

Gross Total Versus Subtotal Surgical Resection in the Management of Craniopharyngiomas

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Abstract

Craniopharyngiomas (CP) are suprasellar tumors that can grow into vital nearby structures and thus cause significant visual, endocrine, and hypothalamic dysfunction. Debate persists as to the optimal treatment strategy for these benign lesions, particularly with regards to the extent of surgical resection. The goals of tumor resection are to eliminate the compressive effect of the tumor on surrounding structures and minimize recurrence. It remains unclear whether a gross total resection (GTR) or subtotal resection (STR) with adjuvant therapy confers a better prognosis. Chemotherapy and radiation therapy (RT) have been explored as both neoadjuvant and adjuvant treatments to decrease tumor burden and prevent recurrence. The objective of this paper is to review the risks and benefits of GTR versus STR, specifically with regard to risk of recurrence and postoperative morbidity. Aggregated data suggest that STR monotherapy is associated with higher rates of recurrence relative to GTR (50.6% ± 22.1% vs 20.2% ± 13.5%), while STR combined with RT leads to recurrence rates similar to GTR. However, both GTR and RT are independently associated with higher rates of comorbidities including panhypopituitarism, diabetes insipidus, and visual deficits. The treatment strategy for CPs should ultimately be tailored to each patient's individual tumor characteristics, risk, symptoms, and therapeutic goals.

Keywords

craniopharyngioma, endoscopic skull base surgery, gross total resection, skull base tumor, subtotal resection

Introduction

Craniopharyngiomas (CPs) comprise 2–4% of intracranial tumors and up to 10% of pediatric brain tumors. The pediatric peak in presentation occurs between 5–15 years of age and is more often the adamantinomatous histopathologic subtype. CPs can also present in adulthood with a second peak between 50–70 years; in this age group, the papillary histopathologic subtype is more common. Though CPs are benign squamous cell epithelial tumors, they are challenging malignancies to manage due to their tenuous location within the brain and the undesirable sequelae of their growth.^{1,2}

CPs develop from Rathke's pouch and expand into the retrochiasmatic suprasellar region where they can impinge on vital nearby structures, including the optic chiasm, Circle of Willis, hypothalamus, and pituitary stalk. Thus CPs often present with severe headaches, progressive vision loss, growth failure in children,

diabetes insipidus (DI), loss of libido and energy, and other hypothalamic-pituitary axis neuroendocrinopathies.³ Unfortunately, these same symptoms are often also the complications of treating CPs due to their proximity to the aforementioned structures, therefore requiring extreme precision with surgery.⁴

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GTR Versus STR Paradigm

Given the invariable proximity to critical neurovascular structures, true complete resection of CPs is challenging, and gross total resection (GTR) has been defined as removal of 95% of the tumor.⁵ Conversely, a subtotal resection (STR) is intended to deliberately leave residual lesion to minimize risk of iatrogenic complication; while there is no uniform residual tumor percentage cutoff to define STR, some studies delineate it around 10%.^{6,7} STR is often combined with adjuvant radiation therapy (RT) to reduce the risk of recurrence, while introducing a distinct set of risks, especially in the pediatric population.⁸

Both GTR and STR have demonstrated success in alleviating the compressive symptoms of CPs.⁹ The optimal treatment strategy therefore depends on individual patient characteristics in addition to tumor location, size, and composition (cystic versus solid). Each approach can be considered with either an endonasal endoscopic approach or an open transcranial approach. As CPs constitute a rare and heterogenous diagnostic entity, there is limited data demonstrating which treatment strategy confers superior outcomes. The aim of this review is to highlight the advantages and disadvantages associated with each treatment approach.

Materials and Methods

A literature search was performed to identify all articles relevant to the topic of interest. PubMed was queried for “craniopharyngioma”, “surgical resection”, “gross total resection,” and “subtotal resection.” Studies were reviewed to determine those with data relevant to CP management. Only articles reporting primary data on the management and outcomes of patients with CPs were included. Articles were excluded if they did not report either recurrence rates or post-treatment morbidities stratified by treatment modality. Previously performed reviews and meta-analyses were cross-referenced to ensure all appropriate studies were included. Eighteen articles that discussed recurrence rates of craniopharyngiomas with respect to surgical treatment modality were identified. An additional four articles that studied post-operative morbidity with respect to treatment modality were also included. The data reported in these articles was tabulated and descriptive statistics were calculated to determine the frequency of recurrence and incidence of post treatment morbidity. The standard deviation of these percentages was also calculated to demonstrate the variance of the data set.

Results

A total of 1,366 patients underwent surgical treatment of craniopharyngioma (Table 1). Of 722 patients who

underwent GTR, the recurrence rate was 20.2% ($\pm 13.5\%$) as compared to 50.6% ($\pm 22.1\%$) in a total of 413 patients who underwent STR. Of the 204 patients treated with STR followed by adjuvant radiation therapy, there was a 22.1% ($\pm 26.2\%$) recurrence rate. Only 12 patients underwent GTR with radiation therapy, but of those 12, none were reported to have recurrence (Table 1, follow up of 2.2-10 years).^{6,7,11-16}

Post-treatment morbidity was reported for a total of 915 patients. Post-operative morbidity after GTR, STR, or STR combined with adjuvant radiation therapy included: endocrine dysfunction ($55\% \pm 5.8\%$, $48.9\% \pm 9.1\%$, $52.4\% \pm 7.7\%$ respectively), diabetes insipidus ($29\% \pm 18.6\%$, $19.5\% \pm 7\%$, $9.7\% \pm 4.6\%$ respectively), obesity (6% , 0% , 4% respectively), panhypopituitarism ($22\% \pm 30.1\%$, $16.1\% \pm 12.5\%$, $26.4\% \pm 2\%$ respectively), visual dysfunction ($8.5\% \pm 7.3\%$, $18\% \pm 19.2\%$, $12.7\% \pm 5.6\%$ respectively), and neurologic dysfunction (11% , 11% , 0% respectively) (Table 2).^{6,20,24,27}

Discussion

GTR Versus STR Recurrence Rates

GTR is associated with more post-operative morbidity but lower recurrence rates when combined with radiation therapy. STR is associated with reduced post-operative complications but an increased rate of recurrence; the addition of adjuvant RT reduces this recurrence rate.⁸ This is evident in multiple case series in which recurrence rates range from 24.8–100% after performing STR, as compared to recurrence rates ranging from 0–52.1% after GTR (Table 1, follow-up 2.2–10 years).^{6,7,10-26} In 1996 Eldevik et al. examined only CP patients who underwent STR and reported that the addition of radiation reduced recurrence from 85.6% to 35%.¹⁵ Multiple other studies have corroborated this finding, demonstrating that the addition of RT to STR reduced recurrence rates to 14–37.5%, which is comparable to the recurrence rates achieved after GTR in multiple series.^{6,12,16,18,20,21,24}

In 2000 Duff et al. published a nonrandomized case series of 121 CP patients in which 66 patients underwent GTR, 30 underwent STR, 3 underwent GTR+RT, and 22 underwent STR+RT. Of these groups, there was a 50% recurrence rate in the patients receiving only STR, and an 18.2% recurrence rate for GTR patients. The addition of RT further decreased recurrence rates to 9.1% and 0% in the STR and GTR groups, respectively.¹⁴ Overall the compiled data demonstrate comparable recurrence rates after GTR or STR+RT (20.2% vs. 22.1% respectively). This rate is considerably lower than the recurrence rate of 50.6% following STR monotherapy. These data suggest the superiority of GTR and STR+RT over STR monotherapy with regard to recurrence rates.

Table 1. Published Case Series of Craniopharyngioma Patients Managed Surgically.

Author(s)	Year	Total Patients	GTR (n)	GTR Recurrence	GTR+RT (n)	GTR+RT Recurrence	STR (n)	STR Recurrence	STR+RT (n)	STR+RT Recurrence
Cabezudo et al. ¹¹	1981	27	13	4 (30%)	–	–	14	10 (71%)	–	–
Crotty et al. ¹²	1995	47	11 ^a	2 (18%)	1 ^a	0 (0%)	19 ^a	14 (74%)	7 ^a	1 (14%)
Eldevik et al. ¹³	1996	41	–	–	–	–	21	18 (85.6%)	20	7 (35%)
Duff et al. ¹⁴	2000	121	66	12 (18%)	3	0 (0%)	30	15 (50%)	22	2 (9%)
Van Effenterre and Boch ¹⁵	2002	122	71 ^a	9 (12.7%)	–	–	46 ^a	20 (43.5%)	–	–
Stripp et al. ¹⁶	2004	75	48	25 (52.1%)	–	–	9	7 (77.8%)	18	3 (16.7%)
Chakrabarti et al. ¹⁷	2005	86	72	5 (6.9%)	–	–	14	6 (43%)	–	–
Tomita and Bowman ¹⁸	2005	54	43	18 (41.8%)	–	–	3	3 (100%)	8	3 (37.5%)
Balde et al. ¹⁹	2007	36	31	8 (25.8%)	–	–	4	1 (25%)	–	–
Kim et al. ²⁰	2012	146	53	10 (19%)	–	–	41	23 (56%)	52	7 (14%)
Lee et al. ²¹	2012	90	61	20 (32.8%)	4	0 (0%)	15	11 (73.3%)	10	5 (50%)
Lopez-Serna et al. ²²	2012	102	46	5 (10.9%)	–	–	56	23 (41.1%)	–	–
Schoenfeld et al. ⁶	2012	122	30	8 (24.8%)	3	N/R	41	26 (63.8%)	48	13 (26.7%)
Koutourousiou et al. ²³	2013	64	24	6 (25%)	–	–	40	16 (40%)	–	–
Lee et al. ⁷	2015	81	71	7 (9.9%)	–	–	10	3 (30%)	–	–
Park et al. ²⁴	2017	116	54	5 (9.3%)	–	–	44	10 (22.7%)	18	3 (16.7%)
Patel et al. ²⁵	2017	16	14	1 (7.1%)	1	N/R	–	–	1	1 (100%)
Schelini et al. ²⁶	2019	20	14	0 (0%)	–	–	6	3 (50%)	–	–
Total		1366	722	146 (20.2% ± 13.6%)	12	0 (0% ± 0%)	413	209 (50.6% ± 22.1%)	204	45 (22.1% ± 26.2%)

Abbreviations: GTR, gross total resection; RT, radiation therapy; STR, sub-total resection.

^aNumbers reflect patients with follow-up.

Table 2. Published Case Series of Craniopharyngioma Post-Op Morbidities.

Author(s)	Year	Total Patients	GTR (n)	GTR Morbidity	STR (n)	STR Morbidity	STR+RT (n)	STR+RT Morbidity
Clark et al. ²⁷	2012	531	191 ^a	ED 108 (59%) DI 46 (25%) Obesity 10 (6%) PH 27 (15%) VD 9 (5%) ND 20 (11%)	46 ^a	ED 27 (59%) DI 6 (13%) Obesity 0 (0%) PH 2 (4%) VD 2 (4%) ND 5 (11%)	24 ^a	ED 11 (46%) DI 1 (4%) Obesity 1 (4%) PH 7 (29%) VD 1 (4%) ND 0 (0%)
Kim et al. ²⁰	2012	146	53	VD 8 (15%)	41	VD 21 (51%)	52	VD 10 (19%)
Schoenfeld et al. ⁶	2012	122	33	DI 18 (55%) PH 21 (64%) VD 7 (21%)	41	DI 11 (27%) PH 12 (29%) VD 6 (15%)	48	DI 6 (13%) PH 12 (25%) VD 5 (10%)
Park et al. ²⁴	2017	116	54	ED 26 (48.1%) VD 4 (7.8%)	44	ED 17 (40.5%) VD 2 (4.5%)	18	ED 11 (61.1%) VD 2 (11.1%)
Total ^b		915	331	ED 134 (55% ± 5.8%) DI 64 (29% ± 18.6%) Obesity 10 (6% ± 0%) PH 49 (22% ± 30.1%) VD 28 (8.5% ± 7.3%) ND 20 (11% ± 0%)	172	ED 44 (48.9% ± 9.1%) DI 17 (19.5% ± 7%) Obesity 0 (0% ± 0%) PH 14 (16.1% ± 12.5%) VD 31 (18% ± 19.2%) ND 5 (11% ± 0%)	142	ED 22 (52.4% ± 7.7%) DI 7 (9.7% ± 4.6%) Obesity 1 (4% ± 0%) PH 19 (26.4% ± 2%) VD 18 (12.7% ± 5.6%) ND 0 (0% ± 0%)

Abbreviations: DI, diabetes insipidus; ED, endocrine dysfunction; ND, neurologic dysfunction; PH, panhypopituitarism; VD, visual dysfunction.

^aNumbers reflect patients with follow-up.

^bTotal percentages were calculated based on the total number of patients in whom the morbidity was evaluated.

GTR Versus STR Post-Operative Morbidity

Consideration of iatrogenic morbidity is essential in determining the optimal treatment plan for management of CP tumors. In 1998, Xu and Shigemori described the

post-operative complications in 56 patients with CPs (20 children and 36 adults): they observed that surgery, while effective in achieving remission in 52 (92.9%) of the patients, also left patients with new permanent

diabetes insipidus (63.5%), hypothyroidism (60.5%), and pan-hypopituitarism (14.3%).⁴ Both GTR and STR with or without RT are associated with these significant post-surgical endocrinopathies. In general, the aggregated data shows that GTR is associated with higher rates of post-treatment endocrinopathy as compared to STR and STR/RT, however the addition of radiation therapy increases complication rates over STR alone for certain endocrinopathies. For example, STR reduced the rates of endocrine dysfunction from 55% to 48.9%, DI from 29% to 19.5%, obesity from 6% to 0%, and panhypopituitarism from 22% to 16.1% as compared to GTR, but the addition of radiation therapy increased the rates of endocrine dysfunction back up to 52.4%, obesity back up to 4%, and panhypopituitarism to 26.4%. Thus while radiation therapy is effective in reducing recurrence rates of STR-treated CPs, it may leave patients with higher rates of post treatment morbidity. The reported complications from adding RT onto STR varies from study to study.

In 2012, Clark et al. explored how post-operative morbidity differed based on the type of surgical treatment in a pediatric population. Of 531 patients, 89 had pre-operative endocrine dysfunction and 96 had pre-operative visual dysfunction. Of the reported GTR patients with adequate follow-up data, 108 of 191 (59%) experienced post-operative endocrine dysfunction, 46 (25%) developed DI, 10 (6%) developed obesity, 27 (15%) developed pan-hypopituitarism, 9 (5%) developed visual deficits, and 20 (11%) developed neurological injury.²⁷ STR+RT reduced the incidence of most of these complications, and significantly reduced the incidence of post-operative DI to 4% (Table 2).^{6,20,24,27}

Schoenfeld et al. further demonstrated that of 122 CP patients treated either with GTR or STR+RT, GTR was associated with significantly increased rates of DI (56.3% vs 13.3%) and pan-hypopituitarism (54.8% versus 26.7%) with no overall difference in 5-year progression free survival.⁶ While adjuvant RT reduces recurrence rates following STR, Clark et al. reported post-op pan-hypopituitarism in 4% of patients undergoing STR alone as compared to 29% in patients undergoing STR+RT.²⁷ Although not statistically significant, Park et al.'s case series further demonstrates the trend of a direct relationship between RT and increased morbidity: post-operative endocrinopathies increased from 40.5% in STR patients to 61.1% in STR+RT patients, superseding the GTR endocrinopathy complication rate of 48.1%. Similarly, visual dysfunction increased from 4.5% in STR patients to 11.1% in STR+RT patients, also superseding 7.8% in GTR patients.²⁴ Radiation therapy has also been reported to carry risk of decreased IQ and other psychosocial issues.⁹ The rates of radiation-induced secondary malignancy in CP patients is not well understood.

Finally, Jensterle et al. report that while 40–87% of pediatric patients and 41–73% of adult patients with CPs have endocrinopathies at diagnosis, this complication increases to 64–100% of children and 48–97% of adults post-treatment, regardless of the treatment modality. In fact, 43–100% of pediatric patients and 59–74% of adult patients experienced post-treatment pan-hypopituitarism, defined as 3 or more anterior pituitary hormone deficiencies.¹

Limitations

This review is inherently limited by the scope of the original studies whose data is compiled here. The papers ranged in publication date from 1981 to 2019, during which endoscopic surgery became a popular approach for the treatment of craniopharyngiomas. For example, a 2012 meta-analysis by Komotar et al. reported on 2967 patients that underwent transcranial management for CPs versus 149 patients who underwent endoscopic management from 1995 to 2010; in this study, endoscopic surgery was not reported until 1997 and did not gain traction as an option until 2006 when its use skyrocketed.²⁸ Although a breakdown of how frequently each approach is used today does not exist, tracking these trends suggests that the advent of endoscopic surgery likely changed treatment options, recurrence rates, and post-operative sequelae in the management of CP's. Furthermore, radiation protocols have become more advanced to limit the amount of radiation to surrounding tissue, thereby minimizing iatrogenic morbidity.²⁹ Different treatment options may alter the associated recurrence and complication rates for this disease. More recent papers may report fewer post treatment complications due to these changes in clinical practice.

The papers examined also demonstrate significant heterogeneity in terms of their sample sizes, as reflected in the wide range in the standard deviations calculated. Finally, publication bias may contribute to an underestimation of post treatment morbidity. Limited follow-up may falsely lower the reported rate of recurrence. Further research is warranted to elucidate the optimal treatment modality for patients with craniopharyngioma tumors.

Conclusion

Craniopharyngiomas are benign suprasellar tumors of Rathke's pouch that can cause severe neuroendocrinopathies and visual deficits as a result of the tumor's proximity to critical intracranial structures. The suprasellar location of CPs predisposes risk of injury to critical neighboring structures including the optic chiasm, hypothalamus, and pituitary stalk. Both surgical and nonsurgical treatment of these lesions are associated with

similar complications, including DI, hypopituitarism, obesity, and visual deficits.

Both GTR and STR have been explored as treatment modalities in CP treatment. GTR is associated with increased risk of surgical complications compared to STR. While STR combined with adjuvant RT reduces the rate of recurrence, it may lead to increased risk of future RT related complications. Ultimately, the management of craniopharyngiomas should be tailored to the individual and will depend on each patient's unique clinical factors. An individual risk-benefit analysis should be performed incorporating the patient and family's preferences to develop a treatment strategy that balances symptoms, treatment morbidity, and risk of recurrence.

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by our institutional review board.

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Statement of Human and Animal Rights

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Statement of Informed Consent

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