ORIGINAL ARTICLE

Population-based Study of Medulloblastoma: Outcomes in Alberta from 1975 to 1996

Gloria Roldán, Penny Brasher, Giacomo Vecil, Donna Senger, Barry Rewcastle, Gregory Cairncross, Peter Forsyth, Mark Hamilton*

ABSTRACT: ***Background:*** The purpose of this study was to determine incidence, survival rate, and prognostic factors as well as the frequency of Collins' Law Violators (CLVs) in an unselected population of medulloblastoma patients. Collins' Law dictates that 'cure' of a child with a tumor occurs after a period that includes the child's age at diagnosis plus 9 months. ***Methods:*** Using the Alberta Cancer Registry a population-based review identified 49 patients with medulloblastoma (19 adults, 30 children) diagnosed from 1975-96. Pathology was reviewed in all cases. All patients had surgical resection, followed by radiotherapy in 47 patients and chemotherapy in 17. ***Results:*** The overall 5-year survival was 50%. There was a trend for the extent of resection to be associated with a longer survival (Long rank test, p< 0.06) but this was not significant. Tumor recurrence occurred a median of 22.4 months (range, 6.4-192.3) after diagnosis and median survival after recurrence was 9.3 months (range, 0.4-64.9). The survival curve did not appear to plateau but was affected by tumor-related deaths in 3 (21.4%) of the 21 long-term survivors diagnosed in childhood. These three patients had recurrences a mean of 11.7 years after diagnosis and are designated as CLVs. ***Conclusions:*** The survival rate in an unselected population of patients with medulloblastoma is poor. Aggressive resection of the tumors prolongs survival. The Collins' Law Violators were relatively common and we suggest this concept be abandoned in medulloblastoma.

RÉSUMÉ: Étude de population sur le médulloblastome en Alberta de 1975 à 1996. ***Contexte :*** Le but de cette étude était d'évaluer l'incidence, le taux de survie et les facteurs influençant le pronostic ainsi que la fréquence des contrevenants à la loi de Collins dans une population non sélectionnée de patients atteints de médulloblastome. Selon la loi de Collins, un enfant atteint d'une tumeur est guéri après un temps défini par l'âge de l'enfant au moment du diagnostic plus 9 mois. ***Méthodes :*** Nous avons identifié 49 patients atteints de médulloblastome (19 adultes et 30 enfants) dans le Alberta Cancer Registry, entre 1975 et 1996. L'anatomopathologie a été révisée dans tous les cas. Tous les patients avaient subi une résection chirurgicale suivie de radiothérapie chez 47 patients et de chimiothérapie chez 17 patients. ***Résultats :*** La survie globale à 5 ans était de 50%. La longueur de la survie avait tendance à être associée à l'étendue de la chirurgie, sans atteindre le seuil de la signification statistique (Long rank test, p < 0,06). La médiane de survie sans récidive était de 22,4 mois (écart de 6,4 à 192,3 mois) après le diagnostic et la survie médiane après la récidive était de 9,3 mois (écart de 0,4 à 64,9 mois). La courbe de suivie ne semblait pas atteindre de plateau et elle était influencée par le décès dû à la tumeur chez 3 des 21 survivants à long terme dont le diagnostic avait été posé dans l'enfance. La moyenne de survie sans récidive chez ces 3 patients était de 11,7 ans après le diagnostic et donc ils sont des contrevenants à la loi de Collins. ***Conclusions :*** Le taux de survie dans une population non sélectionnée de patients atteints de médulloblastome est faible. Une résection agressive de la tumeur prolonge la survie. Les contrevenants à la loi de Collins étaient relativement fréquents et nous proposons que ce concept soit abandonné en ce qui concerne le médulloblastome.

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Medulloblastoma is the most common malignant brain tumor of the central nervous system (CNS) in children, accounting for approximately 20% of all pediatric brain tumors.[1,2] It is comparatively rare in adults, with a reported incidence rate of 0.05/100,000 per year, accounting for 1% of all primary tumors of the CNS.[3,4] There are few reported studies concerning adults and when reported, adults constitute a small part of the study group.[5-7] Previous studies of outcomes in medulloblastoma patients are based on case series or institutional experiences which were limited by referral and selection biases.[8,9] To our knowledge, there are no population-based studies of children and

From the Department of Clinical Neurosciences (GR, DS, BR, GC, PF, MH), Department of Anatomic Pathology (BR), Division of Neurosurgery (MH), Foothills Medical Centre, University of Calgary; Department of Oncology (GR, PB, DS, GC, PF), Clark Smith Integrated Brain Tumor Cancer Centre (GR, GC, PF, MH), Division of Population Health and Information (PB), Heritage Medical Research Building, Calgary, Alberta, Canada; Department of Neurosurgery (GV), University of Texas, Health Science Center, San Antonio, Texas, USA.

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Corresponding Author:* Peter Forsyth, Clark Smith Brain Tumor Center, Rm. 2AA19 Health Research Innovation Center, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1, Canada.

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adults with medulloblastoma in which the histologic sections were reviewed by a single neuropathologist.

Over the past several decades the survival for medulloblastoma in children has improved significantly. The overall survival rate in children with average and high risk medulloblastoma after surgery, cerebrospinal irradiation and adjuvant chemotherapy is approximately 85% and 70% at five years, respectively.[10,11] Taking into account the side effects of radiotherapy in the neurodevelopment of children, systemic treatment has been evaluated to delay the indication of radiotherapy in small children, or even as an intent to avoid it.[12-15]

In 1955, Collins made the observation that tumor recurrence in children with Wilms' tumor usually occurred within a period of the child's age plus nine months.[16] After that time children were considered cured of the tumor. This concept of a "period of risk" for recurrence was later applied to a variety of tumors in children and became known as Collins' Law.[17] This law has been a successful predictor of survival for some children with brain tumor and a poor predictor for others.[18-20]

We noted three unexpected issues while treating medulloblastoma patients, which prompted us to undertake this study. First, we encountered a patient (diagnosed as a child) presenting with a recurrence a very long time after the initial diagnosis thus "violating" Collins Law [hence, the designation "Collin's Law Violator" (CLV)]. Second, we were following a larger portion of adults in our practice than has been reported in the literature. Third, the survival rate in our patient population was not as favorable as published reports and "cure" occurred less commonly. Our review identified that there are no studies of outcomes of medulloblastomas in an entire population in which charts and histological sections were re-reviewed to assure the accuracy of the clinical and histological information. For these reasons we undertook this study of outcomes in medulloblastoma patients in an unselected population-based study.

The objectives of this study include the incidence, natural history, clinical, imaging, and pathological characteristics as well as treatment outcomes in an unselected population of medulloblastoma patients. We also wanted to determine how commonly medulloblastoma patients violated the Collins' Law.

Patients and Methods

Case Ascertainment

Patients with diagnosis of medulloblastoma, or primitive neuroectodermal tumor with topographic codes for the cerebellum, brainstem or fourth ventricle (International Classification of Disease for Oncology Version II Topography codes c71.6-c71.7, and morphology codes 94703-94733)[21,22] were identified in the Alberta Cancer Registry. The Alberta Cancer Registry is a population-based cancer registry for the province of Alberta (population 2.8 million in 1996), which was established by an Act of the Provincial Legislature and has been operational since 1941. Endorsing legislation is in place requiring all physicians, hospitals, pathologic laboratories, radiographic facilities and cancer treatment centers to participate in registering all patients with a clinical, radiographic or histologic diagnosis of cancer (including those diagnosed at autopsy).[23] All patients who were residents of Southern Alberta and diagnosed with histologically confirmed medulloblastoma from January 1, 1975 to December 31, 1996 were included in the review. In addition, we also reviewed hospital records and pathology reports from the only three hospitals in Southern Alberta where neurosurgical procedures were performed between April 1, 1991 and December 31, 1996 and we reviewed the minutes from weekly pediatric and adult neuro-oncology rounds. These meetings are multidisciplinary tumor board rounds where new neuro-oncology patients are reviewed. Virtually all brain tumor patients requiring radio-or chemotherapy are presented and the minutes recorded. The adult and pediatric rounds began on January 1, 1994 and September 1, 1992, respectively. We found no new cases of medulloblastoma using these last two methods that were not otherwise identified by the Alberta Cancer Registry. In total, 49 cases were identified during the 21 year study period.

Pathological Characteristics

A single neuropathologist (NBR) reviewed the histologic sections and microscopic characteristics described. All biopsy material was fixed in neutral buffered formalin, embedded in paraffin, and 3-5 micron sections were stained with hematoxylin and eosin. The tumors were classified according to Burger and Schiethauer.[24] In 46 patients, tissue blocks were available for immunohistochemical staining to identify the tumor phenotype. Special stains used included PGP (protein gene product) 9.5, Synaptophysin, Reticulin, and GFAP (glial fibrillary acidic protein).

Staging and Treatment

Pre- and post-operative radiological evaluation consisted of either computed tomography (CT) (46 cases) and/or magnetic resonance imaging (MRI) (11 cases), which were reviewed by neuroradiologists. Two patients did not have postoperative imaging.

The extent of surgical resection of the tumors was determined from a combination of the surgeon's post-operative report (49 cases) and from the postoperative imaging performed within the first five postoperative days (47 cases). Data was extracted from radiology reports in most of our patients; the films were only available for re-review in 15 patients. Gross total resection was defined as that with a postoperative residual tumor < 1.5 cm^2.

The post-operative risk stage of patients were graded as 'good' or 'poor' risk based on the type of surgical procedure performed and evidence of tumor outside the posterior fossa by craniospinal imaging.[25] Good-risk patients were those whose tumor was confined to the primary area and who had undergone a gross total resection. Poor-risk patients were those who underwent subtotal resection of the primary lesion, those who had evidence of tumor dissemination outside of the posterior fossa, or those who did not have a complete evaluation of their spinal axes. The Chang staging system was also used to assess patients in our study.[26]

Incidence Rates and Statistical Analyses

The two endpoints used in this study were overall survival and progression-free survival. The overall survival was estimated by using the date of death or the last date on which the patient was known to be alive. Survival probabilities were calculated by the Kaplan-Meier method.[27] Log-rank statistics[28]

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were used to test the strength of association between overall survival or disease-free survival and a single variable.

Results

Incidence

The crude annual incidence rate of medulloblastoma was 0.216/100,000 for all ages, 0.557/100,000 for children, and 0.094 /100,000 for adults, respectively. This represented 4% of all malignant brain tumors diagnosed during the period.

Patient Characteristics

A total of 49 patients were included in the study and their medical records were reviewed. Their clinical and treatment characteristics are presented in Table 1. Of the 49 patients, 30 (61%) were children (age <16), and 19 patients (39%) were adults (age≥16). In children, 18 (60%) were male and 12 (40%) were female. In adults, 12 (63%) were male and 7 (37%) were female. The mean ages at the diagnosis of medulloblastoma were seven years for children and 29.2 years for adults. The most common symptoms at the time of initial examination were those associated with increased intracranial pressure and cerebellar dysfunction including headache (80%), nausea /vomiting (78%) and ataxia (73%).

Table 1: Clinical and treatment characteristics in medulloblastoma patients

	# Patients Overall (*n*=49)	# Children (Age <16, *n*=30, 61%)	# Adults (Age ≥ 16, *n*=19, 39%)
Age (years)			
Mean	15.5	6.9	29.2
Range	1.1-44.4	1.1-15.8	16.3-44.4
Sex [*n* (%)]			
Male	30 (61%)	18(60%)	12 (63%)
Female	19 (39%)	12(40%)	7 (37%)
Presenting Symptoms [*n* (%)]			
Duration (median, range)	53 (35 to 112)	44 (23 to 90)	75 (49 to 142)
Headache	39 (80%)	23 (77%)	16 (84%)
Nausea and vomiting	38 (78%)	25 (83%)	13 (68%)
Ataxia	36 (73%)	21 (70%)	15 (79%)
Altered consciousness	17 (35%)	16 (53%)	1 (5%)
Chang Staging [*n* (%)]			
T1	7 (14%)	2 (7%)	5 (26%)
T2	15 (31%)	9 (30%)	6 (32%)
T3	21 (43%)	17 (57%)	4 (21%)
Unknown	6 (12%)	2 (7%)	4 (21%)
Post-Operative Status [*n* (%)]			
Good Risk	13 (27%)	6 (20%)	7 (37%)
Poor Risk	32 (65%)	23 (77%)	9 (47%)
Unknown Risk	4 (8%)	1 (3%)	3 (16%)
Treatment [*n* (%)]			
Surgery			
GTR	16 (33%)	7 (23%)	9 (47%)
RSTR	16 (33%)	13 (43%)	3 (16%)
STR	16 (33%)	10 (34%)	6 (31%)
unknown	1 (1%)	0 (0%)	1 (5%)
Radiation Therapy	47 (96%)	28 (93%)	19 (100%)
Chemotherapy	17 (35%)	14 (47%)	3 (16%)
RT, Chemotherapy & Surgery	15 (31%)	12 (40%)	3 (16%)
Shunting			
Yes	22 (45%)	19 (63%)	3 (16%)
No	22 (45%)	8 (27%)	14 (74%)
Unknown	5 (10%)	3 (10%)	2 (10%)

Abbreviations: GTR - gross total resection, RSTR - radical subtotal resection, RT - radiation therapy, STR - subtotal resection.

Imaging Features

Computed tomography scanning was used in 36 patients (73%), both MR imaging and CT scanning were done in 10 patients, and MRI imaging alone was done in one patient. Contrast enhancement was present in the majority of the CT scans (32). Other radiologic features included mass effect, hydrocephalus, calcification, and cystic components. The tumor size was not available because tumor volumes were not routinely recorded. The presence or absence of hydrocephalus was recorded in all patients: 35 patients (71%) had hydrocephalus, 22 patients (45%) underwent insertion of a ventricular peritoneal shunt before undergoing radiation therapy. The 13 other patients with hydrocephalus did not require a shunt after surgical resection.

Histological Features

All 49 cases were confirmed to be medulloblastoma by histological criteria. The predominant pathology consisted of densely packed cells with round-to-oval hyperchromatic nuclei surrounded by scanty cytoplasm. The cells were often arranged in sheets. Rosettes were typically present (55.1%) but were not a constant feature. The majority of the tumors were undifferentiated (67.4%) and small cell (65.3%). Occasionally a large cell variation was found (8.2%). Some of the tumors demonstrated cellular differentiation along glial, nodular (desmoplastic) and neuronal cell lines, while a few showed mixed characteristics. Necrosis was evident in 34/49 (69.4%). In six tumors the necrosis was extensive and another seven demonstrated palisading type of necrosis. Mitoses were seen in 48/49 (98 %) cases.

Treatment Characteristics

All patients underwent surgery: 16 (33%) had a gross total resection, 16 had a radical subtotal resection, 16 had a subtotal resection and the extension of surgery could not be evaluated in one case. Overall, 13 patients (27%) were classified as "good-risk" and 32 (65%) as "poor-risk; 4 patients (8%) were "unknown-risk" because of missing information. According to the Chang staging system there were 7 patients with stage T1 disease, 15 with T2, 21 with T3, and 6 patients were classified as “unknown”.

Forty-seven patients (96%) underwent adjuvant radiation therapy following surgery (adults, n=19, children n=28). In contrast, only 17 patients (35%) received adjuvant chemotherapy; most of these were children. Only 15 patients (31%) had multi-modality treatment consisting of surgery, radiation and chemotherapy. Twenty two patients (45%) had a ventriculo-peritoneal shunt insertion for hydrocephalus; most of these were children.

Recurrence

Twenty-eight (57%) patients had evidence of disease progression, one additional patient died from their disease but information regarding the details of the recurrence was unavailable. Overall, the median time to recurrence was 22.4 months (range; 6.4-192.3). The median survival time following recurrence was only 9.3 months (range; 0.4-64.9). The sites of tumor recurrence (Table 2) were local (29%), spine only (18%),

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Table 2: Features of medulloblastoma patients at tumor recurrence

	# Patients Overall (*n*=28)	# Children (Age <16, *n*=15, 50%)	# Adults (Age ≥ 16, *n*=13, 68%)
Recurrence Time (months)			
Median (n=23)*	22.4	14.5	33.6
Range	6.4-192.3	6.4-192.3	6.8-83.4
Survival Post-Recurrence (months)			
Median (n=23)*	9.3	9.3	10.1
Range	0.4-64.9	0.4-26.0	1.2-64.9
Recurrence Site [*n* (%)]			
Local	8 (29%)	5 (33%)	3 (23%)
Local & spine	3 (11%)	1 (7%)	2 (15%)
Spine	5 (18%)	2 (13%)	3 (23%)
Subfrontal	3 (11%)	2 (13%)	1 (8%)
Brain	1 (3%)	1 (7%)	0 (0%)
Brain & spine	1 (3%)	0 (0%)	1 (8%)
CSF spread	2 (7%)	2 (13%)	0 (0%)
Unknown	5 (18%)	2 (13%)	3 (24%)

Abbreviations: CSF - cerebrospinal fluid, NAD - no active disease
* information not available for 5 patients

local and spine (11%), sub-frontal (11%), CSF cytology (7%). The success of salvage therapy for recurrent disease was poor in our series. Salvage treatments included surgery, further radiotherapy, chemotherapy, or a combination. Three patients with recurrent tumors also received high dose-chemotherapy and autologous stem cell transplantation. Due to the small number of patients and multiple treatment regimens used, it was not possible to show a benefit for any particular therapy.

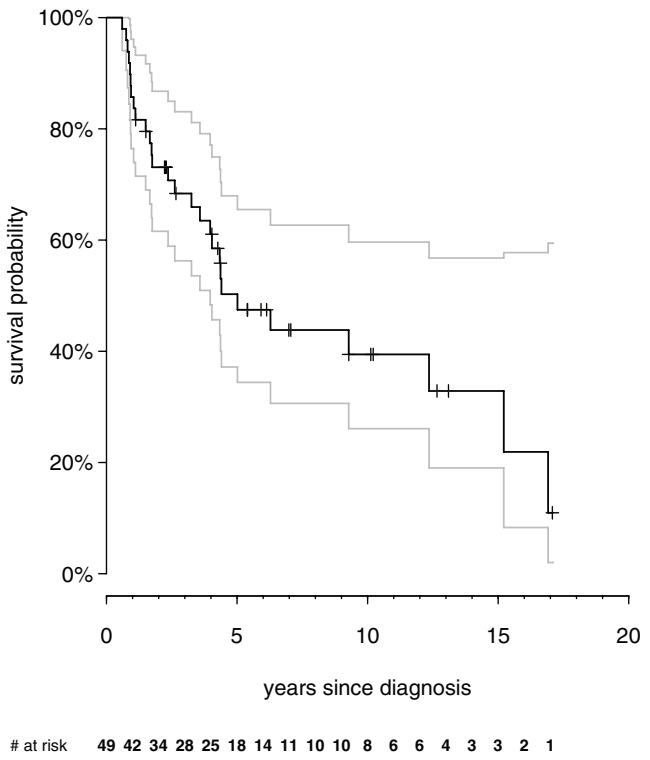

Figure: *Kaplan-Meier survival curve (with 95% confidence intervals) for patients with medulloblastoma diagnosed from 1976 to 1996.*

Survival & Prognostic factors

The five-year actuarial survival rate was 50.3% for entire groups of patients, 55.7% for children and 44.1% for adults (Figure). There was a trend for females to have a longer survival than males (five-year survival rate of 91% versus 19%). Table 3 shows the five-year survival rates according to age, gender, resection, indication of chemotherapy and shunt. These parameters were evaluated for prognostic importance. The only prognostic variable, which only approached statistical significance, was the extent of resection, favoring gross total resection/subtotal resection over less complete resection (p = 0.06, Log Rank Test).

Collin's Law Violators

Three patients (6.1%), all diagnosed as children (10% of <16 years-of-age), developed recurrent tumors following prolonged periods of remission and were considered "Collin's Law Violators" (Table 4). These three patients represented 21.4% of children who were initially thought to be long-term survivors. All patients were male. One patient was classified as good risk, he had a gross total resection of the tumor. The other two were considered poor risk patients, had subtotal tumor resections and both had shunts inserted at first presentation. All three patients had received full craniospinal irradiation with posterior fossa boost; two had adjuvant chemotherapy.

The tumors recurred at 5, 16 and 13 years after their initial diagnosis. Recurrence was either local or limited to the posterior fossa. All of them had repeat surgery. Contrary to our expectations, all patients had recurrent medulloblastomas rather

Table 3: Prognostic variables

	Five Year Survival Estimate (95% CI)	Log Rank Test
All patients (*n* = 49)	50.3% (35.1,65.4)	
Age (years)		
< 16 (*n* = 30)	55.7% (36.4,75.0)	p = 0.26
≥ 16 (*n* = 19)	44.1% (20.6,67.5)	
Gender		
Male (*n* = 30)	47.1% (28.2,65.9)	p = 0.35
Female (*n* = 19)	55.3% (29.4,81.1)	
Resection		
GTR (*n* = 32)	60.5% (44.3,82.5)	p = 0.06
STR/BX/unknown (*n*=17)	35.3% (18.5,67.2)	
Chemotherapy		
Yes (*n* = 17)	61.3% (40.7,92.3)	p = 0.35
No (*n* = 32)	46.2% (31.1,68.6)	
Shunt		
Yes (*n* = 22)	59.9% (41.6,86.2)	p = 0.23
No/unknown (*n* = 27)	42.4% (17.6,65.2)	

Abbreviations: BX - biopsy, GTR - gross total resection, STR - subtotal resection.

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Table 4: Characteristics of Collins' Law Violators

	CLV #1	CLV #2	CLV #3
Initial Features			
Age at diagnosis (years)	1	14	8
Sex	M	M	M
Chang stage - tumor/met	T1/M0	T1/M0	T3A/M0
Good/poor risk	poor	good	poor
Symptom duration (months)	2.0	0.5	2.5
Surgery type	STR	GTR	RSTR
RT field	C-S & PF boost	C-S & PF boost	C-S & PF boost
RT dose in posterior fossa (cGy)	5320	3400	5640
Adjuvant chemotherapy	POG 8633	lomustine	no
Shunt	Yes	no	yes
Recurrence			
Age (delay from onset in years)	6 (5)	31 (16)	21 (13)
Site of recurrence	Local	local	PF
Repeat surgery	STR	biopsy	STR
Repeat radiotherapy	no	no	yes
Chemotherapy	cyclophosphamide	carmustine, vincristine	Stem cell transplant and cisplatin, etoposide, cyclophosphamide
Survival post recurrence (months)	15	11	28

Abbreviations: CLV-Collins Law Violator, C-S-craniospinal, GTR - gross total resection, PF-posterior fossa, RT-radiation therapy, POG-pediatric oncology group, STR-subtotal resection, RSTR-radical subtotal resection.

than radiation-induced neoplasms (eg., sarcoma, [glioblastoma multiforme] GBM and meningiomas). All three patients underwent postoperative chemotherapy, with high dosage chemotherapy and stem cell transplantation in two. The prognosis after recurrence was poor with a median survival of only 15 months with no significant differences between the CLV's and the other non-CLV recurrence patients.

Discussion

We conducted this study to estimate the survival rate, prognostic factors and frequency of CLVs in an unselected, population-based study of patients with medulloblastoma in order to eliminate the selection bias inherent in other case series and institutional reviews. In this study, all histologic and clinical information were reviewed to confirm the accuracy of the data. This is an important issue because histologic diagnoses are often inaccurate in cancer registries. Although our overall incidence of medulloblastomas (0.194/100,000) (population of Alberta in 1996 was 2.8 million) in our population-based study was similar to those reported by others,[29,30] we found a relative higher than expected incidence of medulloblastomas in adults (0.094/100,000). Not surprisingly, the five-year survival rate (50%) in our population-based study was lower than in "single institution" series which found five-year survival rates of 86-93%.[11,15] Our survival rates are similar to other population-based studies that ranged from 36% to 60% at five years.[29,31,32] The most concerning aspect of the survival curves we estimated was that it did not "level off", suggesting patients have a life time risk of tumor recurrence and should not be considered cured. Finally, we did not find Collin's Law to be a useful concept in medulloblastoma patients and suggest it be abandoned.[20,33] The most common cause of a recurrent enhancing mass was recurrent tumor and not radiation-induced necrosis or a radiation-induced neoplasm.

As a retrospective, population-based study spanning 21 years our study has several limitations. First, significant conclusions regarding treatment can't be made since treatment was quite heterogeneous, during this period of time and information regarding some maneuvers is incomplete. For example, the evaluation of extent of resection by neurosurgeons is notoriously inaccurate though other retrospective series have concluded that a gross total resection is associated with favorable survivals.[34,35] In addition, the small size of our study also limits our comments regarding treatment.

Similarly, conclusions regarding other prognostic factors are also limited due to the low statistical power of our study. The power is low because the sample size is small and treatment/staging information is highly variable in retrospective series. For example, we did not detect an effect of gender on survival, as reported by others.[30,36] Nor did we find that tumors arising in the lateral cerebellar hemisphere had a superior prognosis to those arising in the vermis, probably due to the ease of surgical removal in the lateral hemispheres.[37] Definitive conclusions regarding treatment and prognostic factors will await the completion of large prospective clinical trials which include standardized data collection and uniform treatments.

A final limitation of our study is that no molecular analyses were performed as these reagents were not available for paraffin sections when the patients were treated or this study performed. Little is known about the molecular genetic events that lead to the development of medulloblastoma. Mutation in the p53 gene,[38-40] amplification of c-myc[41] and N-myc,[42] upregulation of different PAX genes,[43] and patched[40,44] have all been implicated in the pathogenesis of the tumor. In addition, high levels of expression of TrkC has been associated with a much better prognosis.[45] More recently, with the identification of molecular prognostic factors such as isochromosome 17q[46] and the application of new genomic techniques, the identification of medulloblastoma subgroups that are enriched for specific genetic alterations could be useful in the selection of patients for future clinical trials of molecular targeted therapies.[47]

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