

ORIGINAL ARTICLES

Histologic Features and Prognosis in Pediatric Medulloblastoma

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Received September 24, 2007; accepted January 14, 2008; published online January 17, 2008.

ABSTRACT

Because individual histologic features in childhood medulloblastoma alter survival likelihood, the recent 4th edition of the World Health Organization (WHO) Classification of Brain Tumors recognizes desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, large cell medulloblastoma, and anaplastic medulloblastoma, in addition to medulloblastoma with no other distinguishing features. To identify features affecting survival likelihood, we investigated 33 histologic features in 556 childhood tumors diagnosed as medulloblastoma in the Childhood Brain Tumor Consortium (CBTC) database; all features have CBTC verified read-reread reliability and those features important in the classification of medulloblastoma and its WHO variants regardless of their measured reliability. Nineteen features had no effect on survival likelihood, and 8 features were too prevalent or too rare to measure their effect on survival. Nodules, balls, high cell density, and fine fibrillary stroma improved survival likelihood; necrosis and prominent nucleoli worsened survival likelihood. Of note, the presence of desmoplasia, currently a defining feature (along with nodules) for desmoplastic/nodular medulloblastoma, had no effect on survival likelihood. We conclude that the presence of nodularity in medulloblastoma is important to improved survival likelihood, particularly when combined with balls and fine fibrillary stroma. Given the “overlap” of desmoplastic/nodular medulloblastoma and nodular medulloblastoma, we suggest they be combined into a diagnosis of nodular medulloblastoma, with nodules, balls, and fine fibrillary stroma as defining criteria. We also suggest that because of the considerable overlap of anaplastic medulloblastoma and large cell medulloblastoma they be combined into 1 diagnosis of anaplastic/large cell medulloblastoma, with necrosis and prominent nucleoli among the defining criteria.

Key words: anaplastic medulloblastoma, desmoplastic/nodular medulloblastoma, large cell medulloblastoma, medulloblastoma, medulloblastoma with extensive nodularity

INTRODUCTION

Medulloblastoma is a common, malignant, embryonal childhood tumor located in the cerebellum; it is composed of densely packed cells with round to oval or carrot-shaped nuclei with abundant chromatin and scanty cytoplasm [1–4]. Individual histologic features are used to divide medulloblastomas into several variants thought to modify survival estimates. Thirty-seven years after medulloblastoma was identified [1], a subgroup of these tumors was segregated in 1962 because of desmoplasia and was originally called a sarcoma [5] but was subsequently designated desmoplastic medulloblastoma (DM) [2], with the remaining tumors generically labeled medulloblastoma (M). Nodules were an inherent component of DM tumors since Kernohan’s first description and have been included in most subsequent descriptions, including all previous editions of the World Health Organization (WHO) Classification of Brain Tumors, and DM is now termed desmoplastic/nodular medulloblastoma.

The current WHO classification of these tumors includes desmoplastic/nodular (DM), medulloblastoma with extensive nodularity (N), large cell medulloblastoma (LC), and anaplastic medulloblastoma (A) [6,7].

Reticulin-free nodules or balls of tumor cells characterize DM and N. They contain less or more densely packed cells with neuronal or astrocytic differentiation separated by dense strands of an intercellular network of reticulin fibers [2,5,8]. Chatty and Earle [8] recognized that nodules could be hypocellular or hypercellular relative to surrounding medulloblastoma and that nodules frequently contained the same fine fibrillary stroma as was often present in the surrounding medulloblastoma. Desmoplastic medulloblastoma has been associated with improved survival over medulloblastoma [2,8–12]. Others contradicted this associ-

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ation [13–15]. In no study has the extent of tumor involvement by reticulin or reticulin-free islands—that is, the extent of nodularity—been quantified.

In the WHO 4th edition, N is defined histologically as “differ[ing] from the desmoplastic nodular variant by exhibiting a markedly expanded lobular architecture, due to the fact that the reticulin-free zones become unusually large and rich in neuropil-like tissue The internodular reticulin-rich component, which dominates in the desmoplastic/nodular variant, is markedly reduced” [6]. In the same edition, DM and N are given the same ICD-O code. However, desmoplasia can be produced by tumor merely invading any mesodermally derived structure, such as blood vessels or leptomeninges (and each cerebellar folium is a peninsula surrounded by leptomeninges containing vessels) [2,7]. Thus, confusion has arisen among pathologists with regard to the amount of desmoplasia required for a diagnosis of DM or N.

Large cell medulloblastoma is a variant with cells that have large, round or pleomorphic, molded nuclei with prominent nucleoli and more abundant cytoplasm than non-LC medulloblastomas. Cell-cell wrapping, large areas of necrosis, high mitotic activity, and high apoptotic rate are common findings, and LC is considered highly malignant [6,7]. However, the size of the large cells is not specified.

Anaplastic medulloblastoma is described as containing large tumor cells, prominent nucleoli, abundant mitotic figures, and numerous apoptotic bodies [16,17]. Nuclei are pleomorphic and crowded, with frequent molding [18]. Compared to non-A, A has been shown to be associated with both poorer [14,16–20] and similar rates of survival [21]. Apoptotic rate in these tumors was of no prognostic value [22]. Many studies relating to the outcome of A do not distinguish between A and LC [14,17,18], which further confounds the issue. In the 4th edition of the WHO Classification of Brain Tumors, LC and A share the same ICD-O code [6,7]. Atypical teratoid/rhabdoid tumor had not yet been described at the time of data acquisition for the Childhood Brain Tumor Consortium (CBTC) database.

The boundaries between some of these diagnoses are difficult to define. For instance, A and LC both contain nuclear pleomorphism, apoptosis, and mitosis [18]. In fact, the 4th ed. WHO authors state the following: “The highly malignant large cell medulloblastomas and anaplastic medulloblastomas have considerable cytological overlap” [6]. Nuclear size, mitosis, and apoptosis can be operationally defined, but this was not done in the studies leading to this division of LC and A in the WHO 4th edition. Because of the overlap and because nuclear size, number of mitoses, and amount of apoptosis are not specified, the read-reread reproducibility of the histopathological criteria of this A variant is doubtful, and the widely variable proportions (4% to 24%) of the A variant in various medulloblastoma populations reflect the difficulty in applying these criteria practically [6,18]. Medulloblastomas have also been separated on the basis of amount of anaplasia [14] or the amount of necrosis. Urberuaga et al [15] stratified medulloblastoma by 4 levels of necrosis and in a univariate analysis found worsening survival with increasing proportions of necrosis.

Four problems potentially contribute to the varying

survival results of these diagnoses in the literature. The 1st problem involves study sample sizes; many study sample sizes included less than 100 cases (except for studies like that of McManamy et al [12]). The 2nd problem involves the limitations of single-institution studies. Third, mixing children and adults in survival studies is problematic, as the morphologic phenotype of medulloblastoma in children and adults differs [23]. The 4th problem involves lack of precise definitions of histologic criteria for each diagnosis: for instance, the amount of desmoplasia necessary for a diagnosis of DM or the size of large cells in the LC variant have not been operationally defined. For the A and LC variants, we have assumed a random distribution of the histologic features across the tumor. Hence, biopsy size or amount of resection should make no difference, unlike the situation involving DM, in which the nodules and desmoplasia may not be randomly distributed across the tumor.

The histologic features studied in the CBTC are the same as many of the histologic criteria mentioned in the above descriptions of medulloblastoma variants. We offer this contribution to the ongoing discussion of the survival implications of these histologic variants of medulloblastoma. In this paper on childhood medulloblastomas, we focus on identifying specific histologic features (Glossary) that may be associated with prognosis rather than on clinical or treatment variables.

METHODS

The following results derive from the CBTC database. The CBTC database contains pediatric brain tumors from 10 North American institutions [24]. This database is unique in terms of the following database characteristics: its size, standardized data-acquisition practices, multi-institutional character (to minimize the bias of single-institution studies), use of all brain tumor samples regardless of diagnosis, prestudy agreed-upon operational definitions of histologic features, and read-reread data collection (allowing estimation of CBTC neuropathologists’ reproducibility in making WHO diagnoses and in recognizing histologic features in tumors on 2 occasions).

The CBTC database contains WHO diagnoses as well as clinical, surgical, tumor histology, treatment, and survival information for 3291 unselected children. The mean time from 1st surgical procedure to last follow-up was 5.2 years, with 48.6% of patients lost to follow-up as a result of death. With a brain tumor incidence of approximately 3 per 100 000 children per year [25,26], our sample represents approximately 100 000 000 children-years of observation. Four teams of 2 neuropathologists each reached consensus about the presence or absence of each defined histologic feature in microscopic slides of each case from the 1st surgical procedure. A 5th team of 2 neuropathologists came to consensus about the appropriate WHO diagnosis using original WHO criteria [27]. The neuropathologic teams reviewed cases without clinical information, institutional diagnosis, or knowledge of whether the case had been reviewed by them previously. The same team of 2 readers read 25% of CBTC cases on 2 separate occasions in a randomized and blind design. Reliability estimates were

Table 1. Comparison of survival distributions by diagnosis

WHO diagnosis	Survival estimate			P
	1 Year	5 Years	10 Years	
M ^a	0.71	0.38	0.32	>0.30
DM	0.64	0.32	0.27	

Children with survival of <1 month excluded from survival analysis. WHO indicates World Health Organization.

^aMedulloblastoma (M) includes all medulloblastomas with diagnoses other than desmoplastic medulloblastoma (DM).

Table 2. Comparison of clinical variables by diagnosis

Clinical variable		Diagnosis		
		M ^a (%)	DM (%)	P
Age (years)	Mean (SD)	6.5 (3.8)	5.1 (3.2)	0.003
	Median	6.1	4.4	
	0 to <2	13	16	
	2 to <5	25	39	
	5 to <10	43	36	
	≥10	19	9	
Gender	Male	63	66	0.61
Amount removed	Biopsy only	9	7	0.31
	Partial	68	64	
	Total	23	29	
Treatment	Radiation and/or chemotherapy	81	84	0.54

^aMedulloblastoma (M) includes all medulloblastomas with diagnoses other than desmoplastic medulloblastoma (DM). SD indicates standard deviation.

based on a kappa grading system of observer agreement [28], where a kappa value of <0.50 indicates “poor” reliability and a kappa value of >0.75 indicates “excellent” reproducibility [29]. The CBTC database is the only database with measured read-reread reliability of WHO diagnoses and the many histologic features commonly used by pathologists when diagnosing childhood brain tumors.

For histologic comparison and survival analyses within medulloblastoma, we examined 26 histologic features previously identified as “reliably recognized” in CBTC tumors limited to infratentorial compartment [30]. We also considered an additional 7 features linked to diagnostic groups DM, N, LC, and A [3,8–10,14–23,27,31–34], but with observer agreement slightly below our cutpoint in CBTC: large size nuclei, intermediate size nuclei (we used both large and intermediate nuclear size since “large” nuclear size has not been defined), karyorrhexis (apoptosis), nodules, balls, nests of nuclei, and prominent nucleoli. Four of these 7 histologic features (karyorrhexis, nests of nuclei, balls of nuclei, and nodules) had infratentorial read-reread reliability estimates with an upper confidence limit at or above our cut-off [30] and could be considered borderline reliably recognized. Two of the other 3 features—large size nuclei and prominent nucleoli—had low read-reread reliability estimates because of prevalence issues; large

nuclei (>3 erythrocyte diameters) and prominent nucleoli were found in relatively few cases (see Gilles and colleagues [30] and Childhood Brain Tumor Consortium [35]) for a discussion of prevalence effects on reliability estimates). The remaining feature, intermediate size nuclei, had poor reliability in CBTC. Cases with survival of <1 month after the 1st surgical procedure were omitted from all survival analyses to exclude postoperative deaths. Additionally, 8 reliable histologic features with overall prevalence of <5% in medulloblastomas were excluded from all survival analyses as a result of small sample size for the number of tumors with the feature. These features were: large perivascular pseudorosettes, microcysts, central lumen rosettes, nests of nuclei, thrombosis, Rosenthal fibers, spongy and compact areas, and sheets of ependymal cells.

Statistical analyses were performed using the SAS/STAT statistical software, version 9.1.3 (SAS Institute Inc, Cary, NC, USA). Survival curves were compared using LogRank, Wilcoxon, and –2Log statistics. We required that all 3 measures provide a P value of <0.05 before considering any difference in survival distributions significant.

RESULTS

The database contained 556 cases of medulloblastoma (473 cases of M and 83 cases of DM). By definition, M included all tumors that would currently be diagnosed as A and LC (see 1st paragraph in Introduction). Also, at the time of CBTC data collection, the introduction of N had not been recognized, but it is highly likely that CBTC tumors diagnosed DM would include tumors of this variant. In a previous CBTC study, pathologist reproducibility of these diagnoses was evaluated, yielding kappa estimates of 0.79 (“excellent”) for M and 0.56 (“good”) for DM [35], but the reliability of the other variants, N, LC, and A, could not be evaluated because they were not in early editions of the WHO classification. The elimination of cases with survival of <1 month after 1st surgical procedure resulted in a total of 408 of 473 cases of M and 75 of 83 cases of DM for survival comparisons.

The survival distributions of CBTC children assigned WHO diagnoses of M and DM did not differ ($P > 0.30$) (Table 1). For both diagnoses the survival decreased at approximately the same rate between the 1st and 5th years after 1st surgical procedure. Clinically, children with the diagnosis of M did not differ significantly from those with DM on the variables of gender, amount removed at 1st surgical procedure, or treatment with radiation and/or chemotherapy (Table 2), although there was a slight difference in the distributions of age in the 2 groups. For both M and DM diagnoses, children were more likely male (63% and 66%, respectively), with tumors more likely partially removed (68% and 64%, respectively) and treated (81% and 84%, respectively) (Table 2). Children with M were significantly older at diagnosis than were children with a diagnosis of DM (mean of 6.5 and 5.1 years, respectively). However, age at diagnosis did not result in significant differences in survival between the 2 groups of children (for age groups <2 years, 2 to <5 years, and 5 to <10 years ($P > 0.15, 0.46, \text{ and } 0.21$, respectively) (Table 3).

Table 3. Comparison of survival distributions by age^a

Age (years)	Survival estimate					P
	Diagnosis ^b	n ^c	1 Year	5 Years	10 Years	
0 to <2	M	49	0.53	0.37	0.34	>0.15
	DM	11	0.45	0.27	–	
2 to <5	M	99	0.62	0.29	0.28	>0.46
	DM	29	0.57	0.32	0.28	
5 to <10	M	180	0.76	0.41	0.33	>0.21
	DM	28	0.75	0.28	0.23	
≥10	M	79	0.80	0.45	0.33	–
	DM	6	–	–	–	

^a– Indicates insufficient sample size.

^bMedulloblastoma (M) includes all medulloblastomas with diagnoses other than desmoplastic medulloblastoma (DM).

^cChildren with survival of <1 month excluded from survival analyses.

Table 4. Comparison of prevalence of 26 reliable features and 6 additional features

Histologic feature	Reliability	% of all medulloblastomas
Density, very high	0.72	88.3
Nuclei, hyperchromic	0.53	84.9
Density, high	0.53	83.0
Nuclei, oval	0.62	81.9
Mitosis	0.72	78.3
Karyorrhexis ^a	0.49	77.1
Fine fibrillary stroma	0.63	64.3
Cellularity uniform	0.59	63.5
Intermediate size nuclei ^a	0.35	54.4
Pleomorphic nuclei	0.59	50.7
Necrosis	0.71	48.1
Nuclei, elongated without cytoplasm	0.65	34.4
Density, low	0.57	34.4
Nodules ^a	0.45	27.9
Desmoplasia, parenchymal	0.52	27.5
Rows	0.50	26.3
Balls ^a	0.43	16.9
Astrocytes	0.76	14.8
Nuclei, elongated with cytoplasm	0.51	13.2
Nucleoli, prominent ^a	0.27	13.1
Density, very low	0.60	12.4
Large size nuclei ^a	0.28	12.9
Coarse fibrillary stroma	0.52	9.8
Vacuoles	0.57	7.6
Calcification, parenchymal	0.58	5.8
Rosettes, pseudo, perivascular, large	0.73	2.0
Microcyst	0.80	1.8
Rosettes, central lumen	0.54	1.6
Nests of nuclei ^a	0.48	1.6
Thrombosis	0.60	0.9
Rosenthal fibers	0.82	0.5
Spongy and compact areas	0.67	0.5
Sheets of ependymal cells	0.79	0.4

^aReliability point estimate <0.50.

Since the WHO classification scheme did not include N, LC, or A when the CBTC was formed, they were not included as CBTC choices for tumor diagnoses. However, we were able to use appropriate histologic features to see whether the presence of individual histologic features used in these diagnoses contained additional survival information above and beyond that included in the diagnosis of medulloblastoma alone (Table 4). For the remaining portions of this manuscript, M and DM are joined into a common database.

In univariate analyses, a significant difference in survival distribution between feature absence and feature presence in medulloblastomas was found for 6 features: high cell density, fine fibrillary stroma, necrosis, nodules, balls, and prominent nucleoli (Table 5). The presence of nodules, balls, fine fibrillary stroma, and high cell density in a medulloblastoma improved survival outlook, while the presence of necrosis and prominent nucleoli in a medulloblastoma worsened survival outlook (Table 5). Of note, the

Table 5. Comparison of survival distributions for histologic features

Histologic feature	Survival estimate				P
	1 Year	5 Years	10 Years		
Density, high	–	0.57	0.28	0.25	<0.02
	+	0.72	0.40	0.32	
Fine fibrillary stroma	–	0.58	0.24	–	<0.0001
	+	0.76	0.44	0.36	
Necrosis	–	0.72	0.40	0.35	<0.035
	+	0.65	0.32	0.26	
Nodule ^a	–	0.67	0.33	0.27	<0.0035
	+	0.77	0.46	0.40	
Balls ^a	–	0.68	0.35	0.29	<0.03
	+	0.76	0.45	0.40	
Prominent nucleoli ^a	–	0.72	0.40	–	<0.0017
	+	0.53	0.24	0.24	

Histologic features with overall prevalence of >95% or <5% (Table 4) excluded from survival analyses because of small sample size. Children with survival of <1 month are excluded from survival analyses.

^aReliability <0.50.

Table 6. Comparison of survival distributions of medulloblastomas with fine fibrillary stroma, nodules, and/or balls

Histologic features	n	Survival estimate			P
		1 Year	5 Years	10 Years	
Both fine fibrillary stroma and nodules and/or balls	111	0.82	0.49	0.40	<0.0001
Either fine fibrillary stroma or nodules and/or balls	221	0.71	0.38	0.31	
Neither fine fibrillary stroma nor nodules and/or balls	106	0.55	0.22	0.20	

Children with survival of <1 month are excluded from survival analyses.

histologic features of large or intermediate size nuclei, desmoplasia, very high cell density, oval nuclei, uniform cellularity, elongated nuclei (with or without apparent cytoplasm), low or very low cell density, coarse fibrillary stroma, desmoplasia, vacuoles, calcification, rows, astrocytes, mitoses, karyorrhexis (apoptosis), and pleomorphic nuclei did not provide additional prognostic information beyond that included in the diagnosis of medulloblastoma.

Nodules and balls, while having point estimates of suboptimal reliability, had 95% confidence interval upper bounds that exceeded 0.50. For this reason, and because an early description of DM figured both hypocellular and hypercellular reticulin-free islands in DM [8], we grouped these 2 histologic features into a single feature recording the presence of nodules and/or balls versus the absence of either. This combination should ensure a feature with predicted “good” reliability. The analysis of this combined feature with the reliable features of Table 5 in a stepwise Cox regression model resulted in a finding of fine fibrillary stroma and nodules and/or balls as significant predictors of survival (Table 6). The presence of both fine fibrillary stroma and nodules and/or balls of neoplastic cells in all medulloblastomas combined markedly improved survival likelihood, while their absence implied a worse prognosis (Table 6).

DISCUSSION

Specific histologic features or patterns determine tumor diagnosis or degree of anaplasia and convey information about prognosis. Use of histologic features in tumor diagnosis with low recognition reliability attenuates the process of determining prognosis and reduces the ability of research studies to arrive at unequivocal results [36]. Before ascribing prognostic value to specific histologic features, it is necessary to determine the identification reproducibility of individual histologic features. In our opinion, all brain tumor diagnoses and their defining histologic features should have documented read-reread reproducibility prior to being allowed into national protocols evaluating potential therapeutic efficacy.

We have shown in this study that individual histologic features, when present in medulloblastomas, affect survival. Some improved the survival distribution (for example, nodules/balls and fine fibrillary stroma), while others worsened the survival distribution (necrosis and prominent nucleoli). Many histologic features commonly discussed in literature on medulloblastomas (for example, desmoplasia,

rows, astrocytes, mitoses, karyorrhexis [apoptosis], and pleomorphic nuclei) had no effect on the survival distribution.

In agreement with the findings of some previous studies, the diagnosis of DM (which includes the presence of nodules as well as desmoplasia) in the CBTC database had no survival implication compared to tumors with a diagnosis of M [13–15]. The histologic feature desmoplasia itself also had no effect on the survival. However, the other component of DM, nodules/balls, had a strong and distinct association on the survival distribution of children with medulloblastomas. On examination of features with “good” reliability in infratentorial tumors, the “best” subset of features for predicting survival was fine fibrillary stroma and nodules and/or balls. Nodularity in a medulloblastoma has been increasingly recognized in the last 2 WHO editions [3,6], and in the WHO 4th edition, medulloblastomas showing only desmoplasia without nodules are not classified as DM [7].

As entities, the diagnoses of LC or A are difficult to address since no definitive criteria have been agreed upon. Criteria such as “abundant” mitoses and karyorrhexis, “increased” nuclear size, increased mitoses, increased necroses, and cellular “wrapping,” are not rigorous, and the subjective use and interpretation of different subsets of features with untested reader reliability may account for some of the disparity of results between studies of tumors given these labels. Until agreed-upon and succinct criteria are available and adequate read-reread reliability is demonstrated, we suggest that these diagnoses be used with caution.

Three histologic features important for the diagnoses of LC and A have poor read-reread reliability, namely, large and intermediate size nuclei and prominent nucleoli. Neither large nor intermediate size nuclei, when present, had any effect on the survival distributions of medulloblastoma. Prominent nucleoli occurred in only about 13% of medulloblastomas in the CBTC database, and because of its low prevalence in this population of medulloblastomas, we are unable to say whether the read-reread reproducibility of prominent nucleoli is acceptable. We suggest that it be retained for the present because of its negative effect on the survival distribution of medulloblastomas.

We conclude that the presence of nodularity in medulloblastoma is important to improved survival likelihood, particularly when combined with balls and fine fibrillary stroma. Given the WHO-acknowledged “overlap” of desmoplastic/nodular medulloblastoma and nodular

medulloblastoma, we suggest that these diagnoses be combined into a diagnosis of nodular medulloblastoma, with nodules, balls, and fine fibrillary stroma as defining criteria. We also suggest that as a result of the recognized considerable overlap of anaplastic medulloblastoma and large cell medulloblastoma that they be combined into 1 diagnosis of anaplastic/large cell medulloblastoma, with necrosis and prominent nucleoli among the defining criteria.

Glossary

These are the operational definitions agreed upon and used by the members of the CBTC during data collection.

Astrocyte: The prototype is the normal large glial nucleus in white matter. The nucleus is usually less intensely stained with nuclear stains than oligodendroglia.

Balls: These consist of a collection of hyperchromatic nuclei in a sea of more hypochromic cells. A layer of connective or glial tissue may mark the boundary.

Calcification, parenchymal: Flecks of amphophilic or basophilic material, ranging in size from fine stippling to large calcospherites lying in nonnecrotic regions of tumor. Encrusted cells are included.

Cell density: The following 4 definitions of nuclear density are dependent upon increasing amounts of stroma intervening between tumor nuclei from none for very high cell density to considerable for very low cell density.

Density, very high: Regions of large numbers of overlapping nuclear profiles with little visible internuclear cytoplasm or stroma. Nuclei touching.

Density, high: Small amounts of cytoplasm or internuclear stroma are present. Less than 1 nuclear diameter between nuclei. If cells have considerable cytoplasm, this density means stroma interposed between cells has less than 1 cell diameter in width.

Density, low: The stroma or internuclear cytoplasm separates cells by more than 1 nuclear diameter, but less than 4 diameters. If cells have considerable cytoplasm, low density means greater than 1 cell diameter of stroma between cells.

Density, very low: Stroma or internuclear cytoplasm separates cells by more than 3 diameters.

Cellularity uniform: Lack of prominent variation in cell density, pleomorphism, or cell type.

Desmoplasia, parenchymal: Many isolated or extensive strands of connective tissue within tumor constitute parenchymal desmoplasia, whether diffuse or pattern-forming.

Karyorrhexis: Any fragmentation of nuclei, except mitosis, is included in this category. Karyorrhexis within a region of coagulative necrosis is not included. Pyknosis is not included. This measure of cell death probably is very similar to apoptosis.

Microcyst: A small cavity without limiting membrane containing hyaline, eosinophilic fluid, sometimes vacuolated peripherally. Simple pools of plasma-rich fluid are not included.

Mitosis: Only mitoses in nonendothelial cells, whether or not they are bizarre.

Necrosis: A region of tissue that contains ghosts of

cells or a loss of nuclear or cytoplasmic characteristics with a background of eosinophilic amorphous or granular material.

Nests of nuclei: Focal islands or concentrations of glial nuclei in a relatively hypocellular neoplastic stroma (for example, the pattern in a "subependymoma").

Nodules: These histologic structures reverse the appearance of "balls" and consist of isolated groups of pale neoplastic cells in a sea of more hyperchromic cells.

Nuclei, chromatin hyperchromic: Nuclear chromatin staining greater than that of a normal white-matter astrocyte.

Nuclei, elongated with cytoplasm: Greater than a 2-fold difference in major and minor axes. Includes spindle and fusiform nuclei. The cells have a discernible cytoplasm.

Nuclei, elongated without cytoplasm: Includes the nuclear characteristics above, but without discernible cytoplasm. The prototype is the microglial cell.

Nuclei, oval: Up to a 2-fold difference in major and minor axes in most neoplastic nuclei.

Nuclei, size intermediate: Tumor nuclei 1.5 to 3 erythrocyte diameters.

Nuclei, size large: Tumor nuclei greater than 3 erythrocyte diameters.

Pleomorphic nuclei: Nuclei with a 2-fold variation in size or variation in shape except for multinucleation.

Prominent nucleoli: Large numbers of predominant neoplastic cells contain prominent nucleoli.

Rosenthal fibers: Stout, club-shaped, or linear eosinophilic or amphophilic hyaline bodies.

Rosettes, central lumen: Rosettes of cells with a distinct lumen not containing a blood vessel.

Rosettes, pseudo, perivascular, large: Oval, circular, or cylindrical cellular formations with a central vessel surrounded by a nucleus-free zone greater than 2.5 nuclear diameters.

Rows: Neoplastic cells growing in distinct columns or rows. The rows may be separated by fine fibrillary material, axons, glial fibrils, or connective tissue. These rows of cells do not form the surfaces of clefts.

Sheets of ependymal cells: Extensive regions of neoplastic cells with ependymal nuclear characteristics, but without tubules, rosettes with central lumen, or perivascular pseudorosettes.

Spongy and compact areas: Alternating densities of compact fibrillary and vacuolated structures.

Stroma, coarse fibrillary: This and the next category form the ends of a continuum of stromal characteristics. Stout, gently undulating fibrils similar to collagen, either loosely or densely packed.

Stroma, fine fibrillary: Fine fibrillary refers to a stroma containing serpiginous fine fibrils (glial fibril-like), either loosely or densely packed (as noted by Rubinstein and Northfield [2] as well as by Chatty and Earle [8]).

Thrombosis: Any fibrin/platelet thrombus or thrombus in any stage of organization. Simple blood-filled vessels are not included.

Vacuoles: Small empty spaces of varying size and shape, usually 1 to 4 nuclear diameters in size, not

containing any eosinophilic material. Smaller than microcysts.

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