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Original Investigation

Is the Knowledge Pertaining to Adult Glioblastomas Enough for Pediatric Cases? Prognostic Factors in Childhood

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ABSTRACT

AIM: Pediatric glioblastoma (GBM) is still a topic obscurity. The aim of this study was to explore clinical, radiological and pathological features, and prognostic factors affecting the outcomes.

MATERIAL and METHODS: We retrospectively reviewed our database for prognostic factors for 42 consecutive pediatric patients with histologically proven GBM treated in our hospital.

RESULTS: The study reached at 20 boys and 22 girls, with a mean age of 10.2 years. Almost all patients (97.6%) had supratentorial tumors; lobar/hemispheric (68.3%), thalamic (26.8%) and suprasellar-hypothalamic region (4.8%). Total of 11/42 children had seeding metastases (mean 11.5 months) either preoperatively or postoperatively. Gross total resection (GTR) was achieved in 13 patients (30.9%) in the first surgery. Perioperative mortality and morbidity rates were 4.7% and 19%, respectively. Patients were followed for an average of 18.1 months. The median progression-free and overall survivals were 7.0 (95% CI: 5.9-8.0) and 11.0 (95% CI: 8.9-13.1) months, respectively. 1-year, 2-year and 5-year progression-free survival and overall survivals were 30.9% vs. 50.0%, 11.9% vs. 19.0%, 4.8% vs. 9.5%; respectively.

CONCLUSION: Gross total resection should be safely attempted in pediatric GBM. In addition, a thorough and frequent radiological evaluation of the entire neuraxis for seeding metastases is recommended both at diagnosis and follow-ups.

KEYWORDS: Children, Glioblastoma, Management, Metastasis, Prognosis, Surgery

INTRODUCTION

Glioblastoma (GBM) is the leading and yet the most aggressive primary tumor of the central nervous system (CNS) in adulthood, particularly after the 5th decade of life (8, 21). This predominance is responsible for the general perception regarding GBM as a "tumor of the elderly". Indeed, pediatric cases are rare, accounting for 3-6 % of all glioblastomas. The incidence may be responsible for the underestimation of this devastating pathology in childhood. There is a paucity of information in the literature about age-specific histopathological and molecular biology. This is also true for prognostic factors and therapeutic strategies regarding pediatric glioblastoma. The current understanding is therefore majorly based on adult data.

The incidence and spectrum of pediatric CNS tumors have been addressed in several studies in the literature. Despite geographical differences, the incidence of glioblastoma was updated to 7-12 % of all pediatric brain tumors (12, 30).

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Therefore, there is more to tell about this devastating tumor in the pediatric population, which poses completely different characteristics in management and prognosis. There are some age-specific perspectives in radiotherapy and chemotherapy planning focusing on mental and motor development besides de novo tumor formations.

We retrospectively evaluated our experience with 42 consecutive cranial glioblastoma patients with particular emphasis on prognostic factors and differences from adulthood. We believe that sharing regional experiences and defining distinctive characteristics of glioblastoma in the pediatric population are important in shaping a clinical perspective for the accurate management of this relatively rare entity.

MATERIAL and METHODS

We retrospectively evaluated our database for pediatric glioblastomas and its variants that were operated at the Department of Neurosurgery, Hacettepe University Hospitals, Ankara, Turkey from January 1996 to December 2014. All consecutive patients were included in the evaluation if operated when younger than 18 years of age. Parental consent was obtained for each patient prior to surgical intervention. For the sake of a homogenous and comprehensive evaluation, patients without postoperative follow-up and radiological evaluation were excluded from the study, in addition to spinal and brainstem glioblastomas and those initially operated at other centers. There were 50 cases of consecutive GBM; 6 patients were excluded due to absence of data from follow-up and 2 were excluded for being operated initially at another center and referred to our center due to neurological deterioration in the postoperative period. A total of 42 pediatric cases were evaluated further. The diagnoses were approved based on histopathological features. The patient charts were used to obtain data regarding gender, age, symptoms and signs, radiological and histopathological characteristics, management strategies (surgical approach, radiotherapy and chemotherapy) and prognosis.

Extent of Resection

All patients were evaluated radiologically in the early postoperative period (in first 24 hours) and the extent of resection was determined using 4 grades based on comparisons of the pre- and postoperative gadolinium-enhanced magnetic resonance imaging (MRI) findings; (1) gross-total resection ([GTR], no residual enhancement), (2) near-total resection ([NTR], thin rim of enhancement in resection cavity only), (3) sub-total resection ([STR], residual nodular enhancement) and (4) biopsy ([Bx]). All excisions other than GTR were considered incomplete resections.

Postoperative Management

Upon pathological confirmation, all patients were referred to the departments of Radiation Oncology and Pediatric Oncology for radiotherapy and chemotherapy planning, respectively. However, seven patients could not receive any adjuvant therapy due to poor neurological or general health status in the postoperative period.

Follow-up Protocol

The radiological follow-ups with contrast enhancement were performed in the early postoperative period within 24 hours and then routinely at 3-month intervals after surgery. In case of significant deterioration in neurological status (more than 2 points decrease in the Glasgow coma scale) or when indicated by the other departments, radiological evaluation was performed earlier. The MRI scanning was not limited to the brain, per se. All the spinal column was included in the imaging. Tumor progression was determined by comparing follow-up MRI findings with those at the first postoperative day.

Length of survival and time to tumor progression (treatment failure) were measured in months from the date of initial surgery.

Statistical Analysis

Statistical analysis was done using the IBM SPSS Statistics 22 software. The Kaplan–Meier method was used to estimate the progression-free survival (PFS) and overall survival (OS). The log-rank test was used to test for differences in the PFS and OS distribution for dichotomous variables. Variables associated with survival in a univariate analysis were included in the multivariate Cox model if $p < 0.10$. Variables with probability values > 0.05 were then removed from the multivariate model in a backward stepwise fashion. p-value under 0.05 was considered significant.

RESULTS

The study included 42 consecutive pediatric patients who were operated on for GBMs. There were 20 boys and 22 girls with a mean age of 10.2 years (1 month to 18 years). The patients under 3 years of age made up 11.9% of the study group. The demographic data are presented in Table I.

Clinical Presentation

The demographic features in our series revealed an age-dependent increase in the incidence of GBM in pediatric patients. The figures demonstrated a cut-off point at the age of 6 years. The incidence almost doubles after this year (Table I). There were no significant difference between genders; the male to female ratio was 1:1.1 (20 males, 22 females). Boys presented at a slightly earlier age but this difference was not statistically significant (boys and girls; 9.3 vs. 11.1 respectively; p=0.23).

Signs and symptoms of increased intracranial pressure dominated the clinical presentation in the majority of the patients (64.2%, 27/42). Headache was the leading symptom in half of the cases (21 patients, 50%) (Table I). Alterations in consciousness (11.9%), visual disturbances, gait disturbances and diplopia (7.1% each), aphasia and increasing head circumference (4.8% each) were also observed. Beside these, one patient with hypothalamic tumor suffered from appetite loss, apathy and weight loss.

The mean duration to diagnosis was 20 days (1 day to 365 days) after the initial symptom, the majority (88.1%, 37/42) being diagnosed in less than 3 months (Table I).

Table I: Demographics, Clinical Characteristics and Treatment Modalities of the Patients

	Number of patients	% of Total
Patient Demographics		
Sex		
Male	20	47.6
Female	22	52.4
Age (years)		
0-3	5	12%
4-6	3	7.2%
7-9	9	21.4%
10-12	6	14.2%
13-15	11	26.2%
16-18	8	19%
Clinical Presentation		
Duration of symptoms		
≤1 week	10	23.8
1-4 weeks	13	30.9
1-3 months	14	33.3
>3 months	5	11.9
Presenting symptoms		
Headache	21	50.0
Nausea/vomiting	19	45.2
Seizure	20	47.6
Motor deficits	18	42.9
Other	13	30.9
Hydrocephalus		
Total	21	50.0
Preoperative	15	35.7
Postoperative (follow-up)	6	14.3
Number of operations		
Single	23	54.8
Multiple (2 or 3)	19	45.2
Extent of resection		
Gross total (GTR)	13	31.0
Incomplete (NTR/STR/PR/Bx)	29	69.0
Radiotherapy		
Yes	34	80.9
No	8	19.1
Chemotherapy		
Yes	35	83.3
Conventional	17	40.5
TMZ only	8	19.1
TMZ + others	10	23.8
None	7	16.7
Dissemination (seeding met.)		
Total	11	26.2
Primary	3	7.1
Secondary	8	19.1
< 1 year	4	9.5
> 1 year	4	9.5

Predisposing Factors

A particular predisposing factor could not be determined in 88.1% (37/42) of the cases. However in 3 patients, Neurofibromatosis type 1, a family history for a brain tumor (sister with PNET), and history for cranial irradiation for acute lymphoblastic leukemia were specified as a factor. Moreover, two patients had secondary glioblastoma that progressed from a lower-grade glioma 18 and 43 months after the initial diagnosis.

Tumor Localization

All but one of the tumors were located in the supratentorial region (97.6%, 41/42) (Table II). One infratentorial tumor was situated in the cerebellar vermis. Occipital lobe and suprasellar-hypothalamic localization were exceptional compared to the other sides, observed in 3 (7.1%) and 2 patients (4.8%), respectively. Two newborn had giant tumors, which involved the entire hemisphere.

Radiological Findings

MRI was the preferred imaging modality at both initial and follow-up evaluations. However, computerized tomography (CT) was implemented initially in case of acute alterations in the neurological status.

In general, pediatric glioblastomas presented either as a focal and heterogeneous mass lesion (Figure 1A-F) or as an ill-defined infiltrative lesion particularly on T2 weighted (T2w)

Table II: Lesion Localizations were Detailed with Respect to Overall Numbers and Percentages

Lesion Location	Numbers (percentages)
Supratentorial	41 (97.62%)
Lobar/Hemispheric	28 (66.67%)
Frontal	6 (14.29%)
Fronto-temporal	2 (4.76%)
Fronto-temporo-insular	3 (7.14%)
Temporal	3 (7.14%)
Temporo-parietal	3 (7.14%)
Temporo-insular	1 (2.38%)
Parietal	3 (7.14%)
Parieto-occipital	4 (9.52%)
Occipital	1 (2.38%)
Hemispheric	2 (4.76%)
Thalamic	11 (26.19%)
Suprasellar	2 (4.76%)
Infratentorial-Cerebellar	1 (2.38%)
Total	42 (100.00%)

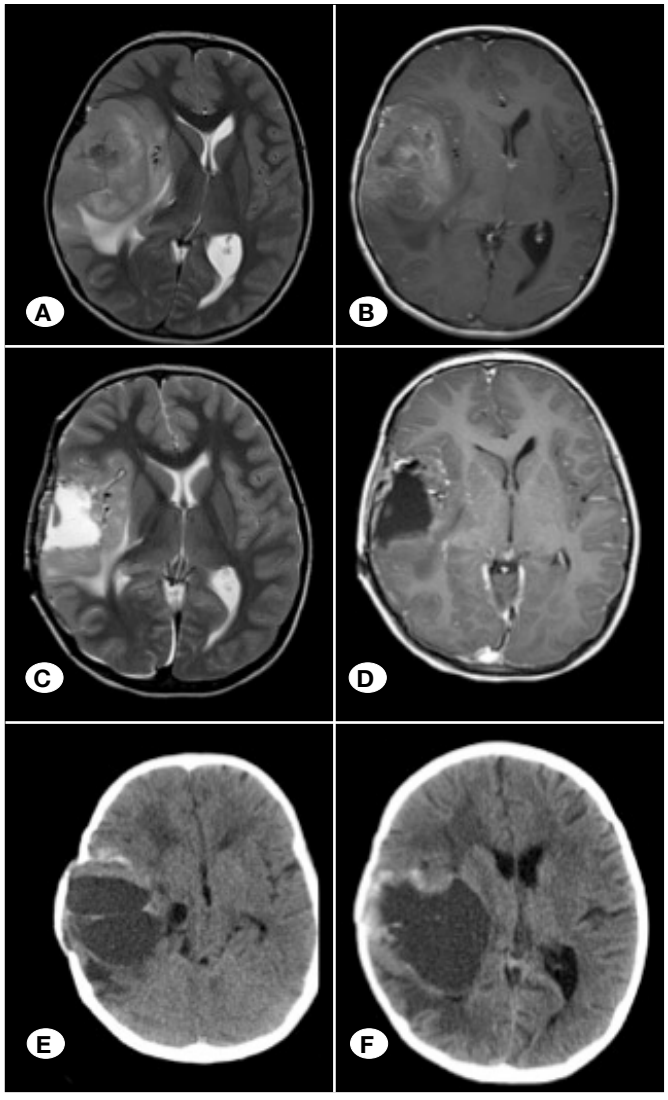

Figure 1: Neuroimaging findings of a 7-year female patient. A huge and heterogeneous mass is seen in the right temporal lobe and insula with compression of the right deep gray matter and lateral ventricle, and subfalcine herniation to the left **(A, B)**. A month after the operation, the resection cavity with adjacent thickening and T2 hyperintensity suggesting edema and/or nonenhancing tumor **(C, D)**. An enhanced cranial CT, obtained 6 months later shows a recurrent cystic, heterogeneous mass with peripheral solid enhancing portions, again with mass effects **(E, F)**.

and Fluid-attenuated inversion recovery (FLAIR) images on MRI (Figure 2A-D). The post- gadolinium enhancement was not uniform among patients with respect to intensity and homogeneity, and varied between mild and moderately high enhancement. Moreover, the contrast uptake could be homogeneously distributed to all tumor tissue or there could be heterogeneous or even, irregular ring enhancement.

Hemorrhage was not evident in this series and only one patient had intraventricular bleeding due to multi-foci hemorrhagic periventricular tumor. Hydrocephalus was evident in 15 patients (35.7%) preoperatively

Surgery and Complications

The surgical technique was shaped based on the philosophy; "maximal resection with best functional status of the patients". This tenet was reflected in the overall rates of tumor resection and half of the patients (21/42 cases) had subtotal removal. Gross total excision could only be achieved in 30.9% (13/42) of the patients (Table I). These figures were concordant with the location of the lesions; the resection rates increased in accordance with localizations such as the frontal or temporal lobe and cerebellum. The tumors were situated in these relatively safer areas in 38% of the cases, which was parallel to rates of overall gross and near total resections (35.7%) in the series.

Surgical interventions were not limited to tumor resections in this series. There were 14 cases that needed ventriculoperitoneal (V/P) shunt placement either in preoperative or postoperative period. Hydrocephalus was associated with glioblastoma in 35.7% (15/42) of the patients in preoperative period but half of them (53%, 8/15) were managed with a V/P shunt. Postoperative hydrocephalus was seen in 6 patients (14.2%) and all needed V/P shunt in a mean duration of 9.5 months (5 months-3 years).

Histopathological Findings

The diagnosis of glioblastoma was established based on histopathological findings according to the World Health Organization (WHO) Classification of Tumours of the Central Nervous System (i.e. vascular proliferation and/or necrosis in addition to the focal or diffuse hypercellularity, nuclear atypia, nuclear pleomorphism, and the presence of mitotic figures) (24).

The variants (all being WHO grade IV) were also included in the evaluation. There were 3 cases of gliosarcoma based on mesenchymal appearance in the specimens. Moreover, there were 7 cases with multinucleated giant cells and abundant eosinophilic cytoplasm, which led to giant cell glioblastoma as the diagnosis (14).

The Ki-67 proliferation index was calculated in the specimens and the mean value was 30.8 (5-90%). Immunohistochemical analysis for p53 and epidermal growth factor receptor (EGFR) was also performed on the specimens; immunoreactivity was observed in 72.7% (59.1% strong/diffuse, 13.6% weak/focal) for p53 expression. This figure decreased to 55.6% in case of EGFR expression.

Adjuvant Therapies

As a part of the standard of care, the patients received adjuvant radio- and chemotherapy after the surgical resection. However, 7 patients (16.7%) received no adjuvant treatment due to poor outcome following surgery. In total, radiotherapy and chemotherapy were applicable in 33 (78.6%) (50-60 Gy) and 35 (83.3%) patients (conventional and/or temozolomide), respectively.

Outcome

In our GBM series, peri-operative mortality occurred in two newborn patients (4.7%) with hemispheric involvement.

There were 8 surgical complications (19%); one patient had postoperative hematoma that warranted a surgical intervention and the other 7 patients experienced either worsening in preoperative neurologic deficits or additional neurological deterioration (16.7%). However, the deficits in three of them gradually improved during the follow-up.

Tumor progression was observed in a mean duration of 7 months (1-68 months) in 90.5% of the patients. Local recurrence was the initial mode of progression in 34 patients (81%). There were 3 patients (2 cases in the periventricular and 1 case in the suprasellar region) with seeding metastases at the time of diagnosis. However, seeding metastases were observed in another 8 patients during the follow-up, half of them occurring in less than a year (mean: 11.5 months, 2-53). When seeding metastases occurred, the prognosis was relatively poor and the outcome doomed at a mean duration of 5 months after the diagnosis. Two newborn patients who died within 30 days of surgery were excluded from survival analyses.

The median durations for progression-free (PFS) and overall survival (OS) were 7.0 (95% CI: 5.9-8.0) and 11.0 (95% CI: 8.9-13.1) months, respectively. The PFS dropped to almost a third after 1-year (30.9%) to 11.9% at 2-years and the figure was just 4.8% at 5 years. However, these trends were not exactly followed in case of overall survivals; half of the patients were alive at the first year (50%). The rate was decreased less abruptly to 19% at 2 years and 4 patients survived beyond 5 years (9.5%). These 4 patients had GBM in the suprasellar region (2 patients), temporoparietal lobe (1 patient) and cerebellum (1 patient).

Statistical Analysis

Kaplan-Meier survival analysis was performed for both PFS and OS survival in this series.

The statistical analysis for prognostic factors were unyielding and revealed no significance pertaining to age, gender, duration of symptoms before diagnosis, hydrocephalus at diagnosis, and histopathological type (glioblastoma vs. its variants). In addition to these, the Ki-67 proliferation index, p53 and EGFR immunoreactivity were not correlated with the outcome.

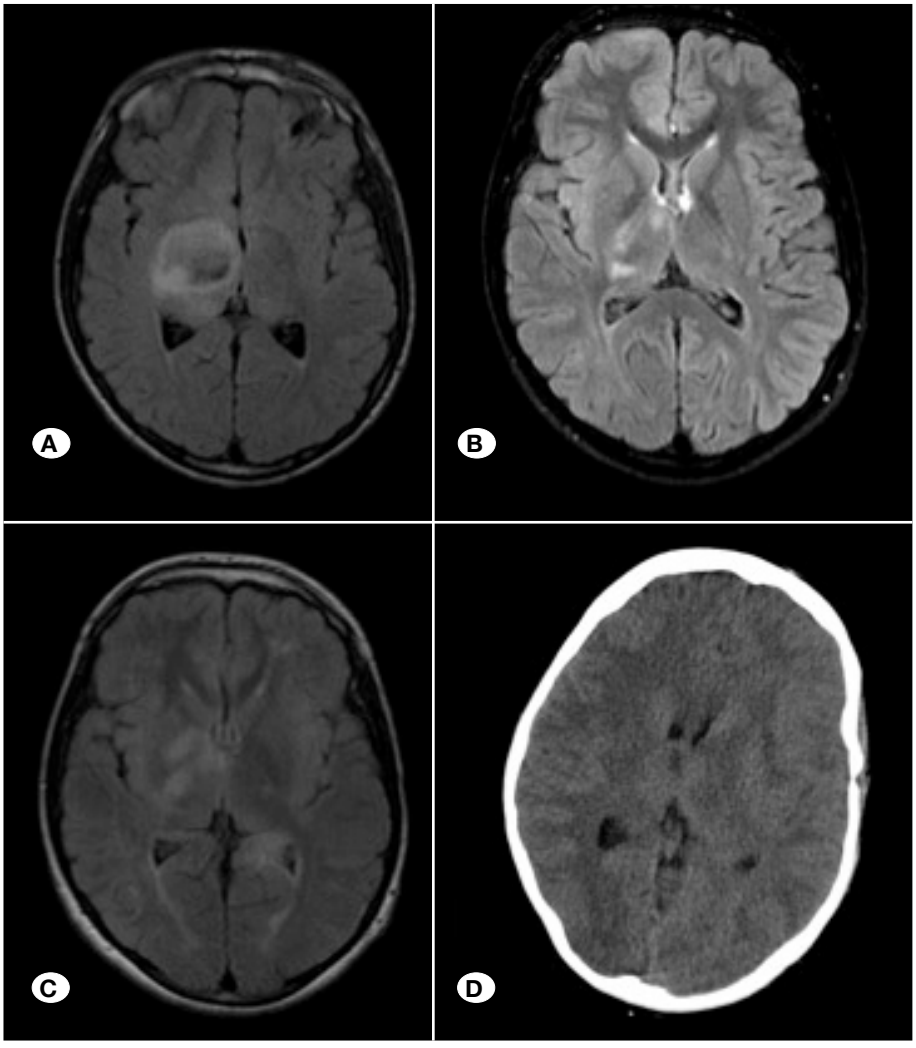

Figure 2: Neuroimaging findings of a 14-year old male patient. Axial FLAIR image of initial MRI shows a right thalamic mass with central necrosis **(A)**. 12 week after the operation and chemo-radiotherapy a marked resolution of the mass is seen with small residual hyperintense focus in the right thalamus and internal capsule **(B)**. However, the FLAIR image obtained another 10 weeks later shows relapse of the right thalamic mass with swelling and extension as well as new cortical lesions in the contralateral parieto-occipital lobe and insula **(C)**. Axial CT of the patient obtained 3 months later shows progression of the left hemispheric infiltrating mass, now lso involving the left thalamus and causing midline shift **(D)**.

There was an association between poor postoperative neurological status and unfavorable prognosis in the Kaplan-Meier analysis, however, this effect could not be confirmed in the multivariate Cox model (Table III). Univariate analysis revealed that lobar localization of the tumor (supratentorial or infratentorial) was associated with a more favorable outcomes compared to thalamic tumors (p=0.046). On the other hand, this association was also not supported in the multivariate analysis.

Gross total resection was associated with better overall and progression-free survivals. Multivariate analysis favored complete resection as an independent prognostic factor in this series (Table III). Chemotherapy and radiotherapy, alone or in combination, were significantly associated with a better prognosis (p<0.001). However, the statistical analysis for chemotherapy and radiotherapy were felt to be biased due to the fact that these therapies cannot be applied to every patient and there was no homogeneity based on age groups. Moreover, patients with poor a postoperative course could not receive radiotherapy or chemotherapy. Hence, RT and chemotherapy were not considered as independent variables in this series and not included in the multivariate analysis.

Presence of seeding metastases either at presentation (p=0.024) or within 3 months (p=0.001) and 6 months (p=0.005) after the surgery was also a predictor for poor overall survival in the Kaplan-Meier analysis. Early seeding metastases (at diagnosis and within 3 months of surgery) was an independent prognostic factor for overall survival in the multivariate analysis (p=0.027) (Table III).

■ DISCUSSION

Pediatric glioblastoma is uncommon with respect to overall incidence. The literature is populated with series that are difficult to concise and to reach a clinically applicable guideline in the management of a pediatric patient. There is a heterogeneity in inclusion criteria, tumor localizations and philosophy in surgical approaches in addition to diagnostic and therapeutic tools. Dohrmann et al. (16) can be credited for the first discussion of pediatric vs. adult GBM. They have reviewed 488 pediatric CNS tumors; GBM was reported in 8.8% of the patients. The incidence is compatible with today's data. Their review concluded that glioblastoma behaved similarly irrespective of the age group (adult vs. pediatric) (16). However, detailed evaluation of the article revealed that there were localization and age-group specific differences between adult and pediatric glioblastomas. Our study concentrated on our institutional experience to define differences from a clinical perspective attributable to daily practice over one of the largest series of pediatric cases in the literature.

There is an age-dependent trend in the incidence of pediatric glial tumors, similar to the adult population (21, 27). Considering the supratentorial region, glial tumors also constitute the majority of primary hemispheric tumors in children. Nevertheless, in contrast to adults, high-grade gliomas are significantly less common than their low-grade counterparts (28). Das et al. reviewed 341 brain tumor cases and concluded that medulloblastomas and ependymomas are followed by astrocytic tumors in terms of the incidence in patients younger than 5 years but the rates of astrocytic tumors increase, making them the second most common tumors in childhood after this age. GBM constituted 12% of their childhood brain tumors (12). We also observed a similar trend; there was a dramatic increase in the incidence of GBM (other than brainstem) after 6 years of age (19% vs. 81%) (Table I). However, a specific age was not unequivocally observed in all studies; Rickert et al. presented a undulating course regarding age-groups; the incidence reached 8-10% at age groups of 3-5, 12-14 and 15-17 years while the figure dramatically decreased to 3.6% between 9 to 11 years (30).

The importance of age in the prognosis was emphasized in adult series. Lacroix et al. examined age (the younger the better) as a clinical factor in their grading system together with the presence of necrosis (on MRI) and Karnofsky performance scale (KPS). In this grading, the higher the score (older patients in particular), the more unfavorable was the prognosis (23). However, such a trend could not been specified in the pediatric group; our series had two perioperative early mortalities; both were newborns with hemispheric GBM. These patients were excluded in the survival analysis because their specific age-related characteristics would cause bias in the results. Moreover our data was not supportive for the conclusion; "*younger age (on the contrary to adults) impose a worse prognosis in childhood*". However, this concern was supported by other studies in the literature (7, 15). Bloom et al. indicated relatively unfavorable prognosis in younger patients after comparing the age groups 0-2 years and 10-15 years in their series (7). Dohramann et al. adopted a different approach and emphasized the occurrence of GBM in rather well developed regions (supratentorial) of the brain in relatively older children (over 12 years), which in turn, supposedly, imposed a longer survival (16).

Glioblastomas mostly involve the supratentorial compartment in childhood. Cerebellar involvement, excluding the brainstem, was seldom reported in institutional series (less than 5% of all glioblastomas) (16). Exceptionally, Mahvash et al. presented a relatively high rate of cerebellar involvement (2 cases), making up of 22% (2/9 cases) of non-brainstem GBMs (26). Our figures were also consistent with the literature in terms of cerebellar GBM (one case). This finding denotes that the infratentorial compartment was reserved for other childhood malignancies such as medulloblastomas. Although there is a similarity in rates of cerebellar involvement in pediatric and elder cases, deep-seated GBMs (thalamus and brainstem) are far more common in childhood. Our series had 11 thalamic and 2 suprasellar GBMs, constituting 30.9% (13/42) of our cases. The literature search yielded a distinct difference in adulthood; Devaux et al. reviewed 263 GBM patients, and thalamic and basal ganglia tumors were diagnosed in only 12.1% (32/263) of their cases (13). The figures varied dramatically depending on the enrolled age group; in a GBM series of patients over 66 years old, the incidence even dropped to 4.7% (33).

Lesion localization is also a prognostically significant factor (5). The thalamic GBMs had slightly a worse prognosis compared

Table III: Univariate and Multivariate Progression-Free (PFS) and Overall Survival (OS) Analysis of Pediatric Glioblastoma Patients by the Cox Proportional Hazards Model

	Progression-free survival (PFS)				Overall survival (OS)			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Gender male *vs* female	1.345 (0.671-2.696)	0.403			1.107 (0.549-2.232)	0.777		
Age (years) <10 *vs* ≥10	1.009 (0.924-1.103)	0.835			1.199 (0.607-2.368)	0.601		
Duration of symptoms (months) ≤1 *vs* >1	1.242 (0.595-2.593)	0.564			0.791 (0.377-1.658)	0.535		
Tumor location lobar/hemispheric *vs* thalamic	0.510 (0.244-1.066)	0.074	0.688 (0.323-1.465)	0.332	0.473 (0.227-0.987)	0.046	0.645 (0.301-1.382)	0.259
Extent of resection complete *vs* incomplete	0.311 (0.136-0.710)	0.006	0.340 (0.146-0.789)	0.012	0.322 (0.140-0.744)	0.008	0.352 (0.150-0.827)	0.017
Surgically acquired deficits yes *vs* no	1.862 (0.822-4.217)	0.136	1.097 (0.421-2.857)	0.849	2.043 (0.902-4.623)	0.087	1.139 (0.390-3.328)	0.813
Seeding metastases within 3 months yes *vs* no	6.768 (2.029-22.583)	0.002	5.041 (1.501-16.926)	0.009	5.251 (1.604-17.185)	0.006	3.914 (1.185-12.927)	0.025
Histological variant giant cell *vs* non-giant cell	1.338 (0.548-3.270)	0.523			1.207 (0.459-3.174)	0.703		

HR: *Hazards ratio,* ***CI:*** *Confidence interval.*

to lobar/hemispheric ones. Univariate analysis in our recent series also supported such a trend among supratentorial GBMs but this conclusion could not be confirmed in multivariate analysis. In accordance with Das et al., this may be due to difficulties in the complete resection of deep-seated tumors (11). The tumor location may not be a direct prognostic factor per se, but rather has an indirect impact on prognosis by determining the extent of resection. On the other hand, a relatively bad prognosis was attributed to aggressive behavior of the tumors near the ventricular system due to progenitor cells in some reports (1).

Complete resection still remains the most efficient and significant factor in the management of adult glioblastomas. We have not observed any significant difference in terms of surgical technique in tumor resection between adult and pediatric cases. There are some reports supporting a similar correlation between gross total resection and long-term survival in pediatric patients (3, 9, 11, 36). In the current series, gross total resection, when possible, stood as the most important and independent prognostic factor for both progression-free and overall survival on multivariate analysis. However, the benefit of radical surgery on survival should be considered in conjunction with the functional neurological status in the postoperative period (20). Although we have adopted the philosophy of "maximal resection with good neurological status", we have unfortunately experienced some degree of worsening in preoperative deficits or appearance of new deficits in the postoperative period in 16.7% of our cases. The overall prognosis was unfavorable in these patients compared to those with good postoperative neurological status. Based on our observations, we have concluded that the gross total resection should be attempted in glioblastoma surgery but not at the expense of functional status.

We have observed local recurrence in 81% of the patients with a mean duration of 7 months after surgery. The surgical complications included one postoperative hematoma at the resection side. There was no other significant complication besides the aforementioned neurological deterioration in 16.7% of the cases.

Maximal resection seemed to preserve its prognostic significance in the pediatric age group, similar to adulthood. Radiotherapy was the leading adjuvant therapy in these patients. However, under the age of 3 years, radiotherapy was held due to apprehension of damage to the developing brain in younger ages. On the other hand, with respect to management strategies, our figures were not supportive for chemotherapy-only regimens without radiotherapy in terms of prognosis. There was a slightly better result in those patients receiving temozolomide in conjunction with radiotherapy, but this finding could not be confirmed on multivariate analysis. There are also some clinical trials emphasizing minimal or no benefit of temozolomide over conventional treatment in the pediatric group (10, 22, 25). Based on these, in this age group, a patient specific-discretion is warranted in balancing the risk of tumor growth with the benefits and complications of radiotherapy. There are relatively newer approaches other than conventional radiotherapy in the management of glioblastomas. Weintraub et al. (35) reviewed their series and indicated failure of any therapeutic strategy in controlling tumor progression in partially resected glioblastomas. They supported the use of a Gamma Knife in management of residual or recurrent glial tumors with judicious control rates. However we have no experience in this regard.

Radiotherapy in the pediatric age group carries particular considerations compared than adulthood. Formation of secondary tumor (other than the primary tumor type) was discussed in the literature before. We have published our experience regarding second primary tumors (6). Our retrospective analysis revealed that there were 2 high-grade glial tumors arising after 6 and 11 years after radiotherapy. We were unable to determine any relationship between radiotherapy and secondary formation of glial tumors in our previous series.

Another factor, possibly conveying prognostic significance different than adulthood, is the presence of seeding (drop) metastases, which we have observed in 26.2% (11/42) of the patients in this series. The metastases involved the thoracic (5 cases), cervical (3 cases) and lumbar (3 cases) regions. These figures were also in accordance with the literature. Ginat et al. reported even distribution of spinal seeding metastases (overlapping 52% thoracic, 41% lumbar and 31% cervical level) (18). Three patients had primary disseminated disease at the time of diagnosis, the remaining 8 having been detected after their surgical intervention. There were seeding metastases even more than 1 year after surgery (4 patients). Mean duration for dissemination was 11.5 months. After the diagnosis, the mortality doomed rather soon at mean 5 months. Our analysis revealed that presence of seeding metastases at the time of diagnosis or its early appearance (in the first 6 months after the diagnosis) was associated with a significantly worse prognosis. This prognostic factor was addressed rarely in the literature; a report of high-grade glial tumors revealed that secondary dissemination was observed in 21-33% of the pediatric patients. An unfavorable outcome was also reported in these patients (mean survival 3-4 months). High mortality rates rendered postoperative evaluation of the craniospinal axis with gadolinium-enhanced MRI (19). In the adult population, leptomeningeal spread is seldom discussed and the numbers are not clear. Awad et al. reported their experience with 191 patients and reported 13 patients (6.8%) with such metastases (4). However in this series, only 5 patients had the diagnosis in the ante mortem period. These figures were reported in higher incidences (14%) in some other articles but the enrolled age group was younger; Arita et al. emphasized that metastases were more common in the first two decades of life (mean: 31 years) (2). This was also supported by Vertosick et al. (mean: 38.5 years), who also reported a shorter mean duration of survival (2.8 months) after the diagnosis of the metastases (34). These findings implied that the incidence for seeding metastases is higher in younger patients with glioblastoma and imposed a bad prognosis.

Besides spinal seeding metastases, another factor worth discussing may be the probable association between the presence of shunt catheters and the risk of metastases.

There were 21 patients (50%) with hydrocephalus in this series. In the literature, there are some case reports regarding distant metastases of glioblastomas via shunt catheters. The peritoneal region and involvement of intracranial organs were reported (17). However, these cases are extremely rare. In our series, there were 21 cases of hydrocephalus, and overall, 8 patients from the preoperative period and 6 patients from the postoperative period needed V/P shunt surgery. Among these, none of the patients complained of intrabdominal discomfort that pertained to metastases from glioblastoma. This may be partly explained by emergence and domination of the clinical findings due to recurrences in the intracranial region far before any possible intraabdominal metastases that could have been diagnosed.

There are some limitations of our study; first of all, our institution is a tertiary center and pediatric patients were referred from other centers. The "more complex" patients would have been encountered and therefore our series should be cautiously evaluated. Moreover, being a retrospective analysis, patient stratification could not be performed; we have observed that there are 2 patients with histologically confirmed suprasellar-hypothalamic GBMs, and their biological behavior was distinct from the rest. They responded favorably to adjuvant therapy and survived longer despite partial surgical excisions. They may constitute a distinct group and further studies may focus on this "benign tempered variant" of GBM. Moreover, our study did not concentrated on histopathological and molecular characteristics of GBMs. In recent years, molecular and genetic/epigenetic variations are widely discussed in the literature. There is accumulating data focusing on the differences between pediatric vs. adult GBMs in this respect (29, 31, 32). However, the authors believed that this topic was out of the scope of this study, which basically dealt with the clinical perspective of the prognostic factors apart from adulthood through an institutional experience. There is a need for future prospective studies with patient stratifications for age- and location-based comparisons, besides reflections of molecular and genetic/epigenetic variations on prognosis.

CONCLUSION

Pediatric GBM cases are distinct from their adult counterparts. The data pertaining to adulthood may help to understand the incidence in childhood to some extent. Based on our results, we observed that the incidence of GBM increases over 6 years of age, the younger patients confronted a more challenging course with respect to treatment regimens and prognosis, and the thalamic and deep-seated lesions were more common in childhood, similar to seeding metastases. The response of pediatric GBMs was limited prognostically. Maximal resection should be attempted in surgical planning but not at the expense of functional status. Due to the poor prognosis attributed to seeding metastases, the patients should be closely evaluated preoperatively and followed by craniospinal MR scanning.

REFERENCES

1. Adeberg S, Bostel T, König L, Welzel T, Debus J, Combs SE: A comparison of long-term and short-term survivors with glioblastoma, subventricular zone involvement: A predictive factor for survival? Radiat Oncol 9:95, 2014
2. Arita N, Taneda M, Hayakawa T: Leptomeningeal dissemination of malignant gliomas. Incidence, diagnosis and outcome. Acta Neurochir (Wien) 126:84-92, 1994
3. Artico M, Cervoni L, Celli P, Salvati M, Palma L: Supratentorial glioblastoma in children: A series of 27 surgically treated cases. Childs Nerv Syst 9:7-9, 1993
4. Awad I, Bay JW, Rogers L: Leptomeningeal metastasis from supratentorial malignant gliomas. Neurosurgery 19:247-251, 1986
5. Bilginer B, Narin F, Isikay I, Oguz KK, Soylemezoglu F, Akalan N: Thalamic tumors in children. Childs Nerv Syst 30:1493-1498, 2014
6. Bilginer B, Turk CC, Narin F, Hazer B, Hanalioglu S, Oguz KK, Soylemezoglu F, Akalan N: De novo formation of brain tumors in pediatric population following therapeutic cranial irradiation. Child Nerv Syst 31:893-899, 2015
7. Bloom HJ, Glees J, Bell J, Ashley SE, Gorman C: The treatment and long-term prognosis of children with intracranial tumors: A study of 610 cases, 1950-1981. Int Radiat Oncol Biol Phys 18: 723-745, 1990
8. Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, Kruchko C, McCarthy BJ, Rajaraman P, Schwartzbaum JA, Sadetzki S, Schlehofer B, Tihan T, Wiemels JL, Wrensch M, Buffler PA: Brain tumor epidemiology: Consensus from the Brain Tumor Epidemiology Consortium. Cancer 113:1953–1968, 2008
9. Campbell JW, Pollack IF, Martinez AJ, Shultz B: High-grade astrocytomas in children: Radiologically complete resection is associated with an excellent long-term prognosis. Neurosurgery 38:258–264, 1996
10. Cohen KJ, Pollack IF, Zhou T, Buxton A, Holmes EJ, Burger PC, Brat DJ, Rosenblum MK, Hamilton RL, Lavey RS, Heideman RL: Temozolomide in the treatment of high-grade gliomas in children: A report from the Children's Oncology Group. Neuro-Oncology 13:317–323, 2011
11. Das KK, Mehrotra A, Nair AP, Kumar S, Srivastava AK, Sahu RN, Kumar R: Pediatric glioblastoma: Clinico-radiological profile and factors affecting the outcome. Childs Nerv Syst 28:2055-2062, 2012
12. Das U, Appaji L, Kumari BS, Sirsath NT, Padma M, Kavitha S, Avinash T, Lakshmaiah KC: Spectrum of pediatric brain tumors: A report of 341 cases from a tertiary cancer centre in India. Indian J Pediatr 81: 1098-1091, 2014
13. Devaux BC, O'Fallon JR, Kelly PJ: Resection, biopsy and survival in malignant glial neoplasms. A retrospective study of clinical parameters, therapy and outcome. J Neurosurg 78:767-775, 1993
14. Dias-Santagata D, Lam Q, Vernovsky K, Vena N, Lennerz JK, Borger DR, Batchelor TT, Ligon KL, Iafrate AJ, Ligon AH, Louis DN, Santagata S: BRAF V600E mutations are common in pleomorphic xanthoastrocytoma: Diagnostic and therapeutic implications. PLoS One 6:e17948, 2011

15. Di Rocco C, Iannelli A, Ceddia A: Intracranial tumors of the first year of life. A cooperative survey of the 1986-1987 Education Committee of the ISPN. Childs Nerv Syst 7:150-153, 1991
16. Dohrmann GJ, Farwell JR, Flannery JT: Glioblastoma multiforme in children. J Neurosurg 44:442-448, 1976
17. Fecteau AH, Penn I, Hanto DW. Peritoneal metastasis of intracranial glioblastoma via a ventriculoperitoneal shunt preventing organ retrieval: Case report and review of the literatüre. Clin Transplant 12:348-350, 1998
18. Ginat DT, Schaefer PW: Imaging guidelines and findings of extracranial glioblastoma. J Neurooncol 118:9-18, 2014
19. Grabb PA, Albright AL, Pang D: Dissemination of supratentorial malignant gliomas via the cerebrospinal fluid in children. Neurosurgery 30:64-71, 1992
20. Gulati S, Jakola AS, Nerland US, Weber C, Solheim O: The risk of getting worse: Surgically acquired deficits, perioperative complications, and functional outcomes after primary resection of glioblastoma. World Neurosurg 76:572-579, 2011
21. Hess KR, Broglio KR, Bondy ML: Adult glioma incidence trends in the United States, 1977-2000. Cancer 101:2293-2299, 2004
22. Jung TY, Kim CY, Kim DS, Ra YS, Kim SH, Baek HJ, Choi HS, Kim IA: Prognosis of pediatric high-grade gliomas with temozolomide treatment: A retrospective, multicenter study. Childs Nerv Syst 28:1033-1039, 2012
23. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, Demonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection and survival. J Neurosurg 95:190-198, 2001
24. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK: World Health Organization Classification of Tumors. Pathology and genetics of tumours of the nervous system. Lyon: IARC, 2007
25. MacDonald TJ, Aguilera D, Kramm CM: Treatment of high-grade glioma in children and adolescents. Neuro Oncol 13:1049-1058, 2011
26. Mahvash M, Hugo HH, Maslehaty H, Mehdorn HM, Stark AM: Glioblastoma multiforme in children: Report of 13 cases and review of the literature. Pediatr Neurol 45:178-180, 2011
27. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C, Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro Oncol Suppl 2:ii1-56, 2013
28. Pollack IF: Brain tumors in children. N Engl J Med 331:1500-1507, 1994
29. Pollack IF, Finkelstein SD, Woods J, Burnham J, Holmes EJ, Hamilton RL, Yates AJ, Boyett JM, Finlay JL, Sposto R: Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med 346:420–427, 2002
30. Rickert CH, Paulus W: Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 17:503-511, 2001
31. Sturm D, Bender S, Jones DT, Lichter P, Grill J, Becher O, Hawkins C, Majewski J, Jones C, Iavarone A, Aldape K, Brennan CW, Jabado N, Pfister SM: Paediatric and adult glioblastoma: Multiform (epi)genomic culprits emerge. Nat Rev Cancer 14:92-107, 2014
32. Suri V, Das P, Pathak P, Jain A, Sharma MC, Borkar SA, Suri A, Gupta D, Sarkar C: Pediatric glioblastomas: A histopathological and molecular genetic study. Neuro Oncol 11:274–280, 2009
33. Tanaka S, Meyer FB, Buckner JC, Uhm JH, Yan ES, Parney IF: Presentation, management and outcome of newly diagnosed glioblastoma in elderly patients. J Neurosurg 118:786-798, 2013
34. Vertosick FT Jr, Selker RG: Brain stem and spinal metastases of supratentorial glioblastoma multiforme: A clinical series. Neurosurgery 27:516-521, 1990
35. Weintraub D, Yen CP, Savage J, Williams B, Sheehan J: Gamma knife surgery of pediatric gliomas. J Neurosurg Pediatr 10:471-477, 2012
36. Yang T, Temkin N, Barber J, Geyer JR, Leary S, Browd S, Ojemann JG, Ellenbogen RG: Gross total resection correlates with long-term survival in pediatric patients with glioblastoma. World Neurosurg 79:537-544, 2013