Introduction
Medulloblastomas are the most common malignant brain tumour of childhood and occur exclusively in the cerebellum. The disease is rare after the fourth decade of life.

Patients with medulloblastoma present with a combination of signs and symptoms of increased intracranial pressure and cerebellar dysfunction evolving over a period of weeks to a few months.

[Picture Credit: Medulloblastoma]

Medulloblastomas by definition occur in the cerebellum, which is the part of brain located at the base of the skull, just above the brainstem. The cerebellum is involved in many functions including coordination of voluntary movements (e.g., walking, fine motor skills) and regulating balance and posture. Medulloblastomas arise from primitive, undeveloped cells in the brain. Most medulloblastomas occur in infants and children. Less commonly, these tumours can develop in adults as well.

Medulloblastoma
Medulloblastoma is a cancerous tumour. It is also called Cerebellar Primitive Neuroectodermal Tumour (PNET) that starts in the region of the brain at the base of the skull, called the posterior fossa. These tumours tend to spread to other parts of the brain and to the spinal cord. Medulloblastoma accounts for 64.3% of all embryonal tumours in paediatric patients (0-19 years old).

Males display a higher incidence rate relative to females (males: 0.16 vs. females: 0.12), except in patients <1 year-old. Overall ratio tend to be 1.5:1 for males. Males also tend to have poorer prognosis.
“Brain tumors are the most common solid tumor malignancies in childhood, and among them, medulloblastoma occurs with the greatest frequency. Because medulloblastomas occur in the posterior fossa, the presenting symptoms often are vague complaints and diagnosis may be delayed. Between 70% and 80% of patients who are diagnosed before metastatic dissemination survive, compared with 30% to 40% of those in higher risk groups. This article reviews the diagnosis, treatment, and prognosis for medulloblastoma.”

“Medulloblastoma (MB) comprises a biologically heterogeneous group of embryonal tumours of the cerebellum. Four subgroups of MB have been described (WNT, sonic hedgehog (SHH), Group 3 and Group 4), each of which is associated with different genetic alterations, age at onset and prognosis. These subgroups have broadly been incorporated into the WHO classification of central nervous system tumours but still need to be accounted for to appropriately tailor disease risk to therapy intensity and to target therapy to disease biology. In this Primer, the epidemiology (including MB predisposition), molecular pathogenesis and integrative diagnosis taking histomorphology, molecular genetics and imaging into account are reviewed. In addition, management strategies, which encompass surgical resection of the tumour, cranio-spinal irradiation and chemotherapy, are discussed, together with the possibility of focusing more on disease biology and robust molecularly driven patient stratification in future clinical trials.”

Incidence of Medulloblastoma in South Africa
The South African National Cancer Registry (2014) does not provide any information regarding the incidence of Medulloblastoma.

- The majority of medulloblastomas occur as sporadic cases, yet hereditary conditions have been associated with medulloblastoma, including:
  - Gorlin syndrome (neviod basal-cell carcinoma syndrome)
  - Blue rubber-bleb nevus syndrome
  - Turcot syndrome (i.e., glioma polyposis syndrome)
  - Rubinstein-Taybi syndrome

Risk Factors for Medulloblastoma
Doctors are gradually understanding what causes most childhood tumours, including medulloblastoma. The following factors are linked with a higher risk of medulloblastoma:

- Gender. Medulloblastoma is more common in boys than in girls.
- Age. Medulloblastoma occurs most often in the first 8 years of life, with about half occurring in children younger than 6 years old.
- Genetics. The following genetic conditions are associated with a higher risk of developing medulloblastoma:
  - Nevoid basal cell carcinoma syndrome (NBCCS)
  - Turcot syndrome (a subtype of familial adenomatous polyposis) – (FAP)
  - BRCA1 gene mutations.
  - genetic conditions, such as Gorlin and Li-Fraumeni syndromes
  - Nearly half of childhood medulloblastomas have a genetic abnormality on chromosome 17
Signs and Symptoms of Medulloblastoma
Symptoms are often progressive over weeks to months, and it is not uncommon for patients to have an extended symptomatic period prior to initial diagnosis. Metastatic disease is commonly present at diagnosis (40%), and imaging of the entire craniospinal axis is an essential part of the initial diagnostic evaluation.

Symptoms usually differ by anatomic location of the tumour, presence of disseminated disease, and by the presence of hydrocephalus (condition in which excess cerebrospinal fluid (CSF) builds up within the brain).

If a child has Medulloblastoma, the following symptoms may occur:
- Headaches
- Morning nausea or vomiting that gradually gets worse
- Clumsiness
- Problems with handwriting
- Visual problems (rare) at the time of diagnosis
- Morning headache or headache that goes away after vomiting.
- Unusual sleepiness or change in energy level.
- Change in personality or behaviour.

If the tumour has spread to the spinal cord, additional symptoms may include:
- Back pain
- Trouble walking
- Problems controlling bladder and bowel functions

Physical signs may include:
- Physiognomy (facial features or expression)
  - Increasing head circumference often is the only presenting symptom in infants.
  - Infants may have also full anterior fontanelles with split cranial sutures.
- Funduscopic examination
  - Visual difficulty usually is due to papilloedema (optic disc swelling); however, it also may originate from cranial nerve palsy (most commonly Cranial Nerve IV or VI).
  - Some studies have found papilloedema (the most common physical finding) to be present in as many as 90% of patients.
- Extraocular examination
  - As a consequence of hydrocephalus, the sixth cranial nerve can be compressed at the petroclival ligament, resulting in diplopia (double vision) and lateral gaze paresis.
  - Fourth cranial nerve palsy can be detected on careful extraocular examination and should be considered in any patient with a head tilt.
  - Patients with fourth cranial nerve dysfunction have greatest difficulty when eyes are rotated medially and depressed (i.e., going down stairs). The fourth cranial nerve usually is compressed by direct tumour extension into the cerebral aqueduct.
  - Examination of the extraocular muscles may detect nystagmus (involuntary eye movement), which, although nonspecific, can be related to a lesion of the cerebellar vermis.
- Cerebellar signs
  - Medulloblastoma most commonly is located midline. Therefore, unilateral dysmetria (lack of coordination of movement typified by the undershoot or overshoot of intended position with the hand, arm, leg, or eye) is less common than either truncal ataxia (impaired balance or
coordination) or a wide-based gait (way of walking). Latter symptoms are easily observable on tandem gait (method of walking or running where the toes of the back foot touch the heel of the front foot at each step).

- Desmoplastic medulloblastoma is more common in adults and usually arises in the cerebellar hemisphere.
- Signs of ipsilateral (belonging to, or occurring on the same side of the body) cerebellar dysfunction in the arm or the leg are more common in this subtype.

- Torticollis: Head tilt can be a manifestation of either accessory nerve (cranial nerve eleven) or trochlear nerve (cranial nerve four) palsy (paralysis).

**Diagnosis of Medulloblastoma**

Magnetic resonance imaging (MRI) typically demonstrates a midline or paramedian cerebellar mass that enhances after contrast administration, and approximately one third of patients will have evidence of tumour dissemination through the subarachnoid space either by imaging or cerebrospinal fluid (CSF) examination.

**Treatment of Medulloblastoma**

Treatment of childhood medulloblastoma in children younger than 3 years of age is usually within a clinical trial and may include the following:

- Surgery followed by chemotherapy to delay radiation therapy.
- Surgery followed by high-dose chemotherapy with stem cell transplant.
- Chemotherapy only.

Nobre, L., Pauck, D., Golbourn, B., Maue, M., Bouffet, E., Remke, M. & Ramaswamy V. 2019. “Most medulloblastoma protocols worldwide include vincristine during radiation and chemotherapy. A significant dose-limiting toxicity is peripheral neuropathy; however, there is a paucity of data to support the view that omission of vincristine does not impact survival. Herein we report two adolescent patients with Group 4 and SHH medulloblastoma, where vinblastine successfully replaced vincristine with resolution of their peripheral neuropathy. We furthermore show vinblastine is highly active in vitro and demonstrates equivalent antitumoral activity compared to vincristine. Substitution of vincristine with vinblastine in future studies should be considered for all patients with medulloblastoma, particularly those with hereditary neuropathy, severe vincristine toxicity, and adults.”

Eckerdt, F., Bell, J.B., Beauchamp, E.M., Clymer, J., Blyth, G.T., Kosciuczuk, E.M., Ma, Q., Chen, D.Z., Horbinski, C., Goldman, S., Munshi, H.G., Hashizume, R. & Platanias, L.C. 2019. “Medulloblastoma is a highly malignant pediatric brain tumor associated with poor outcome. Developing treatments that target the cancer stem cell (CSC) population in medulloblastoma are important to prevent tumor relapse and induce long-lasting clinical responses. We utilized medulloblastoma neurospheres that display CSC characteristics and found activation of the PI3K/AKT pathway in sphere-forming cells. Of all class I PI3Ks, only the PI3Kα isoform was required for sphere formation by medulloblastoma cells. Knockdown of p110α, but not p110β or p110δ, significantly disrupted cancer stem cell frequencies as determined by extreme limiting dilution analysis (ELDA), indicating an essential role for the PI3Kα catalytic isoform in medulloblastoma CSCs. Importantly, pharmacologic inhibition of the MAPK-interacting kinase (MNK) enhanced the antineoplastic effects of targeted PI3Kα inhibition in medulloblastoma. This indicates that MNK
signaling promotes survival in medulloblastoma, suggesting dual PI3Kα and MNK inhibition may provide a novel approach to target and eliminate medulloblastoma CSCs. We also observed a significant reduction in tumor formation in subcutaneous and intracranial mouse xenograft models, which further suggests that this combinatorial approach may represent an efficient therapeutic strategy for medulloblastoma. **Implications:** These findings raise the possibility of a unique therapeutic approach for medulloblastoma, involving MNK targeting to sensitize medulloblastoma CSCs to PI3Kα inhibition.”


**BACKGROUND:** Craniospinal irradiation (CSI) is the standard radiation therapy treatment for medulloblastoma. The aim of this study was to estimate and compare the lifetime risk of radiation-induced secondary cancer in pediatric medulloblastoma patients using three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT).

**MATERIALS AND METHODS:** 3D-CRT and IMRT plans were performed for 10 CSI pediatric patients. The average absorbed doses for organs at risk (OARs) was calculated from dose-volume histograms on the treatment planning system. The average lifetime risk of radiation-induced secondary cancer was then calculated.

**RESULTS:** Lifetime risk of secondary cancer for CSI pediatric patients treated using IMRT decreases in some OARs compared with those treated using 3D-CRT. This is attributable to the decrease in the average absorbed dose in some OARs when using IMRT technique.

**CONCLUSION:** Follow-up of medulloblastoma pediatric patients should be performed after ending the treatment course in order to diagnose early secondary tumors. IMRT technique is substantially better than 3D-CRT in terms of lifetime risk of radiation-induced secondary cancer, probably due to reduced dose to OARs especially to the thyroid, which is the most sensitive organ to radiation.
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Medulloblastoma
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