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Craniopharyngioma: Safe Adequate Resection with Adjuvant Therapy A Better Choice?

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ABSTRACT

Background: Craniopharyngiomas are rare epithelial tumors arising along the path of the craniopharyngeal duct. Craniopharyngiomas are usually treated with surgery, often radical, with or without radiotherapy. Lifelong follow-up is crucial because of the risk of recurrence and the need for ongoing hormone replacement therapy.

Aims: Surgical outcome in cases of craniopharyngioma.

Settings and Design: Retrospective analysis from hospital information system.

Methods: All patients who underwent surgery for craniopharyngioma during January 2001 to October 2014 were included for the retrospective analysis. Age, gender, clinical features, radiological features, extent of resection, adjuvant therapy, endocrinological and clinical outcome were considered for the analysis.

Statistical analysis used: Chi-Square Test, Kaplan-Meier Analysis

Results: A bimodal age distribution, no gender predilection, and pituitary hormone deficiency was seen for this tumour at presentation. Following aggressive surgery, the rate of pituitary hormone deficiencies, diabetes insipidus and chances of injury to surrounding vital structures increases resulting in more morbidity and mortality. Visual deficits are common and post-surgery, there is significant improvement in visual outcome. The Kaplan Meier estimate revealed median recurrence-free survival rate of 186 months after total removal of tumour, 69 months after subtotal and 20 months after partial excision of tumour.

Conclusions: Less aggressive the resection with adjuvant therapy, more better is the functional outcome. The sample size and the follow up period in the current study being relatively short, a larger study sample and a longer follow up study may be needed before any further conclusions can be made. To summarise, there is no universal treatment protocol. We have a long way to go in order to make craniopharyngioma treatment as "once-in-a-lifetime experience" for our patients.

KEYWORDS: Craniopharyngioma, Retrospective Study, Surgical Outcome, Safe Resection.

INTRODUCTION

"There is perhaps no other primary brain tumor that evokes more passion, emotion, and as a result, controversy than does the craniopharyngioma"

– James T. Rutka[1]

Craniopharyngiomas are rare epithelial tumors arising along the path of the craniopharyngeal duct. They are parasellar tumour that constitutes about 3% of all intracranial tumours and up to 10% of childhood brain tumours.[2] Despite their benign histological appearance, their often infiltrative tendency into critical parasellar structures and their aggressive behaviour causes serious morbidity by damaging the optic chiasm, the pituitary and hypothalamic area and sometimes obstructing the third ventricle. Even after apparently successful therapy, may result in significant morbidity and mortality posing a considerable medical and social problem. Craniopharyngiomas are usually treated with surgery, often radical, with or without radiotherapy.

Lifelong follow-up is crucial because of the risk of recurrence and the need for ongoing hormone

replacement therapy. This manuscript highlights the clinical and laboratory features of craniopharyngiomas at presentation and analyzes the pros and cons of the available therapeutic options with respect to endocrinological outcome, tumour recurrence and clinical status.

MATERIALS AND METHODS

It was a retrospective study for surgical outcome in cases of craniopharyngioma. All patients who underwent surgery for craniopharyngioma during January 2001 to October 2014 were included for the retrospective analysis. Age, gender, clinical features, radiological features, extent of resection, adjuvant therapy, endocrinological and clinical outcome were considered for the analysis. Tumor removal was considered complete if postoperative contrast-enhanced MR imaging (or early in the series contrast-enhanced CT scanning) showed no evidence of residual tumor. Removal was considered subtotal when only a small portion of residual tumor remained because of firm attachment to vascular or neural structures or when postoperative imaging revealed a small contrast-enhancing or calcified area. Partial removal was defined as the presence of a larger residual portion of tumor.

Out-patient and In-patient data along with radiological and endocrinological data was reviewed from the hospital information system. Ethical clearance was obtained from institutional review committee.

STATISTICAL ANALYSIS

Categorical data were expressed as rates, ratios and percentages and the comparison was done using chi-square test. Continuous data was expressed as mean ± standard deviation. Probability of recurrence free survival rate was computed applying Kaplan-Meier Analysis.

RESULTS

The result of the study was analysed by appropriate statistical tools. 60 patients were included in the study, out of which 3 patients died immediately during postoperative period due to hypothalamic injury and whose detailed follow up was not possible. The mean and median follow up period was 85 and 78 months respectively.

The age of patient ranged from 3 years to 77 years. 46% of patients were below 20 years and 28% of patients were between 4^{th} and 6^{th} decade. Hence bimodal age distribution was seen. 56% were males and 44% were females. There was no definite gender predilection but slight male preponderance was seen. Features of raised ICP (70%) like headache, vomiting etc. was the most common mode of presentation followed by visual (65%) and endocrinological (49%) symptoms respectively. Bitemporal field defect was the most common visual disturbance. Generalized weakness, lethargy, growth retardation, hypogonadal, hypocortisol and hypothyroidism features were the most common endocrinological symptoms.

In our study, 21% of the tumours were purely cystic, 14% predominantly cystic, 35% predominantly solid and 30% were purely solid in consistency. Following surgery all patients underwent imaging to know the extent of resection. We found 24.5% patients underwent complete excision, 51% subtotal and remaining 24.5% underwent partial excision of the tumour. 3 patients who died due to hypothalamic injury were found to have complete excision on postoperative imaging.

When immediately assessed for diabetes insipidus postoperatively, we found that 61% had transient features of diabetes insipidus which resolved over week's period, 32% had prolonged diabetes insipidus and had to be discharged with medication and 7% had no features of diabetes insipidus. It was observed that 3 (21%) patients with partial excision, 10 (35%) patients with subtotal excision and 5 (36%) patients who had undergone complete excision respectively, had permanent diabetes insipidus immediately following surgery. On long follow up it was found that 40 patients had developed permanent diabetes insipidus over a period of time. Out of 40 patients, 11 (79%) underwent complete excision, 19 (66%) underwent subtotal excision and 10 (71%) patients underwent partial excision. Further it was found that 8 patients who undergone partial excision and 9 patients who had undergone subtotal excision developed permanent diabetes insipidus following adjuvant radiotherapy. Also it was observed that 6 patients who had undergone complete excision later over a period of time developed permanent diabetes insipidus.

Following surgery, 28% patients newly developed thyroid and cortisol hormone deficiencies respectively which were needed to be replaced and were on hormone replacement therapy.[Table-1]

With respect to Karnoffsky performance status scale, we found that 100% patients with partial excision and 90% with subtotal excision had KPS above 90%, whereas only 29% patients with complete excision had above 90% KPS on long follow up.[Table-2]

In the present study, 20 patients who had normal vision preoperatively had same vision post operatively and hence there was no change. Out of 37 patients who had visual disturbance preoperatively, 32 patients improved, 3 patients deteriorated and 2 patients had same vision even following surgery. Out of 32 patients who had improvement in vision following surgery, 9 patients underwent partial and complete excision respectively and 14 patients underwent subtotal excision. Out of 3 patients who had visual deterioration following surgery, each underwent partial, subtotal and complete excision respectively. It was also observed that following partial excision, 1 patient who had visual deterioration was not

immediate following surgery but was after adjuvant radiotherapy. 2 patients whose visual status remained same following surgery had undergone subtotal excision. When the analysis was done statistically using chi square test, P – values were found to be more than 0.05 and hence there was no significant association between the type of resection and various parameters like immediate diabetes insipidus status, long term diabetes insipidus status, hormonal status, karnoffsky performance status scale and visual status.

Table 1: Postoperative need for hormone replacement therapy

Hormone Replacement Therapy		Replacement		
		Present		Absent
		Newly Developed	Pre Existing	
Cortisol Hormone Replacement	No. of cases	16	21	20
	Percentage	28	37	35
Thyroid Hormone Replacement	No. of cases	16	18	23
	Percentage	28	32	40
Growth Hormone Replacement	No. of cases	0	4	53
	Percentage	0	7	93
Sex Hormone Replacement	No. of cases	0	10	47
	Percentage	**0**	**18**	**82**

Table 2: Co-relation Between Excision Status and KPS

Excision status	Karnoffsky Performance Status Scale					Total (n=57)
	60%	70%	80%	90%	100%	
Partial	00 (0%)	00 (0%)	00 (0%)	06 (42%)	08 (58%)	**14 (100%)**
Subtotal	00 (0%)	01 (3%)	02 (7%)	17 (59%)	09 (31%)	**29 (100%)**
Complete	03 (21%)	04 (29%)	03 (21%)	04 (29%)	00 (0%)	**14 (100%)**
Total	**03 (5%)**	**05 (9%)**	**05 (9%)**	**27 (47%)**	**17 (30%)**	**57 (100%)**

Table 3: Co-relation between Excision Status and Recurrence

Excision status	Recurrence		Total
	Present	Absent	
Partial	08 (57%)	06 (43%)	14 (100%)
Subtotal	17 (59%)	12 (41%)	29 (100%)
Complete	04 (29%)	10 (71%)	14 (100%)
Total	29 (51%)	28 (49%)	57 (100%)
(X^2, p = 0.157, p > 0.05 - insignificant)			

Table 4: Co-relation Between Consistency of tumour and Recurrence

Consistency of tumour	Recurrence		Total
	Present	Absent	
Purely Cystic	05 (42%)	07 (58%)	12 (100%)
Predominantly Cystic	04 (50%)	04 (50%)	08 (100%)
Predominantly Solid	11 (55%)	09 (45%)	20 (100%)
Solid	09 (53%)	08 (47%)	17 (100%)
Total	29 (51%)	28 (49%)	57 (100%)
(X^2, p = 0.772, p > 0.05 - insignificant)			

With respect to recurrence in the present study we found that out of 14 patients with complete excision, 04 (29%) patients had recurrence. Also out of 14 patients with partial excision, 08 (57%) had progression of disease and 06 (43%) had stable residue. Out of 29 patients with subtotal excision, 17 (59%) had recurrence and 12 (41%) patients had stable residue. [Table-3]

It was also found that all the patients with stable residue had received adjuvant radiotherapy following surgery. It was also found that 43% patients with purely cystic consistency, 50% with predominantly cystic consistency, 55% with predominantly solid consistency and 53% with purely solid consistency had recurrence on long follow up. [Table-4]

The Kaplan–Meier estimate revealed median recurrence-free survival rates of 186 months after total removal of the tumour. The mean recurrence free survival rate was 150.16 months with standard error of 20.412 with 95% confidence interval with 110.15 and 190.16 as lower and upper limit respectively. 4 patients whose first surgery were done before 2001 outside our institution by our own surgeons but were following up with our institution since 2001 were also included in this study.

The median recurrence-free survival rate was 69 months after subtotal excision of the tumour. The mean recurrence free survival rate was 65.70 months with standard error of 10.70 with 95% confidence interval with 44.72 and 86.67 as lower and upper limit respectively. The median recurrence-free survival rate was 20 months after partial removal of the tumour. The mean recurrence free survival rate was 49.56 months with standard error of 16.768 with 95% confidence interval with 16.70 and 82.43 as lower and upper limit respectively. Here, on applying chi square, the p-value was found to be less than 0.05 and hence there was significant association between extent of resection and recurrence free survival rate. (X^2, $p = 0.002$, $p < 0.05$ - significant). More aggressive was the resection, better was the recurrence free survival period but more were the morbidity and mortality.

DISCUSSION

Craniopharyngiomas are considered WHO Grade I tumors, and gross total resection has been regarded as the primary treatment modality during the past several decades. The overall objective, however, remains tumor cure without causing intolerable patient disability.

The potential proximity to and the subsequent pressure effects of craniopharyngiomas on vital structures of the brain predispose the patients to multiple clinical manifestations.[3,4] The severity of the clinical manifestations depends on the location, the size, and the growth potential of the tumor. At diagnosis 40–87% of patients have been identified to have at least one hormone deficiency.[5-7]

In our series, at diagnosis 60 % of patients have been identified to have at least one hormone deficiency. Post-surgery, the rate of pituitary hormone deficiencies increases and has been reported to be 80–100%.[5,6,8-14] In our series, we found that there was no change in preoperative and postoperative levels of growth hormone, follicle stimulating hormone, luteinizing hormone and testosterone. We also observed that 16 patients newly developed hypocortisolism and hypothyroidism respectively following surgery. Out of 16 patients who newly developed hypocortisolism, 6 (43%) patients underwent complete excision, 8 (28%) subtotal excision and 2 (14%) partial excision.

Out of 16 patients who newly developed hypothyroidism, 7 (50%) patients underwent complete excision, 6 (28%) subtotal excision and 3 (21%) partial excision.

In our series, there was no significant difference between type of resection and pituitary hormone deficiency statistically but grossly we could find that as the resection is aggressive, more is the insult to the endocrinological parameters.

Diabetes Insipidus

Transient post-surgical diabetes insipidus is a prevalent finding that has been described to occur in almost all patients in some series.[6,11,15] Permanent DI after treatment was found in different series to range between 60–90% after aggressive surgery and 50–55% after less aggressive surgery combined with radiation therapy.[5,6,8,9,11,14-18] In our study, we also tried to differentiate with surgical management but there was no statistical significance with respect to type of resection. But this is probably due to less number of cases which prevents actual statistical analysis.

Visual outcome

Visual deficits are common and result either from direct compression of optic pathways or from increased intracranial pressure. Visual field defects are a common presenting sign in patients with craniopharyngioma. Visual fields/visual acuity reportedly improved or stabilized in 74% of patients in a series study by Pereira A. M. et al.[19,20] In our series, 95% of patients had same or improve visual deficits following surgery. However, despite this, the incidence of long-term major visual field defects has been reported to be 48% at 10 year follow-up.[21]

Extent of Tumour Resection

When reviewing the literature, different philosophies are encountered for the surgical management of craniopharyngiomas. Some authors follow a strictly surgical attitude, espousing total tumor removal in all cases. Yasargil et al. has argued: "The strategy is that of complete tumor removal followed by appropriate substitution therapy rather than risking repeated surgical procedures and/or irradiation, with its unpredictable side effects." This attitude carries the risk of higher rates of early morbidity and mortality.[22]

Hoffman and colleagues described their goal as being "total excision of a craniopharyngioma whenever possible" and accomplished total removal in the majority of their cases.[5] Symon and associates suggest that "maximal control of tumour recurrence by removal of all tumour accessible and visible to the surgical microscope is best achieved by a radical excision at the first operation."[23]

With this attitude, in our series complete tumor removal was accomplished in 24.5% of patients who underwent transcranial operations. Only 3 of the patients who underwent transcranial surgery with complete excision of the tumor died in the early postoperative period mainly due to hypothalamic injury. In our series, the

main problems were tight adherence of tumor to the hypothalamus, major calcifications, and adherence of tumor to vascular structures.

Thus far, only a few studies have detailed the intraoperative hazards and the reasons for incomplete tumor removal. Craniopharyngioma tissue and glial tissue are sometimes intimately connected.

The view point that "A firmly attached capsule should not be removed", has found support in a recent publication: the authors demonstrated that removal of tumor adherent to the hypothalamus was directly associated with significant occurrence of operative morbidity. Other authors recommend the concept of conservative or limited surgery plus radiotherapy. The surgical mortality rate of recent large surgical series is generally between 0% and 5%. The mortality rate of 16.7% in the series of Yasargil et al., in which the surgeons aggressively performed total removal in all cases, is an exception.[22]

Tumour Recurrence

Hoffman et al. has demonstrated that residual tumor is relatively often detected during postoperative imaging after what was believed to be a complete tumor removal.[5] This was also experienced by us. With the requirement of postoperative MR imaging and/or CT scanning, only approximately 10 to 30% of totally resected craniopharyngiomas recur, as confirmed by our study. Recurrence rates dramatically increase if craniopharyngiomas are incompletely removed.

Our data impressively demonstrate that freedom from tumor recurrence is closely correlated to the extent of surgical removal. Tumour recurrences mostly occur within the first 5 years and are relatively rare thereafter. The latest instance of recurrence in our series was observed 186 months after surgery. The recurrence rate after complete removal was 7% in Laws' series of 29 patients with a follow-up review lasting at least 5 years.[24,25]

Limited surgery followed by radiation might induce favourable outcomes when compared to more aggressive solely surgical treatments.[8,9,26,27] Radiotherapy might have significant short and long term adverse effects and these pose a major limitation to the use of this treatment modality in children.[6,9,15,26]

Determining the exact prevalence of outcomes for the different treatment modalities is complicated by multiple factors and no randomized control trials exist in the population. Decisions regarding surgery and adjuvant therapy are done based on tumor and patient characteristics as well as the treating team's approach and experience. Despite these limitations, there are data from the literature suggesting improved outcomes for less aggressive surgical approaches combined with radiation in terms of disease recurrence, neurocognitive functioning, and prevalence of diabetes insipidus (DI) and severe obesity. Over the past decade, the surgical approach to craniopharyngioma in some institution has changed to become less aggressive.

Functional Outcome

Our results demonstrate a high rate of independence without any impairment (86%) at the last follow-up examination in patients who underwent primary transcranial surgery. 5% of patients who underwent complete excision had probably some hypothalamic insult and were dependent on relatives for routine activities. Hence we can infer that less aggressive the resection, better is the functional outcome of the patient. A similar result has been shown in other series.[23,28]

At last but not the least, I would like to summarise in nut shell the best possible management for craniopharyngioma which still remains a controversial topic. Currently the debate centers round the merits of radical surgical removal against limited resection followed by adjuvant therapy.

CONCLUSION

After analyzing our data and observations, the following are the conclusions from the present study. More aggressive the resection, higher is the recurrence free survival with increase in morbidity affecting the quality of life. More aggressive the resection, more are the chances of injury to surrounding vital structures resulting in more morbidity and mortality. Less aggressive the resection, better is the functional outcome of the patient. Inspite of complete removal of tumour, there is no 100% cure. Recurrence can occur even after complete excision. Hence in view of associated morbidity and mortality, one should try to achieve safe adequate tumour resection with adjuvant therapy for better postoperative quality of life. Tumours with more solid consistency had higher chances of recurrence compared to the tumors with cystic consistency. Less aggressive resection had better outcome with regards to Karnoffsky Performance Status Scale. Better quality of life is definitely more with less aggressive resection and adjuvant therapy. Pituitary hormone deficiencies are common in patients treated for craniopharyngioma. When patient had underwent aggressive resection and or who underwent partial or subtotal resection with adjuvant therapy had more endocrine insult and required additional hormonal replacement therapy. Visual deficits are common and result either from direct compression of optic pathways. Post-surgery, there is significant improvement in visual outcome. More aggressive the resection, more are the chance of postoperative diabetes insipidus.

In many of the tables, the p value was found to be greater than 0.05, making the association statistically not significant due to inadequacy of the sample size. Volumetric analysis of the tumour was not done due to unavailability of the resource. Imaging differences during the study period i.e. Contrast enhanced CT was used in initial period where as Contrast enhanced MRI

was used to analyse extent of resection in later part of the study, which could produce error in perfect analysis for extent of resection. This could be a limitation of this study.

Though the present study does not show any distinct advantages statistically of type of surgical resection and outcome, in the light of above results, it can be concluded that less aggressive resection with adjuvant therapy gives superior results with no significant increase in post-operative morbidity and mortality. However, the sample size and the follow up period in the current study being relatively short, a larger study sample and a longer follow up study may be needed before any further conclusions can be made.

To summarise, there is no universal treatment protocol for this tumours. Recurrences following excision of this tumour have frustrated surgeons since the inception of modern surgery. In the quest for a perfect technique, various techniques were introduced but none guaranteed zero recurrence. But, the question as to which is the best of all available techniques suitable for all kinds of craniopharyngioma surgery still remains partly unanswered.

At last but not the least, we should try to outline a management for craniopharyngioma which will help us to achieve a goal that includes better quality of life, good disease free survival period and less morbidity and mortality.

Quality assessment of craniopharyngioma surgery is essential. It is necessary for education and for evaluation of new methods. For neurosurgeons and neurosurgical units, quality assessment is necessary for improving and defending achievements.

We have a long way to go in order to make craniopharyngioma treatment as "once-in-a-lifetime experience" for our patients.

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