Original Article

Treatment Outcomes and Prognostic Factors in Pediatric Non-brainstem Astrocytoma in North East of Iran

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Abstract

Background: Central Nervous System (CNS) tumors have accounted for approximately one fourth of all pediatric malignancies. CNS tumors have been the most common solid malignancies among the children. In this study, we have evaluated survival and prognostic factors in children with non-brain stem astrocytoma.

Methods: Children with non-brain stem astrocytoma, referring to radiation oncology centers of Ghaem and Omid hospitals of Mashhad, have included in this retrospective study, in years 2000-2010. Patients' demographic data, past medical history, clinical symptoms, extent of tumor resection and treatment modality have recorded. Disease-free survival and overall survival have measured using Kaplan-Meier method.

Results: We studied 87 patients with male to female ratio of 44/43 (1.02), and median age of 10 yrs (range: 2-15 yrs). Tumor grade distribution was as follows: grade I: 20 (23%) subjects; grade II: 34 (39.1%) subjects; grade III: 20 (23%) subjects; and grade IV: 13 (14.9%) subjects. The median follow-up duration was 38 months (6 to 110), and 16 months (4 to 100) for patients with low- and high-grade tumors. The 2-year survival rates in grades I-IV were 100%, 84.7%, 60% and 10.8%, respectively. Tumor resection less than gross total and non-ambulation have associated with a significantly inferior survival in both groups multivariate analysis, with high- and low-grade tumors.

Conclusion: For all the cases of the pediatric non-brainstem astrocytoma, tumor grade had dramatic influences on their survival. Performing gross total resection was crucial for achieving favorable outcomes in both low-grade and high-grade cases. Moreover, according to the results, having major motor deficits has associated with lower survival.

Keywords: Pediatric; Non-brain stem; Astrocytoma

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Introduction

Central Nervous System (CNS) tumors has accounted for approximately 20-25% of all pediatric malignancies. CNS tumors were the most common solid malignancies in children [1, 2]. Among the pediatric primary brain tumors, low-grade astrocytoma tumors have comprised approximately one third of all cases. In comparison with adults, high-grade gliomas were less common in children, and then have more frequently observed in the brainstem region [3, 4].

Treatment modalities which have included surgery, followed by observation, and chemotherapy or radiotherapy, depending on histological characteristics, the extent of tumor resection, and its site [5-9]. Prognosis and type of treatment have differed among the children and adults with primary brain tumors. Several studies have shown that the grade and extent of tumor resection were the main independent factors that have been affecting the prognosis of glial tumors. Other influential factors were the patient's age, the amount of tumor resection and tumor location [10-12].

This study has conducted to reveal the characteristics of pediatric non-brain stem

astrocytoma including clinicopathologic behavior, treatment outcomes, and prognostic factors.

Materials and Methods

Children with non-brain stem astrocytoma referred to radiation oncology department of Omid Hospital of Mashhad have included in this retrospective study, between the years 2000-2010.

The patients who have met the following criteria have included in the study: 1) age ≤16 yrs, 2) pathologically confirmed astrocytoma, and 3) patients with tumor in non-brain stem region, confirmed by imaging.

The exclusion criteria were as follows: 1) unavailable pathological report, and 2) incomplete medical records.

Statistical analysis

Data have analyzed using SPSS Version 16, and descriptive and analytical methods have utilized. For survival analysis, Kaplan-Meier method has used, and overall survival has calculated from the time of diagnosis until the time of death to any cause or the last visit. Log-rank test has performed to compare survival curves between the groups, and Cox-regression test has used for multivariate analysis.

Results

Of 167 patients with primary brain tumor, 87 cases with the median age of 10 yrs (range: 2-15 yrs) and male/female ratio of 43/44 had pathologically confirmed non-brain stem astrocytoma (Table 1).

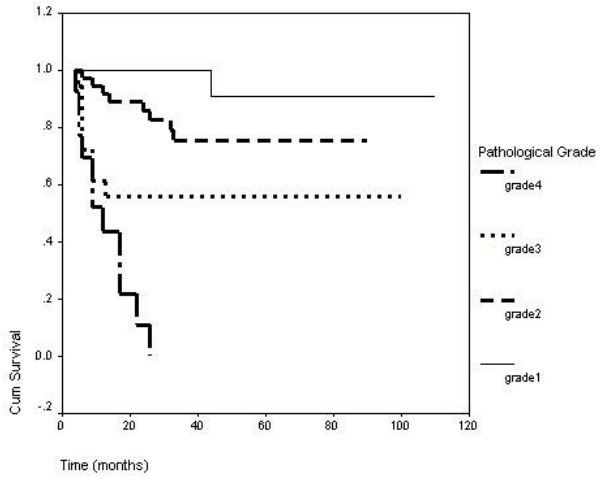

Figure 1. It shows survival curves for patients with non-brain stem astrocytoma and different tumor grades.

Table 1. Primary brain tumors frequency among the children

Primary tumor	Number (%)
Non-brain stem Astrocytoma	87 (52.1)
Brain stem tumor	26 (15.1)
Medullublastoma	26 (15.1)
Pineoblastoma	1 (0.6)
Ependymoma	11 (6.5)
Oligodendroglioma	7 (4.2)
Craniopharyngioma	4 (2.4)
Meningioma	3 (1.8)
Choroid plexus papilloma	2 (1.2)
Total	167

Table 2. Tumor grades

Tumor grade	Patients (%)
Grade I	20 (23.0%)
Grade II	34 (39.1%)
Grade III	20 (23.0%)
Grade IV	13 (14.9%)
Total	87

Table 3. Tumor grades frequency based on anatomical locations

Tumor grades	Supratentorial	Infratentorial
Grade I	2	18 (90%)
Grade II	20	14 (41.2%)
Grade III	15	5 (25%)
Grade IV	13	0

Tumor grades have illustrated in Table 2.

As compared with high-grade cases, low-grade non-brainstem astrocytoma were more common among the younger ages; 34 (63%) and 8 (24.2%) of low- and high-grade patients were younger than 10 years ($p<0.01$), respectively. In comparison with high- grade cases, low-grade astrocytomas have more frequently observed in the infratentorial region (15.2% vs. 59.3%, $p< 0.001$) (Table 3). Eight (9.2%) cases had a history of epilepsy, and 34 (39%) individuals complained of focal neurological symptoms, with paresis and plegia in 21 (24.1%) and 13 (14.9%) subjects, respectively. In addition, 69 (79.3%) cases were ambulatory at the time of referral.

Table 4. Performance status among the patients with high- and low-grade tumors

Tumor grade	Performance		Total
	Ambulatory	Aid-needed	
Low grade	50	4 (7.4%)	54
High grade	19	14 (42.4%)	33
Total	69	18	87

Gross total/near-total resection has performed on 58 (66.6%) patients, while 29 (33.3%) cases have only undergone biopsy. Patients with low-grade tumors (grade I, II) have undergone subtotal or near-total resection more frequently compared to patients with high-grade tumors (75.9% vs. 48.5%, p=0.003). As shown in Table 4, neurologic deficits were significantly more common in children with high-grade tumors (p<0.001).

The intended radiotherapy protocol has completed in 77 (88.5%) subjects. The number of cases who could complete the treatment has slightly higher in patients with low-grade tumors compared to those with high-grade tumors (90.6% vs. 85.3%, p=0.47). Patients with completed treatment and low-grade astrocytoma have undergone radiotherapy with a median dose of 54 Gy (range: 45-57.5 Gy) and those with high-grade tumors have received a median dose of 57 Gy (range: 50-60 Gy).

Evaluation of Survival Curves and Potential Prognostic Factors

The median follow-up time for patients with low-grade and high-grade astrocytoma was 38 months (range: 6-110 months) and 16 months (range: 4-100 months), respectively. We have recorded 28 deaths during the follow-ups, which were significantly higher in cases with high-grade tumors; all deaths were tumor-related. There was a significant difference in overall survival curves between different tumor grades (Table 5, Figure 1).

Table 5. The frequency of patients with 2-5-year overall survival rates based on tumor grades

Grade	Total number	2-year survival % ± 1 SE	5-year survival % ± 1 SE	Number of events (%)
1	20	100	90.9 ± 7.6	1 (5)
2	34	84.7 ± 6.1	73.9 ± 8	8 (23.5)
3	20	60 ± 10.9	60 ± 10.9	8 (40)
4	13	10.8 ± 10	Not Reached	11 (84.6)

In the "low-grade astrocytoma" group, tumor grade (grade I vs. grade II), performance status (ambulatory vs. non-ambulatory) and surgical resection (gross total/near-total resection vs. biopsy) were significant predictors of survival in univariate evaluation.

However, in multivariate analysis, only surgical resection and performance status have remained as independent prognostic factors (Table 6). Likewise, in the group of high-grade astrocytoma, surgical resection and performance status were significant prognostic factors in both univariate and multivariate analysis; but, tumor grade (grade III vs. grade IV) was only effective for survival in the univariate assessment (Table 7).

Table 6. Potential prognostic factors among the Patients with low-grade non-brainstem astrocytomas

Characteristics	No.	5-year survival % ± 1SE	Log-rank p value	Cox-regression p value
Grade				
grade I	20	90.9 ± 8.7	0.04*	0.26
grade II	34	73.9 ± 8.2		
Age:				
<10 yrs	34	81.3 ± 7		-
≥10 yrs	20	76.7± 13	0.69	
Performance:				
Ambulatory	50	84.2± 6.4	0.001*	0.01*
Non-ambulatory	4	25± 21.6		
Resection:				
Total/subtotal	41	94.9 ± 3.5	0.001*	0.001*
Biopsy	13	24.4 ± 18.8		

*significant

Table 7. Potential prognostic factors among the Patients with high-grade non-brainstem astrocytomas

Characteristics	No.	5-year survival % ± 1SE	Log-rank P-value	Cox-regression P-value
Grade				
grade III	20	60 ± 10.9	0.003*	0.5
grade IV	13	Not reached		
Age				
<10 yrs	8	33.1 ± 18		-
>=10 yrs	25	39± 9.9	0.7	
Performance				
Ambulatory	19	56.7± 11.6	0.003*	0.38
Non-ambulatory	14	Not reached		
Resection				
Total/subtotal	17	70.1 ± 11	< 0.001*	0.001*
Biopsy	16	Not reached		

*significant

Discussion

According to the results of the present study, glial tumors were the most common primary brain tumors in our patients. Likewise, Makino K. et al. in a population-based epidemiological study in Japan have shown that among 210 children (younger than 15 years) with primary brain tumor, astrocytoma was the most common pathology (35.7%), with a boy to girl ratio of 1.3 [2]. Compatible results have obtained in India by Jain et al. [5] and in Nigeria by Uche et al. [13]. However, the epidemiological profile might be somehow different in other regions of the world. For example, a retrospective hospital-based study in Morocco by Karkouri et al has shown that medulloblastoma, has been followed by astrocytoma, has diagnosed as the most common brain tumor (34.5%) among children since the birth until the age of 14 [14].

As compatible with previous surveys [3-6], our study has shown that pediatric non-brain stem astrocytomas were usually low-grade tumors; also, glioblastoma multiform has less frequently observed among the children in comparison with adults. Moreover, compared to adults, pediatric astrocytomas have more commonly located in the infratentorial region; gender distribution was almost equal in our study.

Previous trials have revealed tumor grade as a significant prognostic factor in pediatric children with astrocytoma [10-11]. In our study, cases with grade-I astrocytoma (pilocytic astrocytoma) had a very favourable outcome, and only 1 out of 20 patients (5%) experienced failure.

Patients with grade-IV astrocytoma had a very dire prognosis, and all tumors have located in the supratentorial compartment. A plenty of these tumors have associated with significant neurological deficits which have reflected the aggressive nature of the tumor. Surgical resection was not optimal in a significant number of high-grade cases, especially for those with grade-IV tumors. Children with high-grade astrocytoma have even shown much poor prognosis in comparison with adults, with the same pathology, which might root in biological differences [8, 15].

As similar to the present study, the extent of resection, and the effect of neurological deficit on the outcome have been indicated in other trials [5-7]. Hales et al. in a study on 63 children with high-grade astrocytoma, whose have managed at John Hopkins Hospital (in years 1997-2004), has shown that performance status <80%, resection less than gross total, bilaterally, parietal lobe location and radiation dose <50 Gy have associated with inferior survival [6].

A review of 6,212 cases with pediatric glioma by Qaddoumi_et al. revealed tumor grade as the most important prognostic factor in all age groups; although, the extent of resection was the most significant predictor of survival for the youngest ages. The analysis of his study has indicated that inferior survival in younger children with low-grade

gliomas might be related to receiving lower radiation doses; and it might also be related to lower probability for undergoing gross total resection [7].

Conclusion

Tumor grade was the most important prognostic factor in children with non-brainstem astrocytoma, which has signified precise pathological diagnosis. For patients with low-grade astrocytoma, achieving optimal surgical resection is the most important factor in obtaining favorable long-term outcomes. The final treatment results for high-grade astrocytoma, especially grade IV, were not satisfactory. However, performing gross total resection in high-grade cases could improve clinical outcomes in these patients.

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Conflict of Interest

There was no conflict of interest in this article.

Authors' Contribution

Kazem Anvari , Mehdi Seilanian Toussi, and Gholamreza Bahadorkhan have designed the present study. Soodabeh Shahidsales has written the article, and Kazem Anvari , and Mehdi Seilanian Toussi have edited the article. Motahare Bitaghsir, Mozhgan Heidari, and Mitra Fazl Ersi have been responsible for collecting the data, and Kazem Anvari, Mehdi Seilanian Toussi, and Soodabeh Shahidsales have contributed to the analysis and data interpretation.

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