Primary pediatric central nervous system tumor

- ETMR stem-like state and chemo-resistance are supported by perivascular cells at single-cell resolution
- Embryonic Stem Cell Models of Human Brain Tumors
- Radiosurgery for pediatric central nervous system lesions - initial report and insights from a multicenter registry
- Multi-omics dissection of MAPK-driven senescence unveils therapeutic vulnerabilities in KIAA1549::BRAF-fusion pediatric low-grade glioma models
- Delivery of LOXL1-AS1-siRNAs using targeting peptide-engineered extracellular vesicles with focused ultrasound to suppress medulloblastoma metastasis
- Integration of omics data in the diagnosis and therapy of glioblastoma
- Years of life lost due to central nervous system tumor subtypes in the United States
- Patterns, clinical presentations, and time to diagnosis in pediatric central nervous system tumors: insights from a pediatric neuro-oncology tumor board team at a tertiary referral hospital in Ethiopia

---

---

see also Pediatric spinal cord tumor.

Central nervous system tumors represent the most common solid tumors in children and are a leading cause of cancer-related fatalities in this age group.

Genomics of medulloblastoma, ependymoma, and diffuse intrinsic pontine glioma (diffuse midline glioma, with H3-K27M mutation), have refined, if not redefined, the diagnostic classification and therapeutic stratification of patients with these tumors. They detail the substantial genetic heterogeneity across each disease type and, importantly, link genotypic information to clinical course. The most aggressive, treatment-resistant (and also treatment-sensitive) forms within each disease entity are identified, and their potentially actionable targets.

Molecularly based classification of pediatric brain tumors provides a critical framework for the more precise stratification and treatment of children with brain tumors [1].

High-grade pediatric brain tumors display higher CBF in Arterial Spin Labeling than do low-grade tumors, and they may be accurately graded by using presented values. CBF is correlated with tumor microvascular density [2].

Classification

Central nervous system tumor classification

Diagnosis

Primary brain tumors are the most common cause of cancer-related deaths in children and pose difficult questions for the treating physician regarding issues such as the risk/benefit of performing a biopsy, the accuracy of monitoring methods, and the availability of prognostic indicators. It has been recently shown that tumor-specific DNA and proteins can be successfully isolated in liquid biopsies, and it may be possible to exploit this potential as a particularly useful tool for the clinician in addressing these issues.

A review of the current literature was conducted by searching PubMed and Scopus. MeSH terms for the search included “liquid biopsy,” “brain,” “tumor,” and “pediatrics” in all fields. Articles were reviewed to identify the type of brain tumor involved, the method of tumor DNA/protein analysis, and the potential clinical utility. All articles involving primary studies of pediatric brain tumors were included, but reviews were excluded.

The successful isolation of circulating tumor DNA (ctDNA), extracellular vesicles and tumor-specific proteins from liquid biopsies have been consistently demonstrated. This most commonly occurs through CSF analysis, but it has also been successfully demonstrated using plasma and urine samples. Tumor-related gene mutations and alterations in protein expression are identifiable and, in some cases, have been correlated to specific neoplasms. The quantity of ctDNA isolated also appears to have a direct relationship with tumor progression and response to treatment.

The use of liquid biopsies for the diagnosis and monitoring of primary pediatric brain tumors is a foreseeable possibility, as the requisite developmental steps have largely been demonstrated. Increasingly advanced molecular methods are being developed to improve the identification of tumor subtypes and tumor grades, and they may offer a method for monitoring treatment response. These minimally invasive markers will likely be used in the clinical treatment of pediatric brain tumors in the future [3].

Treatment

Primary pediatric central nervous system tumor treatment.

Outcome

Survivors of paediatric Central Nervous System tumours experience cognitive sequelae characterized by significant impairments in the attention domain (52.3%), but also in the other cognitive functions. Future studies in this research field need to implement more cognitive interventions and effective, but less neurotoxic, tumour therapies to preserve or improve neurocognitive functioning and quality of life of this population [4]

Thirty day mortality is increasingly a reference metric regarding surgical outcomes.

Data estimate a 30-day mortality rate of 1.4-2.7% after craniotomy for pediatric central nervous system tumor. No detailed analysis of short-term mortality following a diagnostic neurosurgical procedure (e.g., resection or tissue biopsy) for tumor in the US pediatric population has been conducted.

The Surveillance, Epidemiology and End Results (SEER) data sets identified patients ≤ 21 years who underwent a diagnostic neurosurgical procedure for primary intracranial tumor from 2004 to 2011. One- and two-month mortality was estimated. Standard statistical methods estimated associations between independent variables and mortality.

A total of 5533 patients met criteria for inclusion. Death occurred within the calendar month of surgery in 64 patients (1.16%) and by the conclusion of the calendar month following surgery in 95 patients (1.72%). Within the first calendar month, patients < 1 year of age (n = 318) had a risk of death of 5.66%, while those from 1 to 21 years (n = 5215) had a risk of 0.88% ($p < 0.0001$). By the end of the calendar month following surgery, patients < 1 year (n = 318) had a risk of death of 7.23%, while those from 1 to 21 years (n = 5215) had a risk of 1.38% ($p < 0.0001$). Children < 1 year at diagnosis were more likely to harbor a high-grade lesion than older children (OR 1.9, 95% CI 1.5-2.4).

In the SEER data sets, the risk of death within 30 days of a diagnostic neurosurgical procedure for a primary pediatric brain tumor is between 1.16% and 1.72%, consistent with contemporary data from European populations. The risk of mortality in infants is considerably higher, between 5.66% and 7.23%, and they harbor more aggressive lesions [5].

Case series

Nabbi et al. performed an immunogenomic analysis of RNA-seq data from 925 treatment-naïve pediatric nervous system tumors (pedNST) spanning 12 cancer types from three publicly available data sets.

Within pedNST, they uncovered four broad immune clusters: Paediatric Inflamed (10%), Myeloid Predominant (30%), Immune Neutral (43%) and Immune Desert (17%). We validated these clusters using immunohistochemistry, methylation immune inference, and segmentation analysis of tissue images. They report the shared biology of these immune clusters within and across cancer types and characterization of specific immune cell frequencies as well as T- and B-cell repertoires. We found no associations between immune infiltration levels and tumor mutational burden, although molecular cancer entities were enriched within specific immune clusters.

Given the heterogeneity of immune infiltration within pedNST, the findings suggest personalized immunogenomic profiling is needed to guide the selection of immunotherapeutic strategies [6].

Using a cross-sectional design, young adults (18-39 years) previously treated for pediatric CNS tumors and followed in a survivorship clinic during 2016-2021 were examined. Demographic, BMI, and diagnosis information were extracted from medical records of the most recent clinic visit. Data were assessed using a two-sample t-test, Fisher's exact test, and multivariable logistical regression. 198 survivors (53% female, 84.3% White) with a BMI status of underweight (4.0%), healthy weight (40.9%), overweight (26.8%), obesity (20.2%), and severe obesity (8.1%) were examined. Male sex (OR, 2.414; 95% CI, 1.321 to 4.414), older age at follow-up (OR, 1.103; 95% CI, 1.037 to 1.173), and

craniopharyngioma diagnosis (OR, 5.764; 95% CI, 1.197 to 27.751) were identified as significant ($p < 0.05$) obesity-related (≥25.0 kg/m2) risk factors. The majority of patients were overweight or obese. As such, universal screening efforts with more precise determinants of body composition than BMI, risk stratification, and targeted lifestyle interventions are warranted during survivorship care [7].

2016

27 patients with drug resistant epilepsy and brain tumor, aged up to 19 years at the time of surgery, were studied between 1996 and 2013 and followed up for at least one year. The mean interval between the onset of seizures and the diagnosis of the tumor was 3.6 years, and from diagnosis to the surgery, 18 months. The location of the tumor was in the temporal lobe in 16, with ganglioglioma and dysembryoplastic neuroepithelial tumors being the most frequent. Among the patients, 92.5% and 90.4% were seizure-free in the first and fifth year after surgery, respectively. Twelve of 16 children were successful in becoming drug-free, with complete withdrawal by 3.2 years. Surgery proved to be potentially curative and safe in these cases, suggesting that the tumor diagnosis and surgery cannot be postponed [8].

1)
Vitanza NA, Cho YJ. Advances in the biology and treatment of pediatric central nervous system tumors. Curr Opin Pediatr. 2016 Feb;28(1):34-9. doi: 10.1097/MOP.0000000000000309. PubMed PMID: 26709691.
2)
Dangouloff-Ros V, Deroulers C, Foissac F, Badoual M, Shotar E, Grévent D, Calmon R, Pagès M, Grill J, Dufour C, Blauwblomme T, Puget S, Zerah M, Sainte-Rose C, Brunelle F, Varlet P, Boddaert N. Arterial Spin Labeling to Predict Brain Tumor Grading in Children: Correlations between Histopathologic Vascular Density and Perfusion MR Imaging. Radiology. 2016 Nov;281(2):553-566. PubMed PMID: 27257950.
3)
Bounajem MT, Karsy M, Jensen RL. Liquid biopsies for the diagnosis and surveillance of primary pediatric central nervous system tumors: a review for practicing neurosurgeons. Neurosurg Focus. 2020 Jan 1;48(1):E8. doi: 10.3171/2019.9.FOCUS19712. PubMed PMID: 31896088.
4)
Sciancalepore F, Fabozzi F, Albino G, Del Baldo G, Di Ruscio V, Laus B, Menegatti D, Premuselli R, Secco DE, Tozzi AE, Lacorte E, Vanacore N, Carai A, Mastronuzzi A; Allena-Mente Study Group. Frequency and characterization of cognitive impairments in patients diagnosed with paediatric central nervous system tumours: a systematic review. Front Oncol. 2023 May 19;13:1198521. doi: 10.3389/fonc.2023.1198521. PMID: 37274224; PMCID: PMC10235613.
5)
Hankinson TC, Dudley RW, Torok MR, Patibandla MR, Dorris K, Poonia S, Wilkinson CC, Bruny JL, Handler MH, Liu AK. Short-term mortality following surgical procedures for the diagnosis of pediatric brain tumors: outcome analysis in 5533 children from SEER, 2004-2011. J Neurosurg Pediatr. 2016 Mar;17(3):289-97. doi: 10.3171/2015.7.PEDS15224. Epub 2015 Nov 20. PubMed PMID: 26588456.
6)
Nabbi A, Beck P, Delaidelli A, Oldridge DA, Sudhaman S, Zhu K, Yang SYC, Mulder DT, Bruce JP, Paulson JN, Raman P, Zhu Y, Resnick AC, Sorensen PH, Sill M, Brabetz S, Lambo S, Malkin D, Johann PD, Kool M, Jones DTW, Pfister SM, Jäger N, Pugh TJ. Transcriptional immunogenomic analysis reveals distinct immunological clusters in paediatric nervous system tumours. Genome Med. 2023 Sep 7;15(1):67. doi: 10.1186/s13073-023-01219-x. PMID: 37679810.
7)
Wilson RL, Soja J, Yunker AG, Uno H, Gordon E, Cooney T, Dieli-Conwright CM. Obesity Risk of Pediatric

Central Nervous System Tumor Survivors: A Cross-Sectional Study. Nutrients. 2023 May 11;15(10):2269. doi: 10.3390/nu15102269. PMID: 37242152; PMCID: PMC10222802.
8)

Bernardino MR, Funayama C, Hamad AP, Machado H, Sakamoto A, Thome U, Terra VC, Santos AC. Refractory epilepsy in children with brain tumors. The urgency of neurosurgery. Arq Neuropsiquiatr. 2016 Dec;74(12):1008-1013. doi: 10.1590/0004-282×20160157. PubMed PMID: 27992000.