

44 Embryonal Tumors

44.1 General information for embryonal tumors

Embryonal tumors are a diverse category of malignancies featuring immature tumor cells that resemble neural progenitors. It is divided into medulloblastomas (relatively common, occurring $\approx$ exclusively in the posterior fossa) and “other” rare non medulloblastoma CNS embryonal tumors (p.728), many of which exhibit amplification of the C19MC region of chromosome 19.

Many of these tumors were formerly encompassed by the term primitive neuroectodermal tumor (PNET) which has been eliminated from the diagnostic lexicon.¹

44.2 Medulloblastoma (a subset of embryonal tumors), general aspects

44.2.1 General information: MDB

Key concepts

- A small-cell embryonal WHO grade 4 neuroepithelial tumor that occurs predominantly in the posterior fossa of children (peak: 1st decade). The most common pediatric brain malignancy
- classified on 4 molecular and 4 histologic criteria
 - 4 molecularly defined types: 1) WNT-activated; 2) SHH-activated (TP53-mutant & -wildtype); 3) non-WNT/non-SHH, group 3; 4) non-WNT/non-SHH, group 4
 - 4 histologic types: 1) classic; 2) desmoplastic/nodular (D/N); 3) extensive nodularity (MBEN); 4) large cell/anaplastic (LC/A)
- brainstem invasion usually limits complete surgical excision
- staging: all patients must be evaluated for “drop mets” (imaging the entire neuraxis with contrast - brain + spine, pre-operatively if possible), and postoperatively with LP for CSF cytology.

Medulloblastomas (MDB) are WHO grade 4 embryonal neuroepithelial tumors that typically occur in the posterior fossa (cerebellum or dorsal brainstem) of children. In the cerebellum, they typically arise in the vermis near the apex of the roof of the 4th ventricle (the fastigium [Latin for summit]). They account for 68% of embryonal tumors.²

44.2.2 Seeding and metastases: MDB

$\approx$ 10–35% have seeded the craniospinal axis at the time of diagnosis,³ and extraneural metastases occur in 5% of patients,⁴ sometimes promoted by shunting⁵ (although this is uncommon⁶).

44.2.3 Clinical: MDB

Clinical history is typically brief (6–12 weeks). Predilection for posterior fossa predisposes to early obstructive hydrocephalus. Usual presenting symptoms: H/A, N/V, and ataxia. Infants with hydrocephalus may present with irritability, lethargy, or progressive macrocrania.⁷ Spinal drop mets may produce back pain, urinary retention, or leg weakness.

Common signs: papilledema, truncal and appendicular ataxia, nystagmus, EOM palsies. Macrocrania in infants and young children.

44.2.4 Classification: MDB

Classification of medulloblastomas based on a combination of molecular signatures combined with histopathological findings is recommended and provides optimal prognostic information. Molecularly defined MDBs are associated with specific morphological patterns to a high degree.

Molecular genetics: Transcriptome profiling (analysis of all RNA in a cell population), microRNA analysis and methylome profiling allows MDBs to be segregated into these 4 principal types⁸ (which are covered individually in the following sections). NB: on a more granular level, additional subgroups have been identified and will continue to emerge.

1. WNT-activated (p.723)
2. SHH-activated
 - a) SHH-activated, TP53-wildtype (p.724)
 - b) SHH-activated, TP53-mutant (p.726)
3. non-WNT/non-SHH (p.727), group 3
4. non-WNT/non-SHH (p.727), group 4.

Histology: 4 histologic types are defined; see detailed description (p.722)

1. Classic (p.722)
2. desmoplastic/nodular (p.722) (D/N MDB)
3. extensive nodularity (p.723) (MBEN)
4. large cell/anaplastic (p.723) (LC/A MDB).

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The distribution and prognosis of the histologic variants and prognostic information among the molecularly classified MDBs is depicted graphically in ► Fig. 44.1 (this is not the entire gamut, see reference⁹ for more details).

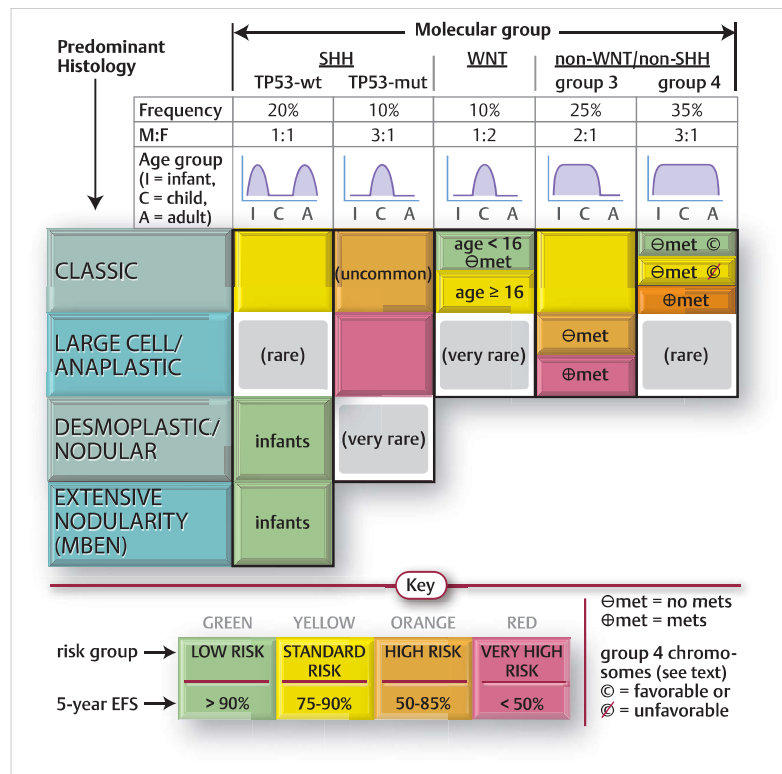


Fig. 44.1 Prognosis and distribution of histologic variants among molecular types of medulloblastoma. Box color indicates prognosis as follows:

5-year EFS rates: **low risk** >90%, **standard risk** 75-90%, **high risk** 50-75%, **very high risk** <50%

(see text for more details).^{8,10,11} No risk is shown for tumors of uncertain clinicopathological significance.

Abbreviations: EFS = event-free survival; MDB = medulloblastoma; SHH = activated sonic hedgehog; TP53 = tumor protein 53; mut = mutant; wt = wildtype; WNT = activated wingless/integrated (signal transduction pathway).

⊙ = favorable chromosomal findings for non-WNT/non-SHH group 4: chromosome 7 gain, chromosome 8 loss, chromosome 11 loss, chromosome 17 gain.

44.2.5 Evaluation

MDBs usually appear as a solid, IV-contrast-enhancing lesion on CT or MRI. Most are located in the midline in the region of the 4th ventricle (laterally situated tumors are more common in adults). Most have hydrocephalus at the time of presentation. Ependymoma (p. 1585) is the main entity from which to differentiate on imaging. MDBs tend to protrude into the 4th ventricle from the posterior aspect (the "roof") of the ventricle, whereas ependymomas more commonly arise from the floor.

CT: noncontrast → typically hyperdense (due to high cellularity). Contrast → most enhance. 20% have calcifications. CT has poor resolution in the posterior fossa due to bone interference

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MRI: Can be variable (► Fig. 44.2). T1WI → hypo- to isointense. T2WI → heterogeneous due to tumor cysts, vessels, and calcifications.¹² Most enhance. MRS: elevated choline and decreased NAA.

Spinal imaging: MRI with IV gadolinium or CT/myelography with water-soluble contrast should be done to rule out "drop mets." Staging is done either pre-op or within 2–3 weeks of surgery.

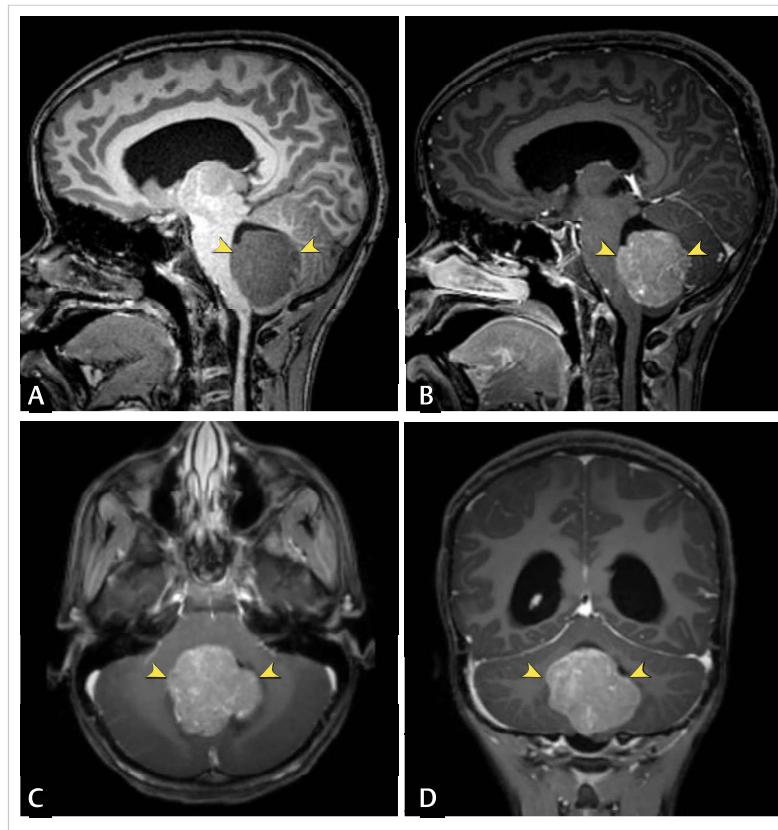


Fig. 44.2 Medulloblastoma. MRI of 10-year-old patient with medulloblastoma (yellow arrowheads) in the 4th ventricle producing obstructive hydrocephalus, presenting with progressive H/A, nausea and acute emesis. Image: A: sagittal T1 FLAIR without contrast, B: sagittal T1 FLAIR with contrast, C: axial T1 with contrast, D: coronal T1 with contrast.

► **Staging.** Preoperatively, staging employs MRI of the entire neuraxis without and with contrast. Postoperatively, CSF cytology obtained by LP is added to MRIs. The grading system of Chang et al. (► Table 44.1) is still used.

Table 44.1 Post-operative staging system for medulloblastoma¹³

Stage	Description
M0	no metastases
M1	microscopic tumor cells in the CSF
M2	gross nodular seeding in the cerebellar/cerebral subarachnoid space or in the third or lateral ventricles
M3	gross nodular seeding in the spinal subarachnoid space
M4	metastases outside the CNS

44.2.6 Treatment: MDB

Surgical intervention: MDB

Maximal safe resection (surgical debulking of as much tumor as possible without causing neurological deficit) to obtain tissue for classification and to improve outcome is considered standard.

Invasion of or attachment to the floor of the fourth ventricle (brainstem in the region of the facial colliculus) often limits excision. It is better to leave a small residual on the brainstem (these patients do fairly well) than it is to chase every last remnant into the brainstem (neurologic deficit is more likely with this).

Surgical exposure of midline cerebellar medulloblastomas requires opening of the foramen magnum, usually removal of the posterior arch of C1, and occasionally the arch of C2. Tumor spread with arachnoidal thickening ("sugar coating") may occur.

Shunts: 30–40% of children require permanent VP shunts following p-fossa resection. The risk of shunt-related seeding has been quoted as high as 10–20%,³ but this is probably overestimated.⁶ In the past, tumor filters were sometimes used. They are less commonly used today because of the high incidence of obstruction.

Post-op adjuvant therapy: MDB

Following surgery, stratification of patients into risk groups guides subsequent therapy. One post-operative stratification scheme is shown in ► Table 44.2. Other systems have been published e.g., for pediatrics (age 3–17 years).⁸

In children: chemotherapy can be used to delay the need for XRT in 20–40% of children <3–4 years of age with non-disseminated MBD.¹⁵

► Low-risk and standard-risk patients

- Especially in pediatrics, may consider reduced dose XRT: 23.4 Gy with a boost to the primary site of 54–55.8 Gy with adjuvant chemotherapy
- or conventional fractionated XRT (see high-risk below).

► High- and very high-risk patients

- Conventional fractionated XRT (once a day) for 54 Gy to the primary tumor and 18 Gy to the craniospinal axis
- chemotherapy¹⁵
 - agents that have been used include: cisplatin, lomustine, vincristine, cyclophosphamide, etoposide, simultaneous high-dose IV methotrexate and/or intrathecal methotrexate of mafosfamide, and/or intraventricular methotrexate
 - in adults: SHH-activated MDBs (which have higher prevalence of PTCH & SMO mutations) may be more responsive to SMO receptor inhibitors and SHH-inhibiting drugs such as vismodegib.¹⁵

44.2.7 Prognosis: MDB

Prognostic details for specific tumor types will be found in the following sections. Poor prognostic factors in general include¹⁶:

- In some cell types younger age (especially if <3 yrs). For other cell types (e.g., desmoplastic/nodular or MBEN, the prognosis for infants is favorable)
- disseminated (metastatic) disease at the time of diagnosis except for MBEN
- inability to perform gross-total removal (especially if residual > 1.5 cm² with localized disease)
- poor Karnofsky performance scale score (p. 1578).

Most common site of recurrence is p-fossa.

Table 44.2 Postoperative risk stratification in medulloblastoma^{11,14,15}

Standard-risk tumors
- total or near total surgical resection^a - no CNS metastases on MRI of brain and spine - no tumor cells on cytospin of lumbar CSF - no clinical evidence of extra-CNS metastases - MDB classification - SHH-activated, TP53-wildtype with classic histology - or non-WNT/non-SHH, group 4, with classic histology and no metastases at diagnosis and no favorable chromosomal findings^b - or non-WNT/non-SHH, group 3 - or WNT with classic histology age ≥ 16 years
Low-risk tumors
- MDB classification - WNT-activated group β-catenin mutation (mandatory testing) β-catenin nuclear immunopositivity by immuno-histochemistry & monosomy 6 (optional testing) - or SHH-activated, TP53-wildtype in infants with - desmoplastic/nodular histology - or extensive nodularity histology - total or near total surgical resection^a
High-risk tumors
- large cell/anaplastic histology non-WNT/non-SHH, group 3 without metastases at diagnosis - classic histology with - SHH-activated, TP53-mutant - or non-WNT/non-SHH, group 4 with metastases at diagnosis - unresectable tumor or residual tumor $> 1.5 \text{ cm}^2$ on axial-plane early post-op MRI - extra-CNS metastases
Very high-risk tumors
- large cell/anaplastic histology with - SHH-activated, TP53-mutant - or non-WNT/non-SHH, group 3 with metastases at diagnosis
^a near total resection: $< 1.5 \text{ cm}^2$ on axial-plane early post-op MRI. This criteria is controversial as much of the data is from CT era ⁸ ^b favorable chromosomal findings for non-WNT/non-SHH group 4: chromosome 7 gain, chromosome 8 loss, chromosome 11 loss, and chromosome 17 gain

Long-term survivors of MDB are at significant risk for permanent endocrinologic, cognitive, and psychological sequelae of treatments. Infants and very young children with MDB remain a difficult therapeutic challenge because they have the most virulent form of the disease and are at highest risk for treatment-related sequelae.

44.3 Medulloblastomas by definition criteria

44.3.1 Medulloblastoma, histologically defined

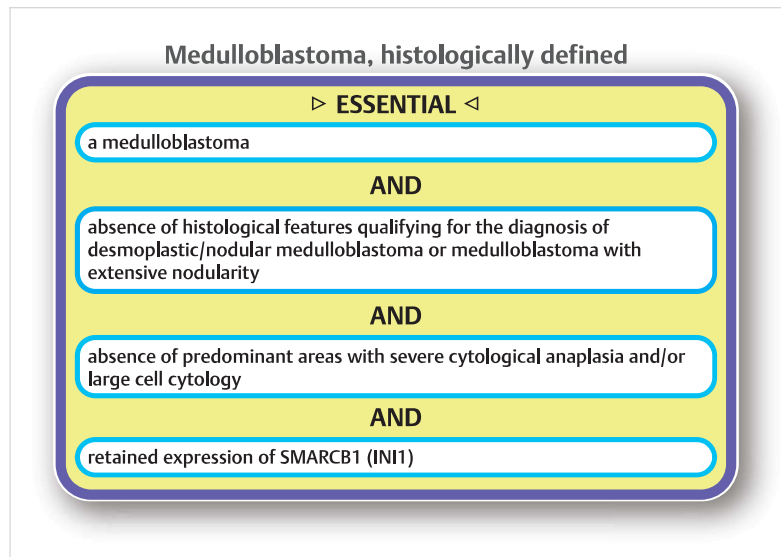
General information: MDB, histologically defined

An embryonal neuroepithelial tumor that occurs in the posterior fossa consisting of small, poorly differentiated cells with a high nuclear to cytoplasmic ratio with profuse mitotic activity and apoptosis. Divided into 4 histologic subtypes described below. On the rare occasion that any subtype shows myogenic and/or melanocytic differentiation, the terms "medullomyoblastoma" and "melanocytic medulloblastoma" respectively may be used in the description.

Diagnostic criteria are shown in ► Fig. 44.3.⁹

Subtypes (histologic/morphologic variants)

- MDB, classic:** densely packed undifferentiated small round cells with mild-to-moderate nuclear pleomorphism and high mitotic count. Comprise $\approx 72\%$ of MDBs. Occur at any age, but predominate in childhood. Found in all 4 molecular MDB types.
- desmoplastic/nodular MDB:** nodular, reticulin-free zones and intervening densely packed, poorly differentiated cells in an intercellular network of reticulin-positive collagen fibers. Account for $\approx 20\%$ of all MDBs. Occurs in cerebellar hemispheres and midline. Bimodal age distribution: 1)



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Fig. 44.3 Diagnostic criteria for medulloblastoma, histologically defined. (Modified with permission from WHO Classification of Tumors Editorial Board, (ed.) World Health Organization classification of tumors of the central nervous system, 5th ed. Bosman F T, Jaffe E S, Lakhani S R, et al. (series eds.): World Health Organization Classification of Tumors series, vol. 6. International Agency for Research on Cancer, Lyon, France, 2021.)

young children and adolescents, 2) adults. Associated with Gorlin syndrome in early childhood. The prognosis in early childhood is excellent with surgery + chemotherapy alone, and is likely better than with any other histologic subtype.

- **MDB with extensive nodularity (MBEN):** numerous reticulin-free neurocytic nodules with a neuropil matrix and narrow internodular strands of poorly differentiated tumor cells in a desmoplastic matrix. Occurs primarily in infants. Accounts for < 5% of MDBs overall, but up to 50% of cases in age < 3 years. Outcome is favorable with near 100% 5-year OS in many (but not all) series. > 80% of these occur in the vermis. The presence of metastases at diagnosis in this group does not affect prognosis.
- **large cell/anaplastic MDB:** Undifferentiated cells with marked nuclear pleomorphism, prominent nucleoli, and high mitotic and apoptotic counts. Accounts for 10% of MDBs. Found in all 4 molecular MDB types. The LC/A morphology is an independent prognosticator of poor outcome (5-year PFS is 30-40%) (very high-risk MDB) justifying aggressive adjuvant therapy. Molecular biology of MDB SHH-activated TP53-mut and non-WNT/non-SHH group 3 with MYC amplification can behave more aggressively.

Staging: MDB, histologically defined

See postoperative staging (p. 720).

Treatment: MDB, histologically defined

For treatment, see treatment for medulloblastomas (p. 721).

44.3.2 Medulloblastomas, molecularly defined

Medulloblastoma, WNT-activated (WHO grade 4)

General information

Typical in older childhood (hardly ever in infancy). Account for ≈ 10% of all MDBs and ≈ 15% of adult MDBs. Male:female = 1:2. Predominant histologic variant: classic (almost all). Favors the cerebellar