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Embryonal Tumors of the Central Nervous System

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Overview

Background

Embryonal tumors are small-cell, malignant tumors showing divergent differentiation of variable degrees along neuronal, glial, or, rarely, mesenchymal lines.

The 2021 WHO classifies CNS embryonal tumors into 2 groups: medulloblastomas and "other" CNS embryonal tumors (the term “primitive neuroectodermal tumor” has been abandoned since 2016).[1]

Medulloblastomas are more common, and the data concerning the different subgroups as well as their treatment options and prognosis is evolving rapidly as our knowledge of medulloblastomas is expanding. A discussion about the different subgroups of medulloblastomas, their diagnosis, and treatment can be found here. The "other" group of embryonal tumors, according to the new classification, includes:

- Atypical teratoid–rhabdoid tumor (ATRT-SHH, ATRT-MYC, and ATRT-TYR, based on DNA methylation and transcriptome signatures)
- Cribriform neuroepithelial tumor (CRINET)
- Embryonal tumor with multilayered rosettes (ETMR)
- CNS neuroblastoma, FOXR2-activated
- CNS tumor with BCOR internal tandem duplication
- CNS embryonal tumor

Only tumors of the CNS are discussed here.[2] This article focuses on CNS embryonal tumors that are non-medulloblastomas.

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Pathophysiology

Considerable controversy exists regarding the histogenesis of embryonal tumors. Initially, these dense, cellular, embryonal tumors were thought to have a common origin from primitive neuroectodermal cells and to differ only in their location, type, and degree of differentiation. In the revised World Health Organization (WHO) classification, however, many of these tumors are given a separate niche based on the assumption that these embryonal tumors also could arise from cells already committed to differentiation.[3]

In the 2021 WHO classification, the following new entities for the "Other" embryonal tumor group were included: cribriform neuroepithelial tumor, CNS neuroblastoma, FOXR2-activated, and CNS tumor with BCOR internal tandem duplication.[4, 5]

Atypical teratoid rhabdoid tumors (ATRTs)

ARTs have quite variable histology. Some known histological features contain at least focal regions of rhabdoid cells with eccentric nuclei with prominent nucleoli and eosinophilic cytoplasm. The histology shows abundant mitosis and necrosis. The main component that is important for diagnosis is loss of INI1; rarely, BRG1 is required for diagnosis. Molecular workup shows homozygous deletion of SMARCB1, which is supposed to encode to create INI1 protein, hence the classic loss of INI1 protein that usually helps to diagnose ATRT. There are other possible genetic and molecular changes, including loss of function mutations, heterozygous deletion of SMARCB1, and alteration of SMARCB4 (related to the creation of BRG1 protein), but those are much less frequent than the loss of INI1. Recent comprehensive molecular profiling of AT/RT has identified three distinct

transcriptional/epigenetic subgroups: (1) TYR, which is found in the infratentorial in infants, expresses tyrosinase and other melanosomal markers (improved survival), (2) MYC, which is mostly supratentorial and is seen in older children, and (3) SHH, which is seen in all locations and demonstrates mutations in SHH and NOTCH pathway.[6]

ATRTs can be found anywhere in the neuroaxis.

Cribriform neuroepithelial tumors (CRINETs)

CRINETs were added to the CNS WHO classification in the 2021 edition as a provisional entity. This group of tumors is usually located around the ventricular system. They have inactivation of SMARCB1 and show loss of INI1. These features make this group of tumors somewhat similar to ATRT, specifically ATRT-TYR. Yet, they don't have the classical rhabdoid features and are arranged in strands and ribbons of cells. Thus, these tumors show some histological resemblance to choroid plexus carcinomas. The clinical behavior and prognosis differ from these tumors.[5] In general, when compared to ATRT these tumors seem to have a better prognosis.[7]

FOXR2-activated CNS neuroblastomas

These have malignant histological features. The diagnosis of this group of tumors is complex because of histological alterations that show complex structural rearrangements for which routine testing is not easily implemented.[8] Hence, advanced molecular techniques (next-generation sequencing or DNA-methylation profiling) are needed to diagnose this subgroup. Any of these tumors contain neurocytic or ganglion cells. These tumors also tend to contain Homer Wright rosettes and perivascular pseudorosettes. The genetic alterations that can be found include FOX2 alterations, 1q gain, and 16q loss.[6]

CNS tumors with BCOR internal tandem duplication

These are another group of tumors that is hard to diagnose solely using histology. Like ependymomas, this group of tumors has perivascular pseudorossetes and palisading necrosis like a glioblastoma. Hence, the diagnosis requires proving tandem duplication at the BCOR gene. This subtype is aggressive and the prognosis is poor. The tumors are usually solid with oval or spindle cells and can also show pseudorosettes.

Embryonal tumors with multilayered rosettes (ETMRs)

ETMR is another newly defined tumor. It was first introduced in the 2016 WHO classification. These rare and highly aggressive brain tumors primarily affect infants and young children. ETMRs were historically classified as ependymoblastoma, medulloepithelioma, and embryonal tumors with abundant neuropil and true rosettes (ETANTRs). These subtypes are still in use to describe the different types of ETMRs.[9] Histologically, ETMRs, as the name implies, show the presence of undifferentiated neuroepithelial cells forming multilayered rosettes. From a genetic perspective, the 2021 classification classified ETMRs into the common C19MC and DICER alteration types. This is based on the known alteration at chromosome 19 (amplification of the chromosome 19 microRNA cluster (C19MC) at 19q13.41–42 and the overexpression of the RNA binding protein Lin28A).[10] The classic characteristics are of C19MC amplification or fusion with TTYH1 gene.[6] Other chromosomal changes that can be found in these tumors include gains of chromosome 2, as well as 7q, 11 q gains, and 6q loss. ETMRs usually will be found in the cerebral hemispheres (classically large supratentorial tumors), although can be found in the posterior fossa as well. They will often be found when they have already reached a significant size and lead to elevated intracranial pressure. They can present with a leptomeningeal spread like the rest of the embryonal tumors and also have extracranial invasive growth and metastases.

Common pathological findings may include cystic changes, although the tumors are usually solid. They may vary from soft to firm in consistency. Geographic necrosis, vascular proliferation, or calcification areas are less common, while hemorrhage is rare.

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Frequency

According to the latest publication of the Central Brain Tumor Registry of the United States (CBTRUS), the incidence of embryonal tumors is about 2.5% in the general population and close to 9.5% in the pediatric and adolescent age group (0–19 years of age).[11]

Medulloblastoma represents the most common type of primary solid malignant brain tumor in children (as many as 30% of all solid brain tumors). In contrast, only 1% of brain tumors in adults are medulloblastomas. Among embryonal tumors, medulloblastoma represents 69.5% of all the tumors for the pediatric population (0–19 years). For pediatric patients 0–14 years of age, medulloblastomas account for 68.3% of all embryonal tumors, atypical teratoid–rhabdoid tumors (ATRTs) for 17.2%, and the rest of the embryonal tumors for 14.8%.[11]

The Swedish Cancer Registry reported, as part of a population-based study, that medulloblastomas represented 21% of all primary brain tumors in children. Similar figures were provided by the British Tumor Registry and from the United States (Surveillance, Epidemiology and End Results Program).

Race-, sex-, and age-related characteristics

According to the latest CBTRUS database publication, embryonal tumors are more common in males and in White vs. Black people.[11] Atypical teratoid–rhabdoid tumors (ATRTs) and embryonal tumors with multilayered rosettes (ETMRs) will usually be diagnosed in patients younger than 2 years old.

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Prognosis

The overall 5-year survival rate for patients with embryonal tumors of the CNS is about 53%.[12]

The following factors worsen the prognosis:

- Presence of metastases at diagnosis
- Infiltrative nature, evidence of glial differentiation, and presence of TP53 mutation
- For medulloblastomas, a genomic study revealed that cases in the WNT group showed a slightly better survival with a more favorable prognosis than those in the SHH or non-WNT/SHH group.[13] WNT-activated medulloblastoma tumors have the lowest rate of metastatic disease and in correlation the highest 5-year survival rate. For SHH-activated medulloblastoma, TP53 mutation is highly related to prognosis. TP53 mutation is usually found in older children and is related to a very poor prognosis, whereas the wild type is usually found in younger children and adolescents and has a good prognosis. For groups 3 and 4, metastatic disease is more common, with group 3 having the poorest outcome of all.[11]
- For non-medulloblastoma embryonal tumors, the presence of C19M amplification as well as the presence of multilayered rosettes is a marker for very aggressive tumors, with an average survival of 12 months after diagnosis.[11]
- For ATRT, close to 25% of the cases will be diagnosed already with leptomeningeal disease, which highly correlates with poor prognosis.
- An unfavorable location that prevents complete resection: Failure at the primary site continues to be the predominant barrier to cure in patients with embryonal tumors.
- Younger age at presentation: Age older than 4 years at the time of initial diagnosis is associated with a a more favorable prognosis than age younger than 4 years. Younger age usually correlates with the diagnosis of embryonal tumors.

A 2022 publication from St Jude Children's research hospital compared two protocols for treating pediatric embryonal tumors (non-medulloblastomas) and included protocols for patients younger and older than 3 years. When considering the whole cohort the prognosis was poor, with survival around 20–35%.[14] It was shown that any work that takes embryonal tumors as one entity gives problematic information, including no survival benefit for CSI, although different results are known for everyday practice. When separating the different tumors by their subgroup and methylation profile, different results emerge.

Patients that tend to show benefit from receiving radiation therapy and multidrug chemotherapy include those with CNS neuroblastoma with FOXR2 activation, which show better results when compared to other embryonal tumors (5-year event-free survival (EFS)/overall survival (OS) of 66.7% ± 19.2%/83.3% ± 15.2%), and CIC rearranged sarcoma (5-year EFS/OS both of 57.1% ± 18.7%). On the other end of the spectrum are the patients with high-grade neuroepithelial tumors with BCOR alteration. This group has a very poor prognosis for those patients receiving only chemotherapy (5-year EFS = 0%). For those patients that can get radiation therapy, a survival benefit can also be seen (5-year OS = 53.6% ± 20.1%). Patients with embryonal tumors with multilayered rosettes (ETMRs) have very poor survival and response regardless of the treatment (5-year EFS/OS = 10.7 ± 5.8%/17.9 ± 7.2%).[14]

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Presentation

History

No pathognomonic signs or symptoms exist. The onset at presentation is insidious in many cases.

The observed symptoms are due to the neuroanatomical location of the tumor or are a consequence of increased intracranial pressure. They include the following:

- Irritability, lethargy, and decreased social interaction
- Intermittent vomiting, sometimes with history of nausea
- Headaches - especially those that lead to waking up in the middle of the night and those that are more pronounced in the morning
- Visual blurring/change
- Neurological deficit - The anatomical location will dictate the possible neurological deficit. In some cases, the neurological deficit is temporary and secondary to either brain edema, mass effect, or even as part of post-seizure deficit (eg, Todd's paralysis)

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Physical

Physical characteristics vary in relation to the anatomical location of the tumor and include the following:

- Papilledema
- Ataxia
- Nystagmus with or without gaze palsy
- Cranial nerve palsy
- Dysdiadochokinesia, hypotonia, dysmetria, particularly in lateralized lesions of the cerebellum
- Increased head circumference in children younger than 2 years
- Bulging fontanelle in infants
- Motor and sensory deficits

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Risk factors

Certain conditions have increased associations with embryonal tumors. They include the following:

- Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is an autosomal dominant disorder with mutations of the PTCH gene.[15] It is characterized by a combination of neoplastic and malformative disorders including nevoid basal cell carcinoma, jaw keratocysts, skeletal abnormalities, ovarian fibromas, and ectopic calcifications. Approximately 5% of mutation carriers develop medulloblastoma at an early age.
- Turcot syndrome is a heterogenous group of autosomal dominant disorders with occurrence of multiple colorectal neoplasms and medulloblastomas or glioblastomas.
- Li-Fraumeni syndrome is an autosomal dominant disorder characterized by multiple tumors in children, including soft-tissue sarcomas, osteosarcomas, breast cancer, and leukemias, and a higher incidence of brain tumors than in the general population.

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Complications

Complications of embryonal tumors may include the following:

- Meningitis (postoperative)
- Hydrocephalus

- Immunosuppression due to chemotherapy and/or radiotherapy
- Paralysis
- Cranial nerve palsy
- Hypothyroidism
- Cognitive dysfunction
- Growth retardation

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Diagnostic Considerations

Other conditions to consider include infectious diseases affecting the brain, such as encephalitis or meningitis, and other brain and spinal tumors, such as ependymoma and astrocytoma.

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Workup

Workup

Laboratory Studies

Lab tests are not helpful in the diagnosis of embryonal tumors affecting the CNS.

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Imaging Studies

Diagnosis of embryonal tumors of the CNS is confirmed or excluded by CT scan and, more importantly, MRI. For the possible diagnosis of leptomeningeal spread, obtaining an MRI of the entire CNS early on in the diagnosis process and a lumbar puncture that will allow sending the CSF for cytology is essential. In case of a large brain mass, it is advisable to avoid early lumbar puncture before surgical resection to minimize the risk of possible herniation.

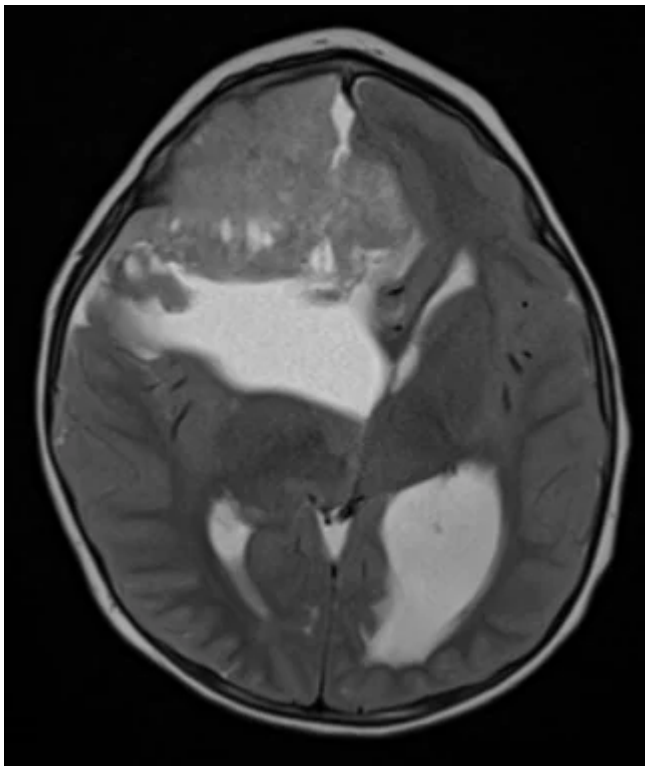
Clinical diagnosis of these tumors is not possible. Radiologic features unique to each type of tumor may be helpful, but the only possible absolute confirmation is by pathologic examination of the surgical specimen.

Magnetic resonance imaging

Non-medullobllastoma embryonal tumors are usually diagnosed when they have reached a considerable size. This is partly because of the early age at which these tumors are usually diagnosed (in children younger than 2–3 years old). In some patients, the anterior fontanelle is still open, which allows for some pressure release, which can lead to a sizeable growth of the tumor before symptoms start. This is usually the case for large hemispheric cerebral tumors; however, for posterior fossa tumors, the presentation can be much more acute because of obstructive hydrocephalus. The tumor appears large, nicely delineated from the surrounding brain, as a solid mass featuring patchy or no contrast enhancement. Surrounding edema is common, with significant mass effects and possible radiographic herniation signs. Some tumors can show cystic components and microcalcifications.

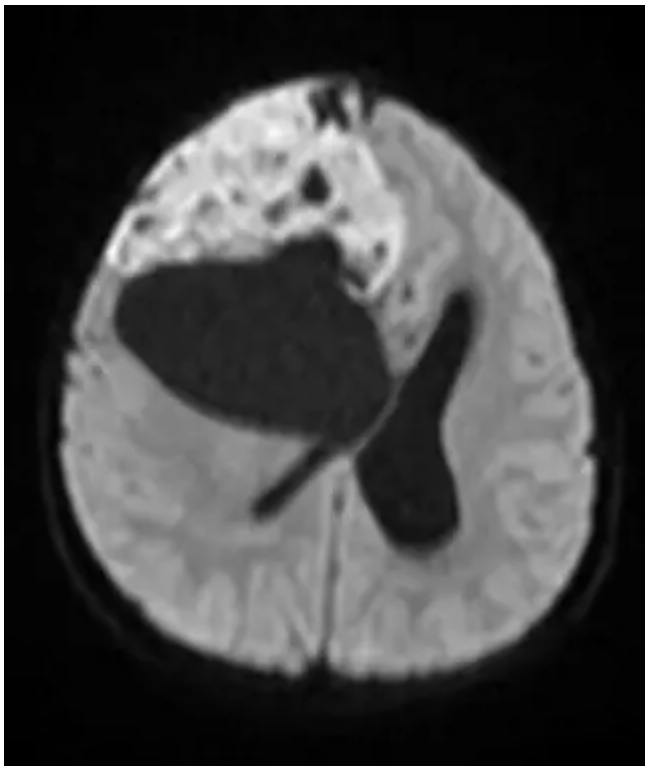
MRI sequences:

1. T1: decreased intensity
2. T2: increased intensity
3. T1 with contrast (gadullinium): patchy or no contrast enhancement
4. DWI: usually, some areas will have diffusion-restricted areas and dark on ADC
5. Spectroscopy shows features suggesting hypercellularity (a choline peak and a high ratio of choline/aspartate).

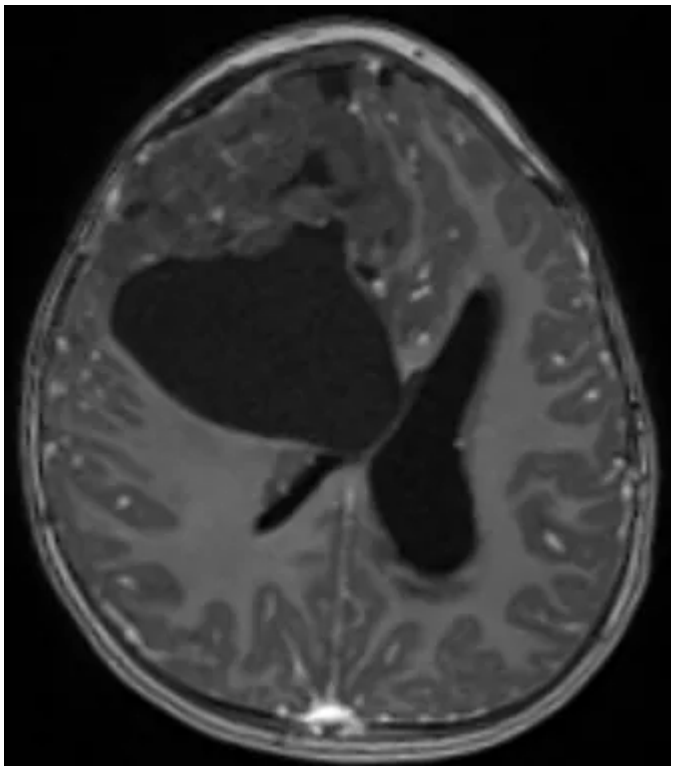


Large supratentorial mass on a toddler. This tumor pathology was of non-medulloblastoma embryonal tumor with final diagnosis of ETMR. On this image, axial T2 with slight hyper intensity

Typical findings include moderate tointense enhancement of the tumor, which is not homogenous (see image below).

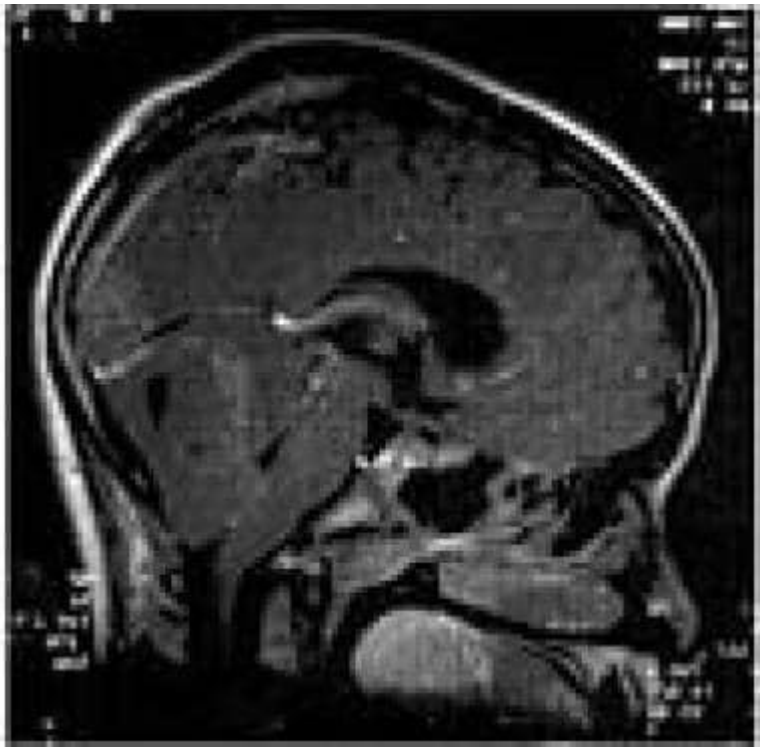


DWI sequence shows restricted diffusion. Matched ADC map (not shown) correlated with dark signal



T1 with contrast of large right frontal tumor, shows very slight patchy enhancement (ETMR)

In case there is a posterior fossa mass, accompanying hydrocephalus is common (see image below), and associated cystic changes can occur (see image below).



Cerebellar medulloblastoma. This sagittal view MRI without contrast demonstrates characteristic midline cerebellar location with mild obstructive hydrocephalus.

The entire neuraxis should be imaged to detect spinal metastases, which may occur via subarachnoid dissemination.

CT scan

In emergent situations, a CT scan is preferred over MRI because of its easy accessibility. However, CT scan resolution is inferior to that of MRI. CT myelogram may rule out spinal dissemination in cases in which MRI is contraindicated. It is important to mention that most of the emergencies related to large embryonal tumors are secondary to either large mass effect or obstructive hydrocephalus. In most cases, measures for alleviation of mass effect, such as steroids, will help to allow MRI scan prior for intervention. For obstructive hydrocephalus, measures for either permanent (shunt, ETV) or temporary (EVD) solutions can be used to allow a more through preoperative workup, including MRI.

Treatment

Medical Care

Preoperative administration of steroids can help to alleviate some of the signs and symptoms of embryonal tumors of the CNS by reducing peritumoral edema.[2]

Radiation therapy

Radiation therapy, usually given adjuvantly, should be performed under the direction of a radiation oncologist. Many series report a clear, dose-dependent relationship between postoperative radiation and local tumor control. Adjuvant radiotherapy alone, with posterior fossa doses of 5000 cGy and neuraxis doses of 3000 cGy, results in a 5-year event-free survival rate of 50-70%. Lower than standard doses of radiation therapy, at least without chemotherapy, are less effective. Craniospinal axis radiation is used for patients with spinal dissemination.

Newer methods are being evaluated, including stereotactic radiosurgery and high fractionation radiotherapy.[16] These methods limit the radiation dose to the local sites and avoid potential adverse effects in children, including cognitive dysfunction or delay in growth, that is seen frequently with conventional radiotherapy.

Radiation therapy by most protocols is reserved for patients older than 3 years old. It is customary to define if the patient is with average or low risk vs. high risk before the initiaion of treatment. CSI is carefully utilized only for selected cases. According to some protocols, for those that are average risk a dose of 23.4 Gy is given whereas 36–39.6 Gy is given for high risk. In both cases a boost to the primary site (55.8-59.4 Gy) is given.[14]

Chemotherapy

Chemotherapy should be administered under the direction of a medical oncologist.

Varying combinations of drugs used in these tumors include, but are not limited to, lomustine (CCNU), vincristine, cisplatin, etoposide (VP-16), topotecan, and cyclophosphamide. Several trials, including those from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG), are underway, evaluating varying combinations of chemotherapy with and without radiotherapy. For children younger than 3 years old "CSI sparing" chemotherapy protocols are being used.

Surgical Care

Surgery aims to achieve radical tumor resection, when possible, and restore normal CSF outflow.

Like in other cases, since the adjuvant treatment has partial success, when feasible, it is important to start the adjuvant treatment when there is no residual tumor (whenever it is feasible in a safe manner). Hence, it is advisable to consider second-look surgeries before the initiation of either radiation therapy or chemotherapy.[17] Recent publication of the Rare Brain Tumor Registry study showed benefit for acheiving GTR.[18]

Permanent CSF diversion in the form of ventriculoperitoneal shunt or endoscopic 3rd ventriculostomy (ETV) is required in as many as 30% of these cases.

Current treatment modalities include surgery, chemotherapy, and/or radiation. Ongoing worldwide research has explored nonconventional therapeutic strategies such as immunotherapy and gene therapy to improve outcomes and survival, although their clinical efficacy is yet to be established.[19] Current publications shows mixed results regarding benefit of GTR, brainstem involvement, metatatic disease, and radiation therapy.[14, 18]

Consultations

Consultation with the following may prove helpful:

- Neurosurgeon
- Neurologist/pediatric neurologist
- Radiation oncologist
- Medical oncologist

These cases are complex and pose complex treatment and diagnosis questions. Hence, it is advisble these cases will be discussed as part of experience center that practice multidisciplinary approach for the treatment of these patients.

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Medication

Medication Summary

No specific medications are used for the treatment of embryonal tumors of the CNS. Steroids may be used for decreasing peritumoral edema.

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Corticosteroids

Class Summary

These agents reduce edema around tumor, frequently leading to symptomatic and objective improvement.

Dexamethasone (Decadron)

Postulated mechanisms of action in brain tumors include reduction in vascular permeability and decreased CSF production.

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