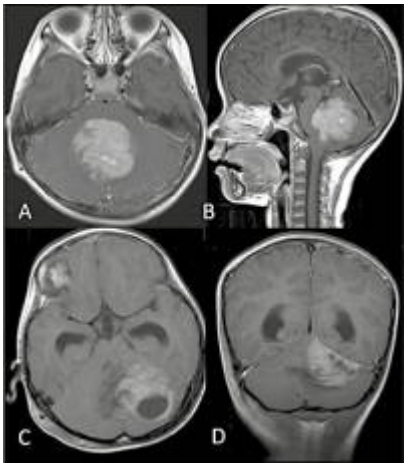
Medulloblastoma prognosis



There is promise of applying radiomics and radiogenomics for advancements in diagnosis, prognostication, and improving patient outcomes in pediatric medulloblastoma. However, there are still challenges in this area, prominently a lack of publicly available studies for computational analysis. However, with the recently launched clinical trials and with data sharing efforts across different institutions as well as data consortiums, this challenge might be mitigated in the coming years, ultimately allowing for building reliable and reproducible machine learning models trained on large multi-institutional cohorts [1)]

Although the current cure rate stands at approximately 70%, the existing treatments that involve a combination of radio- and chemotherapy are highly detrimental to the patients' quality of life. These aggressive therapies often result in a significant reduction in the overall well-being of the patients. Moreover, the most aggressive forms of MB frequently relapse, leading to a fatal outcome in a majority of cases. However, MB is highly vascularized, and both angiogenesis and lymphangiogenesis are believed to play crucial roles in tumor development and spread [2)].

Five-year survival rate is approximately 75% in children with primary disease, but outcomes for relapsed disease are very poor. Recent advances have identified molecular subgroups with excellent prognosis, with 5-year overall survival rates >90%, and subgroups with very poor prognosis with overall survival rates <50% [3)].

All medulloblastomas are WHO grade IV.

Poor prognosticators

● younger age (especially if<3 yrs)

● disseminated (metastatic) disease. see medulloblastoma metastasis

● inability to perform gross-total removal(especially if residual > 1.5cm2 in patient with localized disease)

● histological differentiation along glial, ependymal, or neuronal lines

Medulloblastoma is the most common malignant brain tumor that occurs during childhood. Multimodality treatment regimens have substantially improved survival in this disease; however, the tumour is incurable in about a third of patients with medulloblastoma, and current treatment has a detrimental effect on long-term survivors. Drugs that target cell-signaling pathways provide an alternative to conventional cytotoxic approaches to the treatment of cancer. Several pathways have been implicated in medulloblastoma formation, and knowledge of these is now being used to develop new ways of treating children with medulloblastoma [4)].

Weil et al. [5)] and Prados et al. [6)] found female gender to be a significant favorable prognostic factor in medulloblastoma. Sex did not reveal any bearing on the outcome in the series of Kumar et al. [7)].

Age, hemispheric location of the tumor, the extent of resection, and adjuvant therapy status were the important clinical prognostic factors for survival in the series of Narayan et al. [8)].

Complete resection should be performed if possible as several studies have correlated outcome with the extent of resection and amount of residual tumor [9)].

Gene expression profiling is highly predictive of response to therapy, predicting outcome with much greater accuracy than current staging criteria [10)].

Long-term survivors of MB are at significant risk for permanent endocrinologic, cognitive, and psychological sequelae of treatments. Infants and very young children with MB remain a di cult therapeutic challenge because they have the most virulent form of the disease and are at the highest risk for treatment-related sequelae. Most common site of recurrence is p-fossa. Collins'law has also been used to define the period of the risk of recurrence (PRR) but exceptions to the law have been reported [11)].

Ninety-seven samples of medulloblastoma were collected. Tumor content in samples was judged by frozen section review. Tumor ERBB2 protein and MYCC, MYCN, and TRKC mRNA levels were measured blind to clinical details using Western blotting and real-time polymerase chain reaction, respectively. Histopathologic and clinical review of each case was also performed. All data were subjected to independent statistical analysis.

Sample acquisition and analysis times ranged from 3 to 6 days. Eighty-six samples contained sufficient tumor for analysis, including 38 classic, 30 nodular desmoplastic, and 18 large-cell anaplastic (LCA) medulloblastomas. Protein and mRNA were extracted from 81 and 49 tumors, respectively. ERBB2 was detected in 40% (n=32 of 81) of tumors, most frequently in LCA disease (P=.005), and was independently associated with a poor prognosis (P=.031). A combination of clinical characteristics and ERBB2 expression provided a highly accurate means of discriminating disease risk. One hundred percent (n=26) of children with clinical average-risk, ERBB2-negative disease were alive at 5 years, with a median follow-up of 5.6 years, compared with only 54% for children with average-risk, ERBB2-positive tumors (n=13; P=.0001). TRKC, MYCC, and MYCN expression and histopathologic subtype were not associated with prognosis in this study.

Central and rapid molecular analysis of frozen medulloblastomas collected from multiple institutions is feasible. ERBB2 expression and clinical risk factors together constitute a highly accurate disease risk stratification tool [12)].

The purpose of a study of was to determine the relative contributions of biological and clinical predictors of survival in patients with medulloblastoma (MB).

Clinical presentation and survival information were obtained for 119 patients who had undergone surgery for MB at the Hospital for Sick Children (Toronto, Ontario, Canada) between 1985 and 2001. A tissue microarray was constructed from the tumor samples. The arrays were assayed for immunohistochemical expression of MYC, p53, platelet-derived growth factor receptor-alpha, ErbB2, MIB-1, and TrkC and for apoptosis (terminal deoxynucleotidyl transferase-mediated nick end labeling). Both univariable and multivariable analyses were conducted to characterize the association between survival and both clinical and biological markers. For the strongest predictors of survival, a weighted predictive score was calculated based on their hazard ratios (HRs). The sum of these scores was then used to give an overall prediction of survival using a nomogram.

The four strongest predictors of survival in the final multivariable model were the presence of metastatic disease at presentation (HR, 2.02; P=0.01) and p53 (HR, 2.29; P=0.02), TrkC (HR, 0.65; P=0.14), and ErbB2 (HR, 1.51; P=0.21) immunopositivity. A linear prognostic index was derived, with coefficients equal to the logarithm of these HRs. The 5-year survival rate for patients at the 10th, 50th, and 90th percentiles of the score distribution was 80.0%, 71.0%, and 35.7%, respectively, with radiation therapy and 70.5%, 58.5%, and 20.0%, respectively, without radiation therapy.

In this study, we demonstrate an approach to combining both clinical and biological markers to quantify risk in MB patients. This provides further prognostic information than can be obtained when either clinical factors or biological markers are studied separately and establishes a framework for comparing prognostic markers in future clinical studies [13)].

Two rare subtypes at extreme ends of the histologic spectrum, i.e., medulloblastomas with extensive nodularity and large cell/anaplastic medulloblastomas, are associated with better and worse clinical outcomes, respectively. However, there is little data about correlations between histologic features and clinical outcomes for most patients with medulloblastomas that fall between these histologic extremes of nodularity and anaplasia.

Eberhart et al. evaluated the clinical effects of increasing anaplasia and nodularity in a large group of children with medulloblastomas, hypothesizing that increasing nodularity would predict better clinical outcomes and that increasing anaplasia would presage less favorable results.

Medulloblastomas from 330 Pediatric Oncology Group patients were evaluated histologically with respect to extent of nodularity, presence of desmoplasia, grade of anaplasia, and extent of anaplasia. Pathologic and clinical data were then compared using Kaplan-Meier and log-rank analyses.

Increasing grade of anaplasia and extent of anaplasia were associated strongly with progressively worse clinical outcomes ($P < 0.0001$ for both). Significant anaplasia (moderate or severe) was identified in 24% of medulloblastoma specimens. Neither increasing degrees of nodularity nor desmoplasia were associated significantly with longer survival.

Moderate anaplasia and severe anaplasia were associated with aggressive clinical behavior in patients with medulloblastomas and were detected in a significant number of specimens (24%). Pathologic grading of medulloblastomas with respect to anaplasia may be of clinical utility [14)].

Although surgery, radiation and high-dose chemotherapy have led to increased survival, one-third of patients succumb to their disease, and patients who survive suffer severe long-term side effects as a consequence of treatment.

Through analysis of several well-designed multi-institutional trials, much has been learned about the clinical factors that influence outcome in children with medulloblastomas. Age younger than 3 years, bulky residual disease postoperatively, and metastases constitute adverse prognostic features and indicate patients who are considered “high risk” for recurrence with standard therapy using 3600 cGy craniospinal radiation in conjunction with a posterior fossa dose of 5400 cGy. Patients lacking these features are considered “standard risk.”

Evaluation of biologic predictors of outcome, which may further refine treatment stratification, is in progress.

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