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Five- Year Survival Rate of Children with Central Nervous System Tumors in Shiraz, Iran

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Abstract

Background: Reduced survival and impaired quality of life of the children affected by cancers is one of the most important health problems. In this study, 5-year survival of children affected with Central nervous system (CNS) tumors and its related factors were evaluated.

Materials and Methods: Participants in this historical cohort study consisted of 161children with mean age of diagnosis 72 ± 51 months (median:60 months, range from 1 month to 17 years) who were diagnosed with CNS tumors from 1999 to 2005. All patients had referred to Oncology hospitals of Shiraz University of Medical Sciences, Shiraz, Iran. Data were extracted by checklist from their medical records.

Result: Five-year overall survival (OS) and disease free survival (DFS) of the patients were 59% (standard error: 5%) and 51.7% (standard error: 5%). Moreover, 10- year OS was calculated as 47% (standard error: 7%). Based on tumor histology, OS was 70% for low grade tumors and 52% for high grade tumors (P=0.202). Based on the results, gender (girls had longer survival than boys), recurrence, neurologic deficit and age of diagnosis (60-119 months had longer survival), were determined as the influencing factors on OS rate (HR (95% CI) =0.48 (0.24-0.98), P=0.044, 0.48(0.25-0.93) P=0.031, 0.42 (0.18-0.95), P=0.039, and 0.32 (0.11-0.88), P=0.029, respectively). Moreover, tumor location in diencephalon was determined as poor prognostic factors ((HR (95% CI) =10 (1.9-57), P=0.007).

Conclusion: Aforementioned prognostic factors should be taken into account by oncologists to make better decisions in the management of the patients with CNS tumors. It seems that survival is a multifactorial event and besides these prognostic factors, it might be also related to different clinical settings, ethnicity and type of treatment. Further studies with more focus on different treatment modalities are suggested.

Keywords: Cancer, Central nervous system neoplasm, Pediatric, Survival

Introduction

The central nervous system (CNS) tumors are the largest group of solid neoplasms in pediatrics, and known as the second most common type of cancer after leukemia in this age group. CNS tumors comprise of 25% of all tumors 0-14, and 9% 15-24 years of age, respectively. High mortality and decrease in patients´ survival in one hand, and poor quality of life on the other hand, have signified this issue as one of the most important challenges for health service providers and policy makers (1-4).

Factors such as gender, relapses, age of diagnosis less than 5 years of age, type of adjuvant therapy, tumor location, and tumor grade have been associated with survival of children with CNS tumors (5-8).

In the last decade, due to advancements in surgery, radiotherapy and chemotherapy increased patient's survival has been observed (9, 10). Ten years' survival rate is better in patients who are treated with the combined gross total resection plus radiotherapy, than those with surgery alone (11, 12). Combination of chemotherapy and radiotherapy increases overall survival (OS) (13).

In addition, brain tumor survivors experience broad problems such as cerebellar mutism, cranial nerve deficit, visual impairment, dysarthria, dysphagia, impairment of emotional and behavioral

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function, loss of memories, social dysfunction, and endocrine abnormalities caused by the side effects of treatment and tumor location (14-18). Brain tumors diagnosis and treatment can improve and reduce these complications. Survivors are at risk of developing attention, social, and emotional problems such as anxiety and depression (19).

Survival studies are necessary to evaluate the effectiveness of novel treatments as well as to identify possibilities for further improvements (20).

In this study, 5-year survival rate of children affected by CNS tumors and related factors were assessed during 1999 to 2015 in Shiraz province, Iran.

Materials and Methods

In this historical cohort study, all children with CNS tumors (n=161) who diagnosed during 1999 to 2005 at oncology hospitals affiliated to Shiraz University of Medical Sciences, Iran, were followed-up until 2015. the mean age of diagnosis was 72 ± 51 months. Total of six patients were excluded due to missing data or no possibility of getting in touch with them.Other exclusion criteria included patients who had secondary CNS tumors or their symptoms were caused by tumors outside the nervous system. Finally, 155 patients were investigated in this study.

This study merely included a review of the patients' records. A written informed consent was completed by each individual or their gurdians. The local ethics committee of Shiraz University of Medical Sciences approved the protocol (Grant number=87/1001).

Their diagnosis was based on clinical and laboratory evaluation, pathology report, and radilogy examination, including computerized tomography scan (CT scan) or magnetic resonance imaging (MRI). The participants had undergone various kinds of adjuvant therapies after primary treatment, including radiotherapy, chemotherapy, and combinedradiotherapy and chemotherapy.

In high grade tumors, medulloblastoma and ependymoma, the patients had received craniospinal radiotherapy following surgery, and adjuvant CCNU (Lomustine), vincristin and cisplatinum. Radiotherapy was delayed before the age of 3.

Carboplatin and vincristin were used in patients with newly diagnosed, progressive low grade astrocytoma. In these patients, radiotherapy was used, when chemotherapy had failed in unresectable symptomatic tumors, especially in older childern.

The chemotherapy regimen in the relapsed patients included bevacizumab, irinotecan, temozolomide, and vincristin.

Patients' data was extracted by checklist from their medical records and included gender, age of diagnosis, age of death, age at present, age at the end of treatment, symptoms at the diagnosis time, types of treatment, amount of tumor resection, histology of tumors, location of tumors, recurrences, number of recurrences, number of surgeries, and signs of neurological deficit.

In this study, types of tumors consisted of medulloblastoma, ependymoma, low grade glioma, high grade glioma, primitive neuroectodermal tumor (PNET), craniopharyngioma, pineal, oligodendroglioma, germ cell tumors, and other types of tumors.

Amount of resection in the checklist was classified in 6 categories: unresectable, 25% resection, 50% resection, subtotal resection(75%), near total resection (90%), and gross total resection. Sites of tumors checked in this study included posterior fossa, diencephalon, cerebrum, pineal area, optic nerve, and spinal cord.

Statistical analysis

Data analysis was done using the SPSS (version 21). Survival curves are shown by Kaplan-Meier method. To determin OS, the event was considered as death and in disease free survival (DFS) it was considered as death or the recurrence. Log

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Rank test was used to determine the association between patients' survival and gender, recurrence, neurologic deficit, age of diagnosis, histology and site of tumors, types of treatment, and amount of surgical resection. Finally, a Cox proportional hazards regression model by backward stepwise method was done to determine the independent variables influencing the survival of patients and hazard ratios (HR), estimataed at 95% confidence interval. The variables with P value less than 0.25 in univariate analysis were entered into this model. Two sided p-values less than 0.05 were considered to be significant.

Results

The mean age of the participants was 124 ± 74 months (median:108 months, range: 9-348 months) at the end of the study, and 72 ± 51 months (median:60 months range: 1-204 months) at the time of diagnosis, including 64 girls (41.3%) and 91 boys (58.7%). The most common presentionof symptoms were vomiting, headache, nausea, and imbalance.

Demographic and clinical data and characteristics of tumor are presented in Table I.

The most common type of tumor was medulloblastoma (47cases, 30.3%) followed by low grade glioma 34 cases (21.9%), and ependymoma 26 cases (16.8%). Other types with less frequency included germ cell tumor 5 cases (3.2%), oligodendroglioma 2 cases (1.3%), craniopharyngioma 1 case (0.6%), PNET 8 cases (5.2%), and high grade glioma 7 cases (4.5%). Moreover, there were 25 patients with unspecified low grade tumors (16.1%). Tumors were classified into low (n=62) and high grade (n=93) groups. Low grade tumors consisted of low grade glioma, oligodendroglioma, craniopharyngioma, and other unspecified low grade tumors. High grade tumors included ependymoma, germ cell tumor, medulloblastoma, PNET, and high grade glioma.

The highest frequency of distribution of tumor location in children less than 18 years of age with primary CNS tumor was posterior fossa (58.7%).

The most common type of treatment in this population was combinedsurgery withchemotherapy or radiotherapy (59.4%). Moreover, in tumor resection, the most prevalent type of resection was total or near total resection (59.4%).

Total of 41 patients (26.5%) had experienced at least one episode of recurrence. In addition, neurologic deficit occurred in 99 children (63.9%) during the study.

Univariate analysis was done to determine the relationship of the evaluated variables with OS and DFS of the patients using Log rank test. The results are shown in Table I. In this anlysis, all evaluated variables showed significant association with OS and DFS of the patients, except age at diagnosis, gender, and tumor grade.

At the end of study, 53 patients (34.2%) had died. OS of the patients is shown in Figure1.

Overall, 5-years OS was 0.59 (standard error: 0.05). Patients survival after 98 months was at a steady rate of 0.47 (standard error: 0.07). DFS was 51.7% (standard error: 5%).

OS of the patients based on tumor grade is presented in Figure 2. The difference in survival of the patients was not statistically significant between low grade and high grade tumors (P=0.202). Furthermore, DFS was not significantly different between high garde and low grade tumor (P=0.258). Due to small sample size in some subgroups, comparison of OS among all types of tumors was not possible. Hence, OS and DFS were compared seperately amongst the four groups of patients with frequency of more than 20 patients, which included medulloblastoma, low grade glioma, ependymoma, and unspecified other low grade tumors that revealed no statistically significant differences (P=0.756, P=0.689).

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To determine the independent factors influencing OS rate of the patients, Cox proportional hazards regression model with backward stepwise method was perfomred for OS and DFS and variables with P value less than 0.25 in univariate analysis were entered into the model. In OS analysis, these variables included gender, recurrence, neurologic deficit, treatment, tumor site, tumor resection, age of diagnosis, and tumor grades. Table II shows the results of this analysis. In the final step, gender (girls had longer survival than boys), recurrence, neurologic deficit, and age at diagnosis (60-119 months had longer survival compared to other age groups) showed significant association with survival in affected children (HR (95% CI) =0.48 (0.24-0.98), P=0.044, 0.48(0.25-0.93) P=0.031, 0.42 (0.18-0.95), P=0.039, and 0.32 (0.11-0.88), P=0.029, respectively). Tumor site in diencephalon showed significantly shorter survival in patients ((HR (95% CI) =10 (1.9-57), P=0.007). Moreover, treatment showed a significant association overall, but in subclassification none of the categories had significant correlation with survival. Tumor grade showed no significant association with patients´ OS.

Moreover, in Table II the results of DFS Cox regression analysis are presented. Entered variables into the model consisted of gender, neurologic deficit, treatment, tumor site, tumor resection, and age at diagnosis. Reccurence was not considered because it was used in DFS calcultion. Similar to OS, in the final step, gender (girl had longer survival than boys) and neurologic deficit were determined as prognostic factor with survival (HR (95% CI)=0.41(0.22-0.75), P=0.004, 0.42(0.21-0.82), P=0.011), respectively. On the other hand, tumor resection (unresectable and 25% or less resection) and tumor site (diencephalon) were determined as poor prognostic factors on patients' DFS (HR (95% CI)= 2.59(1.26-5.35), P=0.010, and7.42(1.85-29), P=0.005) . Regarding treatment, it should be mentioned that this analysis was limited to three groups of patients including surgery alone, surgery plus chemotherapy as well as surgery, chemotherapy and radiotherapy, but other groups of treatment including patients who underwent chemotherapy, radiotherapy, combined surgery and radiotherapy and combined chemotherapy, and radiotherapy were excluded due to small sample size. Among the three mentioned treatment groups, patients who underwent surgery and chemotherapy showed significantly worse DFS (HR (95% CI)= 3.47(1.29-9.34), P=0.014).

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Table I: Comparison of 5-year survival rates among different groups of children with central nervous system tumor based on clinical data and characteristics of the tumor

Variables	Number	%	overall survival (Standard error)	P value	Disease free survival (Standard error)	P value
Age at diagnosis (month)						
<60	69	44.5	0.477(0.083)	0.108	0.387(0.076)	0.067
60-119	56	36.1	0.688(0.071)		0.612(0.073)	
≥120	30	19.4	0.653(0.096)		0.653(0.096)	
Gender						
Girl	64	41.3	0.675(0.074)	0.131	0.628(0.074)	0.114
Boy	91	58.7	0.525(0.066)		0.437(0.064)	
Recurrence						
Yes	41	26.5	0.309(0.086)	<0.001	0.171(0.059)	<0.001
No	114	73.5	0.722(0.05)		0.722(0.050)	
Neurological deficit						
Yes	99	63.9	0.502(0.059)	0.001	0.453(0.057)	0.003
No	56	36.1	0.766(0.086)		0.633(0.091)	
Tumor grades						
Low-grade tumors	62	40	0.701(0.067)	0.202	0.598(0.071)	0.258
High grade tumors	93	60	0.522(0.067)		0.464(0.065)	
Tumor site						
Posterior fossa	91	58.7	0.561(0.066)	0.005	0.522(0.066)	0.021
Diencephalon	15	9.7	0.311(0.121)		0.233(0.118)	
Cerebrum	22	14.2	0.648(0.120)		0.530(0.124)	
Pineal and optic nerve	13	8.4	0.738(0.175)		0.506(0.164)	
Spinal cord	14	9	0.851(0.097)		0.750(0.124)	
Tumor resection						
Unresectable and 25% or less resection	18	11.6	0.161(0.133)	0.009	0.129(0.108)	0.001
Partially resection (50-75%)	38	24.5	0.532(0.094)		0.422(0.095)	
Total or near total (90%) resection	92	59.4	0.707(0.054)		0.660(0.056)	
Missing data	7	4.5				
Treatment						
Surgery and chemotherapy	31	20	0.450(0.110)	0.01	0.400(0.108)	0.005
Surgery, chemotherapy and radiotherapy	92	59.4	0.642(0.065)		0.547(0.064)	
Surgery	20	12.9	0. 591(0.125)		0.591(0.125)	
Missing data	12	7.7				

a: Others include germ cell tumor, oligodendroglioma, craniopharyngioma, primitive neuroectodermal tumor (PNET), high grade glioma, and misellaneous

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TableII: Final step of cox regression analysis of covariates on the survival of children affected with central nervous system tumors

	Overall survival		Disease free survival	
Parameters	HR[f](95% CI)	P value	HR[f](95% CI)	P value
Gender[a]	0.48 (0.24-0.98)	0.044	0.41(0.22-0.75)	0.004
Recurrence[a]	0.48 (0.25-0.93)	0.031	------	------
Neurologic deficit[a]	0.42 (0.18-0.95)	0.039	0.42(0.21-0.82)	0.011
Age of diagnosis[b]	------	0.031	------	------
<60 months	0.78 (0.32-1.90)	0.597	------	------
60-119 months	0.32 (0.11-0.88)	0.029	------	------
Treatment[c]	------	0.001	------	0.007
Surgery, chemotherapy	1.84 (0.65-5.2)	0.249	3.47(1.29-9.34)	0.014
Surgery, chemotherapy and radiotherapy	0.46 (0.17-1.21)	0.119	1.26(0.53-2.96)	0.597
Tumor resection	------	------	------	0.020
Unresectable and 25% or less resection	------	------	2.59(1.26-5.35)	0.010
Partially resection (50-75%)	------	------	1.84(0.97-3.47)	0.058
Tumor site[d]	------	0.022	------	0.013
Posterior fossa	2.25 (0.50-10)	0.288	2.45(0.71-8.4)	0.155
Dienceohalon	10 (1.9-57)	0.007	7.42(1.85-29)	0.005
Cerebrum	1.5(0.24-9.3)	0.649	1.62(0.37-6.94)	0.516
Pineal and optic nerve	1.48(0.19-11.3)	0.702	2.14(0.48-9.52)	0.316
Tumor grade	0.45(0.17-1.19)	0.109	------	------

[a] Gender: girl compared to boy; neurologic deficit: no compared to yes; recurrence: no compared to yes, in disease free survival, reccurence was not considered as a variable in cox model because it was used in calcultion of disease free survival. [b] Compared to >=120 months. [c] Compared to surgery (Patients who underwent chemotherapy, radiotherapy, combined surgery and radiotherapy and combined chemotherapy and radiotherapy were not considered in this analysis due to small number of patients in each group). [d] compared to spinal cord
[e] Compared to total or near total (90%) resection. [f]HR: hazard ratio

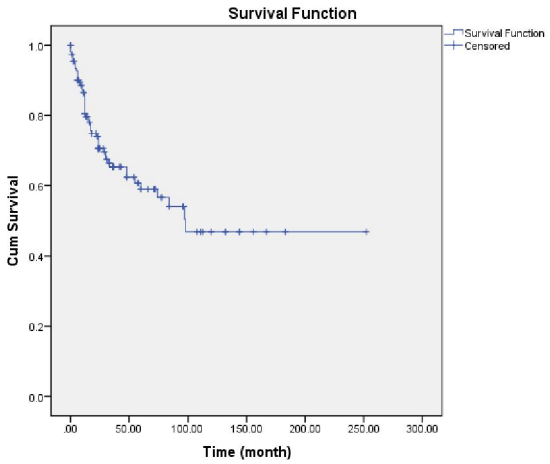

Figure 1: Overall survival of children affected by central nervous system tumors

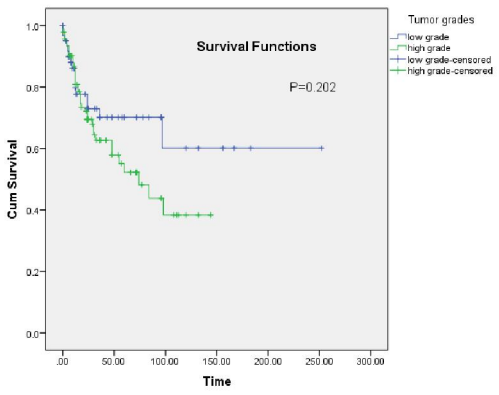

Figure 2: Overall survival of children affected by central nervous system tumors based on tumor grades

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Discussion

In this study, children's survival with CNS tumor who were diagnosed from 1999 to 2005, and were followed-up till 2015, was evaluated. The 5-year OS and DFS of the patients was 59% (standard error=5%) and 51.7% (standard error: 5%). In line with the present study, Pogorzala et al. reported a 5-year survival of 60.9 ± 4.7% in children with brain tumors in Poland (6). Moreover, Magnani and co-workers reported a 5–year survival of 61% in Europe, the authors also estimated 5-year survival in some other countries such as Sweden 73%, Estonia 28%, Iceland 75%, and in Finland 73%(21). It is difficult to compare patients' survival with cancer amongst different countries, because there may be differences in pathological assessment of tumors as well as changes in the management standards over time and places. Jung et al. estimated that the 5-year survival in Korea was 37.5% (22). Another study by Desandes and his coworkers in France showed a 5-year survival of 74.5% in all types of CNS tumors(23).

In two recent studies conducted in Iran, the survival rate of brain tumors was assessed. The 5-year survival rate was reported at 68.5%. and 51.68 ± 5.22 % (24,25). Result of this study is similar to a study conducted in Mahak charity hospital (24), while it was less than what was reported by Rafsanjani et al., (25).

The 10-year OS in the current study was 47%, this result was similar to the study that was done in Poland in which 10-year survival was 58.2±4, however, Lannering et al. showed that it was 72% in their study in Sweden (26).

In the present study, the 5-year OS and DFS of the patients with low grade and high grade tumors was not significantly different. In patients with ependymoma 5-year OS was 47.3 %, which was comparable to several recently published studies. A recent study investigated the survival of children with ependymoma, and found that 5-year survival was 55 ± 6 % (27). Other studies showed the 5 year-survival in children with ependymoma was 24 to 75% and 56.6 ± 16.6% (15, 6).

In this study the 5 year OS in children with medulloblastoma was 61.8%. Johnston et al. reported 5-year survival of 69.2% ± 3.3 in children with medulloblastoma (5). The result of this study was similar to the results of current study, while Duffner et al. showed 5-year- survival of 39% in medulloblastoma and 28% in ependymoma (28).

The 5-year OS in low grade glioma in present study was 70%, in three recently published studies this rate was reported at 71%, 57.7± 9.4% and 83.3±6.2% (6,28,29).

According to the current study, patients with age at diagnosis of 60-119 months had significantly longer survival. Recently published studies have shown that age at diagnosis has been associated with survival rate. Likewise, Johnston and his coworkers showed that age at diagnosis less than 5 years had worser survival, while in the study by Ailon et al. patients with age of diagnosis less than 2 years had poorer survival (5,11,30). In contrast to present study, the Farinotti research showed that age at diagnosis did not have any major impact on survival (31).

In the two recently published studies, the disease affects boys more than girls, which was similar to current study. Although in these two studies, gender did not have any significant association with survival rate, in the present study girls had longer survival compared with boys, and gender was known as an independent factor influencing OS and DFS (5,23).

Considering tumor site, diencephalon was diagnosed as a poor prognostic factor for OS and DFS. Eisenstat et al. showed that tumors involving thalamus and basal ganglion had poorer prognosis in survival (29).

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Based on the current results, DFS was associated with tumor resection as patients whose tumor was unresectable or 25% or less resectable had significantly shorter DFS. Similar to present study, other published studies showed surgical resection, especially gross total and near total resection, to besignificantly associated with longer survival (6, 11,15, 29, 32-34).

Nowadays, treating children with brain tumors is according to the type, tumor location, age of children and other factors. Although surgery is one of the best treatments for children who are affected with brain tumors, often complete removal of the tumors due to its location and other risk factors is next to impossible. Depending on the specific tumor and age, there are severaltreatments that should be added to surgery. Another kind of treatments that may be prescribed after surgery are either chemotherapy or radiotherapy. Overall, treatment plays an important role in children's survival with CNS tumors. In the present study, 12.9% of children underwent surgery, 20% surgery plus chemotherapy, and most of them (59.4%) received combination of surgery, chemotherapy and radiotherapy. Other modalities without surgery were applied for the rest of the children based on the clinical and laboratory evaluation.

In this study, the 5-year OS was 30.9% in patients with recurrence, and 72.2% in patients without recurrence. Recuurence was determined as a poor prognostic factor in survival analysis, whichwas similar to other reports (5,35).

Most of the children affected with CNS tumors experienced neurological deficits. This problem was dependent on type of treatment (surgery, radiotherapy and chemotherapy). Survivors without neurologic deficit showed better survival in current study, and was another independent influencing factor on survival rate.

Mirzadeh et al. reported Leukemia and CNS tumors as the most common cause of death in children aged 0-19 years in Yazd province,Iran 2004-2009; giving the crude cancer death rate of 8.48 and 6.72 in boys and girls per 100,000, respectively. Moreover, they investiagted the Years of Life Lost (YLL) due to premature cancer death that was 3,436 YLL in boys and 2,561 YLL in girls (36).

This study had some limitaions due to data analysis of onlyone center rather than a population based study. In addition, in this study, there was no facility to detect cytogenetic loci implicating malignant brain tumors, which may improvethe treatment decision in tumors such as targeted therapies and unique approaches to molecular subtypes.

Conclusion

According to the current study results, gender (girls had longer survival than boys), recurrence, neurologic deficit and age of diagnosis (60-119 months had longer survival compared to other age groups), were determined as influencing factors on survival. Moreover, location of tumor in diencephalon as well as unresectable and less than 25% unresectable tumors were determined as poor prognostic factors on survival. These factors should be taken into account by oncologists to make better decisions when managing patients. It seems that survival is a multifactorial event, and besides these prognostic factors, it might be also related to different clinical settings, ethnicity and type of treatment. Further studies with more focus on different treatment modalities are suggested.

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Conflict of interest

The author(s) declare that they have no conflict of interests

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