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PEDIATRIC NEUROLOGY (HS SINGER, SECTION EDITOR)

Treatment Options for Medulloblastoma and CNS Primitive Neuroectodermal Tumor (PNET)

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Opinion statement

Medulloblastoma and central nervous system (CNS) primitive neuroectodermal tumor (PNET) are primary pediatric brain tumors that require multidisciplinary therapies. Although often treated similarly in clinical trials, they are biologically different diseases. Even within medulloblastomas and CNS PNETs, there are molecularly distinct subgroups with differing presentations and prognoses. Overall, prognosis is better for medulloblastomas. Specific treatments for these types of cancer are continuously evolving to maximize survival and minimize long-term sequelae of treatment. Patients should be treated on a clinical trial, if eligible, as they may gain benefit with minimal risk over current standard of care. The amount of residual disease after surgery better correlates with survival for medulloblastomas than for CNS PNETs. Maximal surgical resection of tumor should be done, only if additional permanent, neurologic deficits can be spared. Patients should have a staging work-up to assess the extent of disease. This includes postoperative magnetic resonance imaging (MRI) of the brain, MRI of the entire spine and lumbar cerebrospinal fluid (CSF) sampling for cytological examination, if deemed safe. Radiation therapy to the entire CNS axis is required, with a greater dose (boost) given to the region of the primary site or any bulky residual disease for older children. Adjuvant chemotherapy must be given even if no evidence of disease after radiation therapy exists, as the risk of relapse is substantial after radiation alone. Subsets of younger children with medulloblastoma, arbitrarily defined as those younger than

3 years of age in some studies and 4 or even 5 years in other studies, can be effectively treated with chemotherapy alone. Recent genomic studies have revealed further subtypes of disease than previously recognized. Clinical trials to exploit these biologic differences are required to assess potential efficacy of targeted agents. The treatment of medulloblastoma and CNS PNET can cause significant impairment in neurologic function. Evaluations by physical therapy, occupational therapy, speech therapy and neurocognitive assessments should be obtained, as needed. After therapy is completed, survivors need follow-up of endocrine function, surveillance scans and psychosocial support.

Introduction

Medulloblastoma and central nervous system (CNS) primitive neuroectodermal tumor (PNET) are embryonal tumors of the central nervous system. They both consist of small, round blue cells resembling immature neural progenitor cells on pathological examination. They were once thought to be the same disease but arising in different primary locations; medulloblastoma, infratentorial and CNS PNET, supratentorial [1]. Despite histologic similarities, the biology of these tumors are now accepted as separate and distinct [2]. Even within the larger grouping of medulloblastomas and CNS PNETs, biologically distinct subsets exit. Medulloblastomas have recently been subdivided into at least four and possibly more subgroups, and CNS PNETs have been subdivided into three or more subsets (*see section on* New biological insights) [3••, 4••].

Medulloblastoma is the most common malignant primary brain tumor in children and accounts for about 18 % of all brain tumors in children and adolescents [5]. Medulloblastoma can also occur in young adults and accounts for less than 2 % of central nervous system (CNS) tumors in this group [5]. They usually arise from the cerebellar vermis, but can also originate in the lateral hemispheres, particularly in adults. CNS PNET accounts for about 3–5 % of all childhood CNS tumors [4••]. They usually occur in the cerebral hemispheres; however, they also rarely originate within the brainstem and spinal cord.

Headache, nausea, emesis, double vision, gait difficulty and lethargy due to increased intracranial pressure are symptoms seen in patients with either medulloblastoma or CNS PNET. Patients with medulloblastoma are more likely to have cerebellar and brainstem signs. Those with CNS PNET may experience hemiparesis, hemisensory loss, visual field defects or seizures due to cortical involvement.

Patients may present in extremis due to elevated intracranial pressure. The immediate goal of care is stabilization, and frequently necessitates high dose steroids and extra-ventricular drain placement. Once stabilized, all patients should have magnetic resonance imaging (MRI) of the brain with and without contrast.

Tissue diagnosis is critical in patients with brain mass lesions, as clinical features and imaging characteristics of different tumor types can be similar. Gross total resection should be the aim of neurosurgical resection, as patients with minimal residual disease have the best outcomes [6]. This relationship has been shown primarily for those with non-metastatic medulloblastomas; data to support the concept that extent of resection confers a more favorable diagnosis is scarce for those with disseminated medulloblastomas or CNS PNETs. The goal of surgery should be to preserve neurologic function, as well. Radical resection should be preempted if neurologic integrity is threatened.

After neurosurgery, an extent of disease work-up is done to assess for metastatic disease in children with medulloblastoma. This entails a postoperative MRI of the brain, pre-operative or postoperative MRI of the total spine, and lumbar cerebrospinal fluid (CSF) sampling for cytology, if deemed safe. A pre-operative MRI of the total spine is preferred, as blood products from surgery can complicate the diagnosis of metastatic disease. Postoperatively, an MRI of the spine should be done at least 1 week after surgery. If there is no hydrocephalus, a lumbar puncture can be done prior to surgery, but is usually done after surgical resection. If CSF is collected after resection, it is usually after 2 weeks to avoid false positive results from surgery [7]. Similar staging is performed for those with CNS PNET; however, evidence to demonstrate that such staging is useful in determining risk is primarily an extrapolation from medulloblastoma studies.

A modified Chang staging system score is used to grade extent of disease based on these results [8], as follows. M0: no evidence of gross subarachnoid metastasis. M1: microscopic tumor cells found in CSF. M2: gross nodule seedings demonstrated in the cerebellum, cerebral subarachnoid space or in the third or lateral ventricles. M3: gross nodule seedings in the spinal subarachnoid space. M4: extraneural metastasis. Patients are stratified into one of two groups pertaining to risk of recurrent disease in medulloblastoma. Standard risk patients are those with no residual/minimal residual disease (1.5 cm^2 total area of primary tumor) and no metastasis. High-risk patients are those with residual disease and/or metastatic disease. Recently, all patients with anaplastic tumor (defined as greater than 50 % of tissue showing diffuse anaplasia) have been considered high-risk [9].

Patients with high-risk medulloblastoma have a poorer 5-year progression free survival (PFS) of 50–60 % compared to 80–90 % for those with standard risk [10]. M-stage is the most robust clinical prognostic indicator used in risk stratification for medulloblastoma. PFS for patients with CNS PNET is worse, ranging from 20 to 50 % [10]. Despite these differences in outcome, CNS PNET patients are currently treated as per standard high-risk medulloblastoma protocols due to the rarity of this tumor. New insights into the biology of CNS PNET, and medulloblastoma as well, hold the potential for maximizing survival outcomes and minimizing treatment sequelae.

Treatment

Surgery

Tissue must be obtained via neurosurgery to render a definitive diagnosis. Most medulloblastoma tumors are amenable to total resection if they do not extensively infiltrate the cerebellum and brainstem. A biopsy may be done initially, if the presumptive diagnosis is not medulloblastoma, as in the case of an older patient or tumors with atypical imaging characteristics.

Special point

- Extent of tumor resection is predictive of outcome, primarily documented in patients with non-metastatic medulloblastomas (Class II) [6].

Complications

- Aseptic and septic meningitis.
- Development of a pseudomeningocele and/or CSF leak.
- Common post-operative deficits include diplopia and abducens nerve palsies due to brainstem resection that usually resolve several months after posterior fossa surgery [10].
- Ataxia caused by vermian dissection and limb incoordination from cerebellar peduncle dissection, usually resolves in time [10].
- Posterior fossa mutism (PFM) is a side effect which is relatively rare, but is seen in approximately 20–25 % of all patients with posterior fossa surgery now that maximal resection is the goal of surgery [11].
- PFM is characterized by loss of expressive speech, pseudobulbar signs, gait apraxia, severe irritability, and at times, flattening of affect. About 50 % of patients recover, but others will continue to have significant residual symptoms [11].

- PFM is believed to be secondary to surgically-induced disruptions of cortical-cerebellar pathways, including the dentato-rubral-thalamo-cortical pathway [12].

Radiation therapy (RT)

Medulloblastoma and CNS PNET are radiosensitive tumors and RT remains the single most effective postoperative treatment. It is conventional practice to irradiate the entire craniospinal axis. The most significant improvement in survival for children with medulloblastoma was seen with RT delivered to the entire craniospinal axis, independent of the extent of disease at time of diagnosis [10]. The spine and CSF is considered a potential reservoir of tumor cells, even if not clinically detectable. CNS PNET is treated similarly with respect to RT.

Special points

- Post-surgical RT plus local boost is the standard of care for patients greater than 3 years of age (Class I) [13–15].
- The total dose of radiation delivered to the posterior fossa or primary tumor site is 55.8 gray (Gy). The local boost of radiation ranges between 19.8 Gy and 32.4 Gy, depending on the amount of craniospinal irradiation (CSI) administered.
- In those with non-disseminated disease at diagnosis, 23.4 Gy of craniospinal radiotherapy coupled with chemotherapy during and after RT results in 5-year progression-free survival of 85–95 % (Class I) [16].
- In children less than 3 years of age, RT is often not given initially, due to the deleterious effects of RT in the developing nervous system [17, 18].
- Intensity modulated radiation therapy (IMRT) has been shown to decrease hearing loss due to scatter from posterior fossa boost [19].
- RT delivered via proton beam therapy may result in less non-target tissue toxicity, particularly with respect to myelosuppression due to spinal irradiation; however, large cohorts of patients have yet to be treated with this modality, proving its efficacy and safety [20].
- Apart from CSI, additional radiation is also delivered to the temporal lobes and hypothalamus, due to the volume involved in posterior fossa boost for medulloblastoma and internal scatter.

Complications

- 2 to 8 weeks following completion of craniospinal radiation therapy, patients may experience fatigue, increased sleepiness (up to 18 hours per day), nausea and anorexia. This has been called the “somnolence syndrome” and occurs, at least in part, in up to 80 % of children [21, 22]. The syndrome usually does not require treatment, other than reassurance. Believed to be secondary to transient demyelination (although not proven), it may be associated with slowing on elec-

troencephalography and, rarely, a mild cerebrospinal fluid pleocytosis.

- Radiation-induced dermatitis can occur in areas of skin exposed to RT, and responds well to treatment with skin moisturizers.
- Patients recently started on phenytoin or carbamazepine and developing a rash beyond the area of radiation may be heralding early Stevens-Johnson Syndrome (SJS). There is an increased risk of SJS in patients on these anti-epileptics while undergoing RT [23].
- The extent and severity of alopecia induced by radiation varies depending on the dose of RT utilized. Re-growth of hair begins 2–3 months after completing RT; however, the full extent of recovery is not appreciated until several months later. Patients treated with adjuvant chemotherapy will see hair re-growth begin to accelerate only once all therapy is completed.
- Difficulty hearing can be seen due to middle ear effusions from RT. These effusions usually clear spontaneously, but may require myringotomy [24].
- Myelosuppression may occur due to CSI and is more likely in patients being treated with concomitant chemotherapy. Supportive therapy is with blood and/or platelet transfusions. Neutropenia is treated with granulocyte-colony stimulating factor (G-CSF).
- Mucositis and/or esophagitis may be seen in patients treated with CSI. Anesthetic oral rinses with lidocaine, proton pump inhibitors and/or H2 blockers are useful.
- Neurocognitive and endocrinologic outcomes due to CSI have led towards lowering the CSI dose [16, 25].
- Children 3–7 years of age treated with 36 Gy have a 20–30 point decrease in overall intelligence [26].
- Reduced-dose RT of 23.4 Gy still results in a significant decline of 10–15 IQ points and may be even greater in younger patients [27].
- The cumulative incidence of stroke in pediatric brain tumor survivors 25 years from initial diagnosis is approximately 7 % [28].
- The incidence of cerebrovascular disease in survivors is not well known, in patients at particular risk or with clinical symptoms, magnetic resonance angiography (MRA) should be considered.
- Moya-moya disease may occur years after radiotherapy [29].

Chemotherapy

Chemotherapy given during and after RT for patients with standard risk medulloblastoma has resulted in 5-year event free survival and overall survival (OS) of 81 % and 86 % in a cohort of 379 patients treated in prospective, phase III trial [16]. This trial utilized reduced-dose CSI of 23.4 Gy and one of two chemotherapy regimens; Regimen A: vincristine during RT, followed by vincristine, cisplatin and CCNU; or Regimen B: vincristine during RT, followed by vincristine, cisplatin and cyclophosphamide.

For patients with medulloblastoma less than 3 years of age, PFS is 30–40 % at 5 years [30, 31]. These worse outcomes are thought to be due to a different biology and the avoidance of RT in this age group. Patients with a specific subtype of medulloblastoma, desmoplastic medulloblastoma had significantly better outcomes; PFS at 5 years of 85 % even when treated with chemotherapy alone (Class I) [31].

Medulloblastoma is a rare tumor in adolescents and young adults. The utility of chemotherapy in adults has yet to be proven. Survival rates with RT alone versus RT and chemotherapy are both around 50–60 %. These statistics are based on retrospective studies with lack of uniformity in treatment approach [32–34]. Vincristine-induced sensory neuropathy can be very disabling in adults, and usually without motor neuropathy [35]. The only prospective study in adults with medulloblastoma found patients with high-risk disease benefited from RT and adjuvant chemotherapy. Remarkably, they did better than patients with standard risk disease treated with RT alone. This suggests potential benefit of adjuvant chemotherapy in adults (Class III) [36].

Patients with high-risk medulloblastoma are treated with 36 Gy CSI, although data, in non-disseminated patients, to confirm the efficacy of higher-doses of radiotherapy, are lacking. Patients with CNS PNET fair worse than patients with high-risk medulloblastoma. This is due in part to the rarity of this tumor and the convention of treating as if it were high-risk medulloblastoma due to histologic similarities. However, more recent data has elucidated different biologic pathways between these two tumors and potential therapeutic targets [2, 3••, 4••].

Special points

- For infants and young children, defined by some groups as all patients less than 3 and for others less than 4 years of age, children are treated with high-dose chemotherapy using agents including cisplatin, cyclophosphamide and vincristine; often consolidated with thiotepa-based high-dose chemotherapy supported by peripheral stem cell rescue [30, 37, 38]. Some studies have suggested that alternative treatments using intrathecal and high-dose intravenous methotrexate (despite risks of increased neurotoxicity) may be equally or more effective [31, 39]. Biologic agents are being incorporated to try to improve efficacy in infants and young children.
- Infants and children with non-disseminated disease, especially those without residual disease after initial surgery, who maintain disease control after chemotherapy, often are treated without radiotherapy [31, 37, 40]. Long-term disease control is best for those with desmoplastic tumors, ranging from 60–80 % at 5-years [41, 42]. Other histologic subtypes fare less well with chemotherapy alone approaches with 5-year PFS rates of 40 % or less. Some children who fail chemotherapy alone approaches can be salvaged by subsequent treatment with craniospinal and local boost radiotherapy [30].
- A current Children's Oncology Group (COG) trial, COG-ACNS0331, is evaluating lowering the CSI dose to 18 Gy and

decreasing the posterior fossa volume boosted in patients, followed by chemotherapy in patients with standard risk medulloblastoma.

- Another COG trial, COG-ACNS0332, for patients with high-risk medulloblastoma and CNS PNET, is utilizing carboplatin as a radiation sensitizer during RT followed by chemotherapy; it is also randomizing patients between post-radiation therapy treatment with retinoic acid, a maturation agent.

Pharmacologic treatment

Vincristine [43, 44]

Standard dosage	1.5 mg/m2 (maximum 2 mg)
Contraindications	patients with the demyelinating form of Charcot-Marie-Tooth syndrome
Main drug interactions	aminoglutethimide, atazanavir, boceprevir, bosentan, carbamazepine, chloramphenicol, clarithromycin, cobicistat, conivaptan, darunavir, delavirdine, dexamethasone, echinacea, efavirenz, enzalutamide, erythromycin, etravirine, fosamprenavir, indinavir, itraconazole, ketoconazole, leflunomide, lomitapide, lopinavir, mifepristone, nafcillin, natalizumab, nefazodone, nelfinavir, nevirapine, nicardipine, oxcarbazepine, pentobarbital, phenobarbital, pimecrolimus, pimozide, posaconazole, primidone, rifabutin, rifampin, rifapentine, ritonavir, roflumilast, saquinavir, spiramycin, St Johns Wort, tacrolimus, telaprevir, telithromycin, tofacitinib, voriconazole
Main side effects	neurotoxicity: foot drop, severe paresis, disabling paresthesias, ileus, cranial neuropathy, jaw pain; hepatoxicity
Special points	

- emic potential: minimal (<10 %).
- sensory neuropathy without significant motor neuropathy is seen more in late adolescents and adults.
- motor neuropathy without significant sensory neuropathy is seen more in children.
- adolescents and adults tolerate this drug poorly [35].

Cisplatin [43, 44]

Standard dosage	75 mg/m2
Contraindications	contraindicated in pre-existing renal impairment; myelosuppression; hearing impairment
Main drug interactions	cabazitaxel, clozapine, docetaxel, echinacea, leflunomide, natalizumab, paclitaxel, pimecrolimus, roflumilast, tacrolimus (topical), tofacitinib, topotecan
Main side effects	*central nervous system*: neurotoxicity: peripheral neuropathy is dose-dependent and duration-dependent; *gastrointestinal*: nausea and vomiting (76–100 %); *hematologic*: anemia (≤ 40 %), leukopenia, thrombocytopenia; *hepatic*: liver enzymes increased; *renal*: nephrotoxicity (28–36 %; acute renal

failure and chronic renal insufficiency); *otic*: ototoxicity (children 40–60 %; adults 10–31 %; as tinnitus, high frequency hearing loss)

Special points

- emetic potential: high (> 90 %).
- hypomagnesemia: may results from renal tubular wastage of magnesium caused by cisplatin, and manifested by paraesthesias, muscle cramps, weakness and disorientation or seizures.
- peripheral neuropathy may be more common in adults.

Lomustine [43, 44]

Standard dosage 75 mg/m2

Main drug interactions clozapine, echinacea, leflunomide, lomitapide, natalizumab, pimecrolimus, pimozide, roflumilast, tacrolimus, tofacitinib

Main side effects *gastrointestinal*: nausea and vomiting, (onset: 3–6 hours after oral administration; duration: < 24 hours); *hematologic*: myelosuppression (dose-limiting, delayed, cumulative), leukopenia, thrombocytopenia

Special points

- emetic potential: moderate (30–90 %).
- hepatotoxicity: reversible hepatotoxicity (transaminase, alkaline phosphatase and bilirubin elevations) has been reported; use with caution in patients with hepatic impairment.
- pulmonary toxicity: may cause delayed pulmonary toxicity (infiltrates and/or fibrosis); usually related to cumulative doses>1100 mg/m2. May be delayed (has been reported up to 17 years after childhood administration in combination with radiation therapy).
- renal toxicity: kidney damage has been observed and azotemia. Use with caution in patients with renal impairment; may require dosage adjustment.
- fertility: may result in azoospermia or ovarian failure; if concern for childbearing potential exists, consultation with a fertility specialist is advised [45, 46].
- secondary malignancies: long-term use may be associated with the development of secondary malignancies.

Cyclophosphamide [43, 44]

Standard dosage 1000 mg/m2

Contraindications severely depressed bone marrow function

Main drug interactions belimumab, carbamazepine, clozapine, echinacea, etanercept, fosphenytoin, leflunomide, lomitapide, natalizumab, nevirapine, phenobarbital, phenytoin, pimecrolimus, pimozide, primidone, rifampin, roflumilast, succinylcholine, tacrolimus, thiotepa, tofacitinib

Main side effects *dermatologic:* alopecia (reversible; onset: 3–6 weeks after start of treatment); *endocrine* & *metabolic:* amenorrhea, azoospermia, gonadal suppression, oligospermia, oogenesis impaired, sterility; *gastrointestinal:* abdominal pain, anorexia, diarrhea, mucositis, nausea/vomiting (dose-related), stomatitis; *genitourinary:* hemorrhagic cystitis; *hematologic:* anemia, leukopenia, myelosuppression, neutropenia, neutropenic fever, thrombocytopenia

Special points

- emetic potential: moderate (30–90 %).
- nausea and vomiting are likely and prolonged IV fluids may be necessary to prevent dehydration and maintain electrolyte balance.
- fertility: may result in azoospermia or ovarian failure; if concern for childbearing potential exists, consultation with a fertility specialist is advised [45, 46].

Diet and lifestyle

- Supplemental antioxidants during chemotherapy and radiation therapy should be discouraged because of the possibility of reduced survival due to impaired cancer cell death [47].
- About one third of patients treated for medulloblastoma and CNS PNET are at risk for malnutrition, based on evaluation of ideal body weight [48].
- The outcome of malnutrition in children with brain tumors has not been well studied, but those with poor nutrition suffer greater degrees of neuropathy.
- Diet counseling was not found to be an effective mode of nutritional intervention in children receiving chemotherapy [48].
- Cyproheptadine hydrochloride (periactin) and megestrol acetate (megace) can facilitate weight gain in children with cancer/treatment-related cachexia [49].
- Enteral and parenteral feedings may be necessary if weight loss is severe and persistent, particularly if neurologic deficit(s) precludes oral alimentation.

Physical / speech therapy and exercise

- Inpatient rehabilitation after neurosurgery has been shown to improve functional outcome in adults with brain tumors [50].
- Despite lack of evidence dealing in particular with pediatric brain tumor patients, we would recommend early physical, occupational and speech therapy.
- In the outpatient setting, no formal criteria exist for patients that will benefit from rehabilitative services; if in doubt, we recommend referring for evaluation [51].

Long-term follow-up / sequelae of therapy

- Patients are at significant risk for both early and late neurologic or neurosensory sequelae that need to be prospectively monitored [52].
- Neurocognitive sequelae are seen in patients of all age groups due to whole brain RT and possibly local boost radiotherapy. Children less than 8 years appear most vulnerable [26].

- About one third of school-aged patients treated for childhood brain tumors require special education services [53, 54].
- Growth hormone deficiency is the most common endocrinologic sequela of CSI, due to hypothalamic/pituitary dysfunction [55].
- Hypothyroidism is another common endocrinologic problem due to scatter from CSI [55].
- Hearing loss due to RT and therapy with cisplatin may necessitate hearing aids.
- Additional rare complications of therapy include secondary malignancies such as gliomas and meningiomas; however, these can lead to mortality and significant morbidity in survivors [56].
- Psychosocial issues such as obtaining employment, taking care of oneself and forming relationships can be difficult for survivors.
- Follow-up care for survivors is complex and patients should be treated at a long-term survival clinic at a pediatric oncology center, when possible.

New biological insights

Medulloblastoma is subclassified into five histological variants according to the World Health Organization (WHO) 2007 classification scheme: medulloblastoma (often referred to as classic medulloblastoma), desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, large cell medulloblastoma and anaplastic medulloblastoma [57]. Classic medulloblastoma is the most common histological subtype accounting for about 70 % of all diagnoses [58••]. Clinically, the other entities are combined, as they feature common elements expressed in varying degrees. Desmoplastic/nodular medulloblastoma and medulloblastoma with extensive nodularity are distinguished by more lobular formation seen in the latter [57]. Medulloblastoma with extensive nodularity is seen in infants (age less than 3 years). Desmoplastic/nodular medulloblastoma is more common in adults. Large cell medulloblastoma and anaplastic medulloblastoma are combined, as both are clinically aggressive and recur frequently. Risk stratification used to be based on extent of disease and residual disease alone, but patients with anaplasia are now stratified as having high risk disease [9].

The classification and treatment of medulloblastomas is likely to change in the coming years, due to new insights into the molecular biology of medulloblastoma. Whole RNA transcripts of medulloblastoma tumors assayed via gene expression profiling techniques have defined molecular subtypes. A recent consensus statement from an international consortium has established four distinct molecular subgroups of medulloblastoma: WNT, SHH, Group 3 and Group 4 [3••]. Within each of these subgroups there are further subdivisions, as well. The WNT and SHH groups are named after pathways activated in each. Group 3 and 4 tumors do not have key pathways identified as of yet. These four groups appear to have unique features with respect to histology, patient groups at risk and prognosis due to biologic pathways affected. For all the subgroups, RNA whole transcriptome analysis remains

the gold standard for subgroup assignment. The practical application of conventional tests such as cytogenetic analysis, immunohistochemical (IHC) staining and DNA gene mutation analysis remains to be proven in the context of larger cohorts.

WNT subgroup [3••, 58••]

- histology: usually correlates with classic medulloblastoma.
- age group affected: primarily children.
- metastasis: rarely are metastatic.
- prognosis: very good prognosis, > 90 % of patients are long-term survivors.
- testing: cytogenetic analysis: monosomy 6, IHC staining for nuclear β-catenin and DKK1 DNA analysis: mutations in *APC*, *CTNNB1*.

SHH group [3••, 58••]

- histology: predominantly correlates with desmoplastic/nodular pathology, but also found in patients with classic and large cell/anaplastic histology.
- age group affected: seen primarily in infants and adults.
- metastasis: less likely to metastasize.
- prognosis: infants have good prognosis, adults are intermediate.
- testing: cytogenetic analysis: deletion of chromosome 9q, IHC staining: SFRP1, GAB1, DNA analysis: mutations in *PTCH*, *SMO*, *SUFU*; amplifications in *GLI1* and *GLI2*.
- targeted therapy: vismodegib and itraconazole are drugs targeting this pathway and in current clinical trials.

Group 3 [3••, 58••]

- histology: classic and large cell/anaplastic medulloblastoma.
- age group affected: mostly seen in children; extremely rare in adults.
- metastasis: high metastatic potential.
- prognosis: poor.
- testing: cytogenetic analysis: gain of chromosome 1q and/or loss of chromosome 5q and chromosome 10q, isochromosome 17q, isolated 17p deletion, IHC staining: NPR3 DNA analysis: amplification and over-expression of *OTX2*, *MYC* amplification (possibly *MYC* over-expression) [58••].

Group 4 [3••, 58••]

- histology: correlates with classic and large cell/anaplastic medulloblastoma
- age group affected: primarily children, although can be seen in all age groups.
- metastasis: frequently metastasizes.
- prognosis: intermediate.

- testing: cytogenetic analysis: isochromosome 17q, isolated 17p deletion, gain of chromosome 1q and/or loss of chromosome 5q and chromosome 10q, IHC: KCNA.

The IHC antibodies discussed require validation in prospective studies. Furthermore, many are limited to use in biologic research only because they have not been licensed for use in the clinical setting. Issues regarding standardization of antibodies preparations, target-specificity and interpretation of results are some of the requirements for use in the clinical setting.

Three subgroups of CNS PNETs have been identified via analysis of gene copy-number, gene-expression and immunohistochemistry [4••]. This subclassification is likely to lead to stratification and guide potential therapies in future clinical trials for patients with CNS PNET.

- Group 1 (primitive neural) tumors had expression profiles most significantly enriched for genes associated with embryonic or neural stem cells. Survival for this group was the poorest, with median OS of 0.8 years. WNT pathway activation predominates in this tumor type.
- Group 2 (oligoneural) tumors had upregulation of markers of oligoneural differentiation. Patients were least likely to have metastasis in this age group. Median OS was 1.8 years in group 2 patients.
- Group 3 (mesenchymal lineage) had upregulation of epithelial and mesenchymal differentiation genes. Almost 50 % of patients in this group had metastases. In patients less than 4 years of age, no metastatic disease was seen. Median OS was 4.3 years in group 3 patients.

Compliance with Ethics Guidelines

Conflicts of Interest
Kevin C. De Braganca and Roger J. Packer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Retrospective analysis correlating molecular subgroups in medulloblastoma with patients characteristics and outcomes.