 3 trimmed studies increased the prevalence from 26.2% (95% CI: 20.8-32.3) to 27.3% (95% CI: 21.8-33.5).

We calculated ORs by individually comparing each group. Significance was reached when comparing GTR to STR (OR: 0.24, 95% CI: 0.15-0.38, $P < .01$) and STR + XRT to STR (OR: 0.20, 95% CI: 0.10-0.41, $P = .00$; see Table 5). The comparison between GTR and STR + XRT did not reach significance (OR: 0.63, 95% CI: 0.33-1.27, $P = .18$).

Morbidity and Mortality

Only 1 study reported postoperative outcomes (mortality, endocrinopathies, and visual deficits) stratified per extent of resection.[47] Unfortunately, we were not able to extract and analysis data for postoperative morbidities and mortality.

Time of Recurrence

Very few studies, including our center case series (VGH), reported the time of recurrence stratified by groups in terms of months.[34,37,41,44,50] The mean times of recurrence for GTR (n = 21), STR + XRT (n = 4), and STR (n = 24) were 29.1, 81.3, and 23.0 mo, respectively. Given very scant reported data with low number of patients with reported time of recurrence, no analysis could be done to examine the difference.

Sensitivity Analysis

Sensitivity analysis was run to examine the effect of experimental bias (UBC data); thus, we removed our case series (VGH) from this analysis. The random effect model for the global prevalence estimate was 25% (95% CI: 20%-31%; N = 21), and this effect was heterogeneous (I^2: 52.9280). Classic fail-safe N, with alpha 0.05, 2-tailed, and *Z*-score of 1.96, showed that an estimated 594 similar studies would be needed in order to signif-

TABLE 4. Rate of Recurrence Based on Random Effect Model-Patient Level Variables.

Variables	Numbers		Effect size and 95% CI			Heterogeneity			
	Patients	Studies	Event rate	Lower limit	Upper limit	*Q*-value	df (*Q*)	*P*-value	*I*-squared
Global	191/765	22	26%	21%	32%	46.2981	21	.0012	54.6418
GTR	70/434	16	17%	12%	23%	25.2250	15	.0470	40.5360
GTR + XRT	–	3*	–	–	–	–	–	–	–
STR	96/214	17	45%	35%	55%	25.6320	16	.0594	37.5781
STR + XRT	21/99	10	27%	15%	42%	12.9598	9	.1644	30.5546
100% Endo	4/37	6	17	7.7	33	2.4220	5	.7880	0.0000
100% Trans	11/34	3	33	19	51	0.9660	2	.6170	0.0000
Global (pathology)	103/447	7	23	17	31	15.7540	6	.0150	61.9140

*No analysis was performed due to exclusion of single case reports and single studies.

icantly change the prevalence rate of recurrence that we have obtained.

The present reported data left off studies that reported single cases. Here, fitting for the effect of these studies, we ran an average event rate for all sample included. This analysis showed no significant difference from the original analyses and all results were within the 95% CI reported (Global = 25%, N = 22, n = 759; GTR = 16%, N = 18, n = 436; GTR+ = 0, N = 3, n = 6; STR = 46%, N = 18, n = 217; and STR+ = 21%, N = 11, n = 100). Using single-variable meta-regression analysis showed no effect of publication year on the global prevalence estimate (coefficient: −0.0215; 95% CI: −0.0513 to 0.0084; 2-tailed *P*-value: .1586).

For examining the effect of sample size on the prevalence estimate, (A) for global prevalence estimate, the prevalence for studies with sample size equal to 10 and lower was 27.6% (95% CI: 16.4-42.7; N = 8; $I^2 = 0.000$), and for studies with sample size over 10 was 26.2% (95% CI: 20.2-33.2; N = 14; $I^2 = 67.467$), and global prevalence estimate, for studies with sample size equal to 25 and lower was 34.0% (95% CI: 34.0-43.9; N = 14; $I^2 = 11.047$), and for studies with sample size over 25 was 22.6% (95% CI: 16.6-30.1; N = 8; $I^2 = 73.794$). (B) The single-variable meta-regression examining for the effect of sample size was non-significant (coefficient: −0.0027; 95% CI: −0.0098 to 0.0045; 2-tailed *P*-value: .4675).

DISCUSSION

To our knowledge, this is the largest systematic review to examine craniopharyngioma tumors. It is the only quantitative meta-analysis to assess the adult craniopharyngioma population. The main finding of this study is that GTR has a lower rate of recurrence compared to STR + XRT. This new information has to be interpreted in the context that the comparative analysis (OR) did not reach statistical significance. This differs from the pediatric and mixed population. Yang et al[21] concluded that STR + XRT had similar rates of recurrence compared to GTR in a mixed adult and pediatric population with a 5-yr progression-free survival of 67% for the GTR group vs 69% for the STR + XRT group.[21] Clark and colleagues[2] reached the same conclusion in the pediatric population with a 5-yr progression-free survival 77% in the GTR group and 73% in the STR + XRT group. Also, it is the first systematic review to have a minimum duration follow-up. The rates of recurrence might be underestimated in the current literature. Our study offers reliable rates per treatment modality that will guide the patient and the clinician in management decision-making. Although the rates of recurrence are favoring GTR, difference in risk of recurrence did not reach significance between GTR vs STR + XRT (OR: 0.63, 95% CI: 0.33-1.24, *P* = .18). This may be explained by the low number of patients (n = 99) who underwent STR + XRT pooled in our study. More studies reporting patients treated with STR + XRT are needed. Our study shows the superiority of GTR over STR and STR + XRT over STR alone with statistically significant difference in risk of recurrence. GTR should be favored when feasible, especially if radiation is not an option. XRT should be added if an STR has been achieved.

This difference in rate of recurrence between adults and children might be explained by the different prevalence in pathological subtypes, which differ in terms of malignant behavior. Unfortunately, we were unable to assess this. Overall, about 86.2% of craniopharyngioma tumors are classified as adamantinomatous, 11.3% as papillary, and 2.5% as transitional.[12] Pediatric populations typically are entirely classified as adamantinomatous.[12] Previous studies report that papillary subtypes count for 14% to 50% of the tumors in adulthood.[10] Our findings are in keeping with the literature (34.3%). Previous investigators report that papillary histological variant may have better outcome and fewer recurrences.[53] Pekmezci et al[12] described the adamantinomatous subtype as more aggressive than a typical WHO grade I neoplasm.[12] Brain invasion has been associated more significantly with adamantinomatous subtype.[11,54] Prieto et al[14] observed that the adamantinomatous variant was associated with the widest and strongest types of adherence. Overall, a significant proportional relationship was found between adherence severity

Model	Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Total
	Bosnjak et al.	Global	0.056	0.003	0.505	0 / 8
	Leng et al.	Global	0.071	0.004	0.577	0 / 6
	Eui Hyun Kim et al.	Global	0.091	0.013	0.439	1 / 11
	Norris et al.	Global	0.100	0.006	0.674	0 / 4
	Eun Jung Lee et al.	Global	0.122	0.067	0.212	10 / 82
	Chakrabarti et al.	Global	0.128	0.072	0.216	11 / 86
	Crotty et al.	Global	0.146	0.071	0.276	7 / 48
	Frank et al.	Global	0.167	0.010	0.806	0 / 2
	Wang et al.	Global	0.182	0.046	0.507	2 / 11
	Kawano et al.	Global	0.200	0.050	0.541	2 / 10
	Tae-Young Jung et al.	Global	0.256	0.144	0.414	10 / 39
	Baldé et al.	Global	0.257	0.140	0.425	9 / 35
	Young-hoon kim et al.	Global	0.262	0.197	0.340	38 / 146
	Lopez-Serna et al	Global	0.275	0.197	0.369	28 / 102
	Gardner et al.	Global	0.333	0.084	0.732	2 / 6
	Elwatidy et al	Global	0.364	0.143	0.661	4 / 11
	Vyramuthu et al.	Global	0.375	0.125	0.715	3 / 8
	Hoogenhout et al.	Global	0.385	0.170	0.656	5 / 13
	Min Ho Lee et al.	Global	0.400	0.304	0.504	36 / 90
	UBC	Global	0.455	0.265	0.659	10 / 22
	Eldevik et al.	Global	0.500	0.200	0.800	4 / 8
	Cabezudo et al.	Global	0.529	0.303	0.745	9 / 17
Random			0.262	0.208	0.323	191 / 765

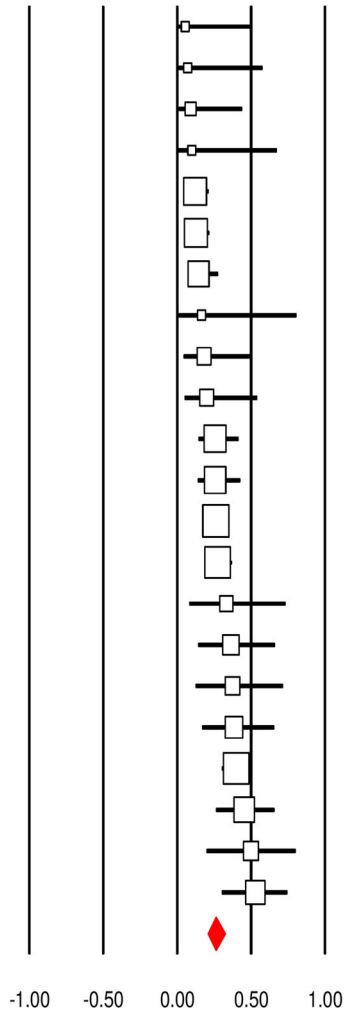

FIGURE 2. *Forest plot showing global frequency estimate:rate of recurrence.*

and poor outcomes.[14] The increased adherence and infiltration by the adamantinomatous subtype may limit the likelihood of achieving GTR. Other differences between the 2 populations beyond histopathological subtypes may exist including expression of specific molecules in recurrent adamantinomatous craniopharyngiomas.[55-57]

It has been well documented that the surgical success rates for recurrences are much less than for primary surgery.[6,7,16,58] Surgery for recurrences is associated with higher rates of peri- and postoperative morbidity and mortality.[6-8,16,58-61] Karavitaki et al[7] reported that mortality was higher in the adult population than in the pediatric population for any surgical intervention for recurrence.

Achieving GTR has to be counterbalanced with possible increased morbidity associated with a more aggressive approach. In a systematic review with a mixed population, Sughrue et al[62] found that GTR had an increased risk of neurological deficits (OR: 5.05) and endocrinopathies (OR: 3.45) compared to STR + XRT on multivariate analysis.[62] On the other hand, worse visual outcomes were observed following STR + XRT compared to GTR and STR alone.[45,62] Tumor recurrence was associated with risk of long-term visual deterioration.[45]

Quality of life has become an increasingly important factor to consider in treatment decision-making. Visual field defects, recurrences, and radiation seem to be a consistent predictor of poor quality of life.[63,64] Patel et al[64] reported higher quality of

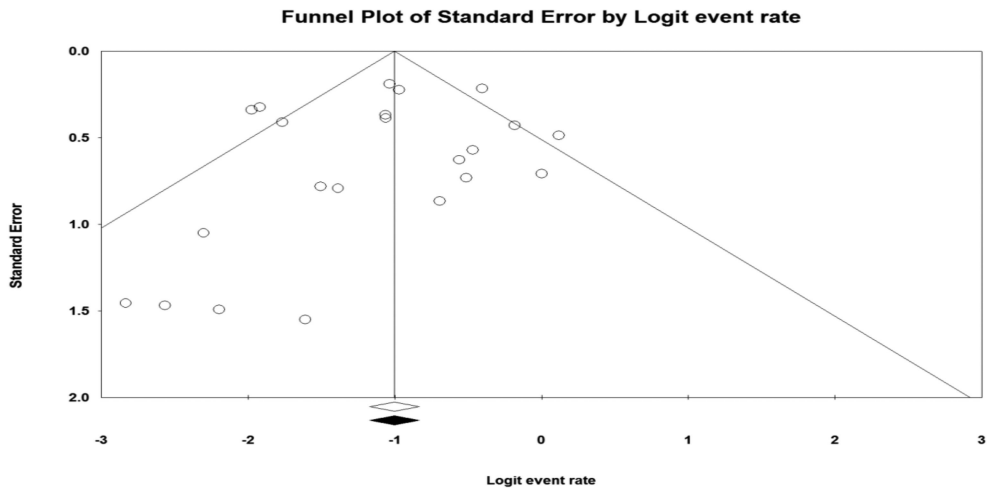

FIGURE 3. *Funnel plot showing study bias examination.*

TABLE 5. Differences in Rate of Recurrence.

		Effect size and 95% CI			Test of null (2-tail)		Heterogeneity			
Group	N	OR	Lower limit	Upper limit	*Z*-value	*P*-value	*Q*-value	df (*Q*)	*P*-value	*I*-squared
GTR vs STR	11	0.24	0.15	0.38	−5.98	.00	6.24	10	.79	0.00
GTR vs STR + XRT	9	0.63	0.33	1.24	−1.34	.18	8.14	8	.42	1.68
STR + XRT vs STR	8	0.20	0.10	0.41	−4.44	.00	4.25	7	.75	0.00

N, number of studies; OR, odd ratio; df, degree of freedom.

life scores associated with GTR. The effect of pituitary hormonal deficiencies on quality of life is inconsistent,[63,64] but quality of life impairment in pituitary disease has been well-documented.[65,66] Optimal hormonal substitution is reported to improve quality of life.[65] However, visual impairment is a permanent handicap. More studies are needed to assess quality of life in relation to extent of resection and treatment-related morbidities. This study highlights the need to report treatment related morbidity in future studies stratified to extent of resection.

The main limitation for safe total removal is hypothalamic invasion, which is associated with higher perioperative morbidity and mortality.[14] The risk of severe morbidity related to hypothalamus injury might outweigh the benefits of GTR. Each patient should be considered on a case-by-case basis given that GTR is not always feasible. Surgeons must take into account patient's characteristics and wishes. The literature reports a wide range (18%-84%) of childhood and adult cases that undergo GTR.[6,7,11,67] This may represent a difference in surgical philosophy. Overall, our study shows that 57.4% of patients in the literature undergo GTR.

Tumor size, location, and surgical approach are interrelated and to determine their individual potential contribution to tumor recurrence is difficult. Tumor size and location will determine surgical approach. In our study, choice of surgical approach did not have an effect on tumor recurrence rate. In a previous study,[12] tumor size was not correlated with recurrence rates. Each patient should have a personalized and tailored approach based on multiple individual factors, notably favorability of anatomy, and good surgical planes.[68,69] The choice of approach should aim at the shortest direct route and adequate exposure of tumor interface and critical structures.[68,69]

Strengths and Limitations

The usefulness of a systematic review is especially acknowledged in research on rare diseases.[70] Our study had an a priori established protocol. We proceeded to a comprehensive literature search with multiple databases. Independent reviewers conducted the process of study selection.

The main limitation of this report is the inability to extract and analyze treatment-related morbidity and mortality. Future research assessing disease for which extent of resection and adjuvant treatment is debatable should stratify and report morbidity and mortality per treatment modality. Should this type of data become available, analysis should be performed. Also,

the quality of the collected publications is of a noncomparative nature. The results of our center case series are not peer-reviewed. The studies included have inevitably an unknown treatment decision-making process. Modalities and neurosurgical technical advances have been made and treatment decision-making has evolved during the course of the published studies. A variation in the definition of tumor recurrence in some studies may result in overestimation or underestimation. Other variables are prone to subjectivity such as histological grade, extent of resection, as well as the appropriateness of XRT. The binary presentation of extent of resection (GTR vs STR) does not account the fact that some STRs with the intent of achieving GTR were probably more extensive resections vs planned STRs. Length of follow-up per treatment modalities was not stratified. A longer length of follow-up for a given treatment modality may increase number of recurrence reported.

Future research should report outcomes, such as recurrences and morbidities, stratified per treatment modalities, pathological subtypes, surgical approach, and type of radiation therapy.

CONCLUSION

This is the first and largest systematic review focusing on the rate of recurrence in adult craniopharyngioma. Based on our results, in the adult population, GTR leads to a lower rate of recurrence than STR + XRT, but statistical significance was not reached when assessing the risk of recurrence compared to STR + XRT. Each patient should be considered on a case-by-case basis. This meta-analysis provides valuable information to clinicians with benchmark numbers. This study provides guidance and directions for future research. Our study highlights the need to stratify outcomes by treatment modalities. A multicenter prospective data gathering could advance the state of the literature and patient care.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

This paper presents a meta-analysis based on a systematic review of the literature on adult craniopharyngioma. Unfortunately, there do not seem to be adequate numbers to make significant conclusions based on the available literature and following the exclusion criteria. As a result of exclusions, several large studies were excluded in favor of a multitude of

smaller case studies or single case reports which are likely to present more favorable outcomes and therefore potentially bias the review, regardless of statistical corrections. Perhaps as a result, their analysis shows that GTR is not statistically significantly different from STR + XRT.

In addition, it is concerning that 33% of patients from the authors' series were excluded. This is an extremely high number and creates concern for complication and follow-up bias. Pathological subtypes were also not available (even retrospectively determined) in their own series or in many of the studies. The impact of pathological subtype could bear significance and is currently lacking in the literature, as noted by absence of its evaluation in this analysis

Finally, the variable length of follow-up was not factored into the analysis. There is a significantly greater length of follow-up for the STR + XRT group which could explain the trend seen which favors GTR.

Despite these criticisms, I applaud the authors for their strenuous effort in this analysis and generally agree with their conclusions. The critiques presented are not of the paper itself, but rather a reflection of the overall inconsistency and quality of current neurosurgical literature on the topic. As molecular analysis of such tumors progresses, even leading to chemotherapeutic options, meticulous reporting of surgical results must become the standard.

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