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# A study of childhood brain tumors based on surgical biopsies from ten North American institutions: sample description

Childhood Brain Tumor Consortium*

*Key words:* brain tumor diagnosis, children, tumor location, pathology, WHO classification

**Summary**

The Childhood Brain Tumor Consortium has collected an extensive amount of neuropathologic and clinical information under rigorously controlled conditions about 3291 children with brain tumors. In this overview of the entire sample, five observations are prominent: 1) many tumors involve more anatomic sites at the time of the first surgical exploration than previously recognized; 2) one-third of infratentorial tumors involve both the brainstem and the cerebellum; 3) the spinal compartment is involved primarily, or in combination with the posterior fossa, in 11% of childhood brain tumors; 4) 43.2% of childhood brain tumors are limited to the posterior fossa; 5) only a few World Health Organization diagnoses account for most brain tumors in children, and 6) there is a male predominance over all ages for infratentorial tumors. Subsequent reports will describe observer variability of participating neuropathologists, correlates of clinical and histologic information, the search for homogeneous subtypes of tumors, and prognostic factors.

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## Introduction

Brain tumors in children differ in location and kind from those in adults. They formed a major focus for Mauthner in 1844 when he first set aside pediatric neurology as an independent discipline (quoted in 1). Starr pointed out their predominance below the tentorium a century ago when about 50% of intracranial masses were tuberculomata, a situation that existed throughout the first third of the 20th century in North America [2, 3]. Schultz's 1926 and Cushing's 1927 recognition that the types of neoplasms also differed from those in adults has been repeatedly confirmed [4–9]. The clinical courses, symptoms, and signs in children with brain tumors were sufficiently distinct to prompt Bailey, Buchanan, and Bucy to introduce their classic monograph with a statement that 'experience... early taught us that in the case of intracranial neoplasms also, one should not reason in the same manner when confronted with a child suffering from such a lesion as when dealing with an adult' [10]. These contrasts between brain tumors in children and adults are still being observed [1, 11–16].

Unfortunately, the estimation of prognosis for children with brain tumors has not kept pace with the advent of new therapeutic regimens, even though these tumors constitute the second most common solid neoplasm in children after leukemia [1, 17]. The greatest impediment to an accurate estimation of prognosis in earlier studies was the singular emphasis on cellular and histologic characteristics of the tumors to the exclusion of all other aspects of their pathology such as clinical evolution, location, operative findings, etc. To address this issue the Childhood Brain Tumor Consortium (CBTC), over the last half decade, has assembled a database containing neuropathologic and clinical information to sort out the effects upon prognosis of tumor type, location, individual histologic features, clusters of histologic features, extent of surgical resection, therapies, progression and clustering of symptoms, gender, and age. Our database is unique for several reasons: its large size; many contributing centers (thus minimizing the bias of single institution studies); standardized methods of data acquisition; and its use of all brain tumors from each of the contributing centers regardless of diagnosis.

We were stimulated towards our efforts by several observations. First, the majority of prior reports of childhood brain tumors and their prognoses do not clarify whether or not: first or subsequent surgical specimens were used; referral cases (pathologic or therapeutic) were included; or, autopsied cases were included. Each of these sources of cases in a study has important influences upon the results. Initial biopsies are less likely than subsequent ones to manifest sequelae of surgery, radiation, and chemotherapy. A large proportion of referral cases may embody the bias of difficult diagnostic or therapeutic problems. Inclusion of autopsied cases may incorporate the bias of more lethal cases as well as the bias of 'who gets autopsied'. Our study was designed specifically with these thoughts in mind. We included only children who had their first surgical specimen examined at one of our collaborating institutions and for whom that specimen as well as a clinical history were available.

Second, there are marked discrepancies in the frequencies and locations of specific tumors cited in earlier reports (e.g., the apparent absence of nonpilocytic astrocytomas of the cerebellum in the large series from the Vienna Neurological Institute [16]). We suspected that among these many studies different diagnostic criteria had been used, and that the marked histologic and site heterogeneity [18] of childhood brain tumors had not been considered. Fortunately, when we began this study the World Health Organization (WHO) classification had become available with its guidelines for diagnostic criteria [19].

Third, while the eventual mastery of childhood brain tumors will rest upon knowledge of etiology and pathogenesis, such knowledge, will not *ipso facto,* provide information about prognosis. The same is true about classifications of brain tumors constructed only upon hypotheses about etiology and pathogenesis. Moreover, despite much work with laboratory models and a few promising epidemiologic leads (e.g., reference 20) over the last four decades, the pathogenesis of brain tumors in children remains largely unknown. Thus, we were concerned that the estimation of prognosis of children with brain tumors, a problem of immense mag-

nitude for parents and clinicians, was being ignored.

In this overview and survey of the entire sample we provide 1) the details of our study design and methods of data acquisition, 2) a preliminary description of these children, and 3) a summary of their tumor types and tumor locations. Subsequent reports will provide: evaluations of observer variability of participating neuropathologists; correlates of clinical and histologic information; delineation of homogenous subtypes of tumors; clusters of histologic features; and prognostic factors.

## Materials and methods

### *Sample size*

Our goal of providing prognostic information about children with brain tumors required data about many clinical, operative, histologic, and therapeutic variables in a large number of children. This was necessary if we were to improve our diagnostic and prognostic ability for tumors not only at common locations but also at the less frequent sites. Our pilot study, which provided a new classification of cerebellar gliomas was based on 132 children [21]. For the present study, we ultimately based our projection of 3000 children on a synthesis of the figures in the report of Koos and Miller [1] and the estimates of the distributions of brain tumor locations in children provided to us by many pediatric neurosurgeons. We expected this number to provide large numbers of children with common brain tumors and 100–250 children with each of the relatively infrequent tumors.

### *Selection of CBTC centers*

North American pediatric pathologists and neuropathologists expressing interest in the goals of the CBTC were invited to join the consortium. Ten centers located in Toronto, Boston, Philadelphia, Pittsburgh, St. Louis, Denver, and Los Angeles enrolled.

### *Identification of potential cases*

The coinvestigators at each of the centers submitted lists of all children with tumors of brain, spinal cord, sella turcica and leptomeninges who had been operated on prior to January 1, 1979 and for whom tissue from the first surgical procedure was available for reexamination. Dermoid and epidermoid cysts, arteriovenous malformations, and nonneoplastic granulomatous processes were excluded. Pathology reports, diagnosis files, tumor registries, neurosurgery files, and case lists from previous studies yielded 3878 potentially eligible cases which were assigned special CBTC study numbers. To protect patient confidentiality, actual patient names were not entered into the data base. Potential cases were deleted during the course of the study for any of the following reasons: inadequate histologic material, inadequate clinical history, case duplication, case not a brain tumor, first surgery not performed at a CBTC center, or autopsy only. The 3291 children remaining at the end of data accrual satisfied the following criteria: 1) a primary nervous system tumor with first tumor surgery performed at a CBTC center before age 21 years, 2) available hematoxylin and eosin stained slides, and 3) a minimal clinical history consisting of year of surgery, age at surgery, and site of tumor.

### *Randomization for slide review*

Cases were randomized in order to avoid problems introduced by temporal trends, education of the reviewer's eyes, selection of cases by institution, and to provide for observational variation studies.

### *Slide review*

Two-member teams of neuropathologists reviewed the slides of brain tumors simultaneously (as a strategy to minimize observational variation [22, 23]) with regard to assigning diagnoses or identifying histologic features. Agreements or disagreements between members were recorded on standard checkoff lists.

*World Health Organization (WHO) diagnoses*

A list of 73 WHO diagnoses and definitions was adapted from the WHO manual [19]. A single team reviewed cases in groups of 300–350 over several days at a time assigning diagnoses from the compiled list. (The members of this team were familiar with the WHO diagnoses since they use them in their daily practices.) In three years this team reviewed in excess of 4000 cases not only recording traditional WHO diagnoses but also providing the database for the estimation of observational variation in assigning these diagnoses. This team did not provide any histologic feature information.

*Histologic features*

A list of 144 histologic features, with operational definitions for each, was developed and tested by the slide readers and coinvestigators with the advice and guidance of Drs. Kenneth Earle and John Kepes. Every team reviewed the same twenty-five practice cases prior to starting the main study. The histologic feature slide review was completed in four years. Four teams combined reviewed a total of 4919 cases providing information about histology as well as data for assessing intrateam and interteam observational variation. These teams did not provide WHO diagnoses.

*Clinical features*

A list of clinical features was developed in conjunction with neurologists, neurosurgeons, oncologists, radiologists, hematologists, and medical records and tumor registry personnel. Tumor location information was obtained by screening the clinical records and operative reports for designations of one or more of 45 possible anatomic loci. We used all positive information about the anatomic location of the tumor, even though computer assisted tomographic information was available for only a few of the 50 years encompassed in our database. For these reasons our localizations are minimal estimates of the extent of these tumors. A CBTC trained Registered Records Administrator reviewed the clinical records on site for the 398 clinical, operative, therapeutic, and follow-up variables. Tumor registries, state vital statistics files, and oncology, radiology, and neurosurgery office records were reviewed as necessary. Clinical record review began in January 1980 and the last follow-up was obtained in February 1984.

*Autopsy features*

The autopsy feature checkoff list included a combination of the histologic features, WHO diagnoses, and location information from the clinical features list. An additional section applicable to autopsy protocol was included. The 460 autopsies were reviewed over one year by a separate sixth team of neuropathologists who reviewed central nervous system slides only.

*Data entry*

The 12743 data forms generated were entered into computer memory. For entry verification, one-tenth of the forms selected randomly by month of entry were reentered by a different person. The error rates for data entry were less than 0.007.

*Final data sets for analyses*

Four data sets were produced by these efforts: The *primary data set* contains clinical and histologic data, as well as a traditional WHO diagnosis for 3291 children and is the basis for this overview. The *intrateam data set* contains cases reviewed twice by the same team for estimates of intrateam observational variation: 822 cases for the histologic features teams and 710 cases for the WHO diagnosis team. The *interteam data set* contains 281 cases read by all histologic feature teams for estimates of observational variation among these teams. An *autopsy data set* contains 460 children who were in the primary data set and came to autopsy.

## Results

The findings reviewed here provide a brief overview of the wealth of information in the CBTC database. They include: gender and age distributions and distributions of WHO diagnoses among the CBTC centers; the locations of these children's tumors; the relationships of age and gender to location; WHO diagnoses and compartments; the interrelation of gender, WHO diagnosis and location; and changes in the WHO diagnoses with age.

### *Gender and age distributions among centers (Table 1)*

The number of cases per center ranged from 54 to 806. The male sex proportion of cases ranged from 47% at St. Louis Children's Hospital to 58% in Pittsburgh. The proportion of children in the first year of life was similar in each center. LAC-USC Medical Center had fewer children between two and six years of age (26% vs. 33%). St. Louis Children's Hospital had a smaller proportion of children in the 6–10 year age group and a larger proportion greater than 14 years of age. The differences in the representation of children older than 14 years presumably reflect the differences in admitting policies among the institutions.

### *Distributions of WHO diagnoses among centers (Tables 2a and 2b)*

Eight WHO diagnoses accounted for 89% of the children. Seven diagnoses accounted for 76% of the supratentorial tumors and 5 for 87% of the infratentorial tumors. However, there were greater than twofold differences among CBTC centers in the proportions of frequent supratentorial tumor types, a phenomenon not present with infratentorial tumors. Unclassified tumors were considerably more frequent in the supratentorial compartment.

*Table 1.* Database of childhood brain tumor consortium: source and percent of cases by gender and age

| | Center | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | STLCH | CG/STL | Boston | Denver | CH/LA | CH/Phil | PITT | Toronto | LAC-USC | STC./Phil | |
| Total number of cases | 198 | 132 | 806 | 199 | 302 | 262 | 443 | 751 | 54 | 144 | 3291 |
| Gender | | | | | | | | | | | |
| Male proportion | 47 | 52 | 55 | 49 | 54 | 49 | 58 | 56 | 54 | 56 | 54 |
| Unknown | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Age last birthday | | | | | | | | | | | |
| <1 yr | 7 | 8 | 6 | 7 | 9 | 7 | 8 | 5 | 9 | 8 | 7 |
| 1 yr | 10 | 6 | 9 | 13 | 10 | 6 | 8 | 5 | 7 | 8 | 8 |
| 2– 5 yr | 29 | 30 | 33 | 33 | 36 | 32 | 33 | 36 | 26 | 33 | 33 |
| 6–10 yr | 21 | 37 | 31 | 33 | 27 | 35 | 31 | 36 | 30 | 34 | 31 |
| 11–13 yr | 12 | 14 | 13 | 11 | 13 | 15 | 14 | 15 | 11 | 11 | 13 |
| 14+ yr | 22 | 5 | 7 | 5 | 6 | 6 | 7 | 7 | 17 | 4 | 7 |
| Unknown | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Total | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

STLCH – Barnes and St. Louis Children's Hospital; CG/STL – Cardinal Glennon Children's Hospital; Boston – Children's Hospital of Boston; Denver – Children's Hospital of Denver; CH/LA – Children's Hospital of Los Angeles; CH/Phil – Children's Hospital of Philadelphia; PITT – Children's Hospital of Pittsburg; Toronto – Hospital for Sick Children; LAC-USC – LAC-USC Medical Center; STC./Phil – St. Christopher's Hospital for Children.

*Table 2a.* Supratentorial tumors: distribution of seven most frequent WHO diagnoses within each center (percent)

| | STLCH | CG/STL | Boston | Denver | CH/LA | CH/Phil | PITT | Toronto | LAC-USC | STC./Phil | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of cases | 86 | 49 | 302 | 66 | 122 | 104 | 153 | 299 | 21 | 53 | 1255 |
| *WHO diagnosis (percent)* | | | | | | | | | | | |
| Fibrillary astrocytoma | 9 | 2 | 8 | 9 | 6 | 17 | 4 | 9 | 14 | 9 | 8 |
| Pilocytic astrocytoma | 7 | 12 | 10 | 8 | 12 | 6 | 19 | 12 | 10 | 13 | 11 |
| Other astrocytoma | 28 | 14 | 21 | 18 | 22 | 14 | 22 | 18 | 38 | 23 | 20 |
| Oligodendroglioma | 6 | 14 | 5 | 5 | 3 | 3 | 3 | 4 | 10 | 2 | 5 |
| Ependymoma | 8 | 14 | 7 | 14 | 7 | 8 | 5 | 8 | 0 | 2 | 7 |
| Craniopharyngioma | 16 | 14 | 19 | 15 | 14 | 11 | 16 | 15 | 5 | 19 | 16 |
| Unclassified tumor | 6 | 8 | 8 | 9 | 10 | 8 | 12 | 8 | 10 | 11 | 9 |
| Total | 80 | 78 | 78 | 78 | 74 | 67 | 81 | 74 | 87 | 79 | 76 |

*Table 2b.* Infratentorial tumors: distribution of five most frequent WHO diagnoses with each center (percent)

| | STLCH | CG/STL | Boston | Denver | CH/LA | CH/Phil | PITT | Toronto | LAC-USC | STC./Phil | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of cases | 87 | 71 | 388 | 117 | 162 | 124 | 244 | 384 | 24 | 80 | 1681 |
| *WHO diagnosis (percent)* | | | | | | | | | | | |
| Pilocytic astrocytoma | 32 | 31 | 27 | 26 | 29 | 31 | 23 | 28 | 25 | 27 | 27 |
| Other astrocytoma | 6 | 7 | 9 | 3 | 9 | 6 | 6 | 6 | 8 | 6 | 7 |
| Ependymoma | 16 | 14 | 13 | 21 | 14 | 12 | 11 | 17 | 13 | 9 | 14 |
| Medulloblastoma | 32 | 37 | 36 | 38 | 39 | 35 | 43 | 35 | 42 | 38 | 37 |
| Unclassified tumor | 1 | 0 | 4 | 1 | 2 | 2 | 2 | 1 | 0 | 2 | 2 |
| Total | 87 | 89 | 89 | 89 | 93 | 86 | 85 | 87 | 88 | 82 | 87 |

### *Tumor location*

We grouped children's tumor locations into the traditional supratentorial, infratentorial, and spinal compartments by mutually exclusive combinations of the 45 neuroanatomic sites (Table 3). We defined the limits of the infratentorial compartment as the union of the aqueduct with the third ventricle at the posterior commissure rostrally and the cervicomedullary junction at the caudal margin of the foramen magnum caudally. Hence, the pineal is considered to have a supratentorial location.

Overall, the vast majority of the 3291 children in our database had tumor limited to one compartment. 40.9% were in the supratentorial compartment, 43.2% were in the infratentorial compartment, and 4.9% were in the spinal compartment. Within the supratentorial compartment, 12.8% were superficially located, 29% were deeper and extended from the surface of the brain to the lateral ventricle, and 28.4% were located in the diencephalon. Within the infratentorial compartment, 49.9% were thought to involve only the cerebellum, 12.7% only the brainstem, and 36.1% both the cerebellum and brainstem. Tumors occupying two or more compartments were distributed as follows: 6.1% involved both the infratentorial and spinal compartments, 3.0% involved both infratentorial and supratentorial compartments, and 1.0% involved all of the compartments as the time of the first hospitalization (Table 3).

### *The relationship of age and gender to the location of the tumor*

The compartment in which the tumor was located changed with age during childhood (Fig. 1 and Ta-

*Table 3.* Tumor location at first operation

| | N | % total group | |
|---|---|---|---|
| A. Single Compartment | | | |
| | | | % supratentorial |
| *Supratentorial* | 1347 | 40.9 | 100.0 |
| Cerebrum, nos | 42 | 1.3 | 3.1 |
| Telencephalon, superficial with temporal lobe | 173 | 5.3 | 12.8 |
| (Temporal lobe only) | (72) | (2.2) | (5.4) |
| Telencephalon, Lateral Ventricle to surface w/o temporal lobe | 291 | 8.8 | 21.6 |
| Telencephalon, Lateral Ventricle to surface with temporal lobe | 99 | 3.0 | 7.4 |
| Diencephalon only | 382 | 11.6 | 28.4 |
| Diencephalon and Telencephalon w/o temporal lobe | 63 | 1.9 | 4.7 |
| Diencephalon and Telencephalon with temporal lobe | 56 | 1.7 | 4.2 |
| Optic nerve only | 48 | 1.5 | 3.6 |
| Optic nerve with diencephalon | 65 | 2.0 | 4.8 |
| Optic nerve, diencephalon and telencephalon | 14 | 0.4 | 1.0 |
| Pituitary only | 15 | 0.5 | 1.1 |
| Pituitary and Diencephalon | 87 | 2.6 | 6.5 |
| Pituitary, Diencephalon and Telencephalon | 12 | 0.4 | 0.9 |
| | | | % infratentorial |
| *Infratentorial* | 1423 | 43.2 | 100.0 |
| Posterior Fossa, nos | 19 | 0.6 | 1.3 |
| Cerebellum alone | 710 | 21.6 | 49.9 |
| Brainstem alone | 180 | 5.5 | 12.7 |
| Cerebellum and brainstem | 514 | 15.6 | 36.1 |
| *Spinal* | 160 | 4.9 | |
| B. Multiple compartments | | | |
| Supratentorial and infratentorial | 99 | 3.0 | |
| Infratentorial and spinal | 199 | 6.1 | |
| Supratentorial, infratentorial, and spinal | 32 | 1.0 | |
| (Pituitary, involved) | (20) | (0.6) | |
| (Pituitary, not involved) | (12) | (0.4) | |
| C. Brain, nos | 31 | 0.9 | |
| Total | 3291 | | |

*Table 4.* The proportion of children in each age group whose tumors were located in each compartment with percent male

| Age category | Compartment | | |
|---|---|---|---|
| | Supratentorial (Male) | Infratentorial (Male) | Spinal (Male) |
| < 1 Year | 54 (53) | 39 (53) | 4 (56) |
| 1 Year | 32 (48) | 63 (57) | 5 (43) |
| 2 – 5 Years | 34 (49) | 61 (58) | 4 (44) |
| 6 – 10 Years | 41 (52) | 54 (54) | 4 (48) |
| 11 – 13 Years | 50 (59) | 42 (54) | 7 (52) |
| 14 + Years | 55 (50) | 36 (63) | 9 (43) |

*Rows do not always total 100% since not all locations were specified.

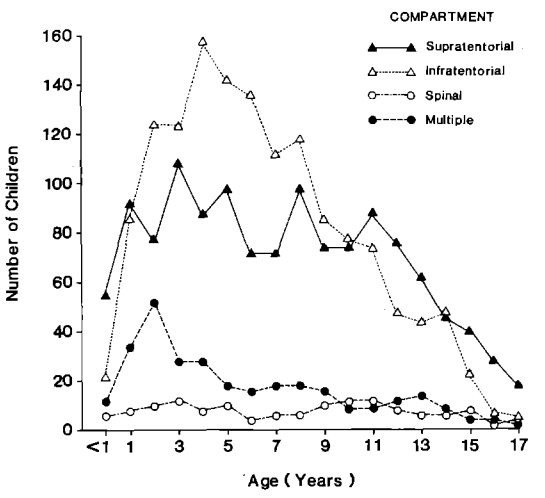


*Fig. 1.* The distributions by age and compartment of the children in the Childhood Brain Tumor Consortium.

ble 4). A male preponderance was present at all ages for infratentorial tumors; during the first and from the seventh year through adolescence for supretentorial tumors; and during the first and from the eleventh year through adolescence for spinal tumors.

### *World Health Organization (WHO) diagnoses and compartments*

Each individual WHO diagnoses was made in less than 10% of children with the two exceptions of pilocytic astrocytoma (18.9%) and medulloblastoma (17.2%) (Table 5). The next most frequent WHO diagnoses, ependymoma, was assigned to 8.3% of children. When the frequencies of WHO diagnoses are examined as proportions of tumors in each com-

*Table 5.* Diagnoses of 3291 tumors and their distributions across anatomic compartments

| Diagnosis | Overall | | Proportion *in* each compartment* (% *within* compartment) | | |
|---|---|---|---|---|---|
| | N | % of all tumors | Supratentorial | Infratentorial | Spinal |
| Astrocytoma, nos | 153 | 4.7 | 35.9 (3.7) | 50.4 (3.7) | 9.4 (9.6) |
| Fibrillary Astrocytoma | 214 | 6.5 | 57.1 (8.9) | 35.0 (3.8) | 5.1 (7.8) |
| Protoplasmic Astrocytoma | 80 | 2.4 | 31.4 (1.9) | 57.1 (2.5) | 7.1 (4.4) |
| Gemistocytic Astrocytoma | 2 | 0.1 | 100.0 (0.1) | 0.0 (0.0) | 0.0 (0.0) |
| Pilocytic Astrocytoma | 622 | 18.9 | 22.5 (12.2) | 74.0 (28.3) | 2.4 (13.0) |
| Subependymal Giant Cell Astrocytoma | 31 | 0.9 | 93.6 (2.6) | 0.0 (0.0) | 0.0 (0.0) |
| Anaplastic Astrocytoma | 194 | 5.9 | 74.0 (12.5) | 19.8 (2.4) | 3.7 (6.1) |
| Glioblastoma | 11 | 0.3 | 70.0 (0.6) | 20.0 (0.1) | 0.0 (0.0) |
| Giant Cell Glioblastoma | 18 | 0.6 | 88.9 (1.4) | 0.0 (0.0) | 0.0 (0.0) |
| Oligodendroglioma | 40 | 1.2 | 71.8 (2.5) | 20.5 (0.5) | 2.6 (0.9) |
| Mixed Oligo-astrocytoma | 29 | 0.9 | 82.8 (2.1) | 10.3 (0.2) | 0.0 (0.0) |
| Anaplastic Oligodendroglioma | 4 | 0.1 | 100.0 (0.4) | 0.0 (0.0) | 0.0 (0.0) |
| Ependymoma | 273 | 8.3 | 21.1 (5.0) | 71.9 (12.0) | 3.0 (7.0) |
| Myxopapillary Ependymoma | 13 | 0.4 | 0.0 (0.0) | 7.7 (0.1) | 92.3 (10.0) |
| Papillary Ependymoma | 11 | 0.3 | 30.0 (0.3) | 40.0 (0.3) | 30.0 (2.6) |
| Subependymoma | 6 | 0.2 | 0.0 (0.0) | 100.0 (0.4) | 0.0 (0.0) |
| Anaplastic Ependymoma | 57 | 1.7 | 48.2 (2.3) | 50.0 (1.7) | 0.0 (0.0) |
| Choroid Plexus Papilloma | 60 | 1.8 | 75.0 (4.0) | 15.0 (0.6) | 1.7 (0.9) |
| Anaplastic Choroid Plexus Papilloma | 6 | 0.2 | 66.7 (0.4) | 16.7 (0.1) | 0.0 (0.0) |
| Gangliocytoma | 1 | 0.0 | 0.0 (0.0) | 100.0 (0.1) | 0.0 (0.0) |
| Ganglioglioma | 36 | 1.1 | 82.9 (2.6) | 5.7 (0.1) | 11.4 (3.5) |
| Ganglioneuroblastoma | 2 | 0.1 | 50.0 (0.1) | 0.0 (0.0) | 0.0 (0.0) |
| Neuroblastoma | 7 | 0.2 | 85.7 (0.5) | 14.3 (0.1) | 0.0 (0.0) |
| Medulloblastoma | 565 | 17.2 | 4.1 (2.0) | 93.7 (32.4) | 0.9 (4.4) |
| Desmoplastic Medulloblastoma | 93 | 2.8 | 1.1 (0.1) | 93.6 (5.4) | 3.2 (2.6) |
| Medulloepithelioma | 3 | 0.1 | 66.7 (0.2) | 33.3 (0.1) | 0.0 (0.0) |
| Pineocytoma | 9 | 0.3 | 33.3 (0.2) | 33.3 (0.1) | 16.7 (0.9) |

*Table 5.* Continued

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pineoblastoma | 25 | 0.8 | 31.8 | (0.6) | 50.0 | (0.7) | 9.1 | (1.7) |
| Germinoma | 44 | 1.3 | 84.1 | (3.3) | 6.8 | (0.2) | 0.0 | (0.0) |
| Embryonal Carcinoma | 11 | 0.3 | 72.7 | (0.7) | 0.0 | (0.0) | 0.0 | (0.0) |
| Choriocarcinoma | 2 | 0.1 | 50.0 | (0.1) | 50.0 | (0.1) | 0.0 | (0.0) |
| Teratoma | 20 | 0.6 | 70.0 | (1.2) | 10.0 | (0.1) | 5.0 | (0.9) |
| Neurilemmoma | 24 | 0.7 | 13.0 | (0.3) | 39.1 | (0.6) | 47.8 | (9.6) |
| Neurofibroma | 3 | 0.1 | 0.0 | (0.0) | 0.0 | (0.0) | 33.3 | (0.9) |
| Anaplastic Neurofibroma | 1 | 0.0 | 0.0 | (0.0) | 0.0 | (0.0) | 100.0 | (0.9) |
| Meningioma, nos | 25 | 0.8 | 85.0 | (1.5) | 10.0 | (0.1) | 0.0 | (0.0) |
| Meningotheliomatous Meningioma | 2 | 0.1 | 100.0 | (0.1) | 0.0 | (0.0) | 0.0 | (0.0) |
| Fibroblastic Meningioma | 3 | 0.1 | 100.0 | (0.1) | 0.0 | (0.0) | 0.0 | (0.0) |
| Transitional (Mixed) Meningioma | 8 | 0.2 | 75.0 | (0.5) | 0.0 | (0.0) | 0.0 | (0.0) |
| Psammomatous Meningioma | 4 | 0.1 | 33.3 | (0.1) | 0.0 | (0.0) | 66.7 | (1.7) |
| Haemangiopericytic Meningioma | 4 | 0.1 | 25.0 | (0.1) | 25.0 | (0.1) | 50.0 | (1.7) |
| Primary Lymphoma | 3 | 0.1 | 66.7 | (0.2) | 33.3 | (0.1) | 0.0 | (0.0) |
| Haemangioblastoma | 6 | 0.2 | 0.0 | (0.0) | 100.0 | (0.4) | 0.0 | (0.0) |
| Craniopharyngioma | 225 | 6.8 | 74.1 | (14.9) | 11.4 | (1.6) | 0.0 | (0.0) |
| Epidermoid Cyst | 9 | 0.3 | 50.0 | (0.4) | 20.0 | (0.1) | 20.0 | (1.7) |
| Dermoid Cyst | 1 | 0.0 | 100.0 | (0.1) | 0.0 | (0.0) | 0.0 | (0.0) |
| Colloid Cyst | 2 | 0.1 | 100.0 | (0.2) | 0.0 | (0.0) | 0.0 | (0.0) |
| Vascular Malformation | 2 | 0.1 | 0.0 | (0.0) | 0.0 | (0.0) | 100.0 | (0.9) |
| Pituitary Adenoma | 8 | 0.2 | 100.0 | (0.7) | 0.0 | (0.0) | 0.0 | (0.0) |
| Chondrosarcoma | 1 | 0.0 | 0.0 | (0.0) | 0.0 | (0.0) | 100.0 | (0.9) |
| Unclassified or unknown | 230 | 7.0 | 73.3 | (8.5) | 16.8 | (1.4) | 4.6 | (5.2) |
| Disagreement between slide reviewers | 88 | 2.7 | | | | | | |

* column or row % may sum to less than 100% or appear inconsistent because some tumors involved multiple compartments, did not have location information, or fell into the last two categories in the table.

[a] the following WHO categories were not present in this group: Anaplastic Gangliocytoma, Anaplastic Ganglioglioma, Angiomatous Meningioma, Anaplastic Neurilemmoma, Astroblastoma, Chondroma, Chordoma, Choristoma (Pituicytoma, Granular Cell), Enterogenous Cyst, Esthesioneuroblastoma, Fibroxanthoma, Gliomatosis Cerebri, Glomus Jugulare Tumor, Haemangioblastic Meningioma, Medullomyoblastoma, Melanoma, Meningeal Melanomatosis, Metastatic, Mixed Glioblastoma and Sarcoma, Monstrocellular Sarcoma, Pituitary Adenocarcinoma, Primitive Polar Spongioblastoma, Xanthosarcoma.

*Table 6.* World Health Organization diagnosis, percent males

| Diagnosis* | Compartment | | | |
|---|---|---|---|---|
| | Overall % | Supratentorial % | Infratentorial % | Spinal % |
| Neurilemmoma | 65 | 100 | 56 | 64 |
| Medulloblastoma | 63 | 43 | 64 | 33 |
| Choroid Plexus Papilloma | 60 | 58 | 64 | 100 |
| Germinoma | 60 | 59 | 75 | – |
| Oligodendroglioma | 60 | 61 | 45 | 100 |
| Pineoblastoma | 59 | 67 | 54 | 33 |
| Ependymoma | 57 | 50 | 60 | 50 |
| Teratoma | 57 | 63 | 50 | – |
| Ganglioglioma | 55 | 53 | 67 | 60 |
| Astrocytoma, nos | 53 | 54 | 51 | 55 |
| Protoplasmic Astrocytoma | 51 | 46 | 54 | 60 |
| Fibrillary Astrocytoma | 50 | 51 | 47 | 44 |
| Unclassified | 50 | 52 | 54 | – |
| Pilocytic Astrocytoma | 49 | 46 | 49 | 53 |
| Craniopharyngioma | 48 | 48 | 52 | – |

* = ≥20 cases.

partment, craniopharyngioma is the most commonly occurring supratentorial tumor (14.9%) with anaplastic astrocytoma at 12.5% and pilocytic astrocytoma at 12.2% closely behind. Two WHO diagnoses accounted for 60.7% of all infratentorial tumors: medulloblastoma (32.4%) and pilocytic astrocytoma (28.3%). The most common spinal compartment tumors were pilocytic astrocytoma (13.0%) myxopapillary ependymoma (10%) and neurilemmoma (9.6%).

*Gender, WHO diagnoses and location*

Some tumors exhibit a high (i.e., 59+%) male sex proportion (Table 6). These include: neurilemmoma, medulloblastoma (infratentorially, particularly), oligodendroglioma, choroid plexus papilloma, and germinoma. A less prominent (55–59%) male sex predominance was seen with pineoblastoma, ependymoma, teratoma, and ganglioglioma. Marked discrepancies, however, appear in sex proportions when tumors are grouped by traditional compartments. Choroid plexus papilloma, neurilemmoma, and germinoma are the only three that occur more commonly in males regardless of whether the tumors are above or below the tentorium in contrast to medulloblastoma. No tumor consistently occurred in all compartments more commonly in girls.

*WHO diagnosis versus age (Table 7)*

Choroid plexus papilloma is dramatically a lesion of early life. Pineoblastoma occurs with increased frequency below the age of two years as do unclassified tumors. Ependymoma and medulloblastoma occur early in life while oligodendroglioma and the astrocytomas are largely tumors of the middle childhood years. Germinoma and glioblastoma, on the other hand, are tumors of late childhood years. Meningioma, although rare, occurs throughout childhood.

## Discussion

Previous childhood brain tumor databases have been subject to the biases of case collections obtained from single institutions as pointed out by Gjerris [24, 25]; studies of single tumor types (e.g.,

*Table 7.* Age distribution (years) of children with selected WHO diagnoses (% all compartments)

| | <1 | 1 | 2–5 | 6–10 | 11–13 | 14+ |
|---|---|---|---|---|---|---|
| Astrocytoma, nos | 5 | 8 | 25 | 33 | 16 | 13 |
| Fibrillary Astrocytoma | 5 | 6 | 36 | 29 | 17 | 7 |
| Protoplasmic Astrocytoma | 7 | 4 | 43 | 34 | 9 | 3 |
| Pilocytic Astrocytoma | 3 | 6 | 39 | 35 | 13 | 5 |
| Ganglioglioma | 11 | 3 | 5 | 42 | 13 | 26 |
| Glioblastoma | 0 | 0 | 17 | 34 | 28 | 21 |
| Oligodendroglioma | 7 | 3 | 28 | 28 | 18 | 17 |
| Medulloblastoma | 7 | 8 | 40 | 33 | 9 | 3 |
| Ependymoma | 6 | 16 | 40 | 24 | 9 | 5 |
| Choroid Plexus Papilloma | 43 | 18 | 20 | 12 | 6 | 0 |
| Pineoblastoma | 7 | 31 | 28 | 21 | 14 | 0 |
| Germinoma | 2 | 4 | 7 | 38 | 42 | 7 |
| Teratoma | 29 | 0 | 24 | 19 | 29 | 0 |
| Neurilemmoma | 13 | 4 | 0 | 35 | 17 | 30 |
| Neurofibroma | 0 | 0 | 0 | 50 | 25 | 25 |
| Meningioma | 16 | 11 | 11 | 29 | 26 | 8 |
| Craniopharyngioma | 1 | 2 | 27 | 43 | 16 | 10 |
| Unclassified tumor | 14 | 17 | 35 | 20 | 10 | 3 |

astrocytoma at one institution); diagnoses provided by numerous pathologists who, because of the relative infrequency of these tumors, are not likely to have had much experience with these diseases (e.g., reference 26); or are case collections in which both autopsy and surgical cases are intermingled [27]. Unfortunately, inconsistent histologic definitions of brain tumors have adversely affected epidemiologic studies [28] and also have resulted in different neuropathologic judgments about tumor diagnoses (compare 29 and 30). When combined with discrepancies in descriptions of location, these limitations make comparisons among reports difficult, can distort estimates of prognosis, and have led to a demand for a large consistent childhood brain tumor database [31]. Our CBTC database of 3291 children with all available brain tumors from ten North American Institutions analysed by a circumscribed group of pathologists and record librarians is less subject to these limitations.

### *Tumor location*

The location of a tumor within the brain has considerable bearing upon prognosis. Further, the biology and evolution of histologically similar neoplastic processes may not be identical at different sites. A preponderance of infratentorial tumors in children was recognized by the end of the last century [2] and most early estimates remained at over 60% [5, 6, 9, 32], with one exception [33]. More recent assessments have been lower, ranging from 50–59% [1, 15, 16, 27] (Table 8). Some of the variation in the early estimates can be accounted for on the basis of different proportions of children and infants; relatively small numbers of children in the tabulations; and differing definitions of the end of adolescence. However, the variation in the more recent estimates is puzzling as each estimate is based on a much larger population. Unfortunately, these recent reports may not be mutually exclusive. For instance, an unknown proportion of the sample of Koos and Miller [1] apparently was included in the report of Jellinger and Machacek [16]. Similarly the samples of Schoenberg *et al.* [26] and Farwell *et al.* [27] are both from the Connecticut tumor registry. Yates *et al.* [15] describe many children who are included in the CBTC sample. Of all tumors in the CBTC database, 49% were found in the posterior fossa or in the posterior fossa and spinal compartment (Table 3), a figure smaller than that cited in other reports except for one [33].

A second major problem with prior reports is their failure to recognize that childhood tumors often involve more than one anatomic compartment or site, with the exception of one report that 3% are both supratentorial and infratentorial in location [16], similar to that in the CBTC material. Cerebellum and brainstem are often spoken of as separate sites of brain tumor and conjoint involvement has been

*Table 8.* Central nervous system tumor locations in children (%)

| | Koos & Miller* | Farwell *et al.* | Gjerris *et al.* | Yates *et al.** | Jellinger & Machacek | CBTC |
|---|---|---|---|---|---|---|
| Supratentorial (midline) | 50.0 | 36.1 | 41.1 | 40.8 | 44.7 | 40.9 |
| | (22.0) | (13.5) | (18.6) | - | (17.3) | (26.2) |
| Multiple compartments | - | - | - | - | 3.0 | 3.0 |
| Infratentorial | 50.0 | 59.4 | 59.0 | 52.4 | 52.3 | 43.2 |
| (cerebellum) | (30.7) | (45.3) | (47.3) | (35.0) | (39.9) | (21.6) |
| (brainstem) | (6.6) | (14.1) | (11.6) | (7.8) | (12.5) | (5.5) |
| (cerebellum and brainstem) | - | - | - | - | - | (15.6) |
| Infratentorial & spinal cord | - | - | - | - | - | 6.1 |
| Spinal cord | - | 4.3 | - | - | - | 4.9 |
| N | *700* | *488* | *533* | *689* | *803* | *3291* |
| Reference # | (1) | (27) | (24) | (15) | (16) | |

*possibly included in another subsequent tabulation, i.e., not necessarily a different population.

virtually ignored in discussions of childhood brain tumors. However, in our experience, 15.6% of all brain tumors in children (or 36.1% of all infratentorial tumors) involve both brainstem and cerebellum at the time of first operation. In a separate report we indicate that children with tumors confined to one compartment have different demographic characteristics and survival than those whose tumor involves multiple compartments [34].

Only two tabulations identify the spinal compartment when considering central nervous system tumors [15, 27]. Two important points are apparent in our data. First, about 5% of central nervous system tumors in children are located in the spinal compartment. Second, an additional 6% of tumors are located both above and below the foramen magnum at the time of first operation. Thus, the spinal compartment is involved in about 11% of all childhood central nervous system tumors.

*Age, gender, and location*

Relationships among age, gender, tumor, and anatomic site have been recognized for the last half century. Ammon in 1932 noted that after the age of 10, the proportion of supratentorial tumors rose rapidly until the age of 15 when they were equal to the proportion of infratentorial tumors [35]. Globus, *et al.* [32], using a relatively small database, added the observations that a supratentorial location predominated in infants up to 1 year, the proportion of supra and infratentorial tumors equalized around 2 years of age and an infratentorial location predominated from 3 to 16 years of age. Our large database confirms and sharpens these observations (Table 4 and Fig. 1). From the second through the fifth year, tumors were located infratentorially by almost a 2:1 margin. After the 6th year, this wide discrepancy diminished until the 10th year and, during adolescence the supratentorial compartment increased in importance. The proportion of tumors limited to the spinal compartment did not change much throughout childhood and adolescence. In the CBTC material, male predominance in infratentorial tumors confirms many prior observations (e.g., 25), but adds the observation that this is most marked during the childhood years of 2 through 6 (Table 4).

*Tumor diagnoses*

Accuracy and reliability of diagnostic categories are of the greatest significance to children with these tumors and necessary to provide unambiguous estimates of prognosis. The importance of the neuropathologist's diagnosis and classification to the therapy for each child with a brain tumor raises three questions. 1) Have neuropathologists provided us with a classification that is reliably reproduced and transmitted to others? 2) Is the classification based upon clearly defined criteria for each diagnostic category? 3) Is the classification based on neuroanatomic location as well as histology of the neoplasm?

The first question cannot be answered fully since neuropathologists have never systematically studied and reported their reliability in assigning tumors to diagnostic categories. Some WHO diagnostic categories are more reliably reproduced than others [36]. Moreover, reliability of recognition of the histologic features upon which these diagnoses rest also varies [37]. The wide variation in proportions of individual tumor diagnoses among various institutions as well as in the Connecticut Tumor Registry (Tables 8, 9) implies that brain tumor classifications have not been uniformly applied by neuropathologists and may explain the discrepancies among and within the larger published series of childhood brain tumors. The third question about the relationship of neuroanatomic location and tumor histology has never been explored in detail. It appears that some histologically similar neoplastic processes evolve quite differently in differing neuroanatomic locations (CBTC, in preparation).

The value of a diagnostic classification lies in its ability to summarize and transmit information, and therefore to assist in the design of individual therapies. The advent of the Bailey-Cushing scheme [38] in 1926 (and its modern codification [30]) offered the promise of a unifying classification for all brain tumors that would satisfy these goals. If it had succeeded then one would have expected similar proportions in the various tabulations of childhood brain tumors offered since its inception.

*Table 9.* Distribution of childhood brain tumors

| Author | Year | Proportion of all brain tumors tabulated | | Proportion of neuroepithelial tumors | | | |
|---|---|---|---|---|---|---|---|
| | | Cranio-pharyngioma | Neuro-epithelial | Astroglial (nonglioblastoma) | Glioblastoma | Medullo-blastoma | Ependymal |
| Cushing [5] | 1927 | ? | 75.3 | 34.5 | 6.0 | 20.7 | 5.2 |
| Craig *et al.* [9] | 1949 | 5.4 | 74.2 | 49.8 | 9.4 | 27.1 | 19.9 |
| Matson* [13] | 1969 | 9.1 | 81.5 | 50.3 | 10.5 | 22.7 | 10.8 |
| Koos & Miller* [1] | 1971 | 8.7 | 71.6 | 46.7 | 6.7 | 25.1 | 12.8 |
| Schoenberg *et al.** [26] | 1976 | 5.6 | 76.8 | 26.8 | 26.4 | 31.5 | 8.5 |
| Farwell *et al.* [27] | 1977 | 8.6 | 75.6 | 42.8 | 10.8 | 31.7 | 11.9 |
| Gjerris *et al.* [24] | 1978 | 4.9 | 73.7 | 48.3 | 0.8 | 22.4 | 17.6 |
| Yates *et al.** [15] | 1979 | 6.0 | 78.5 | 58.4 | 5.0 | 20.7 | 16.3 |
| Jellinger & Machacek [16] | 1982 | 6.2 | 76.7 | 47.4 | 4.1 | 27.6 | 12.7 |
| CBTC | 1987 | 6.8 | 77.8 | 43.0 | 8.7 | 25.7 | 13.8 |

*see Table 8.

Over the last half century the proportion of neuroepithelial childhood brain tumors has remained remarkably constant at approximately three-fourths in various tabulations (Table 9). The craniopharyngioma, a nonneuroepithelial tumor, has also remained proportionally quite constant. Cushing's figure of 13.6% included all congenital tumors and we have no way of knowing the exact number of craniopharyngiomas in his series [5]. Matson's figure of 9.1% probably reflects the large number of children with this tumor referred to him for removal [13]. The 3% difference in the two reports from the same population based registry in Connecticut is likely due to different pathologic interpretations [26, 27].

However, subclassification of the neuroepithelial tumors into aggressive or less aggressive neoplasms is far less consistent among these studies (Table 9). Medulloblastoma, a tumor defined by its dense cellularity, varies widely from a fifth to almost a third of neuroepithelial tumors. Ependymal tumors, defined by the specific morphologic structure of the perivascular pseudorosette [38], range from 5.2% in Cushing's series [85] to 19.9% in Craig *et al.* [9]. Astroglial tumors (not glioblastoma) range even more widely from 26.8% to 58.4% of neuroepithelial tumors.

The range for specifically named glioblastomas from 0.8% (or 2.4% if 'most malignant not classified gliomas' are included) in the Danish series [24] to 26.4% in one report from the Connecticut Tumor Registry [26] is disquieting. Even more bothersome are the discrepancies in the proportions of glioblastomas and astrogliomas in the two reports from the Connecticut Tumor Registry [26, 27]. They exemplify our concern about differing diagnostic criteria for the common brain tumors since the therapies and survivals associated with these two diagnoses are so very different. Both reports rely upon the same population-based registry of all brain tumors, one for the years 1935–1964 (containing 380 children) and the other for the years 1935–1973 (containing 488 children but also including spinal cord tumors). The first report used the already recorded diagnoses while the authors of the second report reviewed the microscopic slides and reclassified an unknown number of cases. The discrepancies between the proportions of astroglial tumors and glioblastomas become less marked if these two categories are combined. Unfortunately, there is insufficient information in all of these reports to make similar comparisons for more than a few of the other subclasses of the astroglial tumors.

Wide discrepancies in location and in histologic typing among various reports were pointed out by Gjerris and his group [24, 25], specifically the different neuropathologic judgments found in Zülch [29] and Russell and Rubinstein [30]. The many, and

sometimes conflicting, histologic definitions were decried by Behrend as interfering with epidemiologic studies [28]. Bailey recognized the reason for these problems in classification in 1927: '... no two gliomas are alike. The gliomas do not fall into distinct groups in which all the members look alike, but consist of variant individuals with certain family resemblances. To find a typical member of each family with which the others may be recognized on comparison is about as difficult as to find a typical member of the Alpine or Dinaric races [39]'.

The distribution of tumor types differs within each compartment. The great majority of posterior fossa tumors are medulloblastomas, pilocytic astrocytomas, and ependymomas. In the supratentorial compartment, by contrast, no single group stands out and a much larger proportion of tumors are unclassified. The astrocytomas together and the craniopharyngiomas account for the majority of these supratentorial neoplastic processes. However an unusual 11% of craniopharyngiomas presented in the posterior fossa. When classified purely on a histologic basis, surprising proportions of neuroblastomas, medulloblastomas, and pineocytomas appeared in compartments not usually associated with these tumors. Since the cases were obtained from ten North American pediatric centers the distribution of diagnostic categories should be reasonably representative of children in North America even though we found considerable variation from center to center.

*Gender, age and diagnosis*

Cushing recognized that a large proportion of children with medulloblastoma were male [5], although this has been both confirmed [15, 32] and denied [26]. Ependymoma occurs more often in males [15, 32] as does the pinealoma [32]. Koos and Miller [1] confirmed these findings and added the observations that astrocytoma in general, spongioblastoma, glioblastoma, oligodendroglioma, and choroid plexus papillomas tended to occur in male children. These observations are largely confirmed in the database of the CBTC (Table 6). In addition, germinoma, ganglioglioma, and teratoma also tend to be tumors of males. Medulloblastoma is strongly male predominant if located infratentorially, but female predominant supratentorially. Protoplasmic and pilocytic (but not fibrillary) astrocytomas are more likely to occur in male children if located infratentorially. Glioblastomas are largely supratentorial tumors of males, but the sex proportions of the remaining astrocytomas are about the same in the three locations. Oligodendrogliomas exhibit a marked male predominance above the tentorium, but not infratentorially, while the ependymoma and choroid plexus papilloma are the reverse. Craniopharyngiomas exhibit no significant male predominance in contrast to the tabulations of Koos and Miller [1] and Yates *et al.* [15].

To paraphrase Harvey Cushing in his 1931 paper [40] on cerebellar astrocytomas, we have completed the tedious process of getting the main facts from a large series of cases in tabular order which is essential for a study of the present type. It will not only show where and how progress has been made but also will bring 'to light the more notable deviations from what proves, on the basis of averages, to represent the common type'. We anticipate a large number of additional insights into the biology and prognosis of brain tumors in children in the subsequent studies from this database.

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