Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2020;45(1):56-62
DOI: 10.17826/cumj.638237

ARAŞTIRMA / RESEARCH

Medulloblastoma in children: 84 patients from a single institution

Çocukluk çağında medulloblastom: Tek merkezden 84 hasta

Serhan Kupeli[1], Gülay Sezgin[1], İbrahim Bayram[1], Atila Tanyeli[1]

[1]Cukurova University Faculty of Medicine, Department of Pediatric Oncology and Pediatric Bone Marrow Transplantation Unit, Adana, Turkey

Cukurova Medical Journal 2020;45(1):56-62

Abstract

Purpose: Medulloblastoma is the most common malignant brain tumor in children. Current treatment strategy for medulloblastoma includes surgery, followed by radiotherapy and chemotherapy. In the present study, we analyze the clinical features, risk categories, treatment, and outcome of the patients with medulloblastoma treated in our institution in the last 15 years.
Materials and Methods: 84 patients with a diagnosis of medulloblastoma at our institution between January 2004 and December 2018 were included in the sudy. Hospital files of the patients were investigated and clinical and epidemiological characteristics, histopathology, treatment modalities, prognostic criteria and survival rates of patients were noted in data form.
Results: There were 45 males and 39 females with a median age of 8 years at the time of diagnosis. Approximately 12% of the patients were Syrian refugees. 54 patients were included in average-risk group and 30 in high-risk group based on the age at the time of diagnosis, extent of the residual tumor after surgery and Chang staging system. Five-year overall survival and event-free survival rates were 58.1% and 57.6% respectively. The prognostic factors having a statistically significant influence on survival were histopathological group, type of surgery and risk group. Only the risk group was found to have an impact on survival in multivariate analysis.
Conclusion: Risk group, utilizing the age of the patient, degree of surgical resection and metastatic disease, is the most important parameter having an impact on survival of patients with medulloblastoma.
Keywords:. Medulloblastoma, treatment, prognosis, children

Öz

Amaç: Medulloblastom, çocuklarda en sık görülen malign beyin tümörüdür. Medulloblastom için mevcut tedavi stratejisi cerrahi, ardından radyoterapi ve kemoterapiyi içerir. Bu çalışmada kurumumuzda son 15 yılda tedavi edilen medulloblastomlu hastaların klinik özellikleri, risk kategorileri, tedavileri ve sonuçlar analiz edilmiştir.
Gereç ve Yöntem: Çalışmamıza Ocak 2004 - Aralık 2018 tarihleri arasında medulloblastom tanısı alan 84 hasta dahil edildi. Hastaların hastane dosyaları incelendi ve klinik ve epidemiyolojik özellikler, histopatoloji, tedavi yöntemleri, prognostik kriterler ve sağkalım oranları veri formunda not edildi.
Bulgular: Tanı anında ortanca yaşı 8 olan 45 erkek ve 39 kadın vardı. Hastaların yaklaşık % 12'si Suriyeli mültecilerdi. Tanı sırasındaki yaşa, cerrahi sonrası rezidüel tümörün boyutuna ve Chang evreleme sistemine bağlı olarak standart risk grubuna 54, yüksek risk grubuna 30 hasta dahil edildi. Beş yıllık genel sağkalım ve olaysız sağkalım oranları sırasıyla% 58.1 ve% 57.6 idi. Sağkalım üzerinde istatistiksel olarak anlamlı bir etkiye sahip prognostik faktörler histopatolojik grup, cerrahi tip ve risk grubuydu. Çok değişkenli analizde, sadece risk grubunun sağkalımı etkilediği bulundu.
Sonuç: Hastanın yaşını, cerrahi rezeksiyon derecesini ve metastaz durumunu kullanan risk grubu parametresi medulloblastomlu hastaların sağkalımına etki eden en önemli faktördür.

Anahtar kelimeler: Medulloblastom, Tedavi, Prognoz, Çocukluk çağı

Yazışma Adresi/Address for Correspondence: Serhan Küpeli, Cukurova University Faculty of Medicine, Department of Pediatric Oncology and Pediatric Bone Marrow Transplantation Unit, Adana, Turkey E-mail: serhankupeli@cu.edu.tr
Geliş tarihi/Received: 25.10.2019 Kabul tarihi/Accepted: 04.12.2019 Published online: 05.01.2020

INTRODUCTION

Medulloblastoma, an embryonal tumor, is the most common malignant brain tumor in children[1]. Medulloblastoma constitutes approximately 40% of the posterior fossa tumors[2]. Contemporary treatment strategy for medulloblastoma includes surgery, followed by radiotherapy and chemotherapy. In recent years, medulloblastoma have been divided into four molecular subtypes according to their clinical characteristics and genetic features[3].

At the moment, examining all the genetic aspects of the tumor specimens is unlikely for most of the institutions in low-income countries. Majority of the clinicians still rely on clinical staging and risk stratification for the treatment of patients with medulloblastoma[4]. In the present study, we analyze the clinical features, risk categories, treatment, and outcome of 84 patients with medulloblastoma treated in our institution in the last 15 years.

MATERIALS AND AND METHODS

We identified 97 patients with a diagnosis of medulloblastoma at our institution between January 2004 and December 2018. The patients who were treated in another hospital, those who discontinued the therapy, and those who died in one month after surgery with surgical complications were excluded. We analyzed hospital files of the remaining 84 patients and their clinical and epidemiological characteristics, histopathology, treatment modalities, prognostic criteria and survival rates were noted in data form.

To evaluate the primary tumor, brain magnetic resonance imaging (MRI) was used. Spinal involvement was investigated with cervical, thoracal, and lumbal MRI preferably before surgery and if it was not possible 3 weeks after surgery. Cerebrospinal fluid analysis (CSF) was made at least 3 weeks after surgery. The amount of resection and presence of residual tumor was evaluated by means of post-operative MRI scans. Gross-total resection was defined as no visible disease after surgery on post-operative imaging studies. Subtotal resection was defined in case of surgical removal that was greater than 50% of the total tumor mass but visible tumor remained. Chang staging system was used for the patients with medulloblastoma[5]. Histologic subtypes of the tumor was defined according to WHO criteria, however, molecular classification could not be done[6].

After surgery all patients older than 3 years of age were given fractionated intensity modulated external beam radiotherapy both to the cranium and medulla spinalis. Radiotherapy started in 2 months after surgery. Generally delivered radiation doses were 36 Gy for the cranium and for the spinal cord and 18 Gy for the posterior fossa boost (total 54 Gy). Chemotherapy protocols were primarily etoposide (100 mg/m^2) and temozolomide (150 mg/m^2) with 3-week-intervals (TEC protocol) between 2004 and 2012, and vincristine (1.5 mg/m^2), etoposide (100 mg/m^2), carboplatin (500 mg/m^2) and vincristine (1.5 mg/m^2), etoposide (100 mg/m^2) and cyclophosphamide+MESNA (1.5 gr/m^2) with a 3-week-interval (VECC protocol) interchangeably thereafter.

Statistical analysis

Mean, median and percentage were used for demographic characteristics. Statistical analysis was performed with the statistical package for social sciences (version 20.0, SPSS, IL, USA). Kaplan–Meier survival analysis was used for subgroups. The patient groups were compared in terms of survival duration using a log-rank test. Cox-regression analysis was used to investigate the effect on survival of all variables with a p value <0.1 in Kaplan–Meier analysis. A 2-tailed p<0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the 84 patients are given in Table 1. There were 45 males and 39 females (M/F = 1.15) with a median age of 8 years (0.3–17 years) at the time of diagnosis. Approximately 12% of the patients were Syrian refugees.

The type of surgery was gross-total in 62 (73.8%) and subtotal in 22 (26.2%). Histopathological subgroups were mainly classic (52.5%), desmoplastic/nodular (27.3%) and medulloblastoma with extensive nodularity (11.9%). 54 patients (64.3%) were included in average-risk group and 30 (35.7%) in high-risk group based on the age at the time of diagnosis, extent of the residual tumor after surgery and Chang staging system.

Craniospinal radiotherapy was delivered to 77 patients (91.7%). Patients who were under age of 3 years (n=7, 8.3%) were not given radiotherapy because of their age. 43 patients (57.3%) were treated with VECC protocol, 20 (26.7%) with TEC, and 12 (16.0%) with other protocols.

Five-year overall survival (OS) and event-free survival (EFS) rates were 58.1% and 57.6% respectively with a mean follow-up time of 53 months. The prognostic factors having a statistically significant influence on survival were histopathological group ($p<0.01$), type of surgery ($p<0.01$) and risk group ($p<0.01$). Among patients with medulloblastoma the survival rate for patients showing the classic type was 79.8%; for those with the desmoplastic/nodular type 66.7%; and for those with anaplastic type 20.0%. High-risk group patients has an inferior survival rate (5.4%) compared to patients in average-risk group.

Gender, nationality, different age groups, chemotherapy schemes and treatment period did not have an impact on survival (Table 2).Age group, histopathological group, risk group and chemotherapy scheme variables with a p value <0.1 in Kaplan–Meier analysis were included in Cox-regression analysis to investigate the effect on survival (Table 3). Only the risk group variable was found to have an impact on survival ($p<0.01$, 95% CI<0.019-0.22). Posterior fossa syndrome developed in 7 patients (8.3%) and resolved in all of them in a maximum 2 weeks.

Table 1. Demographic and clinical characteristics of the patients

Variable		
Age (years)	Median: 8	Range: 0.3-17
Male/female	45/39	Ratio: 1.15
Nationality		
Turkey	74	88.1%
Syria	10	11.9%
Age group (years)		
0-5	22	26.2%
5.1-10	35	41.7%
>10	27	32.1%
Histopathological group		
Classic	44	52.5%
Desmoplastic/nodular	23	27.3%
MBEN	10	11.9%
Large cell	5	5.9%
Anaplastic	2	2.4%
Type of surgery		
Gross-total	62	73.8%
Subtotal	22	26.2%
Risk group		
Average	54	64.3%
High	30	35.7%
Chemotherapy scheme		
VSCE	43	57.3%
TEC	20	26.7%
Other	12	16.0%
Treatment year		
2004-2012	29	34.5%
>2012	55	65.5%

Table 2. Comparison of survival rates

Factor	**Survival rate (%)**	**P value**
Gender		0.262
Male	64.0	
Female	56.2	
Nationality		0.902

Turkey	58.0	
Syria	71.4	
Age group (years)		0.09
0-5	32.0	
5.1-10	63.6	
>10	71.1	
Histopathological group		**<0.01**
Classic	79.8	
Desmoplastic/nodular	66.7	
MBEN	0	
Large cell	0	
Anaplastic	20.0	
Type of surgery		**<0.01**
Gross-total	84.0	
Subtotal	0	
Risk group		**<0.01**
Average	87.7	
High	5.4	
Chemotherapy scheme		0.08
VSCE	63.0	
TEC	38.9	
Other	74.1	
Treatment period		0.89
2004-2012	57.1	
>2012	56.9	

Table 3. Cox regression analysis

Variables in the Equation								
	B	SE	Wald	**df**	**Sig.**	**Exp(B)**	**95.0% CI for Exp(B)**	
							Lower	Upper
Age group			.951	2	.622			
Age group (1)	-.377	.620	.370	1	.543	.686	.204	2.311
Age group (2)	.219	.535	.167	1	.683	1.244	.436	3.555
Histopathology			3.991	4	.407			
Subgroup (1)	-.978	.707	1.916	1	.166	.376	.094	1.502
Subgroup (2)	.036	.754	.002	1	.962	1.037	.237	4.542
Subgroup (3)	-.671	.859	.611	1	.435	.511	.095	2.752
Subgroup (4)	.219	.896	.060	1	.807	1.245	.215	7.203
Risk group	3.100	.809	14.668	1	<.01	.045	.009	.220
Chemotherapy			.866	2	.648			
Group (1)	-.711	.833	.729	1	.393	.491	.096	2.515
Group (2)	-.411	1.013	.165	1	.685	.663	.091	4.824

DISCUSSION

In pediatric age group, nearly 25% of all primary central nervous system (CNS) tumors are embryonal tumors, and the most frequent of them is medulloblastoma[7]. Medulloblastoma is known as the most common malignant brain tumor in children and it occurs essentially in the posterior fossa. Beside the classical medulloblastoma, the most frequently described histopathologic subtype, desmoplastic/nodular, MBEN, large-cell and anaplastic subtypes were defined based on histopathologic characteristics[8]. Some studies have reported that histopathologic subtypes are related with prognosis[9,10]. Consistent with the literature, in our series, patients with classical and desmoplastic/nodular subtypes had better survival rates compared to patients with other medulloblastoma subtypes ($p<0.01$). Recently, medulloblastoma have been divided into four molecular subtypes according to their clinical characteristics and genetic features as Wnt, SHH, Group 3 and Group 4 tumors[3]. Recent studies have revealed that this classification have a significant impact on prognosis of patients with medulloblastoma[10,11]. Unfortunately, genetic analyses were not performed because of limited sources.

Staging of the patients with medulloblastoma basically relies on the extent of the tumor at the time of the diagnosis. Chang staging system is used widely to assign the primary tumor stage (T stage) and metastatic tumor (M stage). Age of the patient, degree of surgical resection and M stage of the disease are utilized for risk stratification[5]. The M stage of the disease is still the most important factor on prognosis[12]. Similarly, the survival rate of average-risk patients (87.7%) was superior compared to high-risk patients (5.4%) in our study ($p<0.01$). Again, in multivariate analysis risk group was the only parameter having an impact on survival ($p<0.01$). In our series, all patients whose tumors resected subtotally have died, whereas survival rate of patients with gross-total resection was 84.0% ($p<0.01$). Since most of the patients with subtotal resection were assigned into the high-risk group, inferior survival rate is not surprising. Younger children at the time of diagnosis also have poorer outcome than older children with medulloblastoma[13]. Higher rate of disease dissemination, incomplete tumor resection, delayed radiotherapy and/or lower doses of craniospinal radiotherapy may be responsible from inferior survival rates of younger patients. Although we obtained better survival rates for patiens >5 years the difference was not significant statistically in the present series ($p=0.09$). Survival analysis of the patients younger than 3 years of age (33.3%) and older than 3 years (59.6%) also resulted insignificant difference ($p=0.31$). Small number of patients in <3 years of age group (n=7) may be responsible from statistically similar results. OS (58.1%) and EFS (57.6%) of our patients are comparable with those of other studies from Turkey and limited-income countries[14-17].

Treatment of patients with medulloblastoma, excluding those younger than 3 years of age, includes surgical resection, craniospinal radiotherapy and chemotherapy. Maximal surgical resection of a posterior fossa tumor may be complicated by posterior fossa syndrome characterized by post-operative mutism with other neurological manifestations, emotional lability and neurobehovioral abnormalities in upto 25% of the patients[18]. Small number of patients (n=7, 8.3%) with posterior fossa syndrome in our series is probably due to retrospective nature of the study. In pediatric age group, generally accepted radiation dose for craniospinal axis and for posterior fossa is 36 Gy and 54-55.8 Gy respectively[19]. Craniospinal radiotherapy (36 Gy) and posterior fossa irradiation (54 Gy) was delivered to majority of patients (91.7%) in our series except those under 3 years of age (8.3%). Clinicians should be aware of long-term side effects of craniospinal radiotherapy on growth, endocrine function, cognition and vascular structures. In a recent study, we have reported cerebral vascular abnormalities in 7 of 53 patients (13.2%) who had received cranial radiotherapy in childhood, mean 3.84 years after radiation therapy[20]. Cranial radiation dose was found to have an impact on developing cerebral vascular abnormalities both in univariate and multivariate analyses. Feasibility of reduction in radiation doses to the craniospinal axis is being investigated in recent studies. Chemotherapy is an important component of treatment for children with medulloblastoma. Studies with different chemotherapeutic agents concluded with good outcome especially for high-risk patients and no survival advantage was reported between pre-irradiation or post- irradiation chemotherapy[21]. In our institution, all patients except younger than 3 years of age were administered post-irradiatin chemotherapy. We did not observe difference in survival ($p=0.08$) between 43 patients (57.3%) treated with VECC protocol and 20 (26.7%) treated with TEC protocol.

Since the onset of the civil war in Syria in March 2011, over 2 million Syrians have migrated to Turkey[22]. Cancer in refugees causes a substantial burden for the health systems of the host countries as well as refugees themselves. Difficulties in shelter and provision of healthy foods, poor adherence to hygiene measures, language and communication problems, difficulties in accessing to drugs in outpatient settings and poor compliance with therapy are tried to overcome by government and with the efforts of health staff. Fortunately, outcomes of patients with medulloblastoma among the Syrian refugee children (71.4%) were similar to the outcome in Turkish children with medulloblastoma (58.0%) in our series ($p=0.902$).

In conclusion, risk group utilizing the age of the patient, degree of surgical resection and M stage of the disease is the most important parameter having an impact on survival of patients with medulloblastoma. Future studies incorporating molecular subtypes according to genetic features of the tumor and clinical characteristics of the patients will help improving outcomes and decreasing treatment related side effects.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SK; Veri toplama: SK, GS, İB, AT; Veri analizi ve yorumlama: SK, GS, İB, AT; Yazı taslağı: SK; İçeriğin eleştirel incelenmesi: SK, GS, İB, AT; Son onay ve sorumluluk: SK, GS, İB, AT; Teknik ve malzeme desteği: SK, GS, İB; Süpervizyon: SK, İB; Fon sağlama (mevcut ise): yok.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Author Contributions: Concept/Design : SK; Data acquisition: SK, GS, İB, AT; Data analysis and interpretation: SK, GS, İB, AT; Drafting manuscript: SK; Critical revision of manuscript: SK, GS, İB, AT; Final approval and accountability: SK, GS, İB, AT; Technical or material support: SK, GS, İB; Supervision: SK, İB; Securing funding (if available): n/a.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Udaka YT, Packer RJ. Pediatric brain tumors. Neurol Clin. 2018;36:533-56.
2. Bautista F, Fioravantti V, de Rojas T, Carceller F, Madero L, Lassaletta A et al. Medulloblastoma in children and adolescents: a systematic review of contemporary phase I and II clinical trials and biology update. Cancer Med. 2017;6:2606-24.
3. Ramaswamy V, Taylor MD. Medulloblastoma: from myth to molecular. J Clin Oncol. 2017;35:2355-2363.
4. Ramaswamy V, Remke M, Bouffet E, Bailey S, Clifford SC, Doz F et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. Acta Neuropathol. 2016;131:821-31.
5. Dufour C, Beaugrand A, Pizer B, Micheli J, Aubelle MS, Fourcade A et al. Metastatic medulloblastoma in childhood: chang's classification revisited. Int J Surg Oncol. 2012;2012:245385.
6. Pickles JC, Hawkins C, Pietsch T, Jacques TS. CNS embryonal tumours: WHO 2016 and beyond. Neuropathol Appl Neurobiol. 2018;44:151-162.
7. Lassaletta A. Medulloblastoma in infants: the never-ending challenge. Lancet Oncol. 2018;19:720-21.
8. Gupta T, Shirsat N, Jalali R. molecular subgrouping of medulloblastoma: impact upon research and clinical practice. Curr Pediatr Rev. 2015;11:106-119.
9. Goschzik T, Schwalbe EC, Hicks D, Smith A, Zur Muehlen A, Figarella-Branger D, et al. Prognostic effect of whole chromosomal aberration signatures in standard-risk, non-WNT/ non-SHH medulloblastoma: a retrospective, molecular analysis of the HIT-SIOP PNET 4 trial. Lancet Oncol. 2018;19:1602-1616.
10. Robinson GW, Rudneva VA, Buchhalter I, Billups CA, Waszak SM, Smith KS et al. Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial. Lancet Oncol. 2018;19:768-84.
11. Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA et al. Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol. 2012;123:473-484.
12. Phi JH, Lee J, Wang KC, Cho BK, Kim IO, Park CK et al. Cerebrospinal fluid M staging for medulloblastoma: reappraisal of Chang's M staging based on the CSF flow. Neuro Oncol. 2011;13:334-44.
13. Robinson GW, Rudneva VA, Buchhalter I, Billups CA, Waszak SM, Smith KS et al. Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial. Lancet Oncol. 2018;19:768-84.
14. Ertan Y, Sezak M, Demirağ B, Kantar M, Cetingül N, Turhan T et al. Medulloblastoma: clinicopathologic evaluation of 42 pediatric cases. Childs Nerv Syst. 2009;25:353-6.
15. Akyüz C, Varan A, Küpeli S, Akalan N, Söylemezoglu F, Zorlu F et al. Medulloblastoma in children: a 32-year experience from a single institution. J Neurooncol. 2008;90:99-103.
16. Mehrvar A, Faranoush M, Hedayati Asl AA, Tashvighi M, Fazeli MA et al. Childhood central nervous system tumors at MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC), Tehran, Iran. Childs Nerv Syst. 2014;30:491-6.
17. Pinho RS, Andreoni S, Silva NS, Cappellano AM, Masruha MR, Cavalheiro S et al. Pediatric central nervous system tumors: a single-center experience from 1989 to 2009. J Pediatr Hematol Oncol. 2011;33:605-9.
18. Küpeli S, Yalçın B, Bilginer B, Akalan N, Haksal P, Büyükpamukçu M. Posterior fossa syndrome after posterior fossa surgery in children with brain tumors. Pediatr Blood Cancer. 2011;56:206-10.
19. Albright AL, Wisoff JH, Zeltzer P, Boyett J, Rorke LB, Stanley P et al. Prognostic factors in children with supratentorial (nonpineal) primitive neuroectodermal tumors. A neurosurgical perspective from the Children's Cancer Group. Pediatr Neurosurg. 1995;22:1-7.
20. Kupeli S, Bicakci K, Sezgin G, Bayram I. Evaluation of late cerebral vascular complications in cranially irradiated pediatric cancer patients with magnetic resonance angiography. Tumori. 2018;104:381-7.

21. Tarbell NJ, Friedman H, Polkinghorn WR, Yock T, Zhou T, Chen Z et al. High-risk medulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031). J Clin Oncol. 2013;31:2936-41.

22. Kebudi R, Bayram I, Yagci-Kupeli B, Kupeli S, Sezgin G, Pekpak E et al. Refugee children with cancer in Turkey. Lancet Oncol. 2016;17:865-7.