Craniopharyngiomas are the most common pituitary masses in children. They represent 6–13% of all childhood brain lesions and are classified as intracranial tumors of benign or unspecified behavior by pediatric cancer registries. The Childhood Cancer Registry of Piedmont, Italy, has postulated an estimated incidence of 1.4 cases per million children per year with similar estimates provided by other cancer registries in Western countries. Epidemiologically, craniopharyngiomas have a bimodal age distribution pattern with a peak between 5 and 14 years and in adults older than 65 years, although the tumor has been reported in all age groups. Over the past few years Haupt et al. have documented dramatic improvements in survival, but craniopharyngiomas continue to pose a challenge for management teams, who must struggle to find that delicate balance between tumor control and the posttreatment quality of life in young children.

Craniopharyngiomas have a propensity to recur after resection, and if left untreated, these recurrences can cause death through their aggressive local behavior in their critical site of origin. Recent data suggest that subtotal resection (STR) followed by adjuvant radiotherapy (XRT) may be an appealing substitute for gross-total resection (GTR), providing similar rates of tumor control without the morbidity associated with aggressive resection. Here, the authors summarize the published literature regarding rates of tumor control with various treatment modalities for craniopharyngiomas.

Object. Craniopharyngiomas have a propensity to recur after resection, potentially causing death through their aggressive local behavior in their critical site of origin. Recent data suggest that subtotal resection (STR) followed by adjuvant radiotherapy (XRT) may be an appealing substitute for gross-total resection (GTR), providing similar rates of tumor control without the morbidity associated with aggressive resection. Here, the authors summarize the published literature regarding rates of tumor control with various treatment modalities for craniopharyngiomas.

Methods. The authors performed a comprehensive search of the English language literature to identify studies publishing outcome data on patients undergoing surgery for craniopharyngioma. Rates of progression-free survival (PFS) and overall survival (OS) were determined through Kaplan-Meier analysis.

Results. There were 442 patients who underwent tumor resection. Among these patients, GTR was achieved in 256 cases (58%), STR in 101 cases (23%), and STR+XRT in 85 cases (19%). The 2- and 5-year PFS rates for the GTR group versus the STR+XRT group were 88 versus 91%, and 67 versus 69%, respectively. The 5- and 10-year OS rates for the GTR group versus the STR+XRT group were 98 versus 99%, and 98 versus 95%, respectively. There was no significant difference in PFS (log-rank test) or OS with GTR (log-rank test).

Conclusions. Given the relative rarity of craniopharyngioma, this study provides estimates of outcome for a variety of treatment combinations, as not all treatments are an option for all patients with these tumors. (DOI: 10.3171/2010.1.FOCUS09307)

Key Words: craniopharyngioma, surgery, gross-total resection, radiotherapy, tumor control

**Abbreviations used in this paper:** fXRT = focal fractionated adjuvant radiotherapy; GTR = gross-total resection; OS = overall survival; PFS = progression-free survival; SRS = stereotactic radiosurgery; STR = subtotal resection; XRT = adjuvant radiotherapy.
treatment paradigms in providing baseline outcomes in patients with craniopharyngiomas.

**Methods**

**Article Selection**

Articles were identified via a PubMed search using the key phrases “craniopharyngioma” alone and in combination with “tumor control,” “recurrence,” “survival,” and “morbidity.” Inclusion criteria were as follows: 1) all patients had to have available follow-up data, and 2) articles had to have enough information for each patient to be disaggregated. Exclusion criteria involved the following: 1) articles that combined the outcomes of patients harboring craniopharyngiomas with those of patients harboring other childhood tumors were excluded, unless there was a clear distinction between the 2 separate groups of patients; and 2) Rathke pouch tumors were excluded from this study. After reviewing these articles, we thoroughly evaluated all referenced sources.

All references that contained disaggregated data specifically addressing tumor control or reporting progression with adequate follow-up in patients who had undergone resection with or without fXRT or SRS, as adjuvant therapy or monotherapy, were included in our analysis. Any paper that did not provide some follow-up imaging data on these patients was excluded, as the absence of such data would not facilitate a Kaplan-Meier analysis.

**Data Extraction**

Our searches yielded 274 studies reporting data for 8058 non-duplicated patients with craniopharyngiomas, the majority of whom were presented in aggregated data sets. Disaggregated data useable for survival and progression analysis was presented for 800 patients. The median largest tumor dimension and median tumor volume were not reportable or analyzable in our analysis, as studies did not consistently report either value. Data were stratified into 5 groups based on the treatment paradigm: STR alone, GTR alone, STR followed by XRT (STR+XRT), biopsy followed by fXRT (fXRT), or biopsy followed by radiosurgery alone (SRS). We hypothesized that tumors treated with SRS or radiotherapy without resection were probably anatomically and volumetrically different from those subjected to some form of surgery. This proposition is supported by the significantly smaller tumor sizes in patients undergoing fXRT. To control for this confounder, we did not directly compare the radiation-only groups (that is, the SRS and fXRT groups) with the surgically treated patients.

Tumor control data were included if adequate radiographic follow-up data were presented in the study, whether demonstrating evidence of recurrence or continued tumor control. The time to progression or recurrence (for simplicity, this idea from this point forward is referred to as “progression” regardless of the extent of resection) was defined as the time from diagnosis to radiographic evidence of progression. Progression-free survival and OS were calculated at the 1- and 5-year time points. Studies that did not present patient data in a way that these variables could be reliably determined were excluded from further analysis.

**Statistical Analysis**

The Pearson chi-square test was used to analyze for differences in categorical factors. The Fisher exact test was applied 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 and tumor size. Post hoc between-group analyses were performed using the Tukey test when the ANOVA demonstrated a p < 0.05. Kaplan-Meier estimates were used to generate time-to-progression curves. Differences in time to progression were analyzed using the log-rank test. Analyses were performed with SPSS, version 16.0 (SPPS, Inc.).

**Results**

**Clinical Characteristics of Included Patients**

As stated above, data for 800 patients were available for survival analysis. We limited our analysis to patients reported in studies since 1990, which limited us to 442 patients undergoing surgery (Table 1). Among these patients, GTR was achieved in 256 cases (58%), STR alone in 101 cases (23%), and STR+XRT in 85 cases (19%). Surgical patients in different cohorts did not differ in their mean age at the time of surgery, sex distribution, or pre-operative tumor size.

The mean overall follow-up for all patients in these studies was 54 ± 1.8 months.

**Gross-Total Resection Provides Improved Tumor Control Compared with STR**

To determine the impact of the extent of resection on tumor control rates, we compared rates of progression and OS in patients who underwent STR with rates in patients who underwent GTR. There were no significant differences between the 2 groups in terms of sex distribution (male sex 49 vs 46%, chi-square test), age (23 ± 1.3 vs 22 ± 1.9 years, ANOVA), or tumor size (3.0 ± 0.2 vs 3.7 ± 0.8 cm, ANOVA Tukey test). The 2- and 5-year PFS rates for the GTR group versus the STR group were 88 versus 67%, and 67 versus 34%, respectively. The 5- and 10-year

| TABLE 1: Clinical characteristics of the study group* |
|------------------|------------------|------------------|
| Characteristic   | GTR              | STR              | STR+XRT          |
| no. of patients  | 256              | 101              | 85               |
| sex (M/F)        | 127:129          | 45:56            | 34:51            |
| mean age in yrs† | 23 ± 1.3         | 22 ± 1.9         | 26 ± 2.0         |
| mean tumor size† | 3.0 ± 0.2        | 3.7 ± 0.8        | 3.5 ± 0.2        |

* The p value was not significant for any of the variables. † Values are expressed as the means ± SEs.
Tumor control in patients with craniopharyngioma

OS rates for the GTR group versus the STR group were 98 versus 96%, and 98 versus 93%, respectively. These values represented a statistically significant improvement in PFS (p < 0.0001, log-rank test), and a trend toward improved OS (p = 0.054, log-rank test; Fig. 1).

Subtotal Resection With Radiotherapy Can Replace GTR for Tumor Control

To determine the impact of the addition of radiotherapy to STR on tumor control rates, we compared rates of progression and OS in patients who underwent STR+XRT with the rates in patients who underwent GTR. There were no significant differences between the 2 groups in terms of sex distribution (male sex 49 vs 40%, chi-square test), age (23 ± 1.3 vs 26 ± 2.0 years, ANOVA), or tumor size (3.0 ± 0.2 vs 3.5 ± 0.2 cm, ANOVA Tukey test). The 2- and 5-year PFS rates for the GTR group versus the STR+XRT group were 88 versus 91%, and 67 versus 69%, respectively. The 5- and 10-year OS rates for the GTR group versus the STR+XRT group were 98 versus 99%, and 98 versus 95%, respectively. There was no significant difference in PFS (log-rank test) or OS with GTR (log-rank test; Fig. 2).

Discussion

Craniopharyngioma is a locally aggressive sellar/suprasellar mass with a high propensity for recurrence. This lesion is associated with decreased survival, demonstrating a 3–6 times higher mortality rate than the general population.31,198 The negative effect of tumor recurrence on the mortality rate is well documented31,124,252 with 10-year survival rates ranging between 29 and 70% depending on what modality of treatment is implemented.125 While there are few definitive studies regarding management strategies for these tumors, the general philosophy toward the treatment of these lesions has shifted toward less aggressive resection in appropriate circumstances, with tumor control after STR being achieved with radiotherapy or radiosurgery, if possible.

In this study, we systematically reviewed the published literature and summarized the rates of tumor control following various surgical and radiation-based treatments. We found that while GTR provides improved tumor control compared with STR alone, the addition of XRT to STR can provide tumor control rates essentially similar to those for GTR.

These data seem to support the idea that STR+XRT is a reasonable approach to achieve tumor control while
limiting hypothalamic and hypophysial morbidity associated with aggressive resection. Many investigators have associated very aggressive attempts at total tumor removal with markedly increased rates of anterior hypopituitarism, diabetes insipidus, growth disturbances, and behavioral and feeding abnormalities. For example, diabetes insipidus has been reported in 59–93% of cases following surgery.58,65,122 Panhypopituitarism occurs in 75–100% of patients who undergo resection.58,122 Hypothalamic obesity occurs in ~40% of patients postoperatively. It is important to consider these complications especially in young patients, who compose a large fraction of those with craniopharyngioma and for whom significant endocrinological problems can yield dramatic adverse effects. While radiotherapy is often not a reasonable option in very young children, when possible, it is generally believed to cause less local hypothalamic/hypophysial morbidity—and based on our analysis it seems to provide similar rates of tumor control.

**Study Limitations**

While these findings represent a helpful summary of the published literature on this topic, an analysis of the data is only as good as the composite studies and may reflect source study biases. It is impossible for us to control for the quality of data reported in the literature, and an overly stringent definition of tumor recurrence in some studies may overestimate rates of tumor control in other studies. Furthermore, subjectively defined variables, such as histological grade, extent of resection, and adequacy of radiation therapy, probably vary among studies, and we cannot independently confirm the validity of these definitions in other investigators’ studies. Moreover, our use of the Kaplan-Meier analysis largely precludes the use of formal meta-analysis, including the calculation of a Q-statistic, which allows one to determine how heterogeneous the data are. The inability to study this by using meta-analysis methods prevents us from addressing this limitation in a statistically meaningful way. Finally, given the diverse range of data presentation, the number of variables capable of being studied and controlled for is limited. Variables that might be of interest that are inconsistently presented across studies cannot be reviewed.

Additionally, we cannot analyze the effect of differences in treatment philosophies between institutions. Given that the extent of resection for craniopharyngiomas is frequently presented as a binary variable (that is, GTR or STR) in the literature, we cannot accurately deduce whether all GTRs were, in fact, GTRs. Furthermore, STRs performed by surgeons with the goal of achieving GTRs were probably more extensive resections than those performed by surgeons who sought to perform STRs only. Given that the goals of surgery for a given clinician are inconsistently published, we cannot control for this factor.

**Conclusions**

In summary, we reported the results of a review of the published literature on control rates of craniopharyngioma after treatment with various modalities. Thus, while we cannot absolutely guarantee that these data definitively predict the expected outcomes of patients undergoing these treatment paradigms, we think that our review provides a useful summary of the existing literature and that analysis of the data can yield useful insights on which to base future inquiries.

**Disclosure**

Dr. Parsa is supported in part by the Reza and Georgiana Khatib endowed chair in skull base tumor surgery. Dr. Sughrue is supported by the American Association of Neurological Surgeons’ Neurosurgery Research and Education Foundation. Mr. Rutkowski is supported by the Doris Duke foundation. Conception and design: AT Parsa, ME Sughrue, D Aranda. Acquisition of data: ME Sughrue, D Aranda. Analysis and interpretation of data: I Yang, ME Sughrue, R Kaur, D Aranda. Drafting the article: AT Parsa, I Yang, ME Sughrue, ME Ivan. Critically revising the article: AT Parsa, I Yang, ME Sughrue, MJ Rutkowski, R Kaur, ME Ivan, IJ Barani. Reviewed final version of the manuscript and approved it for submission: AT Parsa, I Yang, ME Sughrue, MJ Rutkowski, R Kaur, ME Ivan, D Aranda, IJ Barani. Statistical analysis: ME Sughrue, R Kaur, D Aranda. Administrative/technical/material support: ME Sughrue, D Aranda.

**Acknowledgment**

The authors thank statistician Mei Polley for her helpful input on methodological issues associated with systematic reviews of the literature.

**References**

Tumor control in patients with craniopharyngioma


51. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI,

Neurosurg Focus / Volume 28 / April 2010


67. Elwadidy SM, Jamzooin JA, Jamzooin AB, Yakoub AO: Cranio


Tumor control in patients with craniopharyngioma


I. Yang et al.
Neurosurg Focus / Volume 28 / April 2010

Tumor control in patients with craniopharyngioma


219. Sanford RA: Craniopharyngioma: results of survey of the
Tumor control in patients with craniopharyngioma


Address correspondence to: Andrew T. Parsa, M.D., Ph.D., Department of Neurological Surgery, University of California, San Francisco, 400 Parnassus Avenue, A808, San Francisco, California 94143-0350. email: parsaa@neurosurg.ucsf.edu.