MAR Oncology & Hematology (2024) 4:9

Research Article

Outcomes of Glioblastoma in Children and Adolescents Under 21 Years of Age in A Single Tertiary Care Center

Dr Poojashree K S * , Dr Akshay Kamle[1]

1. Dr Akshay Kamle (MD, DNB, FNB), Pediatric Hematoncologist, MGM Medical College Indore.

*__Correspondence to:__ Dr Poojashree K S., MBBS DMRT DNB Radiation oncology, Radiation oncologist, Government Cancer Hospital, Anantapur.

Copyright

© 2024 **Dr Poojashree K S.** This is an open access article distributed under the Creative Commons AttributionLicense, which permits unrestricted use, distribution, and reproduction in any medium, provided the originalwork is properly cited.

Received: 30 August 2024

Published: 04 September 2024

DOI: https://doi.org/10.5281/zenodo.13788856

Abstract

Purpose: *Pediatric Glioblastoma is an aggressive tumor which occurs less often in children and carries a dismal prognosis with median survival of approximately 20 months. Factors including early presentation, complete resection and supratentorial location are associated with better outcomes. Management of Pediatric Glioblastoma is very challenging and includes safe surgical resection along with chemotherapy and radiation. Due to rarity of pediatric data on glioblastoma in low- and middle-income countries, this study will give a comprehensive overview on clinical characteristics and outcomes of pediatric glioblastoma.*

Methods: *In this study, twenty patients who were less than 21 years old, diagnosed as glioblastoma were enrolled at a tertiary care center between January 2015- December 2017 and their clinical characteristics, treatment strategies and outcomes were recorded.*

Results: *Out of 20 patients, 55% were female with mean age of 11.5 years. Vomiting and headache (92%) were commonly found symptoms and supratentorial region (65%) was most common location of the tumor. Subtotal resection (STR) was performed in 55% of patients as compared to gross total resection (GTR) which was performed in 35% of patients. After surgery, only 7 (35%) patients received chemo-radiation, 4 (20%) patients were managed with only radiation and 9(45%) patients didn't receive any therapy. 4 (20%) patients were lost to follow up, 14 (87%) expired whereas 2 (10%) patients are alive with residual disease at 23 months since the time of diagnosis.*

Conclusion: *Pediatric glioblastoma is a rapidly growing aggressive tumor with worst outcomes in children and needs further studies to overcome the challenges in its management and to improve survival.*

Key Words: *Pediatric glioblastoma, Clinical Characteristics, Outcomes*

Abbreviations

Bevacizumab (BV)

Central nervous system (CNS)

Chemotherapy (ChemoRx)

Constitutional Mismatch Repair Deficiency (CMMRD)

Cranio-spinal irradiation (CSI)

Disease progressed and expired (P/ Expired)

Disease relapsed and expired (R/Expired)

Follow up (FU)

Gross total resection (GTR)

Intracranial pressure (ICP)

Low-and middle-income countries (LMICs)

Neurofibromatosis-1 (NF-1)

Not available (NA)

Overall survival (OS)

Patients (Pts)

Radiation therapy (RT)

Subtotal resection (STR)

Temozolomide (TMZ)

Vascular endothelial growth factor (VEGF)

Introduction

A global childhood cancer study across 62 different regions found that the most common cancers were leukemias, central nervous system (CNS) tumors and lymphomas **[**4**]**. Glioblastoma is the most common high-grade glioma in adults but accounts for only approximately 3% of all brain tumors among 0–19 years old, with an estimated incidence of 1.4 per 1,000,000 **[**23,14**]**. It is the most lethal CNS tumor with a median survival of approximately 20 months **[**7**]**. Glioblastoma in children is different from its adult counterpart with respect to different developmental origin and that majority of them harbor somatic mutations in histone gene. Severity of symptoms depends on the site and extension of the tumor. Children usually present with headaches, focal neurologic deficits, seizures and worsening of vision whereas infants have issues with irritability, poor feeding and inability to walk **[**14**]**. Majority of the tumors are located in the supratentorial compartment with frontal lobe being the most common site followed by temporal lobe. Maximal safe surgical resection is the mainstay of treatment followed by radiotherapy and concomitant chemotherapy with temozolomide (TMZ). Treatment outcomes of CNS tumors are much lower in middle-and low-income countries compared to high income countries due to various reasons including lack of a multidisciplinary team, late presentation and associated cancer predisposing syndromes due to higher rates of consanguinity in low- and middle-income countries **[**14**]**. Over 90% of deaths due to pediatric cancer occur in low-and middle-income countries (LMICs) due to inadequate resources **[**4**]** Majority of the research has been done in adult glioblastoma but data on pediatric glioblastoma is very limited. There is only limited data available from developing countries. A study from Thailand (1990 to 2011) reported their age-standardized incidence rate (ASR) was 98.5 per million person-years for all childhood cancers with central nervous system (CNS) being the second most common with an ASR of 12.0 per million person-years **[**4**]**. In Pakistan, there is no data available for childhood glioblastoma and very scarce data for overall pediatric CNS tumors. One study from Karachi, Pakistan depicted a frequency of 22.13% for primary CNS tumors from all solid malignancies in the pediatric age group **[**1**]**. Another study from Rawalpindi, Pakistan found that astrocytic tumors were the most common central nervous system (CNS) tumors in children **[**5**]**. However, no study from Pakistan has exclusively presented data on childhood glioblastoma. Our study highlights the clinical characteristics and outcome of children and young adults with glioblastoma, at a single tertiary health care center, Pakistan. This will help in better understanding of the disease impact and to design support programs for children with glioblastoma.

Materials and Methods

We performed a descriptive, cross sectional study with retrospective analysis at Aga Khan University, Hospital on all patients less than 21 years with histologically proven diagnosis of glioblastoma between January 2015-December 2017 after approval from ethical review committee. A total of 20 patients met the eligibility criteria. All the relevant information about clinical features at presentation, site of the tumor, radiological findings, metastatic workup, histopathology, management and outcome were collected from the medical record on a structured proforma. The data was entered and analyzed using SPSS version 20. The results are presented as mean with standard deviation and frequency with percentage.

Results

From a total of 20 patients who met the eligibility criteria, 55% were female and 45% were male. Majority of the children were between 5-10 years while mean age was 11.15 years. 19 out of 20 patients (95%) had symptoms duration of less than 6 months. Only 2 patients had positive family history of different cancers. Most common presentations were vomiting and headache, present in 92% of the patients, followed by hemiparesis (80%), visual changes (70%), seizures (66.7%) and drowsiness (62.5%). Other modes of presentation involved changes in speech, personality and cranial nerve palsies. Tumors were mainly located in supratentorial region of the brain (65%). Other locations in brain involved were posterior fossa, hypothalamus, brain stem and spinal cord. Metastatic disease in spine was present in only 1 patient at presentation. Subtotal resection (STR) was performed in 11 patients (55%) whereas 7 patients (35%) underwent gross total resection (GTR) and 2 patients (10%) were only biopsied. Combined chemotherapy and radiation were given to 7 (35%) patients and 4 (20%) patients were managed with only radiation. However, 9 patients (45%) didn't receive any chemo-radiation. Median follow up duration was 6 months. Out of 20 patients, 4 (20%) patients were lost to follow up. Of those 16 patients who were followed, 14 (87%) died whereas 2 (10%) patients are alive with residual disease at 23 months after initial diagnosis as showed in table 1 and 2.

S. No	Gender	Age (yr)	SITE	Duration of Symptoms	Family History	Metastas-IS	Performance Scale at Presentation
1.	M	19	Hypothalamus	< 6 months	NO	NO	70
2.	M	17	Right Temporal	< 6 months	NO	NO	40
3.	F	12	Right Frontoparietal	< 6 months	NO	NO	70
4.	M	21	Posterior Fossa	< 6 months	NO	NO	50
5.	F	10	Left Frontotemporal	< 6 months	YES	NO	40
6.	F	9	Posterior Fossa	< 6 months	NO	NO	60
7.	M	15	Spinal Cord	< 6 months	NO	NO	40
8.	F	6	Right Frontal	< 6 months	NO	NO	50
9.	F	10	Right Temporoparietal	< 6 months	NO	NO	90
10.	M	16	Left Parietal	< 6 months	NO	NO	90
11.	F	17	Right Parietal	< 6 months	NO	NO	40
12.	F	08	Posterior Fossa	< 6 months	NO	NO	50
13.	F	6	Brainstem	< 6 months	NO	NO	50
14.	M	16	Left Parietooccipital	> 6 months	YES	YES (SPINE)	50
15.	M	8	Left Frontoparietal	< 6 months	NO	NO	50
16.	M	5	Right Frontal	< 6 months	NO	NO	50
17.	M	11	LEFT TEMPORAL	< 6 months	NO	NO	90
18.	F	14	Posterior Fossa	< 6 months	NO	NO	80
19.	F	2	Right Frontal	< 6 months	NO	NO	70
20.	F	8	Left Parietooccipital	< 6 months	NO	NO	70

Table 1. Patient's characteristics

S. No	SURGERY	Chemotherapy (TMZ)	RT	RT Doses (cGy)	RT SITES	Fractions	OUTCOMES
1.	STR	NO	NO	-	-	-	LOST TO FU
2.	GTR	NO	NO	-	-	-	EXPIRED
3.	STR	NO	YES	5940cGY	RIGHT PARTIAL BRAIN	33	EXPIRED
4.	GTR	NO	NO	-	-	-	R/EXPIRED
5.	GTR	NO	NO	-	-	-	EXPIRED
6.	BIOPSY	YES	YES	5400cGy	PARTIAL BRAIN	30	EXPIRED
7.	GTR	YES	YES	4500cGY	D-SPINE	25	EXPIRED
8.	GTR	NO	NO	-	-	-	ALIVE WITH RESIDUAL DISEASE
9.	GTR	NO	NO	-	-	-	LOST TO FU
10.	STR	YES	YES	5400cGY	CSI	30	EXPIRED
11.	STR	YES	YES	5800cGY	RIGHT BRAIN	29	LOST TO FU
12.	STR	NO	NO	-	-	-	EXPIRED
13.	STR	NO	YES	5400cGy	PARTIAL BRAIN	30	ALIVE WITH RESIDUAL DISEASE
14.	STR	NO	YES	5040cGY	SPINE	28	P/EXPIRED
15.	STR	NO	NO	-	-	-	P/EXPIRED
16.	GTR	YES	YES	6000cGy	NA	NA	R/EXPIRED
17.	STR	YES	YES	6000cGy	LEFT BRAIN	30	P/EXPIRED
18	STR	NO	YES	NA	NA	NA	P/EXPIRED
19.	BIOPSY	NO	NO	-	-	-	LOST TO FU
20.	STR	YES	YES	5940cGy	LEFT BRAIN	33	P/EXPIRED

STR: subtotal resection, GTR: gross total resection, NA: not available, FU:follow up, CSI: cranio-spinal irradiation, R/Expired: Disease relapsed and expired, P/ Expired: Disease progressed and expired.

Table 2(a). Patient Management and Outcome

Yr	Auth-or	Age (yr)	No. Of Pts.	Mean durati-on(mo)	Mean Tumor Size(cm)	Most common site	OS (mo)	GTR	ChemoRx	RT	RT does (Gy)	No. of Alive Pts
1976	Dohrmann GJ	NA	43	NA	NA	Cerebral hemispheres	22	NA	NA	NA	NA	NA
1990	Marchese MJ et al	NA	27	NA	NA	NA	16	NA	NA	27	NA	6
2009	Sánchez Herrera	3–15	16	1.5	5.79	Cerebral hemispheres	54.9	5	NA	NA	45 to 55	3
2009	Suri V	0.9 - 18	45	NA	NA	Cerebral hemispheres	NA	NA	NA	NA	NA	NA
2009	Michael Karremann et al	0-17	178	1	NA	Cerebral hemispheres	12	46	168	154	54–59.4	9
2010	Song KS et al	NA	27	NA	NA	NA	43	12	NA	24	NA	NA
2011	Perkins SM	3 - 20	24	NA	NA	Cerebral hemispheres	13.5	6	14	24	50.4 - 54	2
2012	Mansour Ansari et al	10-20	23	1.5	6.6	Cerebral hemispheres	16	2	10	23	54	2
2016	S. Mallick et al	7-21	27	NA	NA	Cerebral hemispheres	NA	14	20	27	60	7
2018	Present study	<21	20	1.5	NA	Cerebral hemispheres	NA	7	7	11	45-60	2

NA: not available, Pts: patients, OS: overall survival, GTR: gross total resection,

RT: Radiation therapy, ChemoRx: Chemotherapy

Table 3. Major Reported Studies of Pediatric Glioblastoma

Discussion

Since pediatric glioblastomas are rare as compared to adult glioblastomas, there are relatively fewer studies available. In this study, we report characteristics and outcomes of glioblastoma cases at a tertiary care hospital in Karachi, Pakistan. Our center is the only one with existing multidisciplinary teams for pediatric neuro-oncology under one roof including neurosurgery, radiation therapy, physiotherapy and rehabilitation for the management of childhood brain tumors. In our study, 55% of the patients were female. This is in accordance with a study conducted by Perkins et al which also showed a female preponderance **[**7**]**. However most other studies have shown male predilection in pediatric glioblastomas **[**7,18**]**. This difference could be due to smaller number of patients in our study. Female gender is associated with good prognosis in adult glioblastoma however our study did not demonstrate that for pediatric glioblastoma **[**7**]**. Majority of our patients (95%) had symptom duration of less than 6 months. A similar finding was reported by Das et al. where the mean duration of symptoms of 4.8 months **[**7**]**. Most common symptoms in our study were vomiting and headaches (92%), indicating raised intracranial pressure (ICP) and these were also reported from other identical studies **[**18,7**]**. Another study looking at clinical and radiological profile of glioblastoma patients reported that 78.5% of patients presented with signs of raised ICP. This was followed by seizures, focal neurologic deficits and visual disturbances **[**7**]**. Mallick et al reported that 60.8% of patients with glioblastoma presented with signs of raised ICP **[**16**]**.

MRI scan is the diagnostic modality of choice for pediatric glioblastoma for preoperative evaluation as well as post-operative follow up. Our study found that 20% of tumors were occupied in posterior fossa and 30% in frontal and fronto-parietal regions. Most other studies reported that location of most tumors was in the supratentorial region included cerebrum, frontal, temporal, parietal, and occipital followed by brain stem and cerebellum **[**14**]**. Supratentorial tumors have significantly better survival outcomes than infratentorial tumors **[**14**]**.

In our study, two patients had positive family history of multiple cancers. One of the patients had lymphomas, colorectal carcinomas and brain tumors in the family. Genetic testing for Constitutional Mismatch Repair Deficiency (CMMRD) was performed in collaboration with the consortium of CMMRD, which turned out to be negative. The other patient with a positive family history had a sibling who was diagnosed with glioblastoma at the age of three years outside Aga Khan Hospital. He died within a week of diagnosis and no staging workup was done due to clinical instability. Majority of Pediatric Glioblastomas occur sporadically and involve p53, PDGFR and H3K27M mutations among others. A small proportion has

been found to be associated with certain cancer predisposing syndromes and those with Constitutional mismatch repair deficiency (CMMRD) syndrome were found to have a strong tendency to develop glioblastoma at a young age. It arises from biallelic germ line mutations in one of the four MMR genes, MLH1, MSH2, MSH6 or PMS2. These are also the parent genes associated with Lynch syndrome. This condition is autosomal recessive and predisposes to the development of childhood cancers including central nervous system, hematological, colorectal and other malignancies **[**25**]**. This syndrome also predisposes to development of glioblastoma in patients **[**2**]**. Neurofibromatosis-1 (NF-1) occurs due to mutations in NF-1 tumor suppressor gene, which codes for neurofibromin protein. Loss of neurofibromin leads to excessive RAS activity, enhanced cell proliferation and eventually, formation of benign and malignant tumors including glioblastoma, although it is uncommon in NF1**[**10**]**. Turcot syndrome is also associated with the development of central nervous system and colorectal carcinoma at a young age. It is divided into two types based on the type of CNS tumor and the underlying molecular mutations. Type1 (TS1) involves defect in any of the mismatch repair genes (MLH1, MSH2, PMS2 and MSH6) and presence of glial tumors whereas type 2 (TS2) involves mutation in APC gene and occurrence of intestinal polyposis, colorectal carcinoma and medulloblastoma**[**9**]**. A few case reports have also mentioned occurrence of intracranial neoplasms including glioblastoma, in patients with Ollier disease and Maffucci syndrome. These rare syndromes cause dysplasia of cartilage, with involvement of the metaphyses and diaphyses of long bones **[**20**]**.

Management of pediatric glioblastoma involves maximal safe surgical resection followed by adjuvant radiotherapy with concomitant chemotherapy **[**7**]** however, there is no defined standard therapy because of small number of patient population. A study performing analysis of National Cancer data Base, for pediatric (ages 0-19) glioblastoma reported the management commonly involved the combination of surgery, radiotherapy and chemotherapy in most cases (48%). The highest survival benefit was also seen in patients who underwent aggressive surgery, chemotherapy and radiotherapy as their first line of treatment **[**15**]**. Due to different genomic characteristics, pediatric glioblastomas do not show the same response to chemotherapy drugs used for adult glioblastoma **[**14**]**. Temozolomide (TMZ) has been found to improve survival rates in adults with glioblastoma however, its role in improving outcome in pediatric glioblastoma remains unclear**[**11**]**. There has been conflicting data about benefit of TMZ. Cohen et al. compared the results of TMZ in the treatment of glioblastoma in a report from Children`s Oncology Group (ACNS0126 study) to Children`s Cancer Group study (CCG-945), a study that evaluated the role of adjuvant PCV (nitrosourea, vincristine, and prednisolone) for treatment in children.

The 3-year event-free survival rate for glioblastoma was 15 ± 5% in CCG-945 (P = 0.77) compared with 7 ± 4% in ACNS0126, hence this study showed that TMZ failed to improve outcome in pediatric glioblastoma **[**6**]**. In contrast, another study showed that combined adjuvant and concurrent TMZ was associated with better survival, compared to no adjuvant TMZ (median survival 41.9 months vs. 8.06 months; P = 0.0812). The same study also showed some survival benefit with six cycles of adjuvant chemotherapy with TMZ as compared to less than six cycles (median survival not reached (NR) vs. 9.5 months; P = 0.0005) **[**16**]**. A Phase 2 study of concurrent radiotherapy and TMZ followed by TMZ and lomustine (COG ACNS 0423) reported that addition of lomustine to TMZ as adjuvant therapy in ACNS0423 was associated with significantly improved outcome (Event free and overall survival) compared with the preceding COG ACNS0126 HGG study in which participants received temozolomide alone.(3 year event free survival was 0.22 (95% CI, 0.14-0.30) in ACNS0423 compared with 0.11 (95% CI, 0.05-0.18) in ACNS0126)**[**12**]**.

Another chemotherapy drug for recurrent or refractory adult glioblastoma is bevacizumab (BV), a monoclonal antibody against VEGF in combination with irinotecan (CPT11). However, similar results are not seen in children and there are only a few cases of pediatric glioblastoma treated by BV **[**24**]**. **[**8**]** In our study, table 2 shows that seven out of 20 patients (35%) received TMZ along with surgery and radiation. Of those one was lost to follow up and the rest of the patients expired due to rapid progression of the disease. The two patients who survived with residual disease at 23 months, both did not receive chemotherapy.

With the aim to improve care and outcome of pediatric brain tumors in our patient population, we have been discussing individual cases of pediatric brain tumors including glioblastoma with the team at The Hospital for Sick Children in a monthly neuro-oncology video teleconferencing program and implemented their recommendations such as changes in radiation dosages, need for immediate post-operative scans and second look surgeries. As a part of this program, we have also been sending histopathology samples review and molecular subgrouping with the aim of improving patient diagnosis. Recently, we have also started sending samples for bi-allelic mismatch repair gene disorder to identify genetic predisposition to GBM and other CNS tumors.

Glioblastoma has a poor prognosis worldwide with median overall survival rates ranging from 14-55 months and 2-year overall survival between 15-52% **[**14**]**. Table 3 summarizes the data from previous studies on glioblastoma. Median overall survival rate varied among different studies with few reporting 11 months **[**3**]** but majority reported between 43-54 months **[**22,21**]**. Most studies reported that the extent of resection was the most important factor associated with better outcome. GTR was better than STR and biopsy alone

[21,13,22**]**. Prognosis in patients with deep seated and incompletely resected tumors remains poor even with conventional therapy **[**7**]**. Some also reported that superficial and noncentral tumor location had better prognosis than deep and central tumors. **[**22,17**]**. Another study found that younger age, later year of diagnosis, supratentorial location and GTR were associated with better survival **[**14**]**. In one study by Perkins et al, no association was found between outcome and radiation dose and volume **[**19**]**. Similar to other studies published globally, our study also shows a poor prognosis. In table 2, out of sixteen patients who were followed, only 2 patients are alive with residual disease (12.5%) and out of those who survived with residual disease one underwent STR and received radiotherapy whereas the other one patient underwent GTR only. Massive disease on presentation, delayed diagnosis and inability to afford temozolamide due to severe financial constraints were some identified risk factors for poor outcome in our study.

To the best of our knowledge, this is the only study highlighting clinical characteristics and outcome of children and adolescents with glioblastoma, at a single tertiary health care center in Karachi, Pakistan. There are not many studies available locally and this will help us understand the disease impact in our part of the world. This will enable us to develop better pediatric neuro-oncology programs in public hospitals to improve outcomes and quality of life. There are some limitations in our study because of its small sample size and retrospective nature. More large scale studies are warranted locally to assess variation in disease presentation, characteristics, management and outcomes.

Conclusion

Pediatric glioblastoma is a rare entity and carries guarded prognosis with unfavorable outcomes. Further studies on genetic and molecular levels are needed in our part of the world to overcome the challenges in its management and to improve outcomes.

References

1. Ahmed N, Bhurgri Y, Sadiq S, Shakoor KA (2007) Pediatric brain tumours at a tertiary care hospital in Karachi. Asian Pac J Cancer Prev 8:399-404

2. AlHarbi M, Ali Mobark N, AlMubarak L, Aljelaify R, AlSaeed M, Almutairi A, Alqubaishi F, Hussain ME, Balbaid AAO, Said Marie A, AlSubaie L, AlShieban S, alTassan N, Ramkissoon SH, Abedalthagafi M (2018) Durable Response to Nivolumab in a Pediatric Patient with Refractory Glioblastoma and Constitutional Biallelic Mismatch Repair Deficiency. Oncologist 23:1401-1406. doi:10.1634/theoncologist.2018-0163

3. Ansari M, Nasrolahi H, Kani A-A, Mohammadianpanah M, Ahmadloo N, Omidvari S, Mosalaei A (2012) Pediatric glioblastoma multiforme: A single-institution experience. Indian journal of medical and paediatric oncology : official journal of Indian Society of Medical & Paediatric Oncology 33:155-160. doi:10.4103/0971-5851.103142

4. Bidwell SS, Peterson CC, Demanelis K, Zarins KR, Meza R, Sriplung H, Wiangnon S, Chotsampancharoen T, Chitapanarux I, Pongnikorn D, Daoprasert K, Suwanrungruang K, Chansaard W, Rozek LS (2019) Childhood cancer incidence and survival in Thailand: A comprehensive population-based registry analysis, 1990-2011. Pediatric blood & cancer 66:e27428. doi:10.1002/pbc.27428

5. Bilqees F, Samina K, Mohammad T, Khaleeq uz Z (2016) MORPHOLOGICAL PATTERN AND FREQUENCY OF CENTRAL NERVOUS SYSTEM TUMOURS IN CHILDREN. J Ayub Med Coll Abbottabad 28:44-46

6. Cohen KJ, Pollack IF, Zhou T, Buxton A, Holmes EJ, Burger PC, Brat DJ, Rosenblum MK, Hamilton RL, Lavey RS, Heideman RL (2011) Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol 13:317-323. doi:10.1093/neuonc/noq191

7. Das KK, Mehrotra A, Nair AP, Kumar S, Srivastava AK, Sahu RN, Kumar R (2012) Pediatric glioblastoma: clinico-radiological profile and factors affecting the outcome. Childs Nerv Syst 28:2055-2062. doi:10.1007/s00381-012-1890-x

8. Friedman GK, Spiller SE, Harrison DK, Fiveash JB, Reddy AT (2013) Treatment of children with glioblastoma with conformal radiation, temozolomide, and bevacizumab as adjuncts to surgical resection. J Pediatr Hematol Oncol 35:e123-126. doi:10.1097/MPH.0b013e318282cd7f

9. Giunti L, Cetica V, Ricci U, Giglio S, Sardi I, Paglierani M, Andreucci E, Sanzo M, Forni M, Buccoliero AM, Genitori L, Genuardi M (2009) Type A microsatellite instability in pediatric gliomas as an indicator of Turcot syndrome. European journal of human genetics : EJHG 17:919-927. doi:10.1038/ejhg.2008.271

10. Graf N (2010) Glioblastoma in children with NF1: the need for basic research. Pediatr Blood Cancer 54:870-871. doi:10.1002/pbc.22487

11. Immanuel V, Kingsley PA, Negi P, Isaacs R, Grewal SS (2017) Variegated Colors of Pediatric Glioblastoma Multiforme: What to Expect? Rare Tumors 9:6552. doi:10.4081/rt.2017.6552

12. Jakacki RI, Cohen KJ, Buxton A, Krailo MD, Burger PC, Rosenblum MK, Brat DJ, Hamilton RL, Eckel SP, Zhou T, Lavey RS, Pollack IF (2016) Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study. Neuro Oncol 18:1442-1450. doi:10.1093/neuonc/now038

13. Karremann M, Butenhoff S, Rausche U, Pietsch T, Wolff JEA, Kramm CM (2009) Pediatric giant cell glioblastoma: New insights into a rare tumor entity. Neuro Oncol 11:323-329. doi:10.1215/15228517-2008-099

14. Lam S, Lin Y, Zinn P, Su J, Pan IW (2018) Patient and treatment factors associated with survival among pediatric glioblastoma patients: A Surveillance, Epidemiology, and End Results study. J Clin Neurosci 47:285-293. doi:10.1016/j.jocn.2017.10.041

15. Liu M, Thakkar JP, Garcia CR, Dolecek TA, Wagner LM, Dressler EVM, Villano JL (2018) National cancer database analysis of outcomes in pediatric glioblastoma. Cancer medicine 7:1151-1159. doi:10.1002/cam4.1404

16. Mallick S, Gandhi AK, Joshi NP, Kumar A, Puri T, Sharma DN, Haresh KP, Gupta S, Julka PK, Rath GK, Sarkar C (2015) Outcomes of pediatric glioblastoma treated with adjuvant chemoradiation with temozolomide and correlation with prognostic factors. Indian J Med Paediatr Oncol 36:99-104. doi:10.4103/0971-5851.158838

17. Marchese MJ, Chang CH (1990) Malignant astrocytic gliomas in children. Cancer 65:2771-2778

18. Nikitovic M, Stanic D, Pekmezovic T, Gazibara MS, Bokun J, Paripovic L, Grujicic D, Saric M, Miskovic I (2016) Pediatric glioblastoma: a single institution experience. Childs Nerv Syst 32:97-103. doi:10.1007/s00381-015-2945-6

19. Perkins SM, Rubin JB, Leonard JR, Smyth MD, El Naqa I, Michalski JM, Simpson JR, Limbrick DL, Park TS, Mansur DB (2011) Glioblastoma in children: a single-institution experience. Int J Radiat Oncol Biol Phys 80:1117-1121. doi:10.1016/j.ijrobp.2010.03.013

20. Ranger A, Szymczak A, Hammond RR, Zelcer S (2009) Pediatric thalamic glioblastoma associated with Ollier disease (multiple enchondromatosis): a rare case of concurrence. J Neurosurg Pediatr 4:363-367. doi:10.3171/2009.5.peds08422

21. Sanchez-Herrera F, Castro-Sierra E, Gordillo-Dominguez LF, Vaca-Ruiz MA, Santana-Montero B, Perezpena-Diazconti M, Gonzalez-Carranza V, Torres-Garcia S, Chico-Ponce de Leon F (2009) Glioblastoma multiforme in children: experience at Hospital Infantil de Mexico Federico Gomez. Childs Nerv Syst 25:551-557. doi:10.1007/s00381-008-0780-8

22. Song KS, Phi JH, Cho BK, Wang KC, Lee JY, Kim DG, Kim IH, Ahn HS, Park SH, Kim SK (2010) Long-term outcomes in children with glioblastoma. Journal of neurosurgery Pediatrics 6:145-149. doi:10.3171/2010.5.peds09558

23. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, Villano JL (2014) Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev 23:1985-1996. doi:10.1158/1055-9965.epi-14-0275

24. Umeda K, Shibata H, Saida S, Hiramatsu H, Arakawa Y, Mizowaki T, Nishiuchi R, Adachi S, Heike T, Watanabe K (2015) Long-term efficacy of bevacizumab and irinotecan in recurrent pediatric glioblastoma. Pediatr Int 57:169-171. doi:10.1111/ped.12414

25. Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, Gerdes AM, Goldberg Y, Ilencikova D, Muleris M, Duval A, Lavoine N, Ruiz-Ponte C, Slavc I, Burkhardt B, Brugieres L (2014) Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 51:355-365. doi:10.1136/jmedgenet-2014-102284.

Medtronic