Survival and Prognostic Factors in Children with Brain Tumors: Long-term Follow-up Single Center Study in Poland

MONIKA POGORZALA*, JAN STYCZYNSKI* and MARIUSZ WYSOCKI

*Department of Pediatric Hematology and Oncology, Collegium Medicum,
Nicolaus Copernicus University, Bydgoszcz, Poland*

Abstract. *Aim: Analysis of risk factors for survival in long-term follow-up of children treated at a single pediatric center in Poland. Patients and Methods: Out of 623 children diagnosed with cancer between 1995-2005, 110 were treated for brain tumors and followed-up, with a mean survival of 11.4 years. Results: Overall 5-year survival in the whole cohort was 60.9±4.7%, while 10-year survival was 58.2±4.7%. No relapse, progression or death occurred after six years from initial diagnosis. Survival was 48.1±9.6% for patients with medulloblastoma and primitive neuroectodermal tumors; 83.3±6.2% for low-grade astrocytoma; 56.6±16.6% for ependymoma, while 0% at 72 months for high-grade glioma. Patients with cerebellar tumors had a survival rate 69.0±7.1% at 10 years. Multivariate analysis showed that factors predicting poor outcome were: grade III-IV tumor, incomplete surgical resection, and complications after surgical resection, while diagnosis of low-grade glioma was the only factor predicting good outcome. Progression of the disease during therapy was an additional independent adverse risk factor for survival. Conclusion: Long-term survival was achieved by 58% of children with brain tumors. Advanced tumor stage, incomplete surgical resection, complications of surgical treatment, and progression of the disease during treatment predicted poor outcome.*

Central nervous system (CNS) tumors are the second most common type of cancer among children and the most frequent solid tumor in childhood in Europe and in North America (1, 2). They affect approximately 16-27% of all children with malignant diseases, and the annual incidence is 25 cases per one million children (1, 2). Worldwide, they account for 8-15% of pediatric cancer diagnoses and the third most frequent type of childhood cancer, after leukemia (30%) and lymphoma (15%) (3). One third of CNS tumors are diagnosed before three years of age. The incidence of this type of tumor has been progressively increasing, and survival has improved less than for other types of cancer (1-3). After the first year of life, CNS tumors are regarded the most common cause of death due to cancer in adolescence (2). Over the last two decades, adjuvant radiotherapy and chemotherapy were introduced into the therapy of brain tumors in children.

The objective of this study was the analysis of risk factors for survival in long-term follow-up of children treated in a single pediatric center.

Patients and Methods

This retrospective cross-sectional study was performed for the Kujawy-Pomerania region in Poland, which includes 2.1 million inhabitants. Data were collected for all 623 consecutive pediatric patients diagnosed with neoplastic disease between 1995-2005. Diagnosis of brain tumor was made according to the World Health Organization (WHO) classification (4). Patients with secondary or metastatic CNS tumors were excluded from the study. The frequency of brain tumors in the Department was determined based on data reported to the National Cancer Registry over a period of 11 years. The incidence rate of brain tumors in the Kujawy-Pomerania region was determined with regard to the size of population provided by the National Statistic Office in Bydgoszcz. Patients were followed-up until July 2013.

Statistical analysis. Descriptive statistics are used to show the patients' general characteristics. Percentages are reported for categorical variables, median and ranges for continuous variables; overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause, or to the date of the latest follow-up. Death due to any cause was considered as an event. The probabilities of OS were estimated by the Kaplan–Meier method using the log-rank test. The impact of the following variables was analyzed: age, tumor localization, clinical stage, histological diagnosis, degree of

*These Authors contributed equally to this study.

Correspondence to: Jan Styczynski, MD, Ph.D., Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University, ul. Curie-Sklodowskiej 9, 85-094 Bydgoszcz, Poland. Tel: +48 525854860, Fax: +48 525854867, e-mail: jstyczynski@cm.umk.pl

surgical resection, post-operative complications (*i.e.* intracranial hematoma, cerebral edema, meningitis, consciousness clouding, mutism), compliance to treatment protocol, and response to therapy (*i.e.* remission, stable disease, progression/relapse, death). Cox's proportional-hazards regression model was used to correlate each potential prognostic factor with survival in univariate analysis. The factors that appeared to be important were then fitted together in multivariate analysis and dropped one at a time in a backward stepwise manner using the likelihood ratio test at a 0.05 level until all factors in the model were significant. A final check was made to ensure that no excluded factors would improve the fit. A *p*-value below 0.05 was regarded as statistically significant.

Results

Demographic data. Between 1995 and 2005, a total of 623 children aged up to 18 years were diagnosed and treated in our Department. Primary brain tumors were diagnosed in 110 (17.7%) patients, including 49 females and 61 males, aged 0-18 (median 9.8) years. According to the WHO classification, these included the following diagnoses: astrocytic tumors, low-grade glioma (LGG) in 36 (32.7%) patients and high-grade glioma (HGG) in nine cases (8.2%); embryonal tumors [medulloblastoma (MBL) and primitive neuroectodermal tumor, (PNET)] in 27 (24.5%) cases; ependymoma in 9 (8.2%) cases; in 8 (7.3%) cases pineal (n=3) and germinal (n=5) tumors (Table I). Other diagnoses were made in 19.1%, including non-malignant tumors or tumors non-verified histologically (*e.g.* brain stem tumors).

Morbidity expressed as incidence rate (IR) of brain tumors in the area of Kujawy and Pomerania was $19.3/10^6$, and varied in age groups from $22.3/10^6$ (5-9 years), to $18.3/10^6$ (10-14, and 0-4 years), and $17.9/10^6$ (15-18 years).

Survival analysis. A total of 64/110 (58.2%) patients were alive at the end of the follow-up, with a mean survival of 11.4 years (95% confidence intervals, CI=9.8-13.0 years); 37 had died due to disease relapse/progression, while 9 died due to therapy complications. Overall 5-year survival for the whole cohort was 60.9±4.7%, while 10-year survival was 58.2±4.7%. No relapse, progression or death occurred after six years from initial diagnosis. Survival was 48.1±9.6% for patients with medulloblastoma and PNET; 83.3±6.2% for those with low-grade astrocytoma; 56.6±16.6% for those with ependymoma (Figure 1). We found a lower survival rate for patients with high-grade gliomas: 55.6±16% at 12 months, 11.1±10% at 24 months and 0% at 72 months. Patients with brain stem tumors also had a low survival rate, 36.8±11.1% at 24 months. Patients with cerebellar tumors, in contrast, had a survival rate of about 73.8±6.8% at 5 years and 69.0±7.1% at 10 years.

Risk factor analysis of survival. By univariate analysis, factors predicting poor outcome were: brain stem localization, HGG diagnosis, grade III-IV tumors according to the WHO classification, incomplete surgical resection, complications

Table I. *Patients' characteristics*.

Diagnosis	Number of patients (boys/girls)	Rate (%)	Median age, years (range)
Low-grade gliomas	36 (15/21)	32.7	10.2 (0.2-17.7)
Embryonal tumors	27 (21/6)	24.5	9.7 (1.9-17.9)
High-grade gliomas	9 (4/5)	8.2	8.4 (4.4-17.2)
Ependymomas	9 (6/3)	8.2	9.9 (1.1-14.1)
Pineal region tumors	8 (5/3)	7.3	15.1 (0.1-17.9)
Non-verified tumors (brain stem tumors)	8 (5/3)	7.3	5.4 (1.8-17.7)
Non-malignant tumors	13 (5/8)	11.8	11.8 (4.0-17.3)
Total	110 (61/49)	100	9.8 (0.1-17.9)

after surgical resection, and progression of the disease during therapy, while diagnosis of LGG was the only factor predicting for good outcome (Table II). Other factors such as age<3 years, diagnosis of medulloblastoma or PNET, cerebellar localization, presence of metastases or therapy modifications had no prognostic impact on overall survival. By multivariate analysis, factors predicting poor outcome were: grade III-IV tumor according to the WHO classification, incomplete surgical resection, complications after surgical resection, and progression of the disease during therapy, while diagnosis of LGG was the only factor predicting for good outcome (Table II). When progression during therapy was taken as a separate factor in the univariate analysis, it strongly predicted therapy failure (hazard ratio, HR=7.3; 95% CI=3.5-15.4; *p*<0.001). When the additional prognostic model was constructed with this factor, progression during therapy was the strongest independent adverse risk factor for OS (HR=5.6; 95% CI=2.5-12.3; *p*<0.001).

Discussion

This study was aimed analyze factors influencing OS in children with brain tumors diagnosed and treated at a single pediatric Polish center at long-term follow-up. The main independent adverse prognostic factors for the primary outcome for the whole group were tumor grade III-IV, incomplete surgical resection and complications after surgical treatment. Diagnosis of HGG and brain stem tumors were significant adverse risk factors only in univariate analysis. Another finding of our study is that progression of the disease during therapy (chemotherapy or radiotherapy) had a highly negative impact on survival. This observation would seem to be an obvious factor, however its value was not well-documented, and rather presented as 'salvage therapy' (5-7). Diagnosis of LGG was a positive prognostic factor, but other variables did not have any statistically significant effect on survival of the cohort overall.
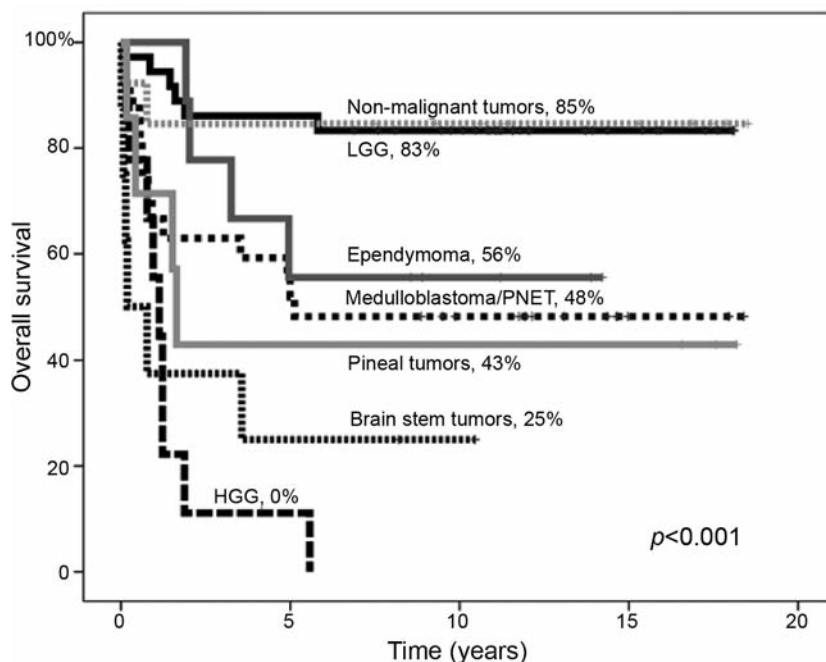
Figure 1. *Probability of overall survival with respect to diagnosis.*

Table II. *Risk factor analysis for overall survival.*

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Diagnosis: Low-grade glioma *vs*. other	0.3	0.1-0.6	0.001	0.3	0.1-0.7	0.008
Tumor grade: T3/T4 *vs*. T1/T2	3.9	2.1-7.6	<0.001	4.1	1.8-8.5	<0.001
Surgical resection: Biopsy/incomplete *vs*. subtotal/total	3.7	2.1-6.8	<0.001	2.5	1.1-6.0	0.047
Complications after surgical resection *vs*. none	4.7	2.5-9.1	<0.001	4.9	2.3-10.4	<0.001
Diagnosis: High-grade glioma *vs*. other	4.8	2.3-10.4	<0.001	1.6	0.7-3.7	0.220
Localization: Brain stem tumors *vs*. other	2.1	1.1-4.1	0.029	1.2	0.5-3.0	0.722
Localization: Cerebellar tumors *vs*. other	0.55	0.3-1.1	0.055			
Age <3 years *vs*. ≥3 years	1.7	0.8-3.9	0.171			
Diagnosis: Medulloblastoma / PNET *vs*. other	0.65	0.4-1.2	0.188			
Metastases: present *vs*. absent	2.0	0.8-5.1	0.135			
Modifications of therapy: yes *vs*. no	1.3	0.7-2.4	0.358			

CI, Confidence interval; PNET, primitive neuroectodermal tumor; HR, hazard risk; HR>1 denotes adverse impact on OS.

Tumor grade, site and histopathological type usually have an important impact on surgical resection, and further therapy. In the study of 6,212 patients younger than 20 years at diagnosis of glioma between 1973-2005 in the USA, the survival of children with gliomas was influenced by tumor grade, age <3 years, histological subtype (*i.e.* HGG), and extent of resection (8).

Surgery other than gross total resection was an independent adverse prognostic factor in our study, in agreement with other reports in the literature (8-11). The complications after surgical treatment were usually not analyzed by other study groups. We found that intracranial hematoma, cerebral edema, meningitis, consciousness clouding, or mutism have negative impact on outcome due to delay of further treatment, necessity for therapy modifications, or permanent disabilities. Impact of these complications has been shown only in a few studies (12-15).

We did not analyze impact of chemotherapy and radiotherapy as these modalities are commonly used depending on histological diagnosis in most national

protocols (16, 17). Radiotherapy is associated with better survival of children (17, 18). It affects the survival of patients with medulloblastoma and PNET or with brain stem tumors, but not of those with low-grade astrocytoma. The indication for radiotherapy in cases of low-grade astrocytoma is usually limited to patients that did not undergo complete resection or had recurrent disease, which limits the evaluation of the role of radiotherapy (3). The role of chemotherapy for pediatric brain tumors is already well-defined, and its positive effect is well-known, especially in medulloblastoma and PNET (17, 19-21).

In conclusion, we have shown that 10-year survival for children with brain tumors was 58%; it was the best for LGG, and the worst for HGG patients. No relapse, progression or death was observed after six years from initial diagnosis. We found that advanced tumor stage, incomplete surgical resection, complications of surgical treatment and progression of the disease during treatment predicted poor outcome.

References

1 Siegel R, Naishadham D and Jemal A: Cancer statistics, 2012. CA Cancer J Clin *62*: 10-29, 2012.

2 Kowalczyk JR, Dudkiewicz E, Balwierz W, Boguslawska-Jaworska J and Rokicka-Milewska R: Incidence of childhood cancers in Poland in 1995-1999. Med Sci Monit *8*: CR587-590, 2002.

3 Araujo OL, Trindade KM, Trompieri NM, Fontenele JB and Felix FH: Analysis of survival and prognostic factors of pediatric patients with brain tumor. J Pediatr (Rio J) *87*: 425-432, 2011.

4 Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW and Kleihues P: The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol *114*: 97-109, 2007.

5 Hu YW, Huang PI, Wong TT, Ho DM, Chang KP, Guo WY, Chang FC, Shiau CY, Liang ML, Lee YY, Chen HH, Yen SH and Chen YW: Salvage treatment for recurrent intracranial germinoma after reduced-volume radiotherapy: A single-institution experience and review of the literature. Int J Radiat Oncol Biol Phys *84*: 639-647, 2012.

6 Rutkowski S, Gerber NU, von Hoff K, Gnekow A, Bode U, Graf N, Berthold F, Henze G, Wolff JE, Warmuth-Metz M, Soerensen N, Emser A, Ottensmeier H, Deinlein F, Schlegel PG, Kortmann RD, Pietsch T and Kuehl J: Treatment of early childhood medulloblastoma by postoperative chemotherapy and deferred radiotherapy. Neuro Oncol *11*: 201-210, 2009.

7 Fisher BJ, Leighton CC, Vujovic O, Macdonald DR and Stitt L: Results of a policy of surveillance alone after surgical management of pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys *51*: 704-710, 2001.

8 Qaddoumi I, Sultan I and Gajjar A: Outcome and prognostic features in pediatric gliomas: A review of 6212 cases from the Surveillance, Epidemiology, and End Results database. Cancer *115*: 5761-5770, 2009.

9 Wisoff JH, Boyett JM, Berger MS, Brant C, Li H, Yates AJ, McGuire-Cullen P, Turski PA, Sutton LN, Allen JC, Packer RJ and Finlay JL: Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: A report of the Children's Cancer Group trial no. CCG-945. J Neurosurg *89*: 52-59, 1998.

10 Robertson PL, Zeltzer PM, Boyett JM, Rorke LB, Allen JC, Geyer JR, Stanley P, Li H, Albright AL, McGuire-Cullen P, Finlay JL, Stevens KR Jr., Milstein JM, Packer RJ and Wisoff J: Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: A report of the Children's Cancer Group. J Neurosurg *88*: 695-703, 1998.

11 Packer RJ and Vezina G: Management of and prognosis with medulloblastoma: Therapy at a crossroads. Arch Neurol *65*: 1419-1424, 2008.

12 Victor S and Lausberg G: Malignant brain glioma – a catamnestic study of 100 operated patients. Zentralbl Neurochir *52*: 59-68, 1991.

13 Di Rocco C, Iannelli A, Papacci F and Tamburrini G: Prognosis of medulloblastoma in infants. Childs Nerv Syst *13*: 388-396, 1997.

14 Suarez C, Llorente JL, Fernandez de Leon R, Cabanillas R, Suarez V and Lopez A: Anterior craniofacial resection: oncologic outcome and complications in a series of 111 cases. Acta Otorrinolaringol Esp *55*: 27-33, 2004.

15 Robertson PL, Muraszko KM, Holmes EJ, Sposto R, Packer RJ, Gajjar A, Dias MS and Allen JC: Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: A prospective study by the Children's Oncology Group. J Neurosurg *105*: 444-451, 2006.

16 Perek D and Perek-Polnik M: Brain tumors in children. Przegl Lek *60(Suppl 5)*: 27-34, 2003.

17 Smith RL, Shi X and Estlin EJ: Chemotherapy dose-intensity and survival for childhood medulloblastoma. Anticancer Res *32*: 3885-3892, 2012.

18 Mohindra P, Robins HI, Tome WA, Hayes L and Howard SP: Wide-field pulsed reduced dose rate radiotherapy (PRDR) for recurrent ependymoma in pediatric and young adult patients. Anticancer Res *33*: 2611-2618, 2013.

19 Butturini AM, Jacob M, Aguajo J, Vander-Walde NA, Villablanca J, Jubran R, Erdreich-Epstein A, Marachelian A, Dhall G and Finlay JL: High-dose chemotherapy and autologous hematopoietic progenitor cell rescue in children with recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors: The impact of prior radiotherapy on outcome. Cancer *115*: 2956-2963, 2009.

20 Fangusaro JR, Jubran RF, Allen J, Gardner S, Dunkel IJ, Rosenblum M, Atlas MP, Gonzalez-Gomez I, Miller D and Finlay JL: Brainstem primitive neuroectodermal tumors (BSTPNET): Results of treatment with intensive induction chemotherapy followed by consolidative chemotherapy with autologous hematopoietic cell rescue. Pediatr Blood Cancer *50*: 715-717, 2008.

21 Siegel MJ, Finlay JL and Zacharoulis S: State of the art chemotherapeutic management of pediatric brain tumors. Expert Rev Neurother *6*: 765-779, 2006.