CranioPharyngioma and Rare Tumors

RARE-01. MANAGEMENT AND OUTCOMES OF PAEDIATRIC CRANIOPHARYNGIOMA: A 15-YEAR EXPERIENCE IN SINGAPORE

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BACKGROUND: CranioPharyngiomas are rare embryonic malformations originating from the sellar region with high survival rates but high morbidity due to long-term sequelae caused by the location of the tumour. We summarise our institution’s experience on the management and outcomes of paediatric cranioPharyngiomas in Singapore. METHODS: This was a retrospective review of all paediatric patients (18 years and below) with histologically diagnosed cranioPharyngioma managed by the National University Hospital, Singapore from January 2002 to June 2017. Data on clinical presentation, imaging, treatments, and outcomes were extracted from the electronic medical record using a standardised data collection form. Data analysis was conducted using RStudio (Version 1.2.5033). Institutional ethics approval was obtained for the study. RESULTS: We identified 12 cases of paediatric cranioPharyngiomas. The majority of cases were male (8, 66.7%) and the median age at presentation was 6.0 (IQR 3.8–9.5). Initial surgical management was attempted in 11 (91.7%) of cases. The excision of a remnant cystic cavity (1, 8.3%) and the cyst cavity (1, 8.3%). All cases had diabetes insipidus, 10 (83.3%) had endocrine dysfunction, and 8 (66.7%) had visual impairment on long term follow up. 7 (58.3%) cases had recurrence, and 3 (25.0%) had demised. Cox-regression showed that females (HR=33.9, p=0.049), and Chinese race (HR=13.3, p=0.034) were at higher risk for recurrence, but age at diagnosis and residual tumor on post-operative MRI was not significant. CONCLUSION: The management of cranioPharyngioma is complex as it is complicated by high recurrence rates and significant long-term morbidity. Further research on treatment strategies focusing on maintaining quality of life is important.

RARE-02. RE-IRRADIATION FOR RECURRENT CRANIOPHARYNGIOMA

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PURPOSE: Patients with recurrent cranioPharyngioma after radiotherapy (RT) have few treatment options. At our institution, re-irradiation has been offered to selected individuals with recurrent cranioPharyngioma not suitable for further surgery, intracystic therapy or targeted agents. METHODS: A retrospective study was performed of patients with cranioPharyngioma treated with two courses of fractionated RT. First RT (RT1) prescriptions ranged from 30–54 Gy in 25–30 fractions; re-irradiation (RT2) prescriptions were 34–41.4 Gy in 34–41 fractions with full, in-field overlap of dose. The maximum dose to organs-at-risk (brainstem and optic structures) were maintained at or below the prescription dose. There was no cumulative dose limit to any structure. RESULTS: We identified four patients. Median RT1-to-RT2 interval was 5.8 years (range, 4.7–20.4). Cumulative maximum doses to optic chiasma and nerves were ≤100 Gy in all four patients. With a median follow-up of 33 months after RT2, three patients had disease control and are alive at 9, 23 and 42 months from RT2; one patient developed progressive disease and died 33 months after RT2. In three evaluable patients, vision remained stable or improved after RT2; the remaining one patient had no light perception prior to re-irradiation. Two patients had neurosurgical testing before and after RT2; neurocognitive domains and residual tumor on post-operative MRI was not significant. CONCLUSIONS: Despite exceeding usual tolerances for further surgery, intracystic therapy or targeted agents, re-irradiation may offer promise for patients with recurrent cranioPharyngioma not suitable for further therapy.

RARE-03. AGGRESSIVE RESECTION FOR PEDIATRIC CRANIOPHARYNGIOMAS VIA ENDOSCOPIC ENDO NASAL APPROACH

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OBJECTIVE: In recent years, the endoscopic endonasal approach (EEA) has been increasingly used for pediatric cranioPharyngiomas. We here present our experience and the outcomes of the EEA resection of pediatric cranioPharyngiomas.

MATERIALS AND METHODS: Between April 2014 and December 2019, 16 cases of pediatric cranioPharyngiomas were operated at the Osaka city university (OUC) hospital. Eight patients were diagnosed with primary cranioPharyngiomas while 8 had a recurrent tumor. There were 5 males and 11 females, with an age of 10.7 years (3–17 years). EEA was selected in all patients and a case of large multinodular tumor was resected by combination of microsurgical transcranial approach. RESULTS: Gross total resection was achieved in 14 patients among 15 cases. Post-operative CSF leak occurred in one patient, which was treated with re-exploitation. Pituitary stalk was preserved intraoperatively in 4 cases, and 15 patients developed diabetes insipidus and anterior hormonal replacement therapy was required in 15 patients at last follow-up. Visual improvement was noted in 4 patients while vision remained unchanged in the rest. Neuropsychological function status was preserved in all patients, and there was no new-onset obesity postoperatively. The mean follow-up duration was 35.1 months (2–69 months) and 4 of 8 recurrent cases had re-recurrence during this period, however there was no re-recurrence in 8 primary cases. CONCLUSIONS: EEA should be the surgical modality of choice for treating pediatric cranioPharyngiomas. It results in better visual and cognitive outcomes with a significantly increased extent of resection.

RARE-04. INTELLECTUAL DEVELOPMENT IN CHILDREN WITH PEDIATRIC CRANIOPHARYNGIOMA AFTER TUMOR REMOVAL

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INTRODUCTION: Intellectual assessment in children with cranioPharyngioma after tumor removal is still unknown. We assessed intellectual development in children who underwent microsurgical resection in our institute over the last twelve years. MATERIALS AND METHODS: Ten children among 41 patients with cranioPharyngioma treated at Kagoshima University Hospital between 2007 and 2019 were reviewed. We also assessed intellectual development in 10 years or younger children with cranioPharyngioma one year after tumor removal. Intelligence was assessed using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). RESULTS: Ten children underwent microsurgical tumor removal. The mean age at surgery was 5.8 (range 1–10) years. Transcranial approach was performed in 8 children, transphenoidal approach in two children. The mean follow-up period was 110 months. Gamma knife surgery was performed in 6 children less than 6 months after first surgery. Regional recurrences occurred in 5 children, and additional GKS was performed in four children, second microsurgical removal in one child. Severe obesity with a transient electrolyte imbalance occurred in one child. Eight children with GH deficiency underwent GH replacement therapy. Eight children were assessed working memory index (WMI), processing speed index (PSI), Perceptual reasoning index (PRI), and verbal comprehension index (VCI) using WISC-IV. Each mean value of WMI, PSI, and PRI was lower than VCI, except PRI in children with normal scale intelligence (N=6). CONCLUSIONS: WMI, PSI and PRI in children with intellectual disabilities were lower tendency than VCI after surgical removal of cranioPharyngiomas in the present study.

RARE-06. OPTIMIZATION OF PROTON RADIATION THERAPY FOR GIANT CRANIOPHARYNGIOMAS

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INTRODUCTION: CranioPharyngiomas are benign intracranial tumors located in the sellar and suprasellar region. Their size and extent of invasion into surrounding structures vary considerably. While the majority of cranioPharyngiomas on presentation are between 1–3 cm without hypothalamic invasion, a significant proportion of patients present with ‘giant’ cranioPharyngiomas of >4cm in dimension with large cystic extension through the 3rd ventricle. These tumors pose a challenge both for surgical resection as well as for radiation therapy. Proton beam therapy (PBT) has become the preferred standard of care after subtotal resection of pediatric cranioPharyngiomas. In the setting of giant cranioPharyngioma, the use of proton therapy allows a reduction of dose to surrounding normal brain, but changes in cyst volume can result in either under-coverage of tumor or excess dose to surrounding brain, an effect further magnified by the sharp gradients associated with proton dose distributions. In this case report we describe the proton treatment planning and intra-treatment monitoring of two patients with giant cranioPharyngiomas with largest pre-operative of dimension 6cm, and 7cm, respectively, and 6cm and 5 cm, respectively, pre-radiation. Both patients had drains inserted to Ommaya reservoirs. We performed surveillance imaging during RT utilizing spiral computer tomography (CT) on a weekly basis and reconstructed the treatment dose on the surveillance CTs to ensure target coverage and normal tissue sparing. We compared the dosimetry in...
these cases for PBT versus intensity-modulated radiation therapy, characterized the cyst evolution during treatment in 3 dimensions, and define an optimized protocol for treatment planning and intra-treatment monitoring.

RARE-07. THE LANDSCAPE OF GENOMIC ALTERATIONS IN ADAMANTINOMATOUS CRANIOPHARYNGIOMAS
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INTRODUCTION: adamantinomatous craniopharyngiomas (ACPs) are characterized by activating mutations in the CTNNB1 gene. Here we perform a comprehensive genomic analysis of 24 ACPs to define the landscape of genomic alterations in this disease. METHODS: We performed whole-genome sequencing of 24 ACPs and their matched normal tissues. We used Mutect 2.0 to detect mutations and indels in our samples. RESULTS: We identified significant mutations. Copy numbers were called using the GATK pipeline and GISTIC 2.0 was applied to identify significant alterations. Finally, svABA was applied to identify genome-wide structural variants. RESULTS: Integration of the data revealed upregulation of WNT/beta-catenin (FDR q-value <0.25) in the CTNNB1 mutant samples compared to CTNNB1 WT samples. CONCLUSION: Our study identified previously described activating CTNNB1 mutations in the majority of ACPs. In addition, we identified several rearrangements and structural variations in these tumors that could play an important role in the pathogenesis of the disease.

RARE-08. CYST FLUID CYTOKINES MAY PROMOTE EPITHELIAL-TO-MESENCHYAL TRANSITION IN PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA
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BACKGROUND: Despite poor clinical outcomes, no targeted therapies have been established for the treatment of adamantinomatous craniopharyngioma (ACP). The only known genetic aberration is a mutation in CTNNB1 that results in the nuclear accumulation of beta-catenin. Nuclear beta-catenin is an established inducer of Epithelial-to-Mesenchymal Transition (EMT). ACP cyst fluid is enriched with pro-inflammatory and SASP cytokines, many of which are also directly implicated in EMT. METHODS: We sought to investigate the role of EMT in ACPs. METHODS: Whole genome sequencing of 24 ACPs and their matched normal tissues. We used Mutect 2.0 to detect mutations and indels in our samples. The ACPs were quiet with regard to copy number alterations and no recurrent amplifications or deletions were detected. 528 structural variations and rearrangements were detected in total in 24 samples with an average of 22 variations per sample. Gene-Set Enrichment Analysis (GSEA) of the RNAseq data revealed upregulation of WNT/beta-catenin (FDR q-value <0.25) in the CTNNB1 mutant samples compared to CTNNB1 WT samples. CONCLUSION: Our study identified previously described activating CTNNB1 mutations in the majority of ACPs. In addition, we identified several rearrangements and structural variations in these tumors that could play an important role in the pathogenesis of the disease.

RARE-09. PRESERVATION OF ENDOCRINE FUNCTION AFTER OMMAVA RESERVOIR INSERTION IN CHILDREN WITH CYSTIC CRANIOPHARYNGIOMA
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INTRODUCTION: Children with craniopharyngiomas (CP) can be subjected to radical surgical resection. however, little is known about the long-term effects of cystic CP on endocrine function. Hypothalamic-pituitary and neuroendocrine function were evaluated in children with CP after Ommaya reservoir insertion (ORI) and median follow-up of 5.1 years. RESULTS: Two of the 13 patients evaluated had significant endocrine dysfunction prior to ORI. Eight patients, including 5 pre-ORI normal, had complete ORI and remained normal post-ORI. One patient with pre-ORI functional hypothyroidism had improvement but remained abnormal. No patients were newly identified with endocrine dysfunction post-ORI.CONCLUSION: ORI is an effective and safe procedure for children with CP that minimizes the risk of postoperative endocrine dysfunction.

RARE-10. ADAMANTINOMATOUS CRANIOPHARYNGIOMA RESIDES OUTSIDE THE BLOOD BRAIN BARRIER
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BACKGROUND: Adamantinomatous craniopharyngioma (ACP) is a devastating skull-base tumor believed to derive from epithelial remnants of the primordial craniopharyngeal duct ( Rathke’s pouch), which gives rise to the anterior pituitary gland. Genetically engineered mouse models of ACP demonstrate that perturbation of the fetal anterior pituitary can generate tumors analogous to ACP. Clinical and preclinical data indicate that IL-6 blockade may contribute to ACP tumor control, with the most common agent being the humanized monoclonal antibody, tocilizumab (Tocilizumab). This agent has demonstrated poor blood-brain barrier (BBB) penetration in primates. We present findings from two children enrolled on a phase 0 clinical trial (NCT03970226) of a single dose of preservative intravenous tocilizumab prior to resection of newly diagnosed ACP. METHODS: Fourteen pediatric patients with newly diagnosed ACP were obtained at multiple timepoints. Serum was isolated via ficoll separation. Tumor tissue and cyst fluid were obtained 4–6 hours following the single IV dose of tocilizumab. Tissue was snap-frozen. Tumor tissue and serum were measured using enzyme-linked immunosorbent assay (ELISA) against a standard curve. RESULTS: Both patients in this trial demonstrated clinically relevant levels of tocilizumab (≥ 4 μg/mL) in serum, cyst fluid, and tumor tissue, compared to undetectable levels in control samples. CONCLUSION: ACP resides outside BBB protection. In addition to demonstrating the feasibility of systemic delivery of tocilizumab, these findings indicate that other large molecules, including those known to have poor BBB penetration, may be systemically delivered as part of an antitumor regimen in the treatment of ACP.

RARE-11. QUANTITATIVE MR IMAGING FEATURES ASSOCIATED WITH UNIQUE TRANSCRIPTIONAL CHARACTERISTICS IN PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA: A POTENTIAL GUIDE FOR THERAPY
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INTRODUCTION: Children with craniopharyngiomas (CP) may have significant morbidity due to radical surgical resection into hypothalamic and anterior pituitary tissue. To date, there are no effective systemic therapies for CP. METHODS: This is a retrospective chart review of children with CP treated at the Hospital for Sick Children between 01/01/2000 and 1/01/2020. Results: In total 72 children with CP were reviewed. Of these, 21 were treated with upfront ORI. CONCLUSION: ORI is associated with significant endocrine, hypothalamic and neuroendocrine dysfunction. In the future, therapies targeting CP should be considered to limit the impact of ORI on patient outcomes.