A Retrospective Analysis of the Treatment Results of 24 Cases of Pediatric Craniopharyngioma. 
A Single Institution Experience. 

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Abstract

This is a retrospective study of all cases of pediatric Craniopharyngioma who attended from January 1992 till January 2002 to the Pediatric Unit of Kasr El-Eini Center of Radiation Oncology and Nuclear Medicine (NEMROCK). All cases were diagnosed by brain CT scan or Magnetic resonance imaging (MRI) and diagnosis was confirmed by pathological examination. Eight cases underwent total surgical excision and 16 cases underwent near total excision of the tumor and postoperative radiation therapy. All cases were followed up clinically every 3 months by assessment of neurological function. Brain MRI and endocrinal functions were assessed every 6 months for 5 years.

The overall survival at 5 years was 90%. The 5 year progression free survival (PFS) was 62.5%, 5 cases developed surgery related complications and 4 cases developed radiation related complications as visual deterioration, pan-hypopituitrism and disturbed cognitive and neuropsychological disorders.

The two standard treatment options in children with craniopharyngioma are primary total surgical excision of the tumor or subtotal resection followed by radiotherapy. In certain subgroups of patients such as those with large tumors and hypothalamic extension, primary surgery is associated with a high incidence of complications and high failure rates. We recommend the utilization of an individualized risk adapted treatment approach which attempts to maximize cure rates without compromising long-term functional outcome. Neuropsychological assessments with a focus on memory recall should be a component of the management of each case.
Key words: Craniopharyngioma, treatment results, complications.

Introduction:
Craniopharyngioma accounts for 6% to 9% of all primary CNS tumors in children with one peak during childhood at approximately 8 to 10 years of age and a second peak in middle age. The tumor is rarely detected before the age of 2 years (Bunin et al., 1998). Although these lesions are predominantly supra-sellar with involvement of the pituitary stalk and hypothalamus, they may also occur within the sella-turcica or third ventricle. Although, craniopharyngioma is a histologically benign tumor composed of well differentiated tissue, it may have a malignant clinical course because of its location and its propensity to infiltrate surrounding normal structures. Grossly, these tumors are smooth, lobulated masses with both solid and cystic components. The cyst contents may range from gelatinous to viscous oily fluid rich in cholesterol crystals. Rupture of a cyst into the CSF may cause intense chemical meningitis. Calcification is frequently apparent. Both the cystic lining and the solid portions of the tumor are characterized by the presence of squamous epithelium, usually with some evidence of keratinization (Russell et al., 1989).

Craniopharyngioma is either treated by complete surgical excision which is associated with long-term neurological complications (Yasargil et al., 1990 and Pang, 1993) or near total excision and post-operative radiation therapy which is associated with a low incidence of long-term neurological complications (Weiss et al., 1989).

The most important prognostic factors reported are the extent of the tumor, the extent of surgery; where total excision is superior to near total excision which in turn is superior to tumour biopsy. Cystic tumours carry a better prognosis than those which are partly solid and cystic. Children older than 5 years have a better prognosis (Russell et al., 1989).

Patients and Methods:
This study is a retrospective analysis of the results of treatment of 24 cases of pediatric craniopharyngioma who had attended to the
pediatric clinic of Kasr-El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 1992 till January 2002. Patient files were reviewed for all criteria; including: history of consanguinity, onset of the disease, duration of symptoms, main presenting symptoms and methods of diagnosis and surgical intervention.

All cases were diagnosed by CT scan or magnetic resonance imaging (MRI), which delineated solid and cystic nature of the tumor, its extent and its relation to the adjacent structures. The diagnosis was confirmed by surgical biopsy. Sixteen cases (66.6%) underwent near total surgical excision of the tumor including removal of the cystic component of the tumor followed by postoperative radiation therapy and 8 cases (33.3%) underwent complete surgical removal of the tumor.

All patients underwent postoperative magnetic resonance imaging (MRI) and performed visual field examination, and fundus examination. All cases were neurologically examined for any cranial nerve affection and any neuro-behavioral abnormalities. All children had endocrine assessment for short stature, and signs of delayed puberty. Pituitary function was evaluated by measuring serum growth hormone (GH), thyroid hormones (T3, T4, TSH) and serum cortisol.

Patients who underwent subtotal surgical excision of the tumor received postoperative radiation therapy 54 Gy, 200 cGy per fraction, 5 fractions per week, for 5 weeks by cobalt machine at a focal skin distance of 80 cms including tumor volume with a 2cm safety margin by a multiple field arrangement (2 or 3 fields depending on the dose distribution to the temporal lobes) with the patient laying supine with Orfit fixation (Hetelekedis et al., 1993 and Regine & Kramer, 1992).

Patients were followed up every 3 months and examined neurologically for any sensory, motor and neurobehavioral abnormalities and performed visual field examination for visual field defects, in addition to assessment of pituitary hormone profile. Radiological assessment was performed by MRI or CT scan of the brain at the same follow-up intervals. Patients were followed up for 5 years; survival was calculated from the date of diagnosis to the date of the last follow-up or death. Disease free survival was
calcula-ted from the date of ending treatment till evidence of disease progression or relapse.

**Statistical methods:**

The Kaplan–Meier method was used to estimate overall survival and disease free survival and log rank test was applied to compare groups. P value is significant at 0.05 levels (Miller et al., 1981).

**Results:**

Pediatric Craniopharyngioma cases represented 5% of the total pediatric CNS tumors that attended our unit (1992-2002 inclusive).

The median age of the patients was 10.5 years (5-16 years range). Sixteen patients were males (66.6%) and 8 cases were females (33.3%).

The most common presenting symptom was increased intracranial tension (↑ICT) documented in 17 cases (70.8%), followed by visual field defects in 13 cases (54.2%) (as homonymous hemianopia and bitemporal hemianopia), delayed puberty in 5 cases (20.8%), vision loss in 4 cases (16.7%) and neuroendocrinal abnormalities in 9 patients (37.5%) as delayed puberty, growth delay and diabetes insipidus.

Radiologically 91.7% of the tumors (22 cases) had mixed solid and cystic components, calcifications were detected in 70.8% of tumors (17 cases) and ventricular dilatation was observed in 50% of the cases (12 cases). The tumor had extended to the posterior fossa in 4 cases (16.7%) and to the middle and posterior fossa in 2 cases (8.3%).

Eight cases (33.3%) underwent complete surgical excision and 16 cases (66.6%) underwent subtotal excision of the tumor and post-operative radiation therapy. Ten cases (62.5%) received 54Gy and 6 cases (25%) received 50Gy (see table I).

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<tr>
<th>Table (I): Demographic Data</th>
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<tr>
<td><strong>Factor</strong></td>
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<td>≤5 years</td>
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<td><strong>Sex:</strong></td>
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<td>Female</td>
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<td><strong>Symptoms:</strong></td>
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<td>↑ICT</td>
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<td>Visual field defects</td>
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The overall survival at 5-years was 90% (Fig. 1). Recurrence occurred in 9/24 patients after disappearance of disease (37.5%) with a median time of relapse of 19 months and a 5-year progression free survival of 62.5% (Fig. 2). There was no statistical difference in median time to progression between children who received 50 Gy and those who received 54 Gy.

The 5-year survival for patients who underwent total tumour resection and those who underwent partial resection and post-operative radiotherapy was 92% and 87.5% respectively (see fig 3). The difference was statistically insignificant (p=0.623).

The 5-year PFS for patients who underwent total tumour resection and those who underwent partial resection and postoperative radiotherapy was 65.5% and 57.4% respectively (see fig 4). The difference was also statistically insignificant (p=0.619).
Fig. (1): Overall Survival of the 24 cases of Craniopharyngioma

Fig. (2): Progression Free Survival of 24 cases of Craniopharyngioma
Fig. (3): Total Actuarial Survival Comparison between Patients treated with Surgery Alone versus Surgery + R/T

Fig. (4): Total Actuarial Progression Free Survival Comparison between Patients treated with Surgery Alone versus Surgery + R/T
Of the nine recurrent cases; 3 had recurred after gross total resection and were salvaged by re-surgery and post-operative radiotherapy. Six others recurred after near total resection and post-operative radiotherapy. Four of those were salvaged by re-surgery and the remaining two cases died a few months later.

Among the 8 cases that underwent total surgical excision, 5 cases (62.5%) developed surgically related morbidities as memory disorders, cognitive dysfunction and appetite disorders. Among 16 cases that underwent subtotal tumor excision and postoperative radiation therapy, 4 cases (25%) developed treatment related complications as visual field deterioration, and panhypopituitarism.

After long-term follow up at the end of the study (mean follow-up period was 7 years, range was 4-10 years), 17/24 cases (70.8%) were neurologically free or stable, 15 cases were free after ending treatment and 2 cases were salvaged after recurrence. All of the 17 cases suffered from cognitive and neuropsychological disorders including school problems, appetite disorders, sleep disorders and attention deficits; in spite of the fact that they were free of disease.

**Discussion:**

This current study is a retrospective analysis of the results of treatment of 24 cases of pediatric craniopharyngioma who had attended to the pediatric unit of NEMROCK from January 1992 to January 2002.

The median age was 10.5 years, 16 cases were males (66.6%) and 8 cases were females (33.3%); these results compare with those reported by Abrams where the median age was 9 years, and males constituted 55.2% of cases and females 44.8% (Abrams et al., 1997).

The main presenting symptom was increased intracranial tension (most probably because of the bulky
nature of the tumour) observed in 17 cases (70.8%), followed by visual field defects in 13 cases (54.2%), then vision loss and finally neuro-behavioral abnormalities. This coincides with the work of El-Watidy where increased intracranial tension was present in 66.7% of cases, reduced vision in 50% of cases and endocrinal problems in 33.3% of cases (El-Watidy et al., 2002).

Most craniopharyngioma patients have an excellent 5-year overall survival as these tumors are slowly growing. In the present series the 5-year overall survival was 90%, which is very close to most of the reported series in the literature (84-93%) (Regine & Kramer, 1992 and Isacc et al., 2001 and Van Effenterre et al., 2002).

Craniopharyngioma is commonly relapsing especially after incomplete surgical excision. This explains why most of the reported series show lower figures of progression free survival compared to overall survival. In the present work, the five-year progression free survival was 62.5% which is very close to the figure of 68% reported by Kalapurakal (Kalapurakal et al., 2003). In contrast to that, Habrand (Habrand et al., 1999) reported a five-year PFS of 91%. This high figure is most probably attributed to a higher proportion of patients in his series who had a total growth surgical resection.

In the current study those patients who received doses of 54Gy had a median time to disease progression better than those who received radiation doses less than 54Gy (19 months versus 15 months respectively). Although the difference was not statistically significant Habrand reported a significant gain of event free survival (EFS) for higher doses of radiation, he further added that the optimum dose was equal to 55Gy (Habrand et al. 1999) (p=0.05). Contrary to this was the work of Isaac (Isacc et al., 2001) where doses of radiotherapy greater than 50Gy had no impact on local control or survival.

In our present study recurrence occurred in 37.5% (9 cases), on the other hand the work of El-Watidy was different as he obtained poorer rates; where tumor recurrence occurred in 50% of his cases, 56% of those were salvaged and alive and free of disease, 33% alive with disease and 11% dead (El-Watidy et al., 2002).

Five cases (62.5%) of the 8 who underwent total surgical excision developed surgery related morbidities as memory loss, cognitive dysfunction and
appetite disorders, and 4 cases (36.3%) of the 16 cases that underwent subtotal tumor removal and radiation therapy developed radiation related complications, as visual field deterioration and panhypopituitrism. These results are in agreement with the work of Villani (Villani et al., 1997) where 20.6% of his cases developed radiation related complications as diminution of visual acuity, endocrinial and neuropsychological function disturbances. In the series of patients treated by Fisher (Fisher et al., 1998); 19 children had visual loss and 15 cases had endocrine deficits before surgery. Moreover, after surgery 21 cases developed visual loss and 29 cases developed endocrine deficits. Riva (Riva et al., 1998) also observed that visual dysfunction occurred in 50% of his cases and frontal lobe malfunction in 26% of his cases after ending treatment.

In the current study after long term follow-up (median follow-up period was 5.5 years) at the end of the study 17/24 cases (70.8%) were neurologically free or stable. Fifteen cases were maintained symptom free and 2 cases were salvaged after recurrence. All of these 17 cases (70.8%) developed neuro-behavioral abnormalities, school problems, sleep disorders and attention deficits. None of the cases developed tumor recurrence at the time of developing neuropsychological complications. Fisher (Fisher et al. 1998) also reported in his series of patients that 9% of his cases developed visual loss, 40% school deficits, neurobehavioral and endocrinial defects.

**Conclusion:**
The two standard treatment options for children with cranioph-aryngioma are either primary complete surgery or subtotal resection followed by adjuvant radiotherapy. Complete primary surgery is associated with a high incidence of morbidity and mortality especially in bulky extensive tumors. Subtotal resection followed by adjuvant radiation avoids the morbidity caused by extensive surgery. However, utmost care is needed for careful planning and high precision radiation delivery techniques are recommended to avoid and minimize the radiation complications and late effects. Care has to be taken to treat by a dose not less than 54Gy to obtain the maximum therapeutic benefit from radiation therapy.

In a certain subgroup of patients such as those with large
tumors and hypothalamic extension, primary surgery is associated with a high incidence of complications and high failure rates. We recommend the utilization of an individualized risk-adapted treatment approach, may be on a neo-adjuvant setting that attempts to maximize cure rates without compromising long-term functional outcome (Carpentieri et al., 2001).

We believe that further research is recommended especially for bulky or advanced cases to achieve better treatment optimization in an attempt to reduce the neuropsychological disability and late effects related to the disease and those related to treatment in a potentially curable disease.

References:


A RETROSPECTIVE ANALYSIS


دراسة تحليلية لعلاج 24 حالة أورام الكرانيوفارنجيوما

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جميع الحالات قد تم عمل لها أشعة مقطعية على المخ أو أطراف مغناطيسية مع إثبات التشخيص بالفحص الباثولوجي. ثماني حالات قد أجريت لها استئصال كامل للورم وستة عشرة حالات قد أجريت لها استئصال غير كامل للورم وثلاعن بعد ذلك علاج إشعاعي. جميع الحالات كانت تحت المتابعة كل ثلاثة أشهر بالفحص الدورى وكل ستة أشهر بعمل أشعات تقييم للغرم الصمام وذلك لمدة خمس سنوات.

العدل البقاء الكلي على حد الحياة بعد 5 سنوات كان 90% ومعدل البقاء بدون تدهور للحالة 62.5% وخمس حالات حدد لها مضاعفات بسبب الجراحة و4 حالات حدد لها مضاعفات بسبب العلاج الإشعاعي.

إن الطريقة التقليدية لعلاج هذه الأورام هي استئصال جراحي كامل للورم أو استئصال غير كامل مصحوب بعلاج اشعاعي. بعض المرضى يعانون من أورام متقدمة تقدم موضعياً وهذه الحالات تعاني من مضاعفات الجراحة وكذلك من فشل نتائج العلاج. وهذه الحالات في حاجة إلى تطوير العلاج بشكل خاص يرفع معدلات الشفاء ويخفض الإعاقة الذهنية للمريض.