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The superiority of conservative resection and adjuvant radiation for craniopharyngiomas

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Abstract

The purpose of this study is to evaluate the roles of resection extent and adjuvant radiation in the treatment of craniopharyngiomas. We reviewed the records of 122 patients ages 11–52 years who received primary treatment for craniopharyngioma between 1980 and 2009 at the University of California, San Francisco (UCSF). Primary endpoints were progression free survival (PFS) and overall survival (OS). Secondary endpoints were development of panhypopituitarism, diabetes insipidus (DI), and visual field defects. Of 122 patients, 30 (24%) were treated with gross total resection (GTR) without radiation therapy (RT), 3 (3%) with GTR + RT, 41 (33.6%) with subtotal resection (STR) without RT, and 48 (39.3%) with STR + RT. Median age at diagnosis was 30 years, with 46 patients 18 years or younger. Median follow-up for all patients was 56.4 months (interquartile range 18.9–144.2 months) and 47 months (interquartile range 12.3–121.8 months) for the 60 patients without progression. Fifty six patients progressed, 10 have died, 6 without progression. Median PFS was 61.1 months for all patients. PFS rate at 2 years was 61.5% (95% CI: 52.1–70.9). OS rate at 10 years was 91.1% (95% CI 84.3–97.9). There was no significant difference in PFS and OS between patients treated with GTR vs. STR + XRT (PFS; $p = 0.544$, OS; $p = 0.735$), but STR alone resulted in significantly shortened PFS compared to STR + RT or GTR ($p < 0.001$ for both). STR was associated with significantly shortened OS compared to STR + RT ($p = 0.050$) and trended to shorter OS compared to GTR ($p = 0.066$). GTR was associated with significantly greater risk of developing DI (56.3 vs. 13.3% with STR + XRT, $p < 0.001$) and panhypopituitarism (54.8 vs. 26.7% with STR + XRT, $p = 0.014$). In conclusion, for patients with craniopharyngioma, STR + RT may provide superior clinical outcome, achieving better disease control than STR and limiting side effects associated with aggressive surgical resection.

Keywords

Craniopharyngioma; Surgical resection; Radiation therapy; Adult; Pediatric

Introduction

Craniopharyngioma is a neuroepithelial tumor that comprises 6–9% of pediatric brain tumors and 1–4% of adult brain tumors [1–4]. The peak incidence is between ages 5 to 14 in childhood, although a second peak occurs during adulthood between 50 to 74 years [1]. Craniopharyngioma is thought to originate from squamous epithelial remnants of Rathke's pouch, an embryonic structure that ultimately forms the anterior pituitary gland [2]. The tumor is most often located in the infrasellar/suprasellar region of the brain and is frequently closely associated with adjacent structures such as the hypothalamus, pituitary gland, optic chiasm and carotid artery [3, 4].

The optimal treatment strategy for craniopharyngioma is controversial. Historically, gross total resection has been the preferred treatment approach, but the tumor's proximity to vital structures may lead to high rates of hypothalamic-pituitary and/or optic impairment [5–8]. Alternative approaches such as subtotal resection followed by adjuvant radiation therapy may have comparable long-term outcomes, while limiting side effects [5, 9–14]. Specifically, Yang et al. [5, 11–14], have shown no significant difference in tumor control rates between patients who received STR + RT vs. GTR and, a number of other studies have demonstrated a significantly higher risk of neurologic, ophthalmic, and endocrine side effects associated with GTR. Conversely, radiation therapy may lead to long-term problems such as vasculopathies, intellectual deficits, and secondary tumors [2, 11, 15, 16]. The issue of long-term toxicity caused by radiation is especially critical in the pediatric population, [11, 15–18].

The current study evaluates a historical cohort of patients treated at the University of California, San Francisco and seeks to examine the efficacy of different treatment approaches in the management of craniopharyngioma in both adult and pediatric patients.

Materials and methods

Existing pathology, neurosurgery, and radiation oncology databases were searched using keywords designed to retrieve all patients with craniopharyngioma treated at University of California, San Francisco between 1980 and 2009. Patients were excluded if: (1) initial surgery was not performed at UCSF; (2) initial treatment was unknown; (3) there was no confirmatory pathology; and/or (4) lost to follow-up within two weeks after initial treatment. The medical records were reviewed and the following data were collected: demographic information, treatment, treatment-related morbidity, and outcome. This study was approved by the UCSF Institutional Review Board.

The degree of resection was determined by reviewing the operative notes and post-operative imaging. All complete resections and near-total resections defined radiologically were classified as GTR, with all other surgical procedures, including biopsy with cyst aspiration, considered as STR. The histologic diagnosis was confirmed by a neuropathologist at UCSF. If progression was not documented, they were assumed to be progression-free upon the last day of documented contact. Patients were followed clinically and with imaging studies (MRI and/or CT). The imaging studies were performed during follow-up period at the discretion of the treating physician and were not done at uniform intervals for all patients. The development of endocrinopathies and visual field defects were documented in UCSF medical records or laboratory studies during the follow-up period after primary treatment.

SPSS version 18.0 was used for all statistical analyses. Progression Free Survival was defined as time between initial surgery and recurrence or death. If the patient was alive with no documented recurrence, the patient was censored for PFS at date of last follow-up. Overall Survival was defined as the time between initial surgery and death. Patients alive were censored at last known follow-up. Curves for PFS and OS were generated using the Kaplan–Meier method. A Cox model was used to assess the association between primary treatment and outcome while allowing for adjustment of other potential prognostic factors including age, gender, histology, and decade of diagnosis. Two-tailed Pearson's chi-square and Fisher exact tests were used to evaluate the relationship between the primary treatment, age, endocrinopathies, visual field defects, and histology.

Results

Patient and treatment characteristics

We identified 225 patients in our search, 122 of whom met our inclusion criteria. Reasons for non-eligibility included initial surgery was performed at an outside institution, initial treatment was unknown, no confirmatory pathology from a UCSF pathology review, and loss to follow-up within 2 weeks of initial treatment (see "Methods and materials" section for details). Patient characteristics are shown in Table 1. The median age at diagnosis was 30 years (inter-quartile range 11–52 years), with 47 patients age 18 or under at diagnosis. Sixty seven (55%) patients were male. There was a significant association between histology and age group ($p = 0.023$). Papillary histology was only detected in patients older than 18, whereas adamantinomatous histology was present in patients of all ages. GTR was performed in 33 patients (27%), 3 of whom received adjuvant RT (3%). Among the 89 patients that underwent STR, adjuvant radiation treatment was given in 48 cases (54%). Extent of resection and adjuvant radiation, according to age group and decade of diagnosis, are shown in Tables 2 and 3. Treatment was significantly associated with age group ($p <$

0.001). Among patients 3 years old or younger, STR + RT was not performed and STR only was performed in seven of 8 patients. In patients between the ages 3 and 18, 48% had a GTR, 26% of patients had STR without RT and 26% of patients had STR with RT whereas in patients older than 18, 17% had a GTR, 32% had STR without RT and 51% of patients had STR with RT. Treatment was not impacted by histological diagnosis ($p = 0.631$).

Over the duration of this historical cohort, five neuro-surgeons performed these surgeries. In general, GTR was done only if minimal morbidity could be achieved. Otherwise, the general philosophy was subtotal resection with XRT. Thirty three surgeries were done through transsphenoidal approaches, while the rest were performed via craniotomies.

Treatment outcomes

Fifty-six patients progressed, 10 died, 6 without known progression. The median follow-up for the 60 patients without progression was 46 months (interquartile range 12.5–119.9 months) and for all 122 patients was 56.4 months (interquartile range 18.5–142.6 months). Sixty patients (48.8%) were followed for a minimum of 5 years, 36 patients (29.3%) were followed for a minimum of 10 years and 13 patients (10.6%) patients were followed for a minimum of 15 years. Patients undergoing GTR had similar follow-up to those undergoing STR and STR + XRT. Median follow-up was 83.3 months (Interquartile range 24–169 months) for GTR, 46.3 months (Interquartile range 7–121 months) for STR, and 56.4 months (Interquartile range 27–144 months) for STR + XRT.

The median PFS was 61.1 months (95% CI 24.3–97.9) and PFS rate at 2 years was 61.5% (95% CI 52.1–70.9). OS rate at 10 years was 91.1% (95% CI 84.3–97.9). Kaplan meier curves for PFS and OS are shown in Fig. 1a, b, respectively.

PFS and OS for patients who received GTR, STR and STR + RT are shown in Fig. 2a, b. The PFS at 2 years for patients who received GTR, STR, and STR + XRT were 75.2% (95% CI 59.3–91.1), 36.2% (95% CI 20.1–52.3), and 73.3% (95% CI 60.4–86.2), respectively. The OS at 10 years for those who received GTR, STR, and STR + XRT were 96.2% (95 CI 88.8–100), 80.8% (95 CI 64.3–97.3), and 95.8% (95 CI 87.8–100), respectively. There was no significant difference in PFS or endocrinopathy with regards to treatment approach. The trans-sphenoidal approach, however, was associated with improved OS ($p = 0.006$).

The seven deaths that occurred in patients who were treated with STR were due to: a hemorrhagic infarct into the basal ganglia and frontal lobe 5 days after surgery; malignant melanoma 90 months after initial treatment; disseminated intravascular coagulation that occurred following salvage surgery 3.2 months after initial treatment; and four cases due to disease progression (9.7, 56.0, 125.1, and 291.2 months, respectively, after initial treatment). In patients treated with STR + XRT, two deaths were documented; one due to progression of disease 60 months after initial treatment and one from leukemia 151.4 months after initial treatment. In patients treated with GTR, there was one death due to a subarachnoid hemorrhage 22.3 months after initial surgery.

Univariate analysis is shown in Table 4. STR without XRT was significantly associated with a shortened progression free survival in comparison to STR + XRT (PFS; HR = 4.152, $p < 0.001$). There were no differences in PFS or OS between GTR and STR + XRT (PFS; HR = 1.240, $p = 0.544$. OS; HR = 0.659, $p = 0.735$). Increasing age at diagnosis as a continuous variable was also associated with decreased OS (HR = 1.35, $p = 0.051$), but not with PFS. Gender, histological diagnosis, and decade of diagnosis did not significantly affect PFS or OS. For PFS, where sufficient data was available, and adjusting for gender, histological diagnosis, age and decade of diagnosis, multivariate analysis was performed and confirmed treatment type as the only factor significantly associated with PFS.

Toxicities of treatment

One hundred and fifteen patients had endocrine data available. A pre-existing diagnosis of panhypopituitarism or diabetes insipidus (DI) prior to treatment in six and 16 patients, led to their exclusion from our evaluations of treatment toxicity. Seven additional patients were excluded from both analyses because there was insufficient data to determine their endocrine status.

For the GTR cohort, 26 and 29 patients, respectively, were assessable for DI and panhypopituitarism; for the STR without XRT cohort 37 were assessable for DI and panhypopituitarism; and for the STR + XRT cohort 44 and 43 patients, respectively, were assessable for DI and panhypopituitarism. Of patients treated with GTR, 18 developed DI and 17 developed panhypopituitarism; in the STR without XRT cohort 11 developed DI and 12 developed panhypopituitarism; and in the STR + XRT cohort six developed DI and 12 developed panhypopituitarism. A significantly higher percentage of patients treated with GTR developed DI and panhypopituitarism than patients who received STR or STR + XRT [(DI two-tailed Fisher's exact test: GTR vs. STR $p = 0.002$, GTR vs. STR + XRT $p < 0.001$, STR vs. STR + XRT $p = 0.100$); (panhypopituitarism two-tailed Fisher's exact test: GTR vs. STR $p = 0.046$, GTR vs. STR + XRT $p = 0.014$, STR vs. STR + XRT $p = 0.634$)].

Data were available on the visual status of 98 patients before and after surgical intervention. Thirty three patients did not have visual defects at baseline and only one (a patient who had a GTR) of these patients developed a worsening deficit after surgery. Of 17 GTR patients who had an initial deficit, 35.3, 29.4, and 35.3% were better, the same, and worse post treatment, respectively. Of 25 STR + XRT patients who had an initial deficit, 60.0, 20.0, and 20.0% were better, the same, and worse post treatment, respectively. Of 23 STR only patients who had an initial deficit, 47.8, 26.1, and 26.1% were better, the same, and worse post treatment, respectively. These differences were not statistically significant.

Other major adverse events included one case of a thalamic infarct post surgery and one case of a subdural hematoma, both occurring in patients who underwent GTR. In the STR + XRT group, one patient developed a left MCA infarct 2 years after treatment, one patient developed a left parietal infarct 7 years after treatment, and one patient had multiple strokes after treatment during a follow-up of 16.5 years. Additionally, 1 patient in STR + XRT developed parathyroid cancer 16 years after STR + XRT.

Discussion

In this report, we describe the UCSF experience for the treatment of craniopharyngiomas between 1980 and 2009. The disease control rates for patients undergoing GTR and STR + XRT were comparable and both were better than STR without adjuvant radiation. However, patients who underwent GTR had an increased rate of long-term endocrine deficits compared to those undergoing STR and STR + XRT.

Previously reported series of craniopharyngioma patients report conflicting results. Yang et al. [9] reviewed 442 patients who underwent tumor resection with a mean follow-up of 54 months, and found no significant difference in PFS and OS between GTR and STR + XRT. Stripp et al. [5] reported significantly better tumor control in patients treated with STR + XRT or GTR, compared to those who received STR only. Other studies maintain better outcomes for patients following GTR only [19, 20]. These inconsistencies among studies may be due to the variable nature of treatment selection at different institutions. Patients with less aggressive tumors may be disproportionately selected for GTR in some studies, accounting for the better GTR outcomes.

Data on treatment with STR only for craniopharyngioma consistently demonstrates that this treatment strategy is associated with poor outcomes. Yang et al. [9], showed a significantly decreased PFS and a trend towards decreased OS in STR only vs. GTR. Stripp et al. [5], found that the majority (78%) of patients who received STRs had tumor recurrences within a year if they did not receive XRT whereas patients who received postoperative radiation had a local control rate of 84% at 10 years. Our results are relatively similar in that 61% of patients who had STR without radiation progressed within 1 year. Karavitaki et al. [19] also found that patients who received STR + XRT had markedly better PFS rates than those who received STR only (77% PFS rate at 10 years for STR + XRT vs. 38% for STR only).

Data on toxicities among treatment approaches are also conflicting. Many studies have shown lower toxicity rates after STR compared with GTR, whereas others maintain no difference in toxicity among treatment approaches. Stripp et al. [5] report a significantly increased risk of DI when GTR is performed rather than STR. Merchant et al. [11, 14] and Thomsett et al. further report that GTR may be associated with higher rates of a number of endocrine disturbances including hypothyroidism, hypogonadism, and growth hormone insufficiency as well as neurologic and ophthalmic side effects. In contrast, Karavitaki et al. [19] and Weiner et al.[20] report no association between endocrine or neurologic side effects and treatment strategy. Studies that report comparable toxicities in STR as compared to GTR may have included a large number of more extensive resections in the STR group, which could explain the lack of association between toxicity and treatment strategy in these studies.

Our study evaluates a relatively large cohort of patients treated at a single institution with long follow-up over a period of 30 years. All patients had pathological confirmation by a UCSF neuropathologist, and regular follow up was documented. However, the inherent constraints of a retrospective study limit the conclusions we can draw from our findings with variability in surgery, radiation, and follow-up. Even longer follow-up may be especially important to assess the impact of long-term toxicity in patients treated at a young age. Furthermore, endocrinopathy from XRT may increase over time whereas endocrinopathy from surgical resection would likely occur closer to surgery. Therefore, the observed difference between GTR and STR + XRT may in actuality be less pronounced. Further studies with long follow-up of irradiated patients are necessary to evaluate endocrinopathy development over time.

We were not able to analyze the efficacy of other treatment modalities currently being used such as stereotactic radiosurgery and fractionated stereotactic radiotherapy since this is not the primary treatment philosophy at our institution. Minniti et al. [21] recently reviewed data in eight published studies for patients who received stereotactic radiosurgery and fractionated stereotactic radiotherapy for craniopharyngiomas (252 patients with a median follow-up of 57 months) and demonstrated the potential efficacy of these as primary treatment modalities. The study reported a control rate of 69% with no differences between children and adult patients in late toxicities (neurological and endocrine) ranging from 0–34%. Still, further prospective studies with long follow-up are needed to directly compare efficacy of stereotactic radiosurgery and fractionated stereotactic radiotherapy to GTR and STR + XRT.

Finally, our evaluation of toxicities following treatment was limited to the toxicities that were readily verifiable from the data available for our patients. Notably, toxicities associated with radiation, including vasculopathies and secondary tumors, did not occur commonly despite the long-term follow-up in this study. A total of five clinically significant vasculopathies occurred, two in the GTR group and three in the STR + XRT group. Only one secondary tumor occurred in the entire cohort–a parathyroid cancer that developed 16

years after radiation. Neuro-cognitive effects that may be associated with radiation therapy were not evaluated in this study.

We highlight and confirm the shortcomings of STR alone as primary treatment for craniopharyngioma. Patients who received STR only were at significantly increased risk of recurrence and death in comparison to patients who received STR + XRT or GTR. Moreover, our study demonstrated that patients who received GTR developed endocrine dysfunction at a significantly higher rate than those who received STR + XRT, with equivalent long-term efficacy, supporting SRT + XRT as an appealing treatment option. Further studies with longer follow-up are necessary to assess the long-term outcomes and morbidities associated with craniopharyngioma treatment, especially in the pediatric subpopulation.

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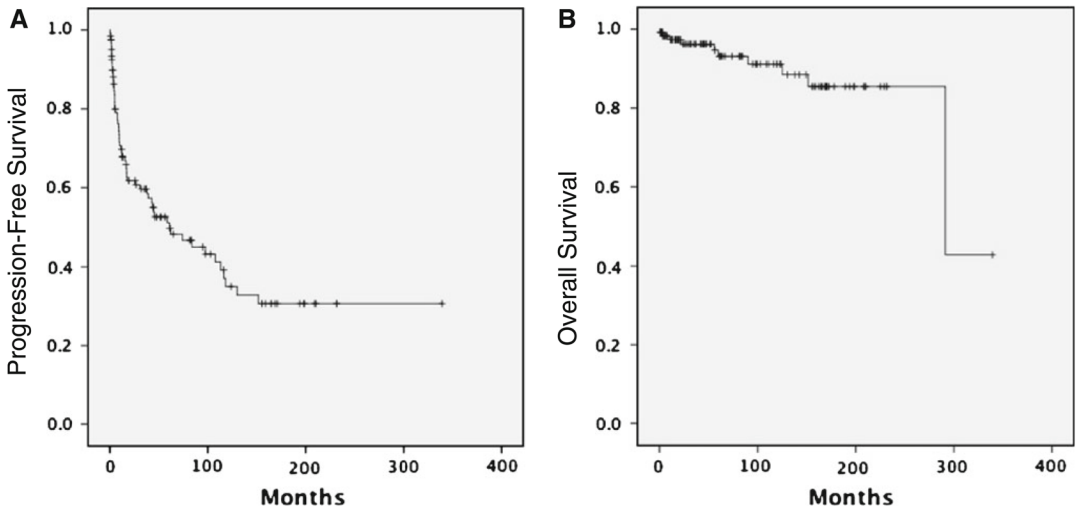

Fig. 1.
a Progression-free survival. **b** Overall survival for all patients (*n* = 122)

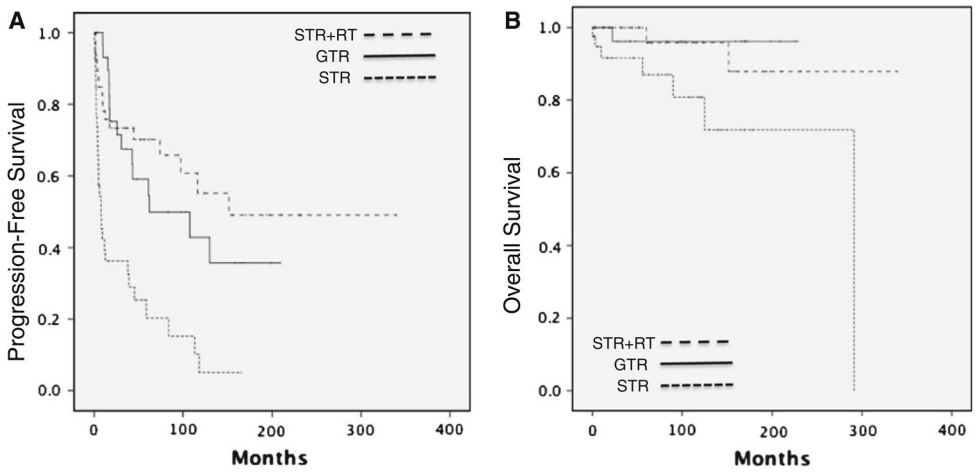

Fig. 2.

a Progression-free survival. **b** Overall survival according to treatment group. Gross total (*GTR*) resection: *solid line*. (*STR*) Subtotal resection plus adjuvant radiation (*RT*): *dashed line*. STR without RT: *dotted line*

Table 1

Patient characteristics and treatment details

Median age (interquartile range) in years	30 (11–52)
Median follow-up (interquartile range) in months	56.4 (18.9–144.2)
Sex M:F	67:55
Histology	
Adamantinomatous	79
Papillary	15
NOS	28
Primary therapy	
GTR alone	30
GTR + XRT	3
STR alone	37
STR + XRT	46
Biopsy or cyst aspiration	6
Decade of diagnosis	
1980s	28
1990s	49
2000s	45

Table 2

Extent of resection/adjuvant radiation by age group

	Number		
	≤3 years (*n* = 8)	**3 years < Age ≤ 18 (*n* = 39)**	**>18 years (*n* = 75)**
GTR	1	19	13
STR	7	10	24
STR + XRT	0	10	38

Table 3

Extent of resection/adjuvant radiation and endocrinopathy by decade of diagnoses

	Number (total)		
	1980s	**1990s**	**2000s**
GTR	6	19	8
Developed DI	4 (6)	10 (18)	4 (8)
Developed panhypopituitarism	4 (6)	11 (17)	6 (8)
Developed worsening visual defect	2 (4)	4 (11)	1 (3)
STR	7	15	19
Developed DI	2 (7)	7 (13)	2 (19)
Developed panhypopituitarism	1 (7)	7 (13)	4 (19)
Developed worsening visual defect	3 (5)	2 (7)	1 (11)
STR + XRT	15	15	18
Developed DI	2 (14)	0 (13)	4 (18)
Developed panhypopituitarism	5 (14)	1 (13)	6 (18)
Developed worsening visual defect	1 (7)	1 (4)	3 (14)

Table 4

Univariate analysis of progression-free survival and overall survival

Parameter	Progression free survival			Overall survival		
	Hazards ratio	95% CI	*p* value	Hazards ratio	95% CI	*p* value
Treatment			< 0.001			0.047
GTR vs. STR + RT	1.240	0.619–2.485	0.544	0.659	0.059–7.398	0.735
STR vs. STR + RT	4.152	2.264–7.614	< 0.001	4.880	1.00–23.740	0.050
GTR vs. STR	0.299	0.159–0.560	< 0.001	0.135	0.16–1.137	0.066
Age (years)	0.999	0.987–1.012	0.901	1.031	1.000–1.064	0.051
Gender (M/F)	1.102	0.665–1.826	0.706	1.319	0.371–4.689	0.669
Decade of diagnosis			0.403			0.160
1980s vs. 2000s	0.649	0.323–1.306	0.226	0.168	0.023–1.234	0.080
1990s vs. 2000s	0.952	0.523–1.733	0.873	0.257	0.048–1.394	0.115
Histology			0.231			0.583
Adamantinomatous vs. NOS	1.474	0.794–2.737	0.219	3.012	0.377–24.099	0.299
Papillary vs. NOS	0.728	0.237–2.235	0.579	0.000	0	0.988