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Medulloblastoma: Tumorigenesis, Current Clinical Paradigm, and Efforts to Improve Risk Stratification

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Summary and Introduction

Summary

Medulloblastoma is the most common brain malignancy in children and tremendous advances have recently been made in understanding the pathogenesis of this tumor. The Hedgehog and Wnt signaling pathways are implicated in medulloblastoma development, and both pathways were discovered as a result of analyses of genetic syndromes associated with the tumor. Over the past 80 years, considerable progress has been made in the treatment of what was once a fatal disease. The first survival reports followed the introduction of craniospinal irradiation, and yet the success of this modality, which continues to be a central component of treatment regimens for patients older than 3 years, comes at a significant cost. The present challenge in medulloblastoma treatment is to improve upon existing survival rates and to minimize the side effects of treatment. The current tools of clinical risk assessment fail to adequately identify patients older than 3 years who require less radiation and those who require more radiation. Significant effort has been made to improve clinical risk stratification and titration of treatment by analyzing properties of the tumor cells themselves for prognostic significance. These efforts include identifying histopathologic, cytogenetic, and molecular features that may correlate with prognosis.

Introduction

Medulloblastoma is the most common brain malignancy in children, with approximately 540 cases in the US diagnosed each year.^[1,2] The peak incidence is at 7 years of age, with a higher incidence in boys than girls.^[3] Classic presenting symptoms include headaches, morning vomiting, and ataxia, and subsequent imaging reveals a mass occupying the posterior fossa (Figure 1). This cerebellar neoplasm typically arises in the midline vermis and often invades and obliterates the fourth ventricle; further invasion through the floor of the ventricle to involve the brainstem can also occur.^[4] In a smaller proportion of patients, usually adolescents, the tumor arises within one of the cerebellar hemispheres.

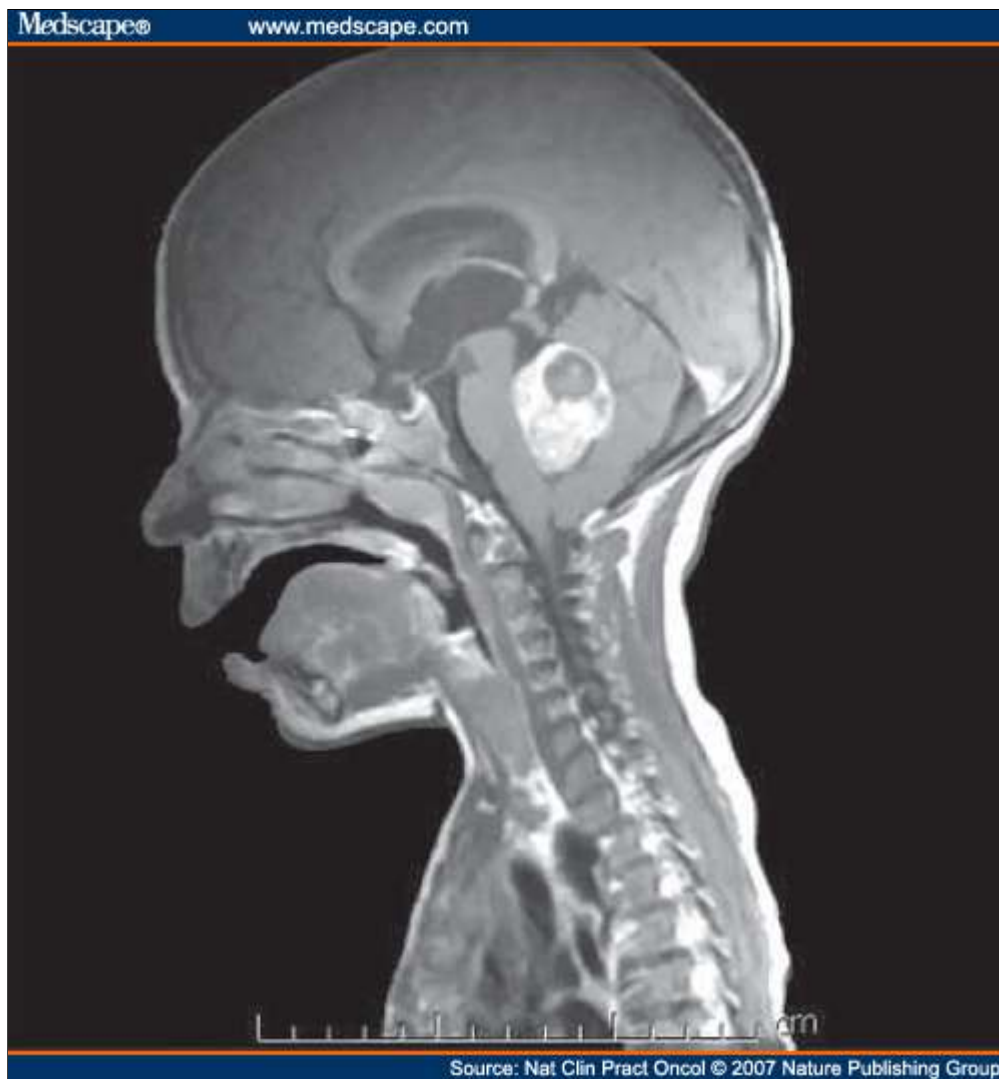


Figure 1. Post-gadolinium MRI of a 4-year-old with medulloblastoma presenting with morning vomiting and ataxia. Note the well-defined enhancing mass obliterating the fourth ventricle.

The WHO classifies medulloblastoma as one of five embryonal tumors, each of which share a primitive 'embryonal' cellular morphology, and are classified as grade IV owing to their aggressive behavior. Classification of such tumors has been a source of great controversy, with many in the past considering medulloblastoma and supratentorial peripheral neuroectodermal tumors to be indistinguishable other than their anatomic location, and, as such, they were collectively called peripheral neuroectodermal tumors or 'PNETs'. Gene-array data from Pomeroy *et al.*, however, confirm that medulloblastoma constitutes a distinct tumor type with a distinguishable molecular phenotype, and this is consistent with the abundant literature describing a unique developmental origin for the tumor, which is discussed below.^[5]

An insidious feature of medulloblastoma is its propensity to metastasize and disseminate through the subarachnoid space, with approximately 30% of children demonstrating cerebrospinal fluid (CSF) metastasis at diagnosis.^[6] Indeed, it was this metastatic feature that foiled treatment attempts for several decades following the original description of medulloblastoma in 1925 by Bailey and Cushing.^[7] Of Cushing's original series of 61 patients, only one patient survived for 3 years following surgery.^[8] It was only following the introduction of intensive craniospinal irradiation (CSI) that significant improvement in survival was reported, with Bloom *et al.* reporting a 32% survival rate at 5 years in 1969.^[4,9] Today, current treatment protocols that include surgery, CSI, and chemotherapy have achieved 5-year overall survival rates of around 60%, and these survival rates are much higher for standard-risk disease. Of those who do survive, however, nearly all experience debilitating side effects from radiation, including cognitive impairment, psychiatric disorders, endocrine dysfunction, and skeletal growth retardation. Despite recent advances in the delivery of radiation therapy using protons as opposed to photons, the late effects of radiation treatment remain a serious concern.^[10]

In the current era of treating medulloblastoma, the challenge is to improve upon existing survival rates, particularly for those with high-risk disease, but also to minimize the life-altering side effects of treatment for those cured of the disease. An individual tumor's aggressiveness and sensitivity to treatment varies considerably, thereby complicating accurate risk assessment and the tailoring of treatment plans that achieve survivability while minimizing side effects. In order to better

address the heterogeneity of tumor behavior, considerable effort has been made to assign risk based upon the biology of each tumor. In this article, we review the pathogenesis of medulloblastoma in order to provide context for the discussion of how the tumor biology might influence treatment decisions. We then discuss the current paradigm of stratifying patients for treatment by clinical parameters, and the shortcomings therein. The remainder of the Review concerns efforts to improve upon clinical risk stratification by using biologic variables, including histopathologic, cytogenetic, and molecular prognostic factors.

Tumorigenesis

The cerebellum constitutes only 10% of the total brain volume, but there are more neurons packed in this small space than in the rest of the brain.^[11] The most abundant of the cerebellar neurons is the granule cell, which during normal development undergoes massive expansion in the external granule layer (EGL) shortly following birth. A number of murine models suggest that perturbations of granule-cell development can result in the formation of medulloblastoma.^[12,13] In these models, medulloblastoma tumors originate from the precursor of the granule cell, called the granule cell progenitor (GCP). The Purkinje cell provides the signal for the GCP to initiate proliferation by secreting the glycoprotein Sonic hedgehog (SHH). Following expansion, GCPs exit the cell cycle and move into the inner zone of the EGL, where they begin to differentiate and migrate inward along Bergmann glial fibers to form the internal granule layer (Figure 2). Postulated mechanisms by which aberrant granule cell development can result in medulloblastoma include excess signaling for GCPs to proliferate or an absence of appropriate signals for GCPs to stop dividing.^[14]

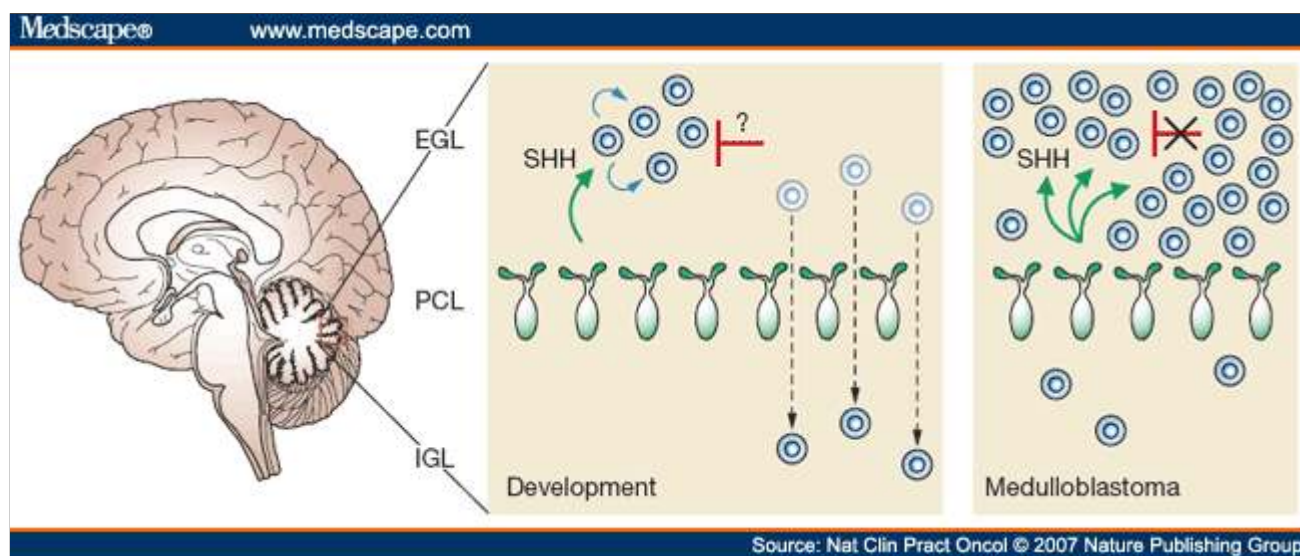


Figure 2. Granule-cell development and tumorigenesis of medulloblastoma. Under normal development, GCPs undergo massive proliferation in the external granule layer upon receiving the SHH signal from the Purkinje cell. GCPs then exit the cell cycle and begin to differentiate and migrate downward to form the IGL. Dysregulated granule cell development, including excessive signals for GCPs to proliferate or an absence of signals to cease dividing, can result in the formation of medulloblastoma. Abbreviations: EGL, external granule layer; GCP, granule cell precursor; IGL, internal granule layer; SHH, sonic hedgehog; PCL, Purkinje cell layer.

Overactive SHH signaling in GCPs in the EGL remains the best characterized of molecular aberrations resulting in medulloblastoma. SHH signaling is initiated when SHH binds to its receptor, Patched 1 (PTCH1), which is a 12 transmembrane-spanning protein. In the absence of SHH ligand, PTCH1 inhibits the effector protein Smoothened (SMO), but when SHH binds to PTCH1, SMO is released from this inhibition, resulting in the downstream activation of the GLI family of transcription factors (Figure 3).^[15,16] Kimura *et al.* recently demonstrated that inactivation of *GLI1* in *PTCH1* heterozygous knockout mice resulted in a significant decrease in medulloblastoma formation, suggesting a fundamental role for GLI1 in SHH-associated tumorigenesis.^[17] A second major mechanism by which SHH signaling exerts a proliferative effect is via the upregulation of *MYCN* (also known as *N-MYC*) expression.^[18,19] *MYCN* upregulation activates D-type cyclins and represses the expression of certain cyclin-dependent kinase inhibitors, and thus also plays an important role in cell-cycle control.^[14] Ultimately, *MYCN* degradation is necessary for GCPs to exit the cell cycle, and its degradation is accomplished via phosphorylation by glycogen synthase kinase-3 beta (GSK3 β). Recent evidence suggests that the insulin-like growth factor (IGF) pathway increases *MYCN* levels via GSK3 β inhibition, thus synergizing with SHH signaling to induce medulloblastoma formation.^[20,21]

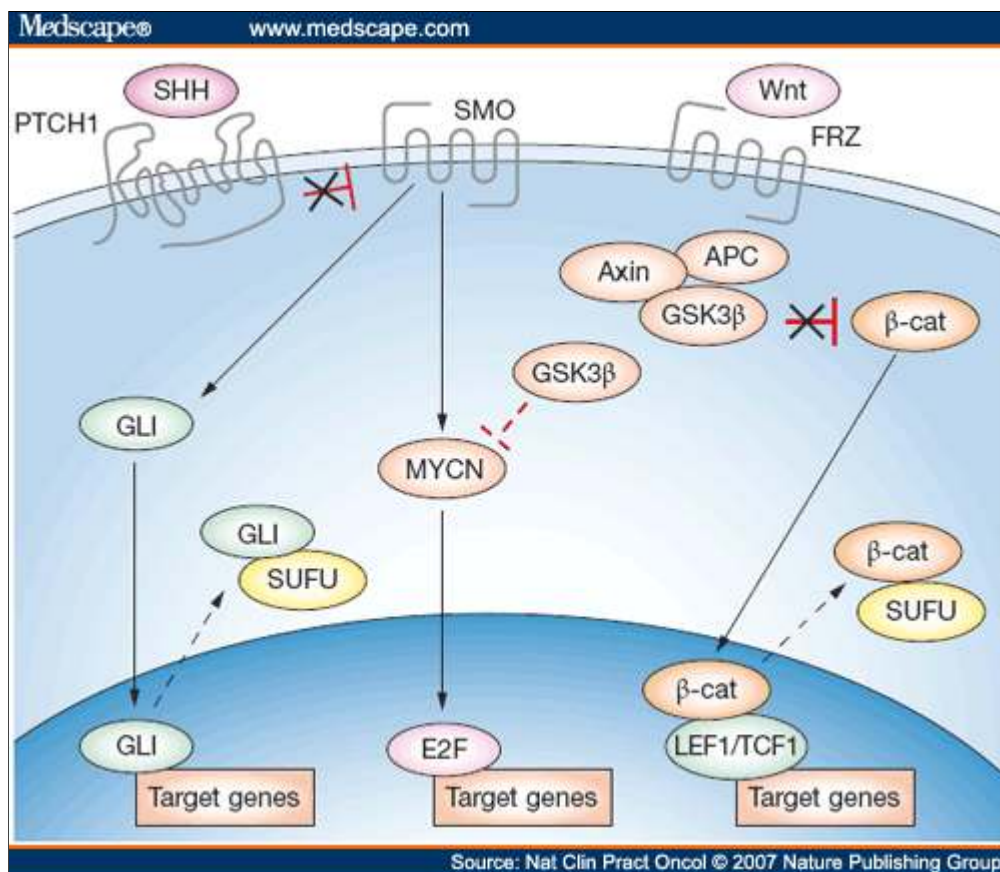


Figure 3. Sonic hedgehog and Wingless signaling pathways implicated in the formation of medulloblastoma. SHH signaling is initiated when SHH binds to its receptor, PTCH1, which releases SMO from inhibition, resulting in the activation of GLI and MYCN. Upon WNT binding to its receptor, FRZ, the APC complex is destabilized, liberating β-catenin to enter the nucleus and activate downstream transcription factors. Note the shared mechanisms of inhibition between the two pathways, SUFU and GSK3β. Permission obtained from Elsevier © Marino S (2005) Trends Mol Med 11: 17–22.[13] Abbreviations: APC, adenomatous polyposis coli; Axin, axis inhibitor protein; β-cat, β-catenin; FRZ, Frizzled; GLI, zinc finger protein GLI1; GSK3β, glycogen synthase kinase 3 β; LEF1/TCF1, lymphoid enhancer-binding factor 1/T-cell specific factor 1; MYCN, N-myc proto-oncogene protein; PTCH1, Patched 1; SHH, Sonic hedgehog; SMO, Smoothed; SUFU, Suppressor of Fused; WNT, Wingless.

SHH signaling was initially implicated in the pathogenesis of medulloblastoma when investigators studied a rare hereditary condition called Gorlin syndrome, which is characterized by skeletal abnormalities, multiple basal-cell carcinomas, and an increased incidence of medulloblastoma. Genetic analysis of Gorlin syndrome revealed a mutation of *PTCH1* that results in constitutive activation of the SHH pathway. In subsequent analyses of sporadic medulloblastomas, mutations in the individual components of the SHH pathway were found in approximately 25% of tumors, with *PTCH1* being the most common mutation.^[22] An additional group of tumors demonstrate increased functional SHH signaling in the absence of a known *PTCH1* mutation, increasing the total percentage of tumors with overactive SHH signaling and indicating alternative mutations and mechanisms of pathway activation.^[23,24]

A role for Wingless (WNT) signaling in the pathogenesis of medulloblastoma was revealed via genetic analysis of a second hereditary syndrome associated with the tumor called Turcot syndrome (a variant of familial adenomatous polyposis). A key component of the canonical WNT signaling pathway is β-catenin, a protein which is stabilized upon WNT signal activation. The binding of WNT to its receptor, Frizzled, destabilizes the multiprotein complex, adenomatous polyposis coli (APC)/AXIN/GSK3β enabling β-catenin to enter the nucleus and activate the LEF1/TCF1 transcription factors, which induce gene expression of downstream targets, including MYC (also known as C-MYC) and cyclin D1. Approximately 15% of medulloblastomas demonstrate WNT signaling mutations.^[25,26,27,28] Interestingly, the SHH and WNT signaling pathways share some similar mechanisms of inhibition. GSK3β, the inhibitory protein of SHH signaling, also has an inhibiting function in the WNT pathway by phosphorylating β-catenin, leading to its degradation. In addition, during SHH signaling, Suppressor of Fused (SUFU) exports both GLI1 and β-catenin out of the nucleus.^[13] Other pathways implicated in the formation of medulloblastoma include increased NOTCH signaling, signaling via the ErbB family of receptors, and, most recently, defective DNA repair mechanisms.^[29,30,31]

The majority of investigation has focused upon GCPs as a source of medulloblastomas, though neural stem cells (NSCs) have become a new focus of attention as a possible independent cell of origin for the tumor. Adult stem cells are characterized by a capacity for self-renewal, and whose progeny can differentiate into one or more distinct cell lineages. NSCs are well described in other parts of the brain, yet a population of cerebellar NSCs was only recently isolated from a murine postnatal cerebellum.^[32] These cerebellar NSCs express the NSC marker CD133 (also called prominin 1), form self-renewing neurospheres, and differentiate into neuronal and glial cells both *in vitro* and after transplantation into another mouse brain. Cerebellar NSCs might provide a potential etiology for a subpopulation of cells that have recently been isolated from human medulloblastoma tumors that are CD133+, self-renewing, and that reproduce a phenocopy of the original tumor following their transplantation—with as few as 100 cells—into immunocompromised mice.^[33,34] Further work is necessary to understand the function of cerebellar NSCs in normal development and to elucidate their relationship with medulloblastoma cancer stem cells and potential role in tumorigenesis.

Current Clinical Paradigm

Despite more than 20 years of insight into the molecular pathogenesis of medulloblastoma, risk assessment continues to be determined solely by clinical parameters. The single greatest prognostic factor is patient age, with those less than 3 years of age—approximately 25–35% of all medulloblastoma cases—facing a worse prognosis. As a result of the severe damage that CSI would inflict upon the immature brain of a child less than 3-years old, it has historically been excluded from treatment regimens in this age group. The exclusion of CSI may explain the disparity in survival rates between those younger and older than 3 years, though others have also speculated that the tumor itself might be more aggressive in younger children.^[35] In addition, it is important to note that before the routine use of immunohistochemistry, another embryonal neoplasm called atypical teratoid/rhabdoid tumor, which generally occurs in children younger than 3 years and has a worse prognosis, was mistaken for medulloblastoma, further lowering survival numbers for the younger age group.^[36] For many years, postoperative chemotherapy for those younger than 3 years yielded disappointing survival rates, in the range 25–45%; however, new strategies, which include intensified chemotherapy, intraventricular chemotherapy, and localized radiation, have produced more promising results—all of which have been recently reviewed in detail by Rutkowski.^[37]

For children older than 3 years, three variables are used to stratify patients into two risk groups, standard risk and high risk, and treatment is determined accordingly. The first variable concerns the presence of tumor cells in the CSF following surgery, with increased risk bestowed upon those with a positive lumbar tap. The second variable assigns increased risk to those with macrometastasis anywhere along the cerebrospinal axis on postoperative imaging, which typically entails a gadolinium-enhanced MRI. The original Chang staging system collapses the latter two variables into the M stage, which summarizes the extent of metastasis from M0—no evidence of micrometastasis or macrometastasis—to M4, evidence of extraneural disease extension (Box 1). The extent of disease beyond the original tumor site has consistently proven to be a highly significant prognostic risk factor.^[38,39,40] Of note, the T stage of the Chang system, relating to tumor size and extent of local invasion at surgery, does not seem to demonstrate prognostic significance and is no longer used. The final clinical variable used to assign risk is residual tumor size following surgery, which is assessed via postoperative imaging; tumors greater than 1.5 cm² confer an increased risk.^[4]

Postsurgical treatment of medulloblastoma in patients older than 3 years is determined by whether the patient is standard risk or high risk (Figure 4). Standard-risk patients receive 'reduced-dose' CSI of 23.4 Gy plus a localized boost to the posterior fossa to a total of 55.8 Gy, combined with concurrent single-drug chemotherapy followed by a multi-drug chemotherapy regimen. The addition of adjuvant chemotherapy allowed the dose of CSI to be reduced from 36.0 Gy to 23.4 Gy without a significant decrease in survival, as demonstrated by an event-free survival of 67–81% at 5 years, while better preserving neurocognitive function.^[41,42,43,44] Nevertheless, loss of neurocognitive function can still occur with the reduced dose, particularly in younger patients.^[45] In the hope of further minimizing neurocognitive loss in standard-risk patients, an ongoing Children's Oncology Group trial is randomizing patients 3–8 years of age to either 18 Gy or 23.4 Gy CSI. Protocols for high-risk patients generally include 'full-dose' CSI of 36.0 Gy plus a similar localized boost to the posterior fossa with concurrent single-drug chemotherapy and a more aggressive adjuvant regimen. Survival rates in the high-risk category are lower, 43–70% event-free survival at 5 years, as well as the degree of compromise of neurocognitive function.^[46,47,48,49]

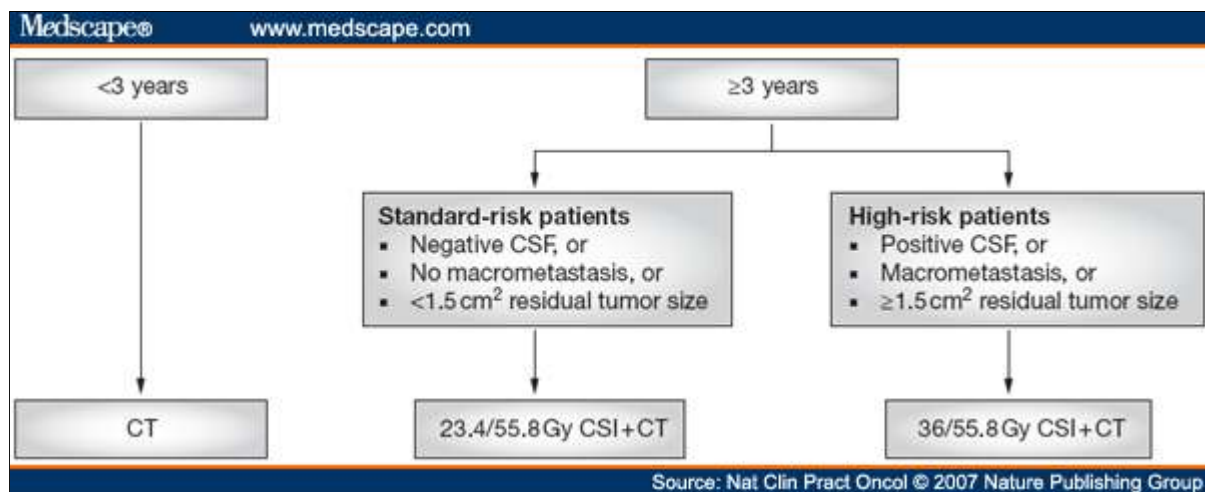


Figure 4. Postoperative risk stratification and treatment of medulloblastoma. Patients younger than 3 years generally receive CT alone, but the role of localized radiation is being investigated. Patients aged 3 years or older are stratified by clinical criteria to receive either 'reduced-dose' or 'full-dose' CSI plus adjuvant CT. Abbreviations: CSI, craniospinal irradiation; CSF, cerebrospinal fluid; CT, chemotherapy.

The current means of clinical risk stratification has several shortcomings. First, the system fails to identify the 20–40% of those meeting standard-risk criteria who are in fact high-risk. As a result, more aggressive therapy is delayed for a substantial number of patients who require it. Second, current risk stratification fails to identify many patients who meet high-risk clinical criteria, but who could be cured with low-risk treatment regimens, and thus avoid unnecessary neurocognitive decline and additional side effects. Third, by categorizing patients into only two risk categories, current clinical risk stratification inappropriately simplifies the true heterogeneity of tumor behaviour, consequently hindering efforts to titrate treatment more accurately.

Histopathologic Prognostics

Four histopathologic subtypes of medulloblastoma are generally described and have been investigated for prognostic potential: medulloblastoma with extensive nodularity (MBEN), desmoplastic, classic, and large cell/anaplastic (LC/A) (Figure 5). Approximately 65% of tumors are classified as classic medulloblastoma, the most common subtype, consisting of uniform sheets of dense, "small, round, blue, cells," which seem undifferentiated under light microscopy but often display neuronal differentiation by immunohistochemistry.^[50]

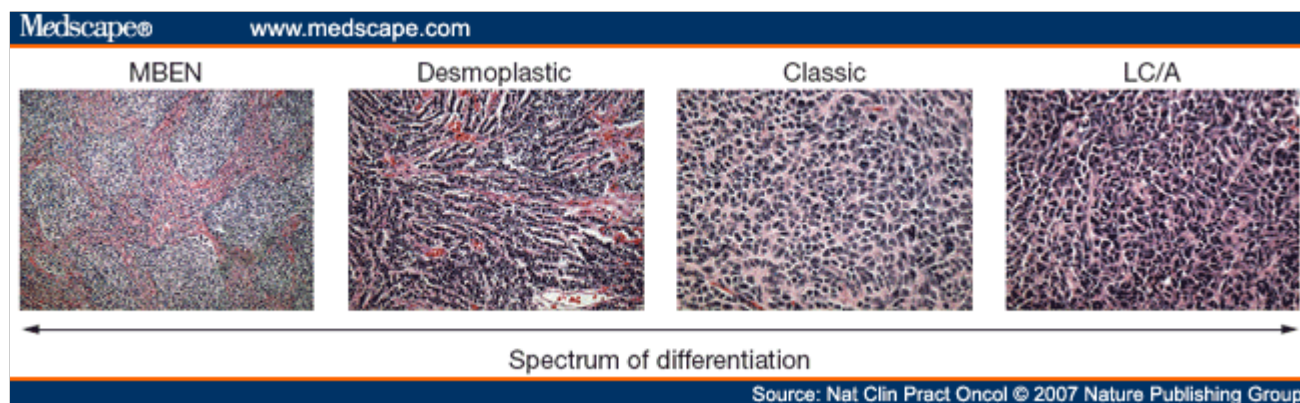


Figure 5. Histopathologic subtypes of medulloblastoma. The histopathologic subtypes of medulloblastoma exist along a spectrum of differentiation and have been investigated for prognostic value, with some studies suggesting an improved prognosis for MBEN and desmoplastic subtypes and other studies showing a worse prognosis for LC/A. Images courtesy of E Tessa Hedley-Whyte, Massachusetts General Hospital Department of Pathology. Abbreviations: LC/A, large cell/anaplastic; MBEN, medulloblastoma with extensive nodularity.

About 25% of tumors are of the desmoplastic subtype, characterized by a tissue pattern consisting of reticulin-free nodules (also called pale islands) surrounded by proliferating cells that produce a reticulin-rich extracellular matrix. The desmoplastic subtype has been linked to mutations in the *PTCH1* gene and overactive SHH signaling, and this subtype is specifically associated with Gorlin syndrome.^[51,52,53] Several series have suggested that desmoplastic medulloblastoma

may have a better prognosis than the classic and LC/A subtypes.^[37,40,54,55] Some consider an extreme variation of the desmoplastic pattern, which exhibits extensive nodularity and advanced neuronal differentiation, to constitute a separate subtype called MBEN. This subtype comprises approximately 5% of tumors, occurs almost exclusively in infants, and is also associated with dysregulated SHH signaling. Of 11 infants reported to have MBEN in an Italian series, all survived.^[56] The fact that MBEN portends a good outcome is surprising considering the fact that younger children generally fare the worst.

The LC/A subtype comprises the most undifferentiated tumors, constituting approximately 5% of tumors. This subtype displays characteristic cells with large nuclei and prominent nucleoli, embedded in a background of cells demonstrating severe nuclear atypia with indistinct nucleoli. Giangaspero and coauthors originally described a highly aggressive 'large cell' variant in a 4-patient case series, all of whom died. Moreover, several large-scale retrospective studies have reported that LC/A medulloblastoma is associated with decreased survival.^[57,58,59,60,61] Hypothesizing that anaplasia and its worse prognosis might exist along a spectrum, Eberhart *et al.* assessed the grade (none, slight, moderate, and severe) and other variables of 330 samples from the Pediatric Oncology Group study.^[62] Moderate and severe anaplasia were associated with decreased survival, suggesting that the impact of the anaplasia on survivability may not be limited to the most severe LC/A subtype.

Since recurrences of medulloblastoma and extra-central nervous system metastases can sometimes demonstrate anaplastic components despite no evidence of anaplasia in the original tumor, some have suggested that the anaplastic phenotype may represent the end stage of a stepwise accumulation of mutations, similar to the colorectal-cancer model.^[62,63] In this model, each medulloblastoma subtype may be capable of progressing to the LC/A subtype. Considering the potential prognostic importance of anaplasia, a number of studies have examined cytogenetic and molecular derangements underlying this phenotype. The two most frequently associated findings are amplification of *MYC* and *MYCN*, but loss of chromosome 17p and aneuploidy have also been noted.^[64,65] A recent study provided insight regarding the role of *MYC* by demonstrating that *MYC* overexpression in medulloblastoma cell lines is sufficient to induce anaplasia.^[66]

Cytogenetic Prognostics

The most common cytogenetic abnormality associated with medulloblastoma is the loss of chromosome 17p, which occurs in 40–50% of tumors. In most cases, the short arm of chromosome 17 is replaced by a duplication of the long arm, creating an isochromosome 17q, but the loss of 17p can also occur without a gain of 17q. Several studies have shown that the loss of 17p is associated with a poorer prognosis.^[61,67,68,69] Other studies, however, have not found a significant association between loss of 17p and survival outcomes.^[70,71] Considering the potential implications of 17p loss on prognosis, many have attempted to identify genes on 17p that when lost or disrupted might contribute to more aggressive behavior. Tumor-suppressor genes on 17p that have been investigated include *KCTD11* (also known as *REN*), *TP53* and *HIC1*.^[72,73,74] *KCTD11* has been shown to inhibit SHH signaling directly, and might provide an important signal for GCPs to cease proliferation.^[75]

Other studies have examined whether aneuploidy can be associated with prognosis. Past results have been mixed, with some authors noting a survival advantage for aneuploidy, while our group demonstrated that aneuploidy correlated with decreased survival.^[76,77,78,79,80] In more recent years, chromosomal instability (CIN) and aneuploidy have been found to have an important role in the pathogenesis and risk assessment of a number of cancers. One study stratified 60 medulloblastoma tumors—in addition to sample sets from other tumor types—into two groups on the basis of a CIN score derived from gene-expression data.^[81] The patients with tumors showing increased CIN were associated with decreased survival, suggesting that aneuploidy may indeed be a negative prognostic feature (Figure 6). It should be noted, however, that the CIN signature derived in this study contains two components that could not be completely separated, one characterizing the level of CIN and the other the proliferative capacity of the tumor cells, both of which were predictive of survival.

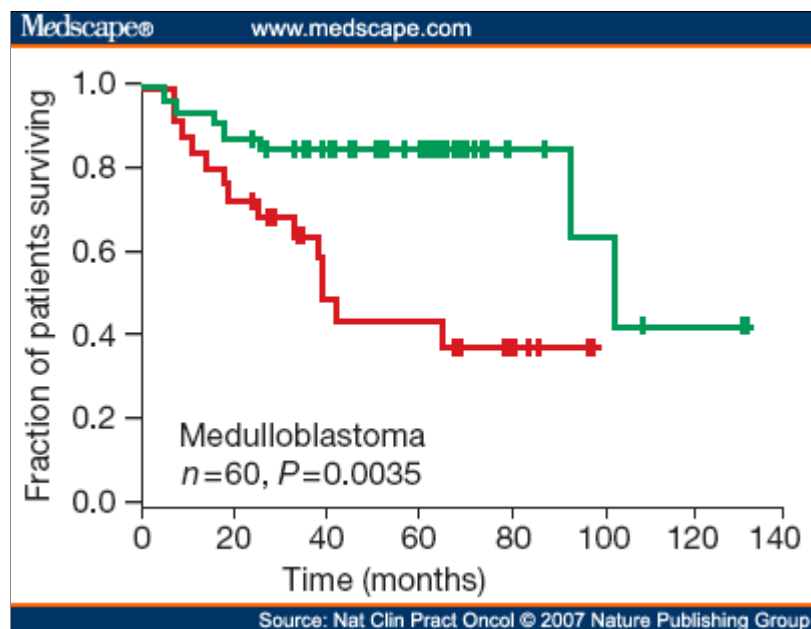


Figure 6. Chromosomal instability and medulloblastoma prognosis. Patients were stratified into two groups on the basis of the expression of a chromosomal instability (CIN) signature. The Kaplan–Meier curve indicates that patients with above average CIN signature (red line) were associated with significantly worse clinical outcome than patients with below average CIN signature (green line). Permission obtained from Nature Publishing Group © Carter SL et al. (2006) *Nat Genet* 38: 1043–1048.[81]

Molecular Prognostics

MYC and MYCN—members of the *MYC* oncogene family that share similar yet unique roles in carcinogenesis—are amplified in a small subset of medulloblastomas. A number of studies have found that *MYC* amplification is independently correlated with a negative outcome, and is also associated with other potential negative prognostic factors such as anaplasia and loss of 17p.^[82,83,84] Furthermore, studies have shown that increased *MYC* mRNA occurs in the absence of gene amplification, and a higher *MYC* expression occurs in a larger percentage of tumors than previously believed. In these studies, levels of *MYC* mRNA independently predicted prognosis.^[85,86] The prognostic value of MYCN, which functions as a downstream target of SHH signaling, remains to be established. In the series reported by Eberhart *et al.*, MYCN could not be significantly associated with outcome, and a more recent study found neither *MYC* nor MYCN to be prognostic.^[84,87]

The EGFR tyrosine kinase family—EGFR, ErbB2, ErbB3, and ErbB4—and the complex signaling pathways that they govern have been implicated in carcinogenesis. Studies have found that the overexpression of ErbB2 in medulloblastoma tumors is associated with a poor clinical outcome and increased metastatic potential.^[87,88,89,90] In the series reported by Gajjar *et al.*, all children with clinically standard-risk disease and ErbB2-negative tumors were alive at 5 years, compared with only 54% of children with ErbB2-positive tumors who similarly met standard-risk criteria.^[87] ErbB2 can upregulate certain prometastatic genes such as *S100A*, suggesting a potential mechanism by which ErbB2 might induce more aggressive tumor behavior.^[91]

In contrast to the other molecular prognostics discussed earlier, overexpression of the TrkC (also known as NTRK3) receptor has been associated with improved survival,^[92,93] although one study by Gajjar *et al.* found no association between survival and TrkC expression.^[87] The Trk receptor family of tyrosine kinases, TrkA, TrkB, and TrkC, are differentially expressed during brain development, and in conjunction with their neurotrophin family of ligands are believed to have an important role in regulating the proliferation and differentiation of neuronal precursor cells. In particular, in the presence of its neurotrophin ligand NT-3, TrkC has been shown to induce apoptosis of medulloblastoma cells via early gene expression of the transcription factors c-Fos and c-Jun.^[94] Another molecular prognostic that has been associated with improved survival is nuclear accumulation of β -catenin.^[95] Upon the binding of the WNT ligand to its receptor, β -catenin enters the nucleus and thus its nuclear immunoreactivity might serve as an assay for active Wnt signaling. The association of an improved outcome with increased Wnt signaling is surprising considering that certain downstream targets of Wnt signaling, such as MYC, have been associated with a poor outcome. This association was confirmed in a recent study that found that patients with tumors demonstrating WNT signaling abnormalities experienced better event-free survival than other patients.^[48]

Conclusion

There is no other brain malignancy for which the molecular mechanisms of pathogenesis have been so abundantly described and modeled. For the newly diagnosed patient and their family, however, this immense knowledge remains largely academic, since it has not influenced clinical management. Of course, the holy grail of medulloblastoma research remains the development of targeted agents such as small molecule inhibitors—the proverbial magic bullet—that would intervene upon tumorigenesis and cause minimal side effects. In the meantime, however, an intermediate goal must be to use our understanding of the biology of medulloblastoma to improve upon a clinical risk stratification system that currently under treats or over treats a significant number of patients, the consequences of which are life-altering. Associations between histopathologic subtypes and clinical outcome show promise, yet for general application can be complicated by subjective criteria. Studies demonstrating prognostic value for certain cytogenetic and molecular findings are also encouraging. However, before histopathologic, cytogenetic, or molecular features can be used to help assign clinical risk more sensitively, their utility must be validated within the context of larger-scale, multicenter, prospective trials. Until then, risk assessment and subsequent treatment decisions will continue to be made on the basis of clinical parameters alone.

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Sidebar: Key Points

- Studies of murine models suggest that aberrant granule-cell development might result in a subset of medulloblastoma tumors; recently identified cerebellar neural stem cells might be another potential cell of origin for the tumor
- Overactive SHH signaling is the best characterized of the molecular aberrations resulting in medulloblastoma, although roles for WNT signaling and other pathways have been described
- Patients diagnosed with medulloblastoma are stratified for treatment by clinical criteria resulting in a significant number of patients being under treated or over treated with significant consequences
- Accurate risk assessment is complicated by the variability of tumor behavior, and consequently considerable effort has been made over the past 20 years to assign risk on the basis of a better understanding of the biology of the tumor
- Biologic parameters investigated for prognostic value include histopathologic, cytogenetic, and molecular features; although promising associations have been demonstrated, none has been used for patient stratification in a clinical trial

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