Turk Neurosurg 32(1):135-142, 2022

Original Investigation

DOI: 10.5137/1019-5149.JTN.34801-21.2

Received: 07.04.2021
Accepted: 17.05.2021

Published Online: 26.10.2021

Clinical Features, Treatment and Outcome of Childhood Glial Tumors

Buket KARA[1], Kubra ERTAN[2], Pinar KARABAGLI[3], Hakan KARABAGLI[4], Guler YAVAS[5], Ahmet Okay CAGLAYAN[6,7], Yavuz KOKSAL[1]

[1]Selcuk University, Faculty of Medicine, Department of Pediatric Hematology and Oncology, Konya, Turkey
[2]Selcuk University, Faculty of Medicine, Department of Pediatrics, Konya, Turkey
[3]Selcuk University, Faculty of Medicine, Department of Pathology, Konya, Turkey
[4]Selcuk University, Faculty of Medicine, Department of Neurosurgery, Konya, Turkey
[5]Selcuk University, Faculty of Medicine, Department of Radiation Oncology, Konya, Turkey
[6]Yale University School of Medicine, Departments of Neurosurgery, Neurobiology, and Genetics, New Haven, CT, USA
[7]Dokuz Eylul University, Department of Medical Genetics, Izmir, Turkey

Corresponding author: Buket KARA ✉ buketkara1001@gmail.com

ABSTRACT

AIM: To evaluate the clinical features, treatment approaches, and outcomes of glial tumors in children.

MATERIAL and METHODS: Files (2006 to 2020) of children diagnosed with glial tumors and followed-up were reviewed retrospectively. Information regarding demographic and clinical characteristics, treatment approaches, and outcomes were retrieved from the patients' files.

RESULTS: Of the total of 180 pediatric patients diagnosed with brain tumors, 73 (40.6%) had glial tumors. The children with astrocytoma were in the age range of 2–18 years (median age: 8.7 years), while the ages of children with ependymoma ranged from three months to 10 years (median age: 3 years). This difference was statistically significant ($p<0.0001$). The male to female ratio was 1.6. The most common symptoms or signs were headaches (n=34, 46.6%), abnormal gait or coordination (n=22, 30.2%), vomiting (n=21, 28.8%), and cranial nerve palsies (n=20, 27.4%). The pathological diagnoses were astrocytomas (n=53, 72.6%), oligodendroglial tumors (n=2, 2.7%), ependymoma (n=15, 20.7%), and other glial tumors (n=3, 4.1%). The most common tumor location was supratentorial (n=42, 57.5%), while midline glioma was detected in seven patients. The 5-year overall survival (OS) rate of all glial tumors, astrocytoma, and ependymoma was 42%, 40%, and 55%, respectively. The 5-year OS rate of the tumor Grade I, II, III, and IV was 77.2%, 45%, 32%, and 0%, respectively ($p<0.0001$). The 5-year OS rate of supratentorial, infratentorial, and spinal tumors was 25.6%, 63.6%, and 50%, respectively ($p=0.021$). In Cox regression analysis, it was found that the tumor resection and grade had an effect on the tumor prognosis.

CONCLUSION: Treatment results are not satisfactory in high-grade astrocytomas. There is a need for new treatment approaches that would take cognizance of molecular features and adopt multidisciplinary approaches.

KEYWORDS: Glial tumors, Children, Treatment approaches, Outcome

ABBREVIATIONS: CNS: Central nervous system, **OS:** Overall survival

Buket KARA : 0000-0003-4737-1901
Kubra ERTAN : 0000-0002-9981-8413
Pinar KARABAGLI : 0000-0002-5558-0175
Hakan KARABAGLI : 0000-0002-1184-3965
Guler YAVAS : 0000-0001-9481-6307
Ahmet Okay CAGLAYAN : 0000-0002-2332-322X
Yavuz KOKSAL : 0000-0002-9190-7817

INTRODUCTION

Central nervous system (CNS) tumors are the second most common malignancy in children (after leukemia) in developed countries. In Turkey, they are the third most common malignancy after leukemia and lymphoma, accounting for 13.3% of all malignancy in children (9). Childhood glial tumors can be classified as astrocytoma, oligodendrogliomas, ependymomas, and other glial tumors (5). In children, astrocytomas and ependymomas are responsible for approximately 50% and 9% of all CNS tumors, respectively (6). In Turkey, the prevalence of asyrocytoma and ependymoma in childhood was found to be 19% and 7.6% by Varan et al. (13), and Akyuz et al. (2), respectively.

The symptoms and signs of CNS tumors are related to their location, growth rate, size, and age of patient at the time of diagnosis. Headache, vomiting without nausea, disturbances of gait and balance, cranial nerve palsies, impaired vision, altered mental status, seizures, endocrine abnormalities, and cranial enlargement in infancy are common symptoms or signs in children with CNS tumor (6).

In contrast to the high-grade glial tumors, outcomes are very promising in low-grade astrocytomas using multidisciplinary approaches. In ependymomas, the main prognosis determinant is complete removal of the tumor. While the 5-year overall survival (OS) rate is 64%–86% in patients with complete resection, it is much lower in patients with subtotal resection (1,6).

In this study, we aimed to evaluate the clinical features, treatment approaches, and outcomes in children with glial tumors.

MATERIAL and METHODS

Approval for the study was obtained from the local ethics committee of Selcuk University (No: 2021/176, Date: Apr 07, 2021). Informed consent was not obtained from the patients included in the study or their guardians, since it was a retrospective study. In addition, this study was conducted in accordance to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines.

Patients

From 2006 to 2020, children diagnosed with glial tumor and followed-up at our clinic were included in this study. Pontine and optic gliomas, which are both diagnosed by clinical and radiological findings, were excluded from the study. The patients' demographic and clinical features, surgery notes, pathological features, treatment approaches, and outcomes were retrieved from the patients' files. The location, diagnosis, and grade of the tumor were noted. In addition, accompanying conditions, such as neurofibromatosis type 1 or constitutional mismatch repair deficiency, were noted. The criteria of European consortium for constitutional mismatch repair deficiency were used for constitutional mismatch repair deficiency syndrome (15).

The patients were divided into two groups according to their age: < 3 years old and ≥ 3 years old.

Pathological diagnoses were divided into astrocytoma, oligodendroglioma, ependymoma, and other glial tumors. In addition, they were divided according to their grades into low (Grade I and II) and high grade (Grade III and IV).

According to the localization of the tumors, they were divided into supratentorial, infratentorial, spinal, and widespread.

Surgical resection was the first line therapy in patients with glial tumors. If possible, the primary goal was complete removal of the tumor. In patients with low-grade astrocytomas, if total or gross total resection were performed, radiotherapy and/or chemotherapy was generally preferred in order to avoid relapse or progression. However, radiotherapy and chemotherapy were routinely used in high-grade astrocytic tumors. In children younger than three years of age, if possible, radiotherapy was postponed until the age of three. Also, if possible, radiotherapy was omitted.

Gross total resection was defined as the removal of all tumors, as gauged by magnetic resonance imaging. Subtotal resection was defined as the removal of less than 90% of the tumor volume. Biopsy only was defined as the removal of less than 25% of the tumor volume. Our patients were grouped according to surgical findings as those who underwent gross total resection, subtotal resection, and biopsy.

Generally, if necessary, the preferred chemotherapy in low-grade astrocytic tumors comprised of carboplatin and vincristine (6). Chemotherapy protocols containing cisplatin and etoposide, or temozolomide were preferred in high-grade glial tumors (6). For ependymomas, after surgery, generally cranial radiotherapy and chemotherapy regimens containing cisplatin and etoposide were preferred (6).

Statistical Analysis

SPSS software for Windows, Version 16.0 was used for the statistical analysis. For categorical data, frequencies and percentages were computed. The range value (minimum and maximum values), together with the median value, was given for numerical data, since their distribution was not normal. Chi-square test or Fischer exact test was used for comparison of categorical data and Mann Whitney *U* test was used for comparison of numerical data. Kaplan–Meier survival analysis was used for survival analysis. Log-rank test and Cox regression analysis were used to investigate factors affecting survival. Since the number of patients diagnosed with oligodendroglial tumors and other glial tumors was low, they were not included in the survival analysis. A statistically significant difference was accepted if the alpha (p) value was less than 0.05.

RESULTS

Demographic Features

During the study period, 180 of 950 children (19%) with malignant disease had CNS tumors, while 73 of 180 pediatric patients with brain tumors had glial tumors (40.6%). The age of all patients ranged from three months to 18 years. Of the 73 patients with glial tumor, 45 were male (61.6%), while 28 were female (38.4%), with a male to female ratio of 1.6.

Table I: The Patients' Clinical Manifestations

Symptoms & Signs	n	%
Headaches	34	46.6
Abnormal gait or coordination	22	30.2
Vomiting	21	28.8
Cranial nerve palsies	20	27.4
Lethargy/fatigue	14	19.2
Hemiparesis	14	19.2
Seizures	13	17.8
Dysdiadochokinesia	11	15.1
Dismetria	11	15.1
Cranial nerve palsies	10	13.7
Cafe au lait spots	10	13.7
Ataxia	5	6.8
Babinski sign	4	5.5
Nistagmus	4	5.5
Altered level of consciousness	3	4.1
Behavior changes and/or declining school performance	2	2.7
Papilledema	2	2.7
Macrocephaly	1	1.4
Paraparesis	1	1.4
Axillary freckling	1	1.4
Bulging fontanelle	1	1.4

Oligodendroglial tumors and other glial tumors were not included in the age comparison analysis, since the number of patients in these groups was low. The children with astrocytomas were in the age range of 2–18 years (median age: 8.7 years), while the ages of children with ependymoma ranged from three months to 10 years (median age: 3 years). Mann Whitney *U* test showed that there was a statistical difference between the ages of children with astrocytic tumors and those with ependymoma (U=86,000; $p<0.0001$, $r=0.56$). The effect size was large.

Clinical Features

The most common symptoms or signs were headaches (n=34, 46.6%), abnormal gait or coordination (n=22, 30.2%), vomiting (n=21, 28.8%), and cranial nerve palsies (n=20, 27.4%) (Table I). Ten patients had *cafe au lait* spots (13.7%) and three of these patients were neurofibromatosis type 1, while the other seven had CMMRD syndrome (4).

The most common tumor locations were supratentorial (n=42, 57.5%) and infratentorial (n=28, 34.4%). Midline glioma was detected in seven patients.

A total of 33 patients underwent gross total tumor resection (45.2%), 29 patients underwent surgery for subtotal tumor resection (39.7%), and biopsy was performed for 11 patients (15.1%). In patients with midline glial tumor, biopsy (n=3) and subtotal resection (n=4) were performed.

Pathological diagnoses were astrocytomas (n=53, 72.6%), oligodendroglial tumors (n=2, 2.7%), ependymoma (n=15, 20.7%), and other glial tumors (n=3, 4.1%). Pathological diagnosis and pathological subgroups are listed in Table II.

Table II: Pathologic Groups of the Patients with Glial Tumor

		n (n=73)	%
Astrocytomas (n=53, 72.6%)	Anaplastic astrocytoma	10	13.7
	Glioblastoma	11	15.1
	Pilocytic astrocytoma	23	31.5
	Subependymal giant cell astrocytoma	1	1.4
	Diffuse astrocytoma	3	4.1
	Astrocytoma, NOS	2	2.7
	Astroblastoma	1	1.4
	Anaplastic pleomorphic xanthoastrocytoma	1	1.4
Oligodendroglial tumors (n=2, 2.7%)	Anaplastic oligodendroglioma, NOS	1	1.4
	Oligodendroglioma	2	2.7
Ependymomas (n=15, 20.7%)	Ependymoma	7	9.6
	Anaplastic ependymoma	8	10.9
Other glial tumors (n=3, 4.1%)	High grade glial tumor	3	4.1

Constitutional Mismatch Repair Deficiency Syndrome

Constitutional mismatch repair deficiency syndrome diagnosis was done by whole exome sequencing on DNA samples extracted from peripheral blood materials in six children with high-grade astrocytoma from three families. Three children of the first family had the bi-allelic *MSH6* mutation [c.478C>T, (p.Gln160Ter)] (4), two children of the second family had the bi-allelic *MSH6* [c.2871dupC (p.Phe958LeufsTer5)]. The first malignant disease was hepatoblastoma in the first child of the second family, while acute lymphoblastic leukemia was the first malignant disease in the second child (7). Their mandatory heterozygous parents have been followed-up by Lynch syndrome' surveillance program. In the index case from the third family, probably the novel bi-allelic *MLH1* [c.236G>A. (p.Arg79Lys)] mutation was identified. However, we were not able to perform Sanger sequencing to confirm zygosity status and its segregation.

In five patients with high-grade astrocytoma, immunohistochemistry performed to detect the loss of mismatch repair protein expression. The result revealed that none of the patients had the loss of mismatch repair protein expression detected by immunohistochemistry.

Table III: Five Years' Survival of Patients With Glial Tumor (Univariate Analyses)

	5-year overall survival (%)	p
All patients	42	
Astrocytomas	40	
Epandimomas	55	
Grades		**< 0.0001**
Grade I	77.2	
Grade II	45	
Grade III	32	
Grade IV	0	
Localization		**0.021**
Supratentorial	25.6	
Infratentorial	63.6	
Spinal	50	
Resection		0.59
Gross total	49.4	
Subtotal	42.6	
Biopsy	25	

Survival Analyses

The 5-year OS rates of all glial tumors, astrocytomas, and ependymomas were 42%, 40%, and 55%, respectively (Table III) (Figure 1). For all glial tumors, the 5-year OS rates of Grade I, II, III, and IV were 77.2%, 45%, 32%, and 0%, respectively. A statistically significant difference was found between them by log-rank analysis (p<0.0001) (Figure 2 and 3). The 5-year OS rates of supratentorial, infratentorial, and spinal tumors were 25.6%, 63.6%, and 50%, respectively. There was a statistically significant difference between them by log-rank analysis (p=0.021) (Figure 4). According to the resection status, the 5-year OS rates of gross total, subtotal, and biopsy were 49.4%, 42.6%, and 25%, respectively (Figure 5). Although the 5-year OS rate was higher in patients who underwent gross total and subtotal resection than those who underwent biopsy, the difference was not statistically significant (p=0.59).

In the Cox regression analysis, it was observed that the tumor resection and grade had an effect on the tumor prognosis (Table IV).

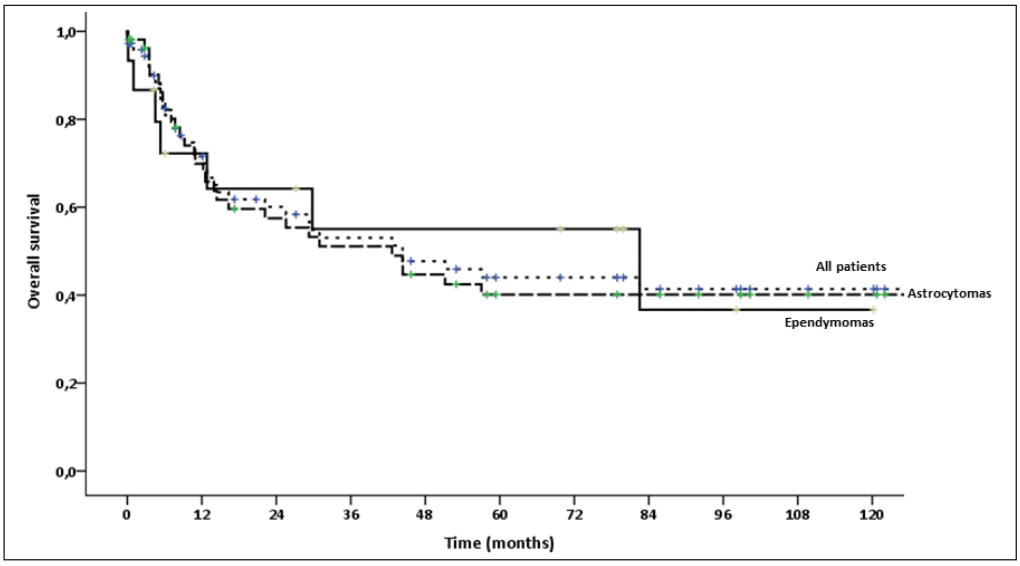

Figure 1: The overall survival of all glial tumor, astrocytomas and ependimomas.

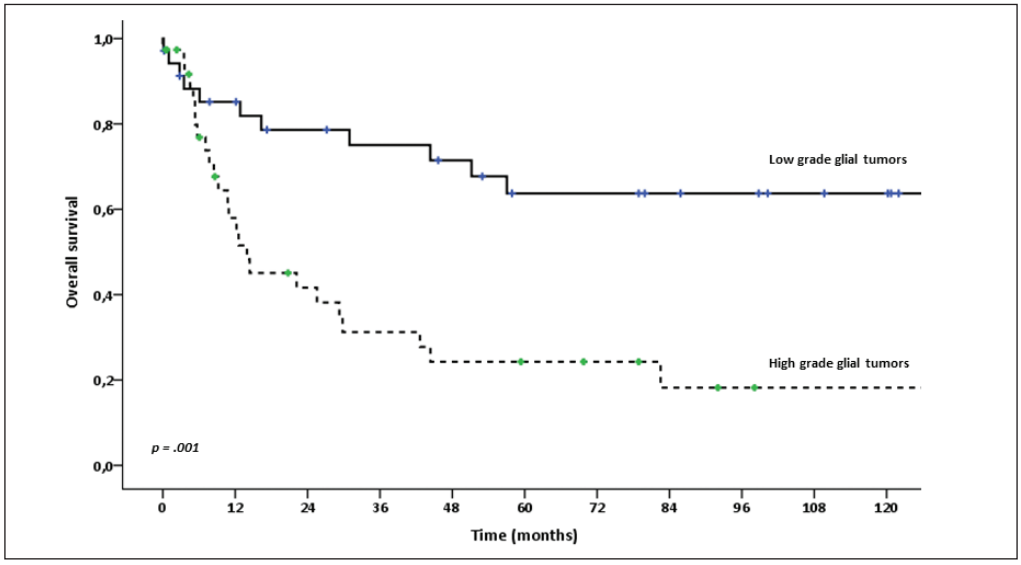

Figure 2: Overall survival according to grades.

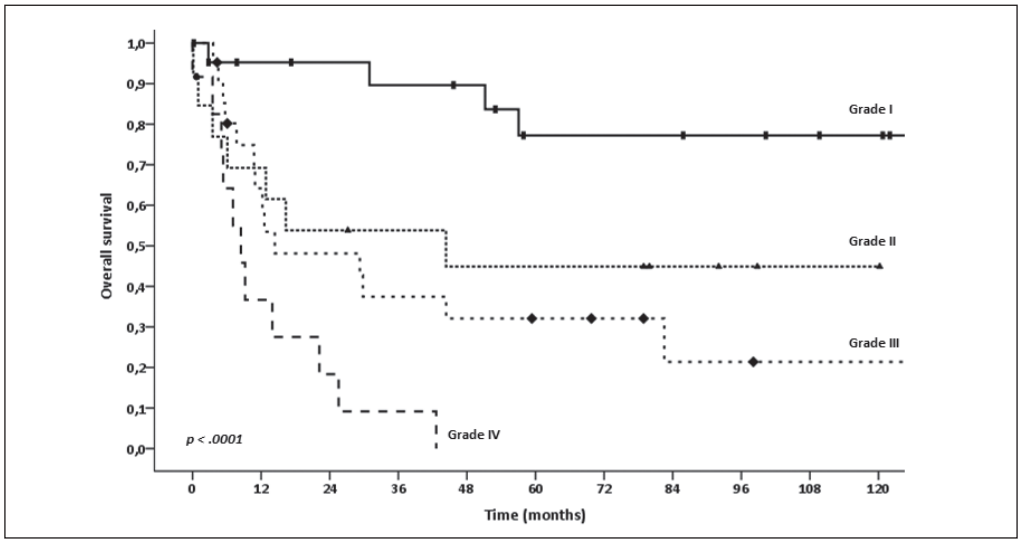

Figure 3: Overall survival of low- and high grade glial tumor.

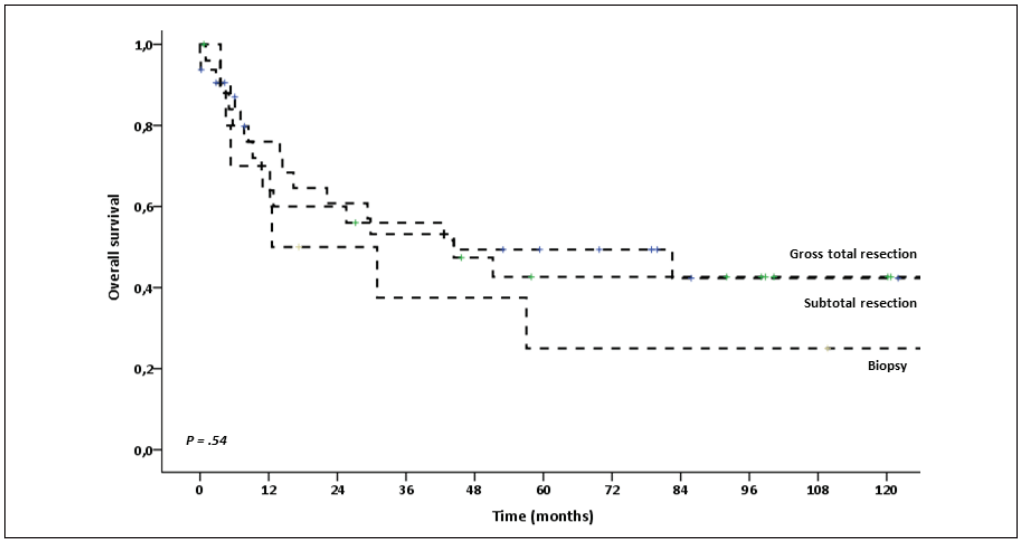

Figure 4: Overall survival of localization.

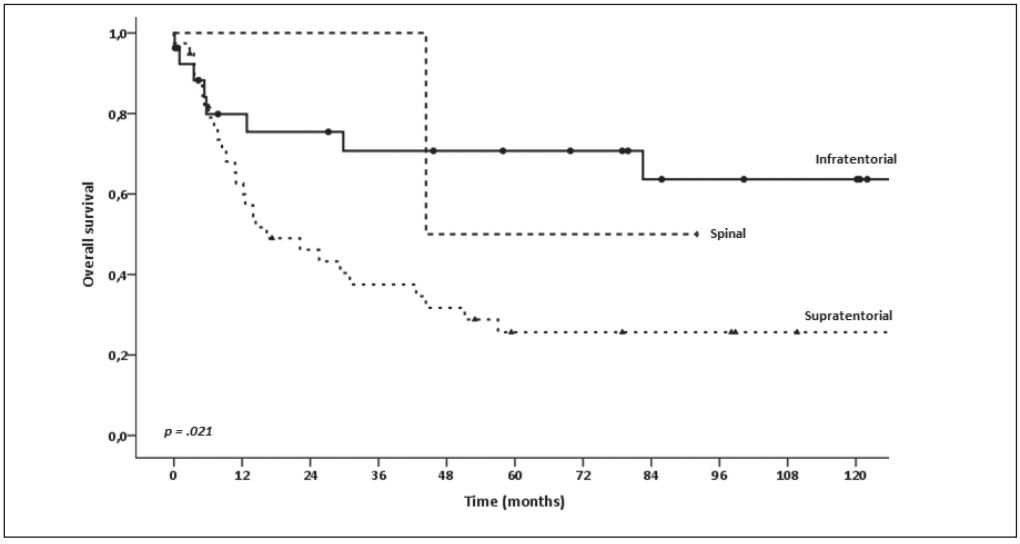

Figure 5: Overall survival of resection status.

Table IV: Multivariate Analysis of the Patients with Glial Tumors

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp (B)	
							Lower	Upper
Diagnosis (astrocytomas / ependimoma)	.357	.549	.424	1	0.515	1.429	.488	4.188
Gender (male/female)	-.150	.357	.177	1	0.674	.861	.427	1.734
Tumor localization								
Supratentorial			1.049	2	0.592			
Infratentorial	.756	1.134	.445	1	0.505	2.130	.231	19.664
Spinal	.990	1.054	.883	1	0.347	2.692	.341	21.228
Surgery								
Gross total			6.078	2	**0.048**			
Subtotal	-1.255	.519	5.854	1	**0.016**	.285	.103	.788
Biopsy	-1.147	.557	4.239	1	**0.040**	.318	.107	.946
Grade								
Grade I			21.162	3	**<0.0001**			
Grade II	-3.122	.680	21.076	1	**<0.0001**	.044	.012	.167
Grade III	-.995	.544	3.346	1	0.067	.370	.127	1.074
Grade IV	-.847	.489	2.998	1	0.083	.429	.164	1.118

DISCUSSION

While CNS tumors are the second most common malignancy after leukemia in developed countries, they are the third most common malignancy in Turkey (9). For children, either *World Health Organization* classification (based on tumor histology and molecular parameters) or the classification proposed by the *International Classification of Childhood Cancer* (based on tumor location and morphology) is used for CNS tumors.

Gliomas are CNS tumors that originate from astrocytes, oligodendrocytes, and ependymal cells. They account for about half of all CNS tumors in children and adolescents. Astrocytomas and ependymomas constitute the majority of gliomas in children (11). In this retrospective study, we aimed to evaluate the clinical characteristics, treatment approaches, outcomes, and factors affecting outcomes in pediatric patients with glial tumors.

As emphasized above, it is possible to classify glial tumors under three main headings: astrocytomas, oligodendrogliomas, and ependymomas (5). In our series, CNS tumors constituted approximately 19% of all childhood malignancies and glial tumors constituted approximately 40.6% of all childhood CNS tumors. Astrocytomas and ependymomas constituted 93.3% of the patients with glial tumors in our study. Oligodendrogliomas or other glial tumors constituted a very small proportion of our series. One of the important limitations in our study is that molecular genetics and cytogenetics features of tumors were not performed due to lack of availability of genetic data or genetic techniques in our center during study period.

In children, symptoms or signs, such as increased intracranial pressure, motor and visual system abnormalities, weight loss, macrocephaly, growth failure, and precocious puberty, are warning signs for CNS tumors (14). The most common symptoms or signs of our patients were headaches, abnormal gait or coordination, vomiting, and cranial nerve palsies.

In children, the locations of CNS tumors are infratentorial (60%) and supratentorial (40%) (6). In childhood, midline glial tumors constitute approximately 10% of all pediatric CNS tumors; however, the most important challenge is that curative surgery is not possible in these patients. At least a stereotactic biopsy should be performed, so that the diagnosis and treatment can be planned as much as possible (8,12). In our study, midline glioma was detected in seven patients.

The excision of the mass is the initial treatment for both low-grade and high-grade glial tumors. The main purpose of excision is complete removal of the mass, if possible. Gross total resection is desirable. While gross total resection is generally possible in hemispheric tumors, it is unlikely possible in midline glial tumors. Another determining factor in resection is the grade. Gross total resection is possible in low-grade tumors, especially if they are hemispherically located. However, in high-grade tumors, it is not possible due to the infiltrative nature of the tumor. Another problem in high-grade glial tumors is being deep-seated and multifocal (1-3,6,12).

In low-grade astrocytoma, while the general treatment approach is surgery, radiotherapy and/or chemotherapy is usually an option for progression or relapse. Also, while only surgery is usually sufficient for grade I ependymomas, radiotherapy is recommended in addition to surgery for grade II and III. Although the benefit of chemotherapy in these patients cannot be fully demonstrated, there are studies demonstrating that the use of chemotherapy provides a significant survival advantage for patients with postoperative residual tumors (2,6,10). In our patients with low-grade astrocytomas, only resection was performed. In ependymomas, platinum-based chemotherapies were used in patients with grade II or III and in whom complete resection could not be performed. Chemotherapy was not used in only three patients. One of our most important challenges in these patients and even in all CNS tumors is that surgeries are performed by neurosurgeons who have no experience in neuro-oncology, although nowadays it is gradually decreasing.

General treatment approaches in high-grade astrocytomas are surgery, radiotherapy or concomitant chemo-radiotherapy, and adjuvant chemotherapy (6,13,16). Various adjuvant chemotherapy regimens can be used. In our patients with high-grade astrocytic tumors, a chemotherapy protocol containing cisplatin and etoposide was used in all patients, except in one patient who used temozolomide as adjuvant therapy.

In patients whose tumor were totally resected, treatment outcomes of low-grade astrocytomas located posterior fossa and supratentorial region are 100% and 76%–100%, respectively, and treatment outcomes are good in low-grade astrocytic tumors that cannot be fully resected (3,6,13). However, high-grade astrocytic tumors have a worse outcome. In our study, 5-year OS rates of all glial tumors, astrocytomas, and ependymomas were 42%, 40%, and 55%, respectively. The 5-year OS rates of Grade I, II, III, and IV were 77.2%, 45%, 32%, and 0%, respectively ($p<0.0001$). The 5-year OS rates of supratentorial, infratentorial, and spinal tumors were 25.6%, 63.6% and 50%, respectively ($p=0.021$). In the Cox regression analysis, it was observed that resection type and tumor grade had an effect on prognosis. Our outcomes are consonant with the data in literature. However, especially in high-grade astrocytomas, our patients' outcomes were not satisfactory as in the whole world.

CONCLUSION

Treatment outcomes are good in low-grade glial tumors, even if complete resection cannot be performed. However, the treatment outcomes in patients with high-grade astrocytomas are not satisfactory. There is a need for new treatment approaches that would take cognizance of molecular features and adopt multidisciplinary approaches.

ACKNOWLEDGMENTS

We thank all the medical doctors and health care team who contributed in the diagnosis, treatment and follow up of the children with cancer over the years in the Selcuk University, Faculty of Medicine.

Genetic analysis of CMMRD patients included in this study was supported by the Gregory M. Kiez and Mehmet Kutman Foundation.

AUTHORSHIP CONTRIBUTION

Study conception and design: YK, HK

Data collection: BK, KE

Analysis and interpretation of results: YK, PK

Draft manuscript preparation: YK, PK

Critical revision of the article: HK, PK, GY, AOC

All authors (BK, KE, PK, HK, GY, AOC, YK) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Agaoglu FY, Ayan I, Dizdar Y, Kebudi R, Gorgun O, Darendeliler E: Ependymal tumors in childhood. Pediatr Blood Cancer 45: 298-303, 2005
2. Akyuz C, Emir S, Akalan N, Soylemezoglu F, Kutluk T, Buyukpamukcu M: Intracranial ependymomas in childhood--a retrospective review of sixty-two children. Acta Oncol 39: 97-100, 2000
3. Bilginer B, Narin F, Oguz KK, Uzun S, Soylemezoglu F, Akalan N: Benign cerebellar pilocytic astrocytomas in children. Turk Neurosurg 21:22-26, 2011
4. Erson-Omay EZ, Çağlayan AO, Schultz N, Weinhold N, Omay SB, Ozduman K, Koksal Y, Li J, Serin Harmancı A, Clark V, Carrión-Grant G, Baranoski J, Caglar C, Barak T, Coskun S, Baran B, Kose D, Sun J, Bakircioglu M, Moliterno Gunel J, Pamir MN, Mishra-Gorur K, Bilguvar K, Yasuno K, Vortmeyer A, Huttner AJ, Sander C, Gunel M: Somatic POLE mutations cause an ultramutated giant cell high-grade glioma subtype with better prognosis. Neuro Oncol 17:1356-1364, 2015
5. Frosch MP: Central nervous system. In: Kumar V, Abbas AK, Aster JC (eds), Robins Basic Pathology Philadelphia: Elsevier-Saunders, 2013:811-850
6. Hanson DR, Atlas MP: Central nervous system malignancies. In: Lanzkowsky P, Lipton JM, Fish JD (eds), Lanskowsky's Manual of Pediatric Hematology and Oncology. Amsterdam, Elsevier, 2016: 453-472
7. Kara B, Koksal Y: Pediatric lymphoma and solid tumors associated with cancer susceptibility syndromes. J Pediatr Hematol Oncol 42:438-445, 2020
8. Khalid SI, Kelly R, Adogwa O, Carlton A, Tam E, Naqvi S, Kushkuley J, Ahmad S, Woodward J, Khanna R, Davison M, Munoz L, Byrne R: Pediatric brainstem gliomas: A retrospective study of 180 patients from the SEER database. Pediatr Neurosurg 54:151-164, 2019
9. Kutluk MT, Yesilipek A: Pediatric cancer registry in Turkey 2009-2018 (TPOG & TPHD). J Clin Oncol 37 Supply 15: e21510, 2019
10. Needle MN, Goldwein JW, Grass J, Cnaan A, Bergman I, Molloy P, Sutton L, Zhao H, Garvin JH Jr, Phillips PC: Adjuvant chemotherapy for the treatment of intracranial ependymoma of childhood. Cancer 80:341-347, 1997
11. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol 20 Suppl 4: iv1-iv86, 2018
12. Tanrikulu B, Ozek MM: Current clinical practice about pediatric midline gliomas in the scope of molecular era. Turk Neurosurg 30: 595-603, 2020
13. Varan A, Akyuz C, Akalan N, Atahan L, Soylemezoglu F, Selek U, Yalcin B, Kutluk T, Buyukpamukcu M: Astrocytic tumors in children: Treatment results from a single institution. Childs Nerv Syst 23:315-319, 2007
14. Wilne S, Collier J, Kennedy C, Koller K, Grundy R, Walker D: Presentation of childhood CNS tumours: A systematic review and meta-analysis. Lancet Oncol 8:685-695, 2007
15. 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; EU-Consortium Care for CMMRD (C4CMMRD): Diagnostic criteria for constitutional mismatch repair deficiency syndrome: Suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 51:355-365, 2014
16. Yazici G, Zorlu F, Cengiz M, Ozyigit G, Eren G, Yuce D, Varan A, Akyuz C, Akalan N, Gurkaynak M: High-grade glioma in children and adolescents: A single-center experience. Childs Nerv Syst 32:291-297, 2016