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Nodule Formation and Desmoplasia in Medulloblastomas—Defining the Nodular/Desmoplastic Variant and Its Biological Behavior

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Among the variants of medulloblastoma in the current WHO classification of nervous system tumors, the desmoplastic variant, which has been reported to constitute 5%–25% of pediatric medulloblastomas, is defined by its nodular collections of neurocytic cells bounded by desmoplastic internodular zones. We have studied the frequency, morphological features and biological behavior of medulloblastomas in two contemporaneous SIOP/UKCCSG trial cohorts of children with medulloblastomas, CNS9102 (n = 315) and CNS9204 (n = 35), focusing on tumors with nodular and desmoplastic phenotypes. In children aged 3–16 years (CNS9102), the nodular/desmoplastic medulloblastoma represented 5% of all tumors, while in infants aged <3 years (CNS9204) this variant represented 57% of medulloblastomas. Using iFISH to detect molecular cytogenetic abnormalities in medulloblastomas with a nodular architecture, we demonstrated distinct genetic profiles in desmoplastic and non-desmoplastic (classic and anaplastic) tumors; in particular, abnormalities of chromosome 17 occurred in the latter, but not the former. Significantly different outcomes were demonstrated for classic, nodular/desmoplastic and large cell/anaplastic medulloblastomas in both cohorts. In conclusion, the nodular/desmoplastic medulloblastoma appears to have clinical, genetic and biological characteristics that set it apart from other variants of this tumor.

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INTRODUCTION

Consensus agreement on a clinically applicable histopathological classification of a tumor and its variants provides a foundation upon which enhanced therapeutic stratification can be built. Improved therapeutic stratification and the search for novel therapies represent the current focus and challenge of pediatric medulloblastoma. While the developing molecular classification of medulloblastoma will clearly play a critical role in achieving these aims, it is important to set such advances against a refined, usable and biologically relevant scheme of histopathological assessment (10, 40).

Medulloblastoma, an embryonal neuroepithelial tumor, is the most common central nervous system (CNS) tumor of childhood, with an incidence of $0.6/10^5$ in children aged under 15 years in the UK. Advances in all aspects of medulloblastoma management have contributed to a current progression-free survival (PFS) rate of 60% at 5 years (26). In children with localized, maximally resected disease, PFS may be as high as 80% in some trials (29, 39). However, survival comes at a cost; radiotherapy, especially to the young developing brain, has significant long-term neuropsychological and neuroendocrine consequences, and current chemotherapeutic regimens have significant toxicities (14, 16, 17, 22, 23).

Based on our current understanding of the behavior of medulloblastomas, children aged over 3 years are assigned to standard or high-risk groups, and treatment is tailored accordingly (10, 41). Separate protocols, with omitted or delayed radiotherapy, exist for those aged less than 3 years. Unfortunately, survival rates in recent trials have leveled out for all age groups, suggesting that further refinements in treatment stratification are necessary, if we are to improve survival in the high-risk group and spare those in the standard-risk group from unnecessarily harsh treatment regimens and avoidable long-term sequelae.

The current World Health Organisation (WHO) classification of nervous system tumors (2000) recognizes classic, desmoplastic, large cell, melanotic and medullomyoblastic variants of medulloblastoma (19). However, nearly all (>95%) medulloblastomas are classic or desmoplastic tumors (9). The incidence of desmoplastic medulloblastoma, which is characterized by a nodular architecture and a network of internodular collagen fibers, varies substantially between series (5%–25%), but it appears to be greater in infants and adult patients than in children (1, 6, 13, 24, 35).

Neither classic nor desmoplastic medulloblastomas are uniform entities; both show a range of architectural and

cytological features (9), and some of these features have biological significance. For example, extensive and marked nuclear pleomorphism in up to a quarter of classic medulloblastomas was the principal characteristic used in recent studies to define the biologically aggressive anaplastic medulloblastoma (6, 25), and the widespread nodularity seen in a type of infantile desmoplastic medulloblastoma, the medulloblastoma with extensive nodularity (MBEN), is associated with a good prognosis (12, 38).

Through the process of central pathology review attached to International Society for Pediatric Oncology (SIOP)/United Kingdom Children's Cancer Study Group (UKCCSG) trials, it has become clear that medulloblastomas can express the nodular phenotype to varying degrees, and that the presence and pattern of desmoplasia, or the laying down of collagen, can also vary. In particular, we have observed that nodules of differentiation can occur both with and without encircling desmoplasia. In addition, it has long been recognized that desmoplasia may occur in any medulloblastoma variant as a normal reactive phenomenon when tumor cells invade the leptomeninges (34). Such variability can make subclassification difficult (9), and could contribute to discrepant data on the biological significance of nodular and desmoplastic phenotypes (3, 27, 28, 37).

This study of histopathological heterogeneity in childhood medulloblastoma and its biological significance therefore sought to:

(i) Record the complete central histopathological review of 350 medulloblastomas from the SIOP/UKCCSG PNET3 (CNS9102) and SIOP/UKCCSG CNS9204 trials, focusing particularly on the phenomena of nodule formation and desmoplasia
(ii) Illustrate the diverse nature of nodular regions of neuronal differentiation in medulloblastomas
(iii) Test the hypothesis that nodular medulloblastomas with or without internodular desmoplasia represent distinct tumor variants by analyzing their molecular cytogenetic profiles
(iv) Analyze the clinical characteristics and outcome data of histopathological subtypes

Our data show that: (i) nodular regions characterized by a neurocytic phenotype and reduced cell proliferation can occur in desmoplastic, classic and (rarely) anaplastic medulloblastomas, and that nodular/desmoplastic and nodular/non-desmoplastic variants are distinguished by their molecular cytogenetic profiles, (ii) the nodular/desmoplastic variant contributes 5% of our series of 315 children aged 3–16 years with medulloblastomas from the CNS9102 cohort, but 57% of our series of 35 infants from the CNS9204 cohort, and (iii) the presence of nodules, particularly in the context of the nodular/desmoplastic variant, confers a survival advantage to children of all ages with medulloblastoma.

MATERIALS AND METHODS

Patient/tumor cohorts

CNS9102 (SIOP/UKCCSG PNET3)—children aged 3–16 years inclusive. Cerebellar/posterior fossa tumors (n = 347) from children registered on the CNS9102 trial were provided by SIOP/UKCCSG centers for central pathology review according to protocol (39). Of these tumors, 19 (5.5%) were not assessable, either because the amount of tissue in proffered sections was insufficient for diagnostic purposes or because tissue artefacts precluded an adequate evaluation. The central review diagnosis was medulloblastoma in 322 of the 328 assessable tumors (98%); other pathological diagnoses being ependymoma (n = 3), high-grade glioma (n = 2), and atypical teratoid/rhabdoid tumor (n = 1). Of these 322 children with medulloblastoma, five received non-protocol therapy and two died before therapy could begin, leaving 315 in the present study's cohort.

Of these 315 patients with medulloblastoma, 154 were part of the randomized trial of "sandwich" chemotherapy followed by radiotherapy vs. radiotherapy alone, the remainder having been treated according to one or other arm of the protocol. Clinical data, including current status, were available from the UKCCSG data center. There was a preponderance of boys (1.7:1). Median age at diagnosis was 8.1 years (range 2.7–16.4 years). Median follow-up is 8.0 years (range 1.4–12.4 years). Tumor resection was total in 152 patients and subtotal in 152. Inoperable tumors were present in seven patients, and the extent of resection was unknown in four cases. Of 154 randomized patients, 76 received both chemotherapy and radiotherapy, while 78 received radiotherapy alone. Among the 161 non-randomized patients, 87 were given chemotherapy and radiotherapy, while 74 received radiotherapy alone. Metastatic disease at presentation (Chang stage M2–3) was demonstrated at central radiological review in 60 cases. Overall survival at 5 years is 70.9% [95% confidence interval (CI): 65.8%–76.0%].

CNS9204 (SIOP/UKCCSG infant brain tumor)—infants aged <3 years. This trial investigated chemotherapy as the primary adjuvant therapy for infants with various high-grade CNS tumors, including medulloblastoma/primitive neuroectodermal tumor (PNET), with the intention of avoiding or delaying the use of radiotherapy. Recruitment of PNETs was halted after 4 years. CNS9102 ran contemporaneously with this trial, so that nearly all eligible children up to the age of 17 years with a medulloblastoma would have been registered on one of these trials. Medulloblastomas (n = 35) from children registered on CNS9204 were provided for central pathology review by several UKCCSG centers. There was a slight male preponderance (1.2:1) among these patients. Median age at diagnosis was 1.7 years.

Histology/immunohistochemistry. Medulloblastomas were first examined using standard histological preparations (hematoxylin/eosin and reticulin). Subsequently, focal morphological neurocytic differentiation, mainly in nodules, was evaluated using immunohistochemistry with antibodies to synaptophysin and neuronal nuclear antigen (NEU-N). Regional variation in p27 expression and tumor cells in cycle were demonstrated using p27 and MiB-1 (Ki-67) antibodies, respectively, as previously described (25). Histopathological evaluation focused particularly on the localization and nature of reticulin-positive desmoplasia, Ki-67 nuclear immunolabeling, and the presence of ganglionic and neurocytic differentiation associated with both a neuronal immunophenotype and enhanced p27 expression. Appropriate tissues were used as positive controls for each

antibody, while omission of primary antibody served as a negative control.

Medulloblastomas were first classified on the basis of having or not having reticulin-positive desmoplastic regions that were unrelated to invasion of the subarachnoid space by tumor cells. All desmoplastic tumors so defined contained nodular reticulin-free areas of neurocytic differentiation, and encompassed typical nodular/desmoplastic medulloblastomas, MBENs, and some "paucinodular" desmoplastic medulloblastomas. Paucinodular medulloblastomas contained just a few synaptophysin-immunopositive reticulin-negative nodules that showed virtually no decrease in nuclear : cytoplasmic ratio.

Non-desmoplastic medulloblastomas included classic and large cell/anaplastic (LC/A) medulloblastomas. LC/A medulloblastomas were identified as previously described (6, 25); anaplastic tumors have extensive groups of cells with pleomorphic polyhedral molded nuclei and high mitotic and apoptotic indices. In our experience, all large cell medulloblastomas have an anaplastic phenotype, plus their characteristic foci of uniform large cells with a prominent single nucleolus.

Because they mimic nodular/desmoplastic medulloblastomas, classic and anaplastic medulloblastomas with foci of neurocytic differentiation were classified separately in this study and labeled "biphasic". Critically, biphasic tumors differ from nodular/desmoplastic tumors in not having reticulin-positive internodular regions.

Some non-desmoplastic medulloblastomas contained multiple irregular regions, in which many ganglion cells were admixed with neurocytic cells. These were labeled ganglioneuroblastomas, because of their similarity to supratentorial tumors with the same designation.

Interphase fluorescence* in situ *hybridization (iFISH). iFISH was undertaken, as previously described (21), on subsets of nodular/desmoplastic (n = 8) and biphasic (n = 9) CNS9102 tumors, in order to compare the molecular cytogenetic profiles of these two nodular medulloblastoma variants. The number of tumors in each category was limited by availability of tissue. The following loci were assessed: *MYCC*, *MYCN*, 9q22, 17p13.3, and 17q12. Specific probes for regions 2p24.3 (*MYCN*, bA355H10), 8q24.21 (*MYCC*, dJ968N11), 9q22 (bA172F4), 17p13.3 (bA356I18) and 17q12 (bA249G4) were generated from DNA isolated from pBACe3.6 (except dJ968N11, which was pCYPAC2) using the NucleoBond BAC100 DNA extraction kit (ABGene, Surrey, UK). Control probes to the centromeric regions of chromosomes 2 (pBS4D), 8 (pZ8.4), 9 (pMR9A) and 17 (D17Z1) were generated from DNA isolated from plasmids (Cytogenetics Unit, University of Bari, Bari, Italy) using the Qiagen Hi-speed DNA extraction kit (Qiagen, Sussex, UK). Probes were subsequently used in two-color iFISH to assess losses, gains or amplification at loci of interest. Isolated DNAs were indirectly labeled with digoxigenin (arm) and biotin (centromere) using a Vysis nick translation kit (Vysis, Richmond, UK).

Statistics. Survival curves were produced and log-rank tests performed to compare overall survival (OS) and event-free survival (EFS), with respect to various potential prognostic indicators. An event was defined either as a recurrence or death. In those cases where death followed recurrence, the event was the recurrence. EFS was defined as the time between date of diagnosis and date of first event. OS was defined as the time between date of diagnosis and date of death. Patients still alive at the end of the study were censored at date of last follow-up. CIs for OS and EFS were calculated using Greenwood's formula. All prognostic variables observed were tested individually in a Cox proportional hazards model using the change in log likelihood from the null model (30). Those shown to be significant ($P < 0.05$) were entered into a multivariate model, alongside clinical variables, in a stepwise procedure taking a P-value of 0.05 to enter and 0.05 to be removed (4). The database was frozen on December 7, 2005, and the final analysis performed in January 2006.

RESULTS

Histopathological heterogeneity in childhood medulloblastoma

CNS9102—children aged 3–16 years inclusive. Among 315 medulloblastomas from this trial cohort, histopathological evaluation showed that 225 (71%) had classic histopathological features and 52 (17%) were large cell/anaplastic (LC/A) tumors (Table 1). These 277 tumors included all 273 classic and LC/A medulloblastomas analyzed in our previous report of the clinicopathological significance of anaplasia (25).

A focal nodular architecture characterized 35 tumors from this series of 315

Main category		Sub-category		Variant		Sub-variant	
Non-desmoplastic	299 (95%)	Non-nodular	280 (89%)	Classic	225 (71%)		
				GNB	3 (1%)	GNB classic	2 (<1%)
						GNB anaplastic	1 (<1%)
				LC/A	52 (17%)	Large cell	5 (2%)
						Anaplastic	47 (15%)
		Nodular	19 (6%)	Biphasic (nodular/non-desmoplastic)	19 (6%)	Biphasic anaplastic	3 (1%)
						Biphasic classic	16 (5%)
Desmoplastic	16 (5%)	Nodular	16 (5%)	N/D	14 (4%)	Typical N/D	11 (3%)
						Paucinodular N/D	3 (1%)
				MBEN	2 (<1%)		

Table 1. Histopathological classification of childhood medulloblastomas. GNB = ganglioneuroblastoma; LC/A = large cell/anaplastic; MBEN = medulloblastoma with extensive nodularity; N/D = nodular/desmoplastic. The gray hatching encompasses tumors with an anaplastic phenotype.

medulloblastomas (11%). However, these tumors appeared heterogeneous; in particular, the nature and the extent of the nodular phenotype were variable, and nodules might or might not occur against a background of desmoplasia.

Of the nodular medulloblastomas, 11 (31% of nodular tumours; 3% of CNS9102 medulloblastomas) conformed to textbook descriptions of the desmoplastic variant (Table 1). These contained scattered round or ovoid nodules separated by desmoplastic internodular regions (Figure 1A–C). Intranodular cells had neurocytic features, with monomorphic bare round nuclei against a fibrillary neuropil-like background, and a lower nuclear : cytoplasmic ratio than internodular cells. Internodular cells, with polyhedral rather than round nuclei, appeared more pleomorphic than intranodular cells, occasionally demonstrating a focal anaplastic phenotype. Mitotic figures were identified in internodular regions, but not within the nodules themselves. In contrast, apoptotic bodies were frequently found in nodules. Defined by a reticulin-positive boundary (Figure 1C), the border between nodules and surrounding desmoplastic regions was usually sharp, but could occasionally break down (Figure 1D). In this situation, either pleomorphic cells would spill into the periphery of the nodule, or the features of the two cell populations would merge, a process involving intermediate morphologies.

Intranodular and internodular cells in typical nodular/desmoplastic medulloblastomas demonstrated distinct immunophenotypes, consistent with the principle that nodules represent micro-environments in which cells stop proliferating and show neuronal differentiation (Figure 1E and F). Intranodular cells were immunoreactive for synaptophysin, NEU-N and p27, while the Ki-67 labeling index was much higher in internodular regions.

Set apart from typical nodular/desmoplastic tumors by the extensive formation of large irregularly shaped nodules (Figure 1G), MBENs (n = 2) were rare among the CNS9102 series of medulloblastomas, accounting for only 0.6%. Slightly more frequent, though still rare (0.9%), were tumors (n = 3) that showed regions of extensive desmoplasia interrupted by only a few small nodules (Figure 1H). Superfi-

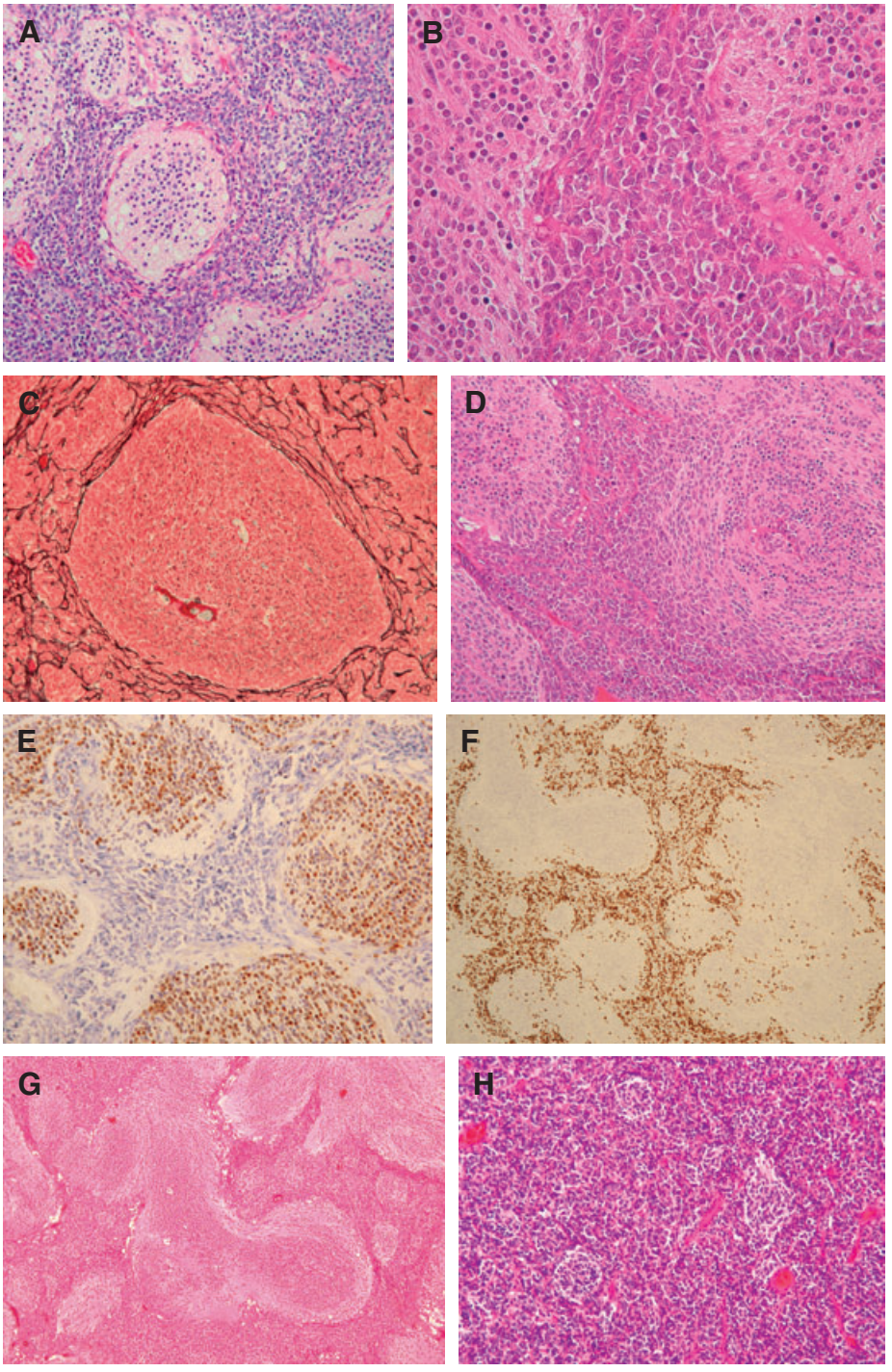

Figure 1. This textbook nodular/desmoplastic medulloblastoma contains nodules (**A,B**), in which neurocytic cells are set against a fibrillary background. Internodular regions are desmoplastic (**C**, reticulin preparation), and harbor cells with more nuclear pleomorphism and a higher mitotic count than intranodular cells. The border around nodules is usually sharp, but cells with an internodular phenotype can occasionally spill into nodules (**D**) making the border around nodules somewhat indisctinct. Differentiation along neuronal lines accompanies the neurocytic morphophenotype of intranodular cells (**E**, NEU-N antibody). The growth fraction of nodules, as assessed by Ki-67 immunolabeling, is much less than in internodular regions (**F**, MIB-1 antibody). The MBEN is characterized by large nodules (**G**), and contrasts with the paucinodular medulloblastoma (**H**), in which nodules were hard to discern without the use of a reticulin preparation.

cially, these "paucinodular" medulloblastomas resembled classic medulloblastomas, but genuine desmoplasia involved some areas of these tumors and their nodules did show evidence of a neuronal immunophenotype. Cell density in the small nodules was greater than in typical nodular/desmoplastic medulloblastomas, and did not differ significantly from the cell density in surrounding desmoplastic internodular regions. Overall, nodular/desmoplastic tumors of the three subtypes described above (n = 16) accounted for 5.0% of the series (Table 1).

A nodular architecture was also present in a separate small group (n = 19; 6%) of tumors characterized by a lack of perinodular desmoplasia (Figure 2A–D). Though a focal phenomenon, nodule formation in these tumors could be just as striking as in the desmoplastic variants. However, borders around nodules were less delineated and often irregularly contoured, rather than round (Figure 2C). In other respects, the nodules, and the neurocytic cells therein, reproduced the phenotype of nodular/desmoplastic medulloblastomas, showing a neuronal immunophenotype and reduced growth fraction (Figure 2E and F). Because these non-desmoplastic tumors contained juxtaposed regions of differentiated and undifferentiated cells, we initially labeled them "biphasic" medulloblastomas (Table 1), for the purposes of this study. In 3/19 biphasic tumors, the majority of cells in nonnodular regions showed an anaplastic morphology (Figure 2G). The extent of this type of non-desmoplastic nodularity could be variable. In some tumors, it appeared as a very focal feature of an otherwise classic medulloblastoma. Occasionally and in addition to oval nodules, biphasic medulloblastomas contained enlarged rosette-like structures (Figure 2H).

Two idiosyncratic tumors diverged slightly from the phenotype described above for biphasic (non-desmoplastic nodular) medulloblastomas, but were nevertheless included in this category. One contained such widespread areas of nodule formation and cytological differentiation that the islands of undifferentiated proliferating cells became the minor element of the tumor (Figure 3). Ganglion cells were occasionally detected in the differentiating regions, but they were exceptional, and the morphophenotype of the dominant cell population appeared neurocytic. Focally in this tumor, perivascular clusters of morphologically undifferentiated cells with polyhedral nuclei and a high mitotic count would often be surrounded by a rim of densely packed neurocytic cells, which were surrounded in turn by hypocellular neuropil-like areas with rare ganglion cells (Figure 3C and D). The second idiosyncratic tumor was a non-desmoplastic medulloblastoma with a classic phenotype that was interrupted in a several areas by nodules of condensed small round cells

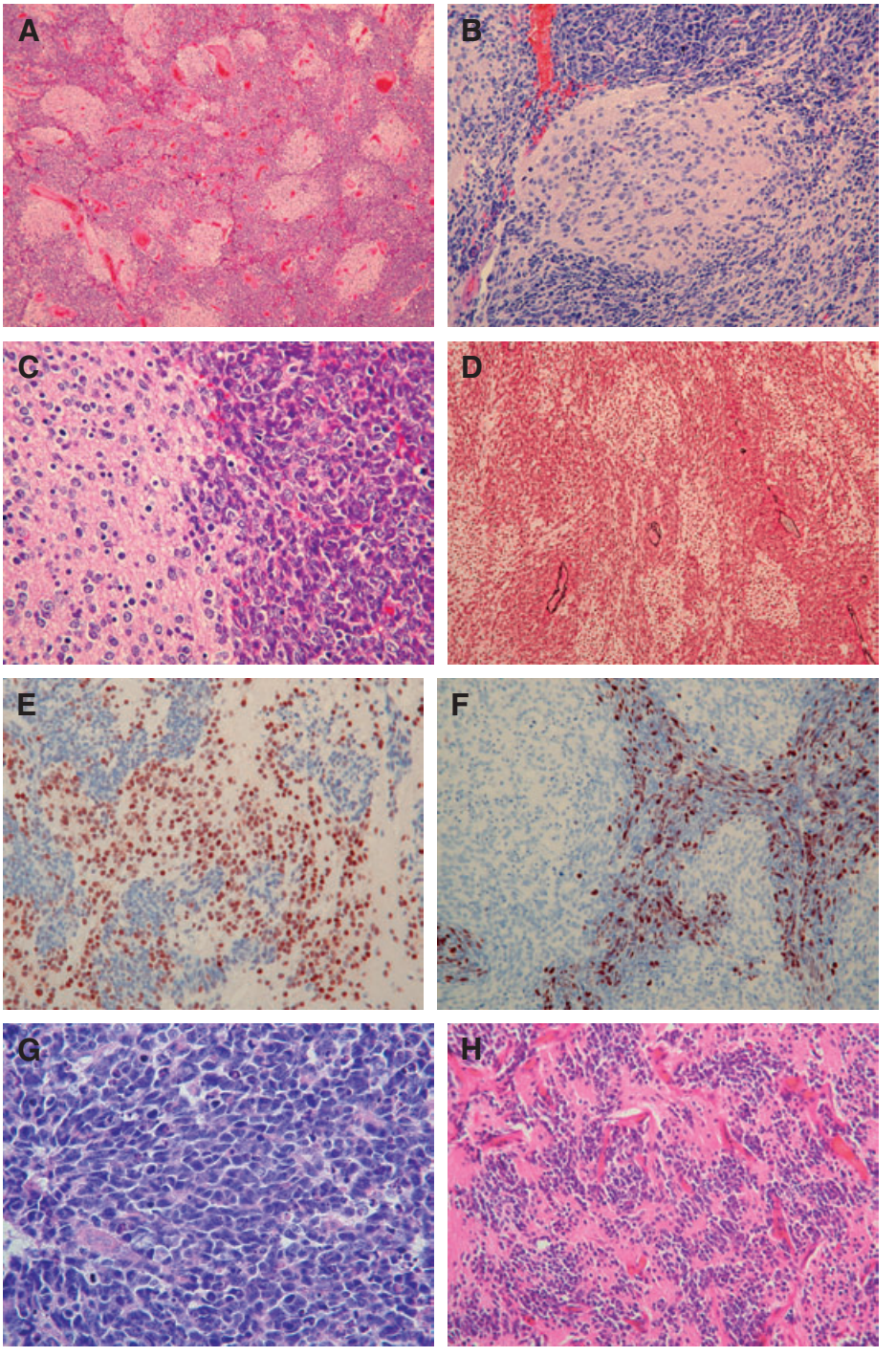

Figure 2. This biphasic medulloblastoma contains nodules (**A–C**) with the same phenotype as nodules in a nodular/desmoplastic medulloblastoma, but they lack perinodular and internodular desmoplasia (**D**, reticulin preparation). Intranodular tumor cells express NEU-N and P27 (**E**, P27 antibody), and have a much lower Ki-67 immunolabeling index than surrounding internodular regions (**F**, MIB-1 antibody). An anaplastic phenotype characterized the internodular regions of some biphasic medulloblastomas (**G**). A pattern of "enlarged" rosettes was evident in a few biphasic tumors (**H**).

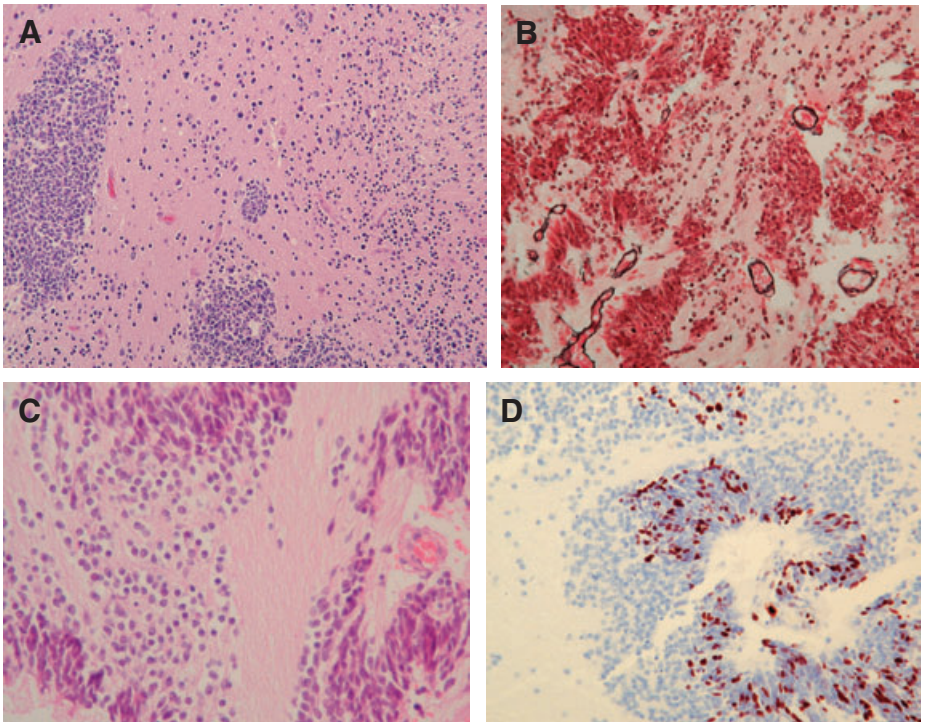

Figure 3. One biphasic medulloblastoma was characterized by extensive regions of neurocytic differentiation (**A**), in which the cell density was low and ganglion cells were occasionally found. The tumor lacked internodular desmoplasia (**B**, reticulin preparation). In some regions of this tumor, islands of undifferentiated cells (**C**), with a high mitotic count and Ki-67 immunolabeling index (**D**, MIB-1 antibody), tended to occur around small blood vessels, but were in turn surrounded by a concentric arrangement of neurocytic cells and hypocellular neurofibrillary areas (**C**).

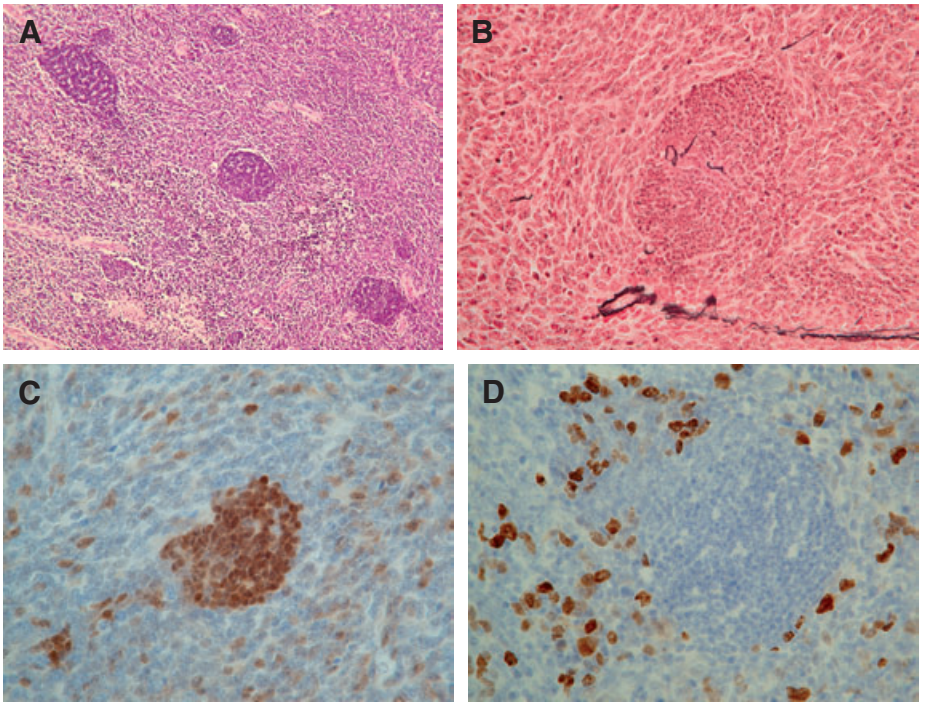

Figure 4. This idiosyncratic biphasic medulloblastoma looked like a classic tumor in many areas, but also contained small nodules (**A**), without internodular desmoplasia (**B**, reticulin preparation), in which the condensed cells were unexpectedly characterized by a neuronal immunophenotype (**C**, NEU-N antibody), and no Ki-67 labeling (**D**, MIB-1 antibody).

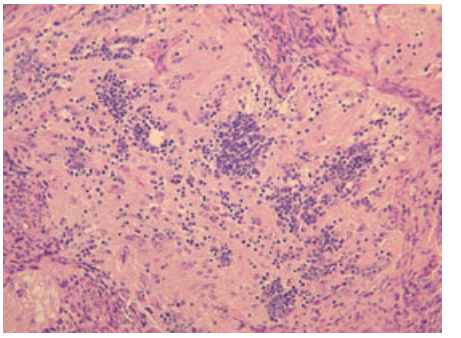

Figure 5. This and two other non-desmoplastic medulloblastomas were characterized by foci of ganglion cell formation, and were termed ganglioneuroblastomas.

(Figure 4). Unexpectedly, these cells exhibited a neuronal immunophenotype, with immunoreactivities for synaptophysin and NEU-N, nuclear accumulation of p27, and a negligible growth fraction (Figure 4C and D).

There were three further non-desmoplastic non-nodular medulloblastomas distinctively characterized by widespread irregular foci of ganglion cell differentiation among their embryonal cells (Figure 5). If these tumors had been in the cerebrum, they would have conformed to the WHO classification's description of a ganglioneuroblastoma (19), and we have used this term here (Table 1).

CNS9204 infants aged <3 years. In striking contrast to the situation for older children, desmoplastic tumors dominated the series of medulloblastomas from infants aged <3 years (Table 2), contributing 20/35 (57%). Of these, MBENs accounted for 8/20 (23% of the total). Among non-desmoplastic medulloblastomas, the LC/A and biphasic variants made up 17% and 6% of the total, identical to the corresponding figures for the CNS9102 cohort. However, the proportion of "classic" medulloblastomas was much lower in CNS9204 (17%) than in CNS9102 (Table 1).

Combined cohorts CNS9102 and CNS9204—all children with medulloblastomas. Pathological review of the combined contemporaneous cohorts encompassed 350 medulloblastomas. The main histopathological variants made up the following proportions of these 350 tumors: classic—66%, LC/A—17%, nodular/desmoplastic—8%, biphasic—6%, MBEN—2%, ganglioneuroblastoma—1%. However, while the incidence of LC/A or

Main category		Sub-category		Variant	
Non-desmoplastic	15 (43%)	Non-nodular	13 (37%)	Classic	6 (17%)
				GNB	1 (3%)
				LC/A	6 (17%)
		Nodular	2 (6%)	Biphasic (nodular/non-desmoplastic)	2 (6%)
Desmoplastic	20 (57%)	Nodular	20 (57%)	Typical N/D	12 (34%)
				MBEN	8 (23%)

Table 2. Histopathological classification of infant medulloblastomas. GNB = ganglioneuroblastoma; LC/A = large cell/anaplastic; MBEN = medulloblastoma with extensive nodularity; N/D = nodular/desmoplastic.

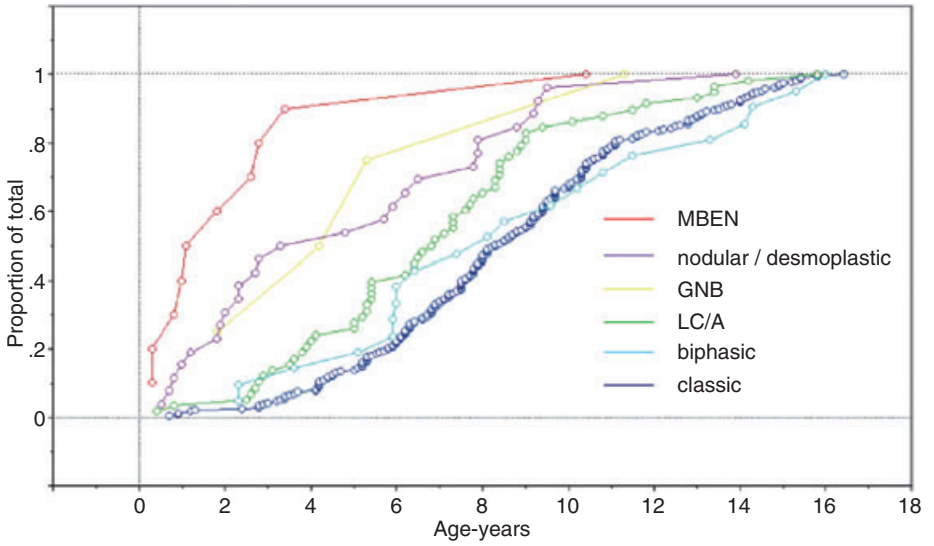

Figure 6. This charts the age at presentation of medulloblastoma variants. Age is plotted against the cumulative proportion of tumors in each variant's cohort. GNB = ganglioneuroblastoma; LC/A = large cell/anaplastic; MBEN = medulloblastoma with extensive nodularity.

biphasic tumors appeared not to vary between the two trial cohorts, many nodular/desmoplastic tumors, including MBENs, presented in infancy. Classic tumors predominated among older children (Tables 1 and 2). These trends are reinforced in a chart that relates age at presentation to the cumulative proportion of tumors for each histological variant (Figure 6). From these plots, it is clear that the MBEN is a tumor of infancy and that nodular/desmoplastic medulloblastomas present earlier than classic tumors. In contrast, the line for biphasic tumors straddles those for LC/A and classic medulloblastomas, reinforcing the proposition that biphasic tumors are just classic or anaplastic medulloblastomas with foci of differentiation and reduced cell proliferation.

Molecular cytogenetic analysis of desmoplastic and biphasic medulloblastomas. iFISH evaluation of chromosomal status at the 17p13.3, 17q12, 9q22, *MYCC* and *MYCN* loci, all of which are characterized by abnormalities in a proportion of medulloblastomas, demonstrated fewer chromosomal abnormalities in nodular/desmoplastic tumors than in biphasic tumors (Table 3). This difference was related mainly to a large incidence of copy number change among the biphasic tumors, which often manifested as a variable increase in centromeric signals, ranging from 3 to 8 per probe, with an equal number of target signals (described in Table 3 as hyperploidy). Hyperploidy was linked to relative loss of 17p in one biphasic tumor and to relative gain of 17q in another. Abnormalities of chromosome 17, including copy number change, were detected in 6/9 biphasic tumors, but in none of the nodular/desmoplastic medulloblastomas ($P = 0.009$). In contrast, a profile of loss at 9q22 was found in 4/8 nodular/desmoplastic medulloblastomas, but in none of the biphasic tumors ($P = 0.03$). *MYC* amplification was more frequent among biphasic than nodular/desmoplastic tumors, occurring in only one MBEN. Overall, the pattern of molecular abnormalities across targeted loci in biphasic tumors resembled those reported by us for the range of classic medulloblastomas and appeared distinct from that shown by nodular/desmoplastic medulloblastomas (21).

Biological behavior of childhood medulloblastoma

CNS9102—children aged 3–16 years inclusive. Categorizing tumors from children in the PNET3 cohort according to age, sex and treatment regimen revealed no significant outcome indicators, either in terms of OS or EFS (Table 4). However, extent of surgical resection and presence of metastatic disease at diagnosis were both prognostic variables. In univariate analyses, OS and EFS at 5 years were 76.4% and 72.0% for totally resected tumors, but 67.2% and 56.0% for partially resected tumors, respectively (OS $P = 0.037$; EFS $P = 0.005$). OS and EFS at 5 years were 51.7% and 41.6% for children with metastatic disease, but 75.4% and 68.5% for those without (OS $P < 0.001$; EFS $P < 0.001$).

The principal histopathological phenotypes of medulloblastoma showed significantly different outcomes in children from the CNS9102 trial, both in terms of OS and EFS (Table 4; Figure 7). In these analyses, which are presented in three ways to give a perspective of the survival associated with different tumor phenotypes, widespread anaplasia or a large cell phenotype in non-nodular tumors conferred a relatively poor outcome (n = 53; Tables 1 and 4—classification A, C), while a nodular/desmoplastic (n = 16) or biphasic (n = 19) phenotype conferred a relatively good outcome (Tables 1 and 4—classification A), when compared with classic tumors (OS $P = 0.023$; EFS $P = 0.018$). However, OS and EFS curves for biphasic and classic

Variant	9q22	17p13.3/17q12	*MYCC*	*MYCN*
N/D MB	Loss 1:2	N	N	N
N/D MB	Loss 1:2	N	N	N
N/D MB	Loss 1:2	N	N	N
N/D MB	N	N	Monosomy	N
N/D MB	N	N	N	N
N/D MB	N	N	N	N
N/D MB	N	N	N	N
MBEN	Monosomy	N	N	lo-freq. amplification*
Biphasic classic MB	N	i(17q)	N	N
Biphasic classic MB	N	i(17q)	Monosomy	N
Biphasic classic MB	Hyperploidy	p loss/hyperploidy	Hyperploidy	hi-freq. amplification*
Biphasic classic MB	N	N	lo-freq. amplification*	N
Biphasic classic MB	N	N	Hyperploidy	Hyperploidy
Biphasic classic MB	N	Trisomy	N	N
Biphasic classic MB	Tetrasomy	N	N	Hyperploidy
Biphasic classic MB	Tetrasomy	q gain/hyperploidy	Hyperploidy	Gain
Biphasic anaplastic MB	N	Monosomy	N	hi-freq. amplification*

Table 3. Molecular cytogenetic abnormalities in nodular/desmoplastic and biphasic medulloblastomas by interphase fluorescence *in situ* hybridization. i (17q) = isochromosome 17q; hi-freq. = high frequency; lo-freq. = low frequency; MBEN = medulloblastoma with extensive nodularity; MB = medulloblastoma; N/D = nodular/desmoplastic; Loss 1:2 = Hemizygous deletion; N = normal. * = See reference 21.

	Number	OS at 5 years		EFS at 5 years	
Clinical variables					
Male	200	67.6% (CI: 61.1–74.1)	NS	59.6% (CI: 52.8–66.5)	NS
Female	115	76.7% (CI: 68.8–84.6)		69.9% (CI: 61.4–78.4)	
Age 3–7 years	151	68.4% (CI: 60.9–75.9)	NS	59.9% (CI: 52.0–67.7)	NS
Age 8–11 years	114	73.7% (CI: 65.5–82.0)		64.9% (CI: 56.0–73.9)	
Age 12–16 years	50	71.9% (CI: 59.5–84.4)		69.9% (CI: 57.2–82.7)	
Sandwich chemotherapy	163	69.6% (CI: 62.5–76.7)	NS	62.1% (CI: 54.6–69.6)	NS
Radiotherapy alone	152	72.3% (CI: 65.1–79.5)		64.6% (CI: 57.0–72.3)	
Total resection	152	76.4% (CI: 69.6–83.3)	P = 0.0373	72.0% (CI: 64.8–79.2)	P = 0.0050
Subtotal resection	152	67.2% (CI: 59.7–74.8)		56.0% (CI: 48.0–64.0)	
Metastatic disease	60	51.7% (CI: 39.0–64.3)	P < 0.0001	41.6% (CI: 29.2–54.1)	P < 0.0001
No metastatic disease	255	75.4% (CI: 70.0–80.8)		68.5% (CI: 62.7–74.2)	
Pathological variables					
Classification A					
Classic phenotype	227	72.6% (CI: 66.8–78.5)	P = 0.0233	64.1% (CI: 57.8–70.4)	P = 0.0177
LC/A phenotype	53	55.8% (CI: 42.3–69.4)		50.9% (CI: 37.5–64.4)	
N/D phenotype	16	87.1% (CI: 70.3–100)		87.5% (CI: 71.3–100)	
Biphasic phenotype	19	78.9% (CI: 60.6–97.3)		68.4% (CI: 47.5–89.3)	
Classification B					
Classic phenotype	243	73.6% (CI: 68.0–79.2)	P = 0.0068	64.9% (CI: 58.8–70.9)	P = 0.0045
LC/A phenotype	56	54.7% (CI: 41.4–67.9)		50.0% (CI: 36.9–63.1)	
N/D phenotype	16	87.1% (CI: 70.3–100)		87.5% (CI: 71.3–100)	
Classification C					
Classic phenotype	227	72.6% (CI: 66.8–78.5)	P = 0.0097	64.1% (CI: 57.8–70.4)	P = 0.0101
LC/A phenotype	53	55.8% (CI: 42.3–69.4)		50.9% (CI: 37.5–64.4)	
Nodular phenotype	35	82.7% (CI: 70.0–95.3)		77.0% (CI: 63.1–91.0)	

Table 4. Univariate analyses of OS and EFS for clinicopathological variables among the CNS9102 cohort. CI = 95% confidence interval; EFS = event-free survival; LC/A = large cell/anaplastic; N/D = nodular/desmoplastic; NS = not significant; OS = overall survival.

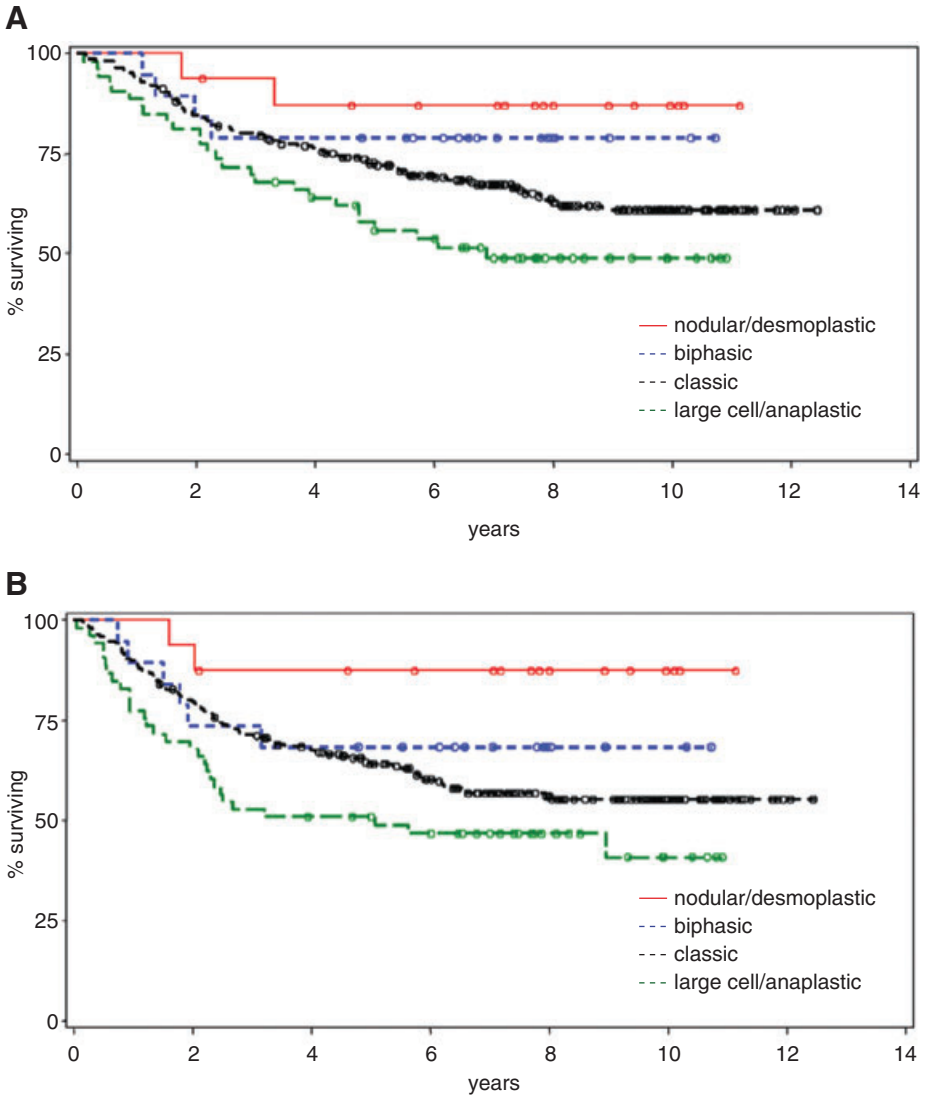

Figure 7. Survival curves (A—OS; B—EFS) relating to children from the CNS9102 trial for the four principal histopathological variants of medulloblastoma.

		OS		EFS	
		Hazard ratio	***P*-value**	**Hazard ratio**	***P*-value**
Metastatic disease at presentation	Yes	2.59	$P < 0.001$	2.15	$P < 0.001$
	No	1.00		1.00	
Pathological variant	LC/A	5.21	$P = 0.024$	5.80	$P = 0.016$
	Classic	3.02	$P = 0.123$	3.28	$P = 0.098$
	N/D	1.00		1.00	
Radiotherapy schedule	RT not given	3.60	$P < 0.001$	3.10	$P = 0.002$
	>50 days	1.29	$P = 0.255$	1.29	$P = 0.253$
	<50 days	1.00		1.00	
Extent of resection	Subtotal			1.58	$P = 0.017$
	Total			1.00	

Table 5. Multivariate analysis of clinicopathological variables among children in the CNS9102 cohort. EFS = event-free survival; LC/A = large cell/anaplastic; N/D = nodular/desmoplastic; OS = overall survival.

variants only diverge beyond 4 years (Figure 7).

Whether the biphasic tumor is considered to represent a type of classic tumor, on genetic grounds, or a type of nodular tumor, on morphological grounds, and classes of medulloblastoma are amalgamated accordingly, then OS and EFS at 5 years remain significantly different for histopathological variant in logrank analyses (Table 4—classification B, C). The former approach (Table 4—classification B) produces three classes of medulloblastoma: classic (n = 243), including 16 biphasic classic tumors (see Table 1), LC/A (n = 56), including three biphasic anaplastic tumors (see Table 1), and nodular/desmoplastic (n = 16) (OS $P = 0.007$; EFS $P = 0.005$). The latter (Table 4—classification C) produces three classes of medulloblastoma: classic (n = 227), LC/A (n = 53), and nodular tumors (n = 35), which combine nodular/desmoplastic and biphasic tumors (OS $P = 0.010$; EFS $P = 0.010$).

Cox proportional hazards modeling for clinicopathological variables in the trial data set showed that metastatic disease at presentation, time to complete radiotherapy and histopathological classification into three variants—classic, LC/A, and nodular/desmoplastic (biphasic tumors and ganglioneuroblastomas are incorporated into classic and LC/A categories according to the scheme in Table 1)—remained significant indicators of OS and EFS in multivariate analyses. Extent of resection was a significant indicator of EFS, but not OS, in these analyses (Table 5).

CNS9204—infants aged <3 years. From this younger cohort, outcome data were available on 28 infants with a centrally reviewed diagnosis of medulloblastoma. Of the 28 medulloblastomas, 17 (61%) were classified as nodular/desmoplastic (MBENs = 7/17), 6 (21%) as classic and 5 (18%) as LC/A variants. A nodular/desmoplastic phenotype was associated with improved OS and EFS. OS at 5 years was 52.9% (95% CI: 29.2%–76.7%) for children with nodular/desmoplastic tumors and 16.7% (95% CI: 0%–46.5%) for those with classic medulloblastomas, EFS at 5 years being 35.3% (95% CI: 12.6%–58.0%) and 16.7% (95% CI: 0%–46.5%),

respectively. All children with LC/A medulloblastomas were dead within 2 years of diagnosis. There was no clear association between histopathological variant and the presence of metastatic disease at diagnosis.

DISCUSSION

Our present data represent the definitive histopathological review of medulloblastomas from children in the SIOP/UKCCSG CNS9102 trial, and are supplemented by an analysis of medulloblastomas from infants entered into the contemporaneous SIOP/UKCCSG CNS9204 trial, so providing information on the full range of pediatric medulloblastomas. In addition, our investigation of histopathological heterogeneity in medulloblastomas follows on from an evaluation of anaplasia in the CNS9102 cohort (25), and focuses on the definition and biological behavior of the nodular/desmoplastic variant.

We have demonstrated in the present study that nodular regions of neurocytic differentiation, conforming to the WHO classification's description of "pale islands", can occur in the presence or absence of internodular desmoplasia, and that nodular medulloblastomas so divided also have distinct molecular cytogenetic profiles. A combination of nodular regions and internodular desmoplasia, as demonstrated by a reticulin preparation, and a molecular cytogenetic profile that does not show chromosome 17 abnormalities defines the nodular/desmoplastic medulloblastoma. In contrast, the non-desmoplastic nodular (biphasic) tumor, with a molecular cytogenetic profile matching that of the classic or anaplastic variant (21), merely represents focal neurocytic differentiation in the range of classic—anaplastic medulloblastomas.

Having defined the pediatric nodular/desmoplastic medulloblastoma, we note that, from a clinicopathological standpoint, this variant is distinctive in two ways; it is particularly prevalent in infancy, unlike the non-desmoplastic nodular (biphasic) tumor (Figure 6), and appears to have a better outcome than classic medulloblastomas across the pediatric age range.

The nodular/desmoplastic variant of medulloblastoma. Historically, there had been controversy over the appropriate term for poorly differentiated desmoplastic tumors of the cerebellum, but this was largely settled when Lucien Rubinstein and Douglas Northfield demonstrated in a range of embryonal cerebellar tumors from children and adults that there was no clinicopathological justification for distinguishing so-called "arachnoidal cerebellar sarcomas" from what they termed a desmoplastic variant of medulloblastoma (34). Since then, the desmoplastic medulloblastoma has been included regularly in WHO classifications (18, 19). It is defined as having a heterogeneous architecture consisting of regions with dense intercellular reticulin and nodular reticulin-free zones ("pale islands"), in which tumor cells may show a neuronal phenotype. While neuropathologists would acknowledge the importance of identifying "pale islands" when making a diagnosis of desmoplastic medulloblastoma, and this is stressed in the WHO classification (2000), there is disagreement about whether the correct designation for this tumor should be desmoplastic medulloblastoma, nodular medulloblastoma or nodular/desmoplastic medulloblastoma.

Desmoplasia, a pericellular depostion of collagen in this context, and a nodular architecture may occur together or separately in medulloblastomas. Desmoplasia can be a reactive phenomenon when medulloblastoma cells invade the leptomeninges (9, 34). The resultant copious collagen can dominate the histopathological picture, but the phenomenon declares itself when the pathologist observes elements of the leptomeninges, including large blood vessels of the subarachnoid space, entrapped by tumor cells. All variants of medulloblastoma have the potential to invade the leptomeninges; so it is important for accurate subclassification to assess mass-forming intraparenchymal elements of a tumor.

The presence, extent and nature of architectural "nodularity" in medulloblastomas can be variable, but we would propose that nodules are distinct microenvironments, in which cells show evidence of neurocytic differentiation and a reduced growth fraction (9). They are thus distinct from, though biologically related to, neuroblastic rosettes and foci of ganglionic differentiation. At one extreme, the MBEN contains nodules that are extensive and polymorphous, resembling a central neurocytoma, while the nodular phenotype can be subtle in the paucinodular medulloblastomas described above and elsewhere (2). MBENs were previously labeled "cerebellar neuroblastomas" (31). As our data affirm, the MBEN occurs almost exclusively in infancy, and has a good prognosis (12). Internodular desmoplasia in MBENs may be variable in its extent, but it is clearly a feature of this variant. Between the MBEN and paucinodular medulloblastomas lies the typical nodular/desmoplastic medulloblastoma (2, 9), but we have used the term nodular/desmoplastic medulloblastoma to encompass all three desmoplastic variants.

During the central pathological review of medulloblastomas from children in the CNS9102 and CNS9204 trials, we noted a few tumors with a focal nodular architecture in the absence of internodular desmoplasia. Most of these tumors, especially those cases in which profuse desmoplasia had been produced by tumor cell invasion of the leptomeninges, had received a primary (local center) diagnosis of nodular/desmoplastic medulloblastoma. At first glance, such evaluations appeared reasonable. In other respects, these nodules show all the characteristics displayed by nodules in desmoplastic medulloblastomas; they are microenvironments of neurocytic differentiation and reduced proliferation. However, a nodular architecture is only a focal phenomenon in these non-desmoplastic medulloblastomas, which appear elsewhere in histological sections as classic or anaplastic variants. Such observations prompted us to test the hypothesis that desmoplastic medulloblastomas (nodular/desmoplastic tumors and MBENs) have a different molecular cytogenetic profile from what we termed, just for the purposes of this study, biphasic medulloblastomas, which essentially belong to the range of non-desmoplastic classic and anaplastic medulloblastomas. The hypothesis is supported by our data, which suggest that biphasic and nodular/desmoplastic medulloblastomas are genetically distinct, but share the capacity to produce small microenvironments of neurocytic differentiation and reduced proliferation. Whether the same biological pathways are activated to produce these phenotypically similar

microenvironments is unknown. The phenomena we describe here have been noted before (1), but we think that it is important for the accurate subclassification of medulloblastomas to highlight their existence.

Other variations on the basic medulloblastoma phenotype were identified in the trial cohorts. Out of 350 medulloblastomas, there were four tumors with scattered foci of ganglion cell formation. A cerebral tumor with this morphology is termed a ganglioneuroblastoma, and recognized as a variant of supratentorial PNET, in the WHO classification (19). While such a tumor is also recognized in the cerebellum (2, 9), it is not accorded the status of a distinct medulloblastoma variant in the WHO classification. In cerebellar ganglioneuroblastomas, a few neurocytic tumor cells may be scattered among the ganglion cells, but these tumors do not contain nodules of neurocytic cells or regions of desmoplasia. We believe that cerebellar ganglioneuroblastomas and non-desmoplastic nodular (biphasic) medulloblastomas are aligned with regard to their shared propensity for producing foci of neuronal differentiation, and that away from these regions, they both resemble a classic medulloblastoma or, in the case of one ganglioneuroblastoma and three biphasic tumors, an anaplastic medulloblastoma.

Two idiosyncratic tumors were found in the CNS9102 cohort, and to our knowledge their features have not been previously described. In one case, there was such widespread differentiation along neuronal lines that the embyronal component of the tumor, with its high growth fraction, was restricted to perivascular regions, while the remainder of the tumor was characterized by numerous neurocytic and ganglion cells with a negligible growth fraction and relatively low cell density. There was no desmoplasia. The tendency for proliferating undifferentiated cells to congregate around blood vessels is reminiscent of cancer stem cells in a niche. This phenotype is also reminiscent of the pediatric neuroblastic tumors of the brain described by Eberhart, Brat, Cohen and Burger (5); however, our tumors did not contain rosettes. The other tumor contained scattered nodules of densely packed small cells with a neuronal immunophenotype and a low growth fraction. It resembled a biphasic medulloblastoma, apart from the "reversed" nuclear : cytoplasmic ratio of the nodules.

Molecular analysis alongside histopathological evaluation of medulloblastomas. We believe that future classifications of CNS tumors should feature an optimal combination of histopathological evaluation and targeted molecular analysis (9, 10). Molecular analysis can be used in a variety of ways; when histopathological variants of a tumor have particular molecular signatures, it can aid classification when tissue availability is limited. Alternatively, molecular analysis can be used to subclassify tumors with the same morphophenotype. With medulloblastomas, there is some evidence to suggest that genetic profiles do segregate with histopathological variants, though this is not an absolute phenomenon. Amplification of the *MYCC* and *MYCN* genes appears more prevalent among LC/A tumors than classic tumors (7, 21). Although it is somewhat controversial, there is also a reported association between desmoplastic medulloblastomas and mutations of the *PTCH* gene, loss of heterozygosity at 9q22 (the *PTCH* locus), and activation of the Shh pathway (28, 32, 33, 36, 40).

Where tissue was available, we used iFISH to examine nodular medulloblastomas, with and without desmoplasia, for chromosomal imbalance indicative of isochromosome 17q (i17q) and of losses at 9q22 or 17p13.3, and for amplification of the *MYCC* and *MYCN* genes. While the number of analyzed tumors in each group was small, the genetic profiles for nodular/desmoplastic and biphasic tumors appeared significantly distinct, supporting our hypothesis that these medulloblastoma variants can be separated on both histopathological and genetic grounds. In addition, the types and frequencies of genetic abnormalities found in the biphasic tumors would align them with classic or anaplastic medulloblastomas. In particular, abnormalities of chromosome 17, including i(17q), were found exclusively in the non-desmoplastic nodular tumors. Loss of 17p and i(17q) are characteristic of classic and anaplastic medulloblastomas and rare in nodular/desmoplastic tumors, according to data from our group and others (8, 21, 28). Loss of 9q22, whether due to an interstitial deletion or monosomy 9, was a feature of half the nodular/desmoplastic medulloblastomas, yet was found in none of the non-desmoplastic nodular tumors. While our data set does provide support for an association between loss at 9q22 and the nodular/desmoplastic medulloblastoma, it is small, and more study of this phenomenon is required. However, it is possible that the discrepant data to be found in the literature on this subject might reflect the inclusion of biphasic tumors in cohorts of desmoplastic medulloblastomas.

Clinical correlates of medulloblastoma variants. Our histopathological review of medulloblastomas from the SIOP/UKCCSG CNS9102 and CNS9204 cohorts has allowed a robust appraisal of various clinicopathological correlates. Because the trials ran contemporaneously and are thus unlikely to be affected by ascertainment bias, we have combined the data from them for some analyses. Analysis of age at presentation across both cohorts revealed several trends. Nearly all MBENs presented in infancy, which bears out previous reports of this variant (12, 38). Nodular/desmoplastic medulloblastomas appeared to present at an earlier age than LC/A or classic tumors, about half occurring in infancy. In this respect, our data complement those of the German and French studies of infant medulloblastoma, from which it is clear that nodular/desmoplastic tumors make up a large proportion of medulloblastomas presenting in the first 5 years of life. We found that nodular/desmoplastic medulloblastomas, including MBENs, constitute 57% of infant tumors, comparable with the figures of 47% and 33% in the HIT and SFOP studies, respectively (15, 35). Given our CNS9102 data, the lower figure for the French study probably reflects the inclusion of children aged up to 5 years, rather than 3 years for the CNS9204 and HIT trials. In children aged 3–16 years from the CNS9102 PNET3 trial, nodular/desmoplastic tumors represented only 5% of medulloblastomas. Across both trials and representing an age range of 0–16 years, 8% is the proportion of 350 medulloblastomas that fulfills our criteria for the nodular/desmoplastic variant. This figure is considerably less than the 21% reported in the 1971 study by Chatty and Earle (3), but accords well with

SIOP data presented by Burger, Grahmann, Bliestle and Kleihues in 1987 (1). These authors reported a frequency of 8% for the "desmoplastic" variant of medulloblastoma, and also described non-desmoplastic tumors with "lucent islands" of cells showing increased expression of neuron-specific enolase (NSE), which correspond with our "biphasic" tumors.

Our study represents the first attempt to examine, in trial-based patient cohorts, the prognostic relevance of subclassifying medulloblastomas from across the pediatric age range. Our data show that it is worthwhile to distinguish the nodular/desmoplastic and LC/A variants of medulloblastoma, which have better and worse outcomes, respectively, than the classic tumor. The favorable biological behavior of the MBEN has been recorded previously (12), but we also found that other childhood nodular/desmoplastic medulloblastomas, whether presenting in infancy or later, are associated with a relatively good outcome, when compared with classic or LC/A tumors. This result accords with recent data from the German Pediatric Brain Tumor Study Group (35), which showed a significantly better OS at 5 years for infants with desmoplastic medulloblastoma (95%) than for those with classic medulloblastoma (41%). Histopathological review of medulloblastomas in that study took into account the presence of a reticulin-positive internodular desmoplasia (T. Pietsch, pers. comm.), which further reinforces the correspondence between the data sets. Similarly, our results agree with separate data for older children (6, 20).

We have provided data to indicate a favorable prognosis for the nodular/desmoplastic medulloblastoma, but the biological basis for this remains unclear. One possibility is that this variant's phenotype reflects a propensity to differentiation that is associated with reduced growth potential. Other possibilities include an enhanced susceptibility to adjuvant therapy or even that, with its tendency to occur in a more lateral position within the cerebellum, it is more amenable to surgery, with a higher chance of complete resection (37). If the nodular/desmoplastic medulloblastoma's biological behavior is related to focal differentiation, then one might expect a similar phenomenon with the biphasic tumor and ganglioneuroblastoma. The latter was too rare in our series for a judgment about this, and the survival curve for children with biphasic tumors does not allow any firm conclusions to be drawn; it appears intermediate between those for the classic and nodular/desmoplastic tumors. However, by combining nodular/desmoplastic and biphasic medulloblastomas to create a group of "nodular" tumors and comparing its outcome with those of classic and LC/A medulloblastomas, we did find a significant difference ($P = 0.01$) for OS at 5 years between nodular (83%), classic (73%), and LC/A (57%) tumors and for EFS at 5 years ($P = 0.01$) between nodular (77%), classic (64%), and LC/A (51%) tumors. While this finding supports the utility of identifying "nodular" medulloblastomas, our molecular cytogenetic data suggest that this would be a heterogeneous group. Unfortunately, we have insufficient molecular data to determine whether non-desmoplastic nodular (biphasic) medulloblastomas with loss of 17p or *MYC* amplification behave more aggressively than those without these molecular signatures.

Histopathological heterogeneity in the medulloblastoma. While this and our earlier studies have made a thorough analysis of histopathological heterogeneity in medulloblastomas, we do not deem that our present data identify a new variant of medulloblastoma. The terms "biphasic" and "paucinodular" were included simply to facilitate description. However, we hope that the detailed descriptions in this account will help neuropathologists and pediatric pathologists to recognize more readily the distinction between nodular/desmoplastic medulloblastomas and classic or anaplastic medulloblastomas with focal nodule formation.

We believe that future classifications of CNS tumors should feature an optimal combination of histopathological evaluation and targeted molecular analysis, and that a scheme with clinicopathological utility is beginning to emerge for the medulloblastoma. In this study, we have provided data to indicate that histopathological classification can usefully distinguish several variants of medulloblastoma. The nodular/desmoplastic variant, including the MBEN, and the LC/A variant have better and worse outcomes than the classic variant, respectively. In addition (Table 6), our studies of molecular prognostic indicators have shown the utility of identifying good-outcome medulloblastomas with nuclear accumulation of β-catenin and poor-outcome medulloblastomas with loss of 17p or *MYC* amplification (11, 21). Combining a scheme like this alongside important clinical determinants of outcome, such as metastatic disease at presentation, should eventually provide a means of stratifying patients into low-, standard- and high-risk groups for therapeutic purposes.

In conclusion, we have presented the definitive histopathological review of medulloblastomas from children entered into the SIOP/UKCCSG CNS9102 trial, combining the data set with a histopathological review of medulloblastomas from infants entered into the SIOP/UKCCSG CNS9204 trial to give an overview of the histopathological heterogeneity among childhood medulloblastomas. We have defined the nodular/desmoplastic variant of medulloblastoma, distinguishing it from the non-desmoplastic nodular medulloblastoma on molecular cytogenetic grounds. Finally, we have demonstrated that nodular/desmoplastic medulloblastomas have a better prognosis than classic

Good prognosis tumours:
Medulloblastoma with extensive nodularity
Nodular/desmoplastic medulloblastoma—particularly infantile
Medulloblastoma with β-catenin nuclear immunoreactivity—mainly classic variant
Poor prognosis tumours:
Medulloblastoma with metastatic disease at presentation
Large cell/anaplastic medulloblastoma
Medulloblastoma with loss of chromosome 17p—often classic variant
Medulloblastoma with high frequency *MYCC* or *MYCN* amplification—often LC/A variant

Table 6. Histopathological/molecular classification of medulloblastoma and outcome relative to the standard-risk classic variant.

medulloblastomas and present at an earlier age.

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