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ORIGINAL ARTICLE

Outcome of childhood brain tumors in Serbia

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Summary

Purpose: *To present the results of treatment for childhood brain tumors in Serbia.*

Methods: *The medical records of patients with brain tumors diagnosed and operated at the Institute of Neurosurgery, Clinical Center of Serbia and treated with postoperative radiotherapy and chemotherapy at the Institute of Oncology and Radiology of Serbia, Belgrade, between January 1995 and December 2004, were reviewed. Of the 247 patients who were identified, 212 formed the basis of this study. Overall survival (OS) was determined by the Kaplan-Maier method, using log-rank test for comparisons.*

Results: *With a mean follow up of 46.9±33.6 months (range 7-120), the 5-and 8-year OS rates were 70.0% and 61.5%, respectively. At the time of evaluation 119 (60.1%) patients had no evidence of disease. Among 79 patients who failed therapy, most of them (n=61; 77.2%) had local failure only. According to histologic tumor type most of them (n=27; 34.2%) were in the group of malignant medulloblastoma.*

Girls had better survival than boys, but without statistical significance (p=0.185). Also, no significant difference in survival in relation to age was seen (p=0.291).

Patients with supratentorial tumors had significantly better survival than those with infratentorial localizations (p=0.036). Patients with low grade astrocytomas had significantly better survival than malignant gliomas, ependymomas and primitive neuroectodermal tumors (PNETs) (p=0.0001).

Conclusion: *OS rates were concordant with the results of other modern series. Although the survival rates were encouraging, there is still significant room for improvement in the management of childhood brain tumors.*

Key words: brain tumors, pediatric, treatment results

Introduction

With an incidence of 2 per 100,000 per year, brain tumors represent the commonest solid tumors of the childhood, the second commonest cause of cancer death in children and constitute approximately 20% of malignant diseases in the childhood [1,2].

Over the past decades there has been progressive improvement in the results of treatment of children with intracranial tumors with overall survival rates approaching 70% [3].

There are several reasons for this which include advances in neuro-radiological imaging leading to more accurate localization, improvements in neuro-surgical techniques, better perioperative care, improvement in radiotherapy equipment and techniques including greater and more precise dosage delivered to the tumor and refinements in the timing and dosing of chemotherapy. Despite all of these improvements childhood brain tumors remain a challenging oncologic condition [4].

The improved survival of children treated successfully for brain tumors had created more interest in possible late effects of cancer treatment especially affecting neurological function, intelligence, behavior and somatic development [5,6].

This would provide lifelong medical and psychological surveillance and support for survivors and their families. For all these reasons pediatric brain tumors have a major public health impact [7].

The aim of our study was to evaluate and present for the first time the results of OS of children treated for brain tumors (excluding brainstem tumors) in Serbia.

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We have previously presented our results on disease-free survival [8,9]; now, data are mature to present the results on overall survival.

Methods

During the period 1995-2004, 247 patients with brain tumors (excluding brainstem tumors), were identified from the hospital records at the Institute of Neurosurgery, Clinical Center of Serbia and the Institute of Oncology and Radiology of Serbia (IORS), Belgrade and 212 patients remained and formed the basis of the current study according to the inclusion criteria. These institutions are the national referral centers in Serbia for diagnosis and treatment of childhood brain tumors. Patients were diagnosed and operated at the Institute of Neurosurgery, Clinical Center of Serbia, and treated with postoperative radiotherapy and chemotherapy in selected cases at IORS.

Inclusion criteria were histologically proven diagnosis, no evidence of metastatic spread at the time of diagnosis, no history of previous malignant disease and age under 18. The main characteristics of the group are shown in Table 1.

Patients were aged 2.5-18 years (mean 9.7±4.5) at the time of diagnosis. There were 133 boys and 79 girls (sex ratio 1.7:1). The majority of patients were in the 4-16 year age group (179 patients), supratentorial tumors were diagnosed in 118 patients and infratentorial in 94 patients and, histologically the majority of patients (n=52) had low grade astrocytomas (32 supratentorial vs. 20 infratentorial) and medulloblastomas (n=55). Postoperatively all of the patients had CT and/or MRI of the brain to assess the degree of resection and, for some histological types, potential subarachnoid metastasis. For patients with tumors spreading into the ventricular system and the cerebrospinal fluid (CSF), imaging of the spine by gadolinium-enhanced MRI or by contrast CT plus lumbar CSF cytology were performed.

Table 1. Patient characteristics

Characteristics	*No. of patients*	*%*
Gender		
Male	133	62.7
Female	79	37.3
Age group (years)		
0-3	13	6.1
4-16	179	84.4
16+	20	9.4
Tumor location		
Supratentorial	118	55.7
Infratentorial	94	44.3
Histologic type		
Supratentorial	118	55.7
Low-grade astrocytomas	32	15.1
Optic pathway gliomas	16	7.5
Craniopharyngioma	10	4.7
Malignant gliomas	25	11.8
PNET	10	4.7
Pineal region tumors	9	4.3
Ependymomas	7	3.3
Oligodendroglioma	4	1.9
Other	5	2.4
Infratentorial	94	44.3
Medulloblastoma (PNET)	55	25.9
Astrocytomas	20	9.4
Ependymomas	18	8.5
Chorioid plexus carcinoma	1	0.5

PNET: primitive neuroectodermal tumors

After completing the staging procedures, treatment continued with postoperative conventionally fractionated radiotherapy. Radiotherapy was delivered using linear accelerator-based megavoltage radiation through a variety of techniques, including craniospinal treatment with standard methods (96 patients) and either opposed lateral portals or other multifield methods for focal treatment (116 patients).

Patients with PNETs (supratentorial and infratentorial), high-grade ependymomas (supratentorial and infratentorial), germ cell tumors and choroid plexus carcinoma had craniospinal irradiation. Craniospinal irradiation was performed with doses of 30-36 Gy conventionally fractionated at 150-180 cGy once daily. A local "boost" to 50-56 Gy was utilized.

For focal irradiation, 3 cm margin around the target volume for high grade tumors, and 1.5-2 cm margin for low grade tumor were used, with different radiotherapy techniques. This protocol was used until 2005 when we introduced in our Institute three-dimensional conformal radiotherapy (3-DCRT) which is now commonly used. This is one of the reasons why we have decided to present results until 2004. Doses were 50-56 Gy at 150-180 cGy per fraction, reduction to 45-50 Gy at 150 cGy daily for youngster less than 3 years old. For children older than 12 years with malignant gliomas a dose of 45-54 Gy to the wide local volume, with "boost" defined as a 1 cm margin, to a cumulative dose of 60 Gy was delivered. Adjuvant chemotherapy was administered to 91 (42.9%) patients according to histologic tumor type, tumor size, age and response to radiotherapy. Different chemotherapy regimens were administered. In the group of patients with medulloblastoma the majority of them received CCNU and vicristine (SIOP I regimen). The "8 in 1" regimen was used in patients who were considered to have poor prognosis and also in the group of patients with malignant gliomas. Several patients received other regimens (cisplatin, CCNU, vincristine or vincristine, CCNU and prednisolone). In

patients with PNETs vincristine, lomustine, cisplatin or vincristine, cyclophosphamide, carboplatin and etoposide chemotherapy regimens were used, and also variants of BEP and PVB regimens like in germ cell tumors.

The survival rates were calculated using the Kaplan-Meier method and differences between curves with log-rang test. In this analysis, we defined time of operation/biopsy as zero time and death as end-point time.

Results

At the time of evaluation 119 (60.1%) patients were without evidence of disease. Seventy-nine (39.9%) patients failed therapy and 14 (6.6%) patients were lost to follow-up. Fifty-six patients died, 54 because of tumor spread, 1 with shunt infection and no evidence of tumor and 1 in a car accident.

Among the 79 patients who failed therapy most of them had local relapse only (61 patients; 77.2%), intracranial (2 patients, 2.5%), local and intracranial (2 patients; 2.5%), spinal (5 patients; 6.3%), spinal and intracranial (6 patients; 7.6%), local and spinal (1 patient; 1.3%) and diffuse bone metastases (2 patients; 2.6%). Among the groups of patients who relapsed, 45 (57%) patients were with supratentorial tumors and 34 (43%) with infratentorial localization, and according to histologic tumor type most of them were in the group of malignant gliomas (14 patients) and medulloblastoma (27 patients).

During the follow-up period (mean 46.9±33.6 months, range 1-120 months), 5- and 8-year OS rates were 70.0% and 61.5%, respectively (Figure 1).

Survival and gender

Although in our study girls had better survival than boys (5-year OS for girls was 76.9% and for boys 66.3%), this difference was not statistically significant (log rank = 2.38, p=0.185) (Figure 2).

Survival and age

There were 13 patients in the 0-3 years age group, 20 were older than 16 years and the majority of patients (n=179) were in the 4-16 years age group.

There was no statistically significant difference in OS in these 3 groups of patients (log rank=2.47, p=0.291) (Figure 3).

Survival and tumor location

Among 212 patients, supratentorial tumors were diagnosed in 118 patients and infratentorial in 94 (brainstem tumors were excluded from this study). Five- and 8-year OS rates for patients with supratentorial tumors were 75 and 71.9% respectively vs. 63.7% and 49% for those with infrantentorial tumors.

Patients with supratentorial tumors had statistically significant better OS (log rank=4.39, p=0.036) (Figure 4).

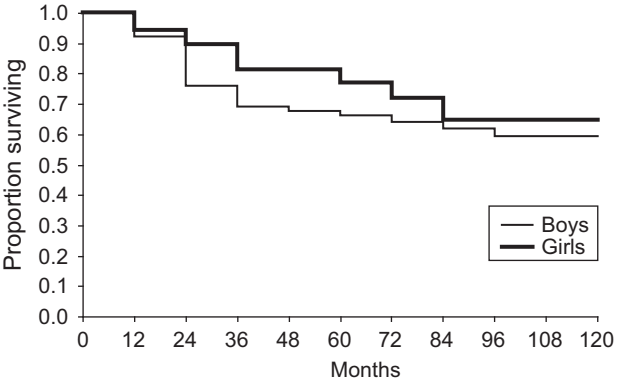

Figure 2. Overall survival of 212 patients with childhood brain tumors according to gender (p=0.185).

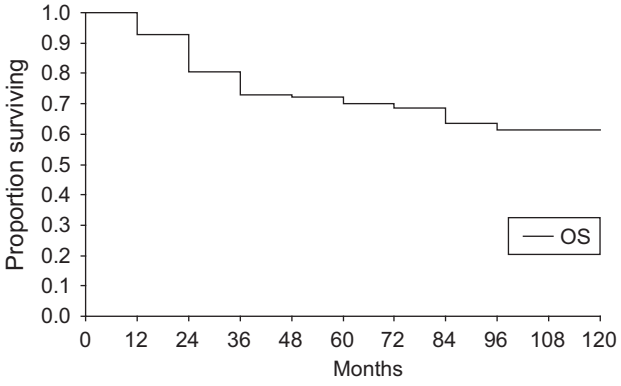

Figure 1. Overall survival of 212 patients with childhood brain tumors.

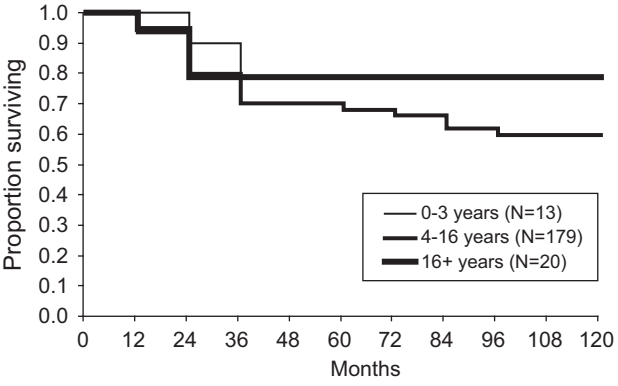

Figure 3. Overall survival of 212 patients with childhood brain tumors according to age (p=0.291).

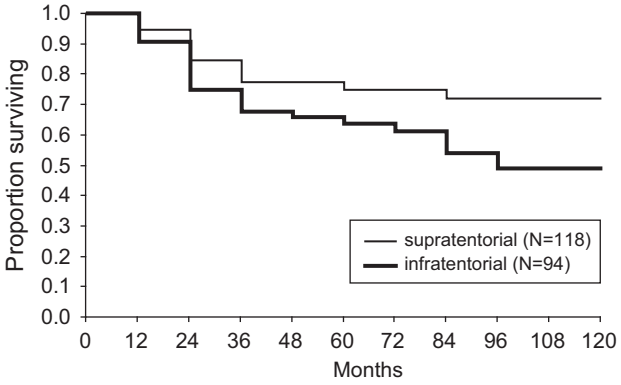

Figure 4. Overall survival of 212 patients with childhood brain tumors according to tumor location (p=0.036).

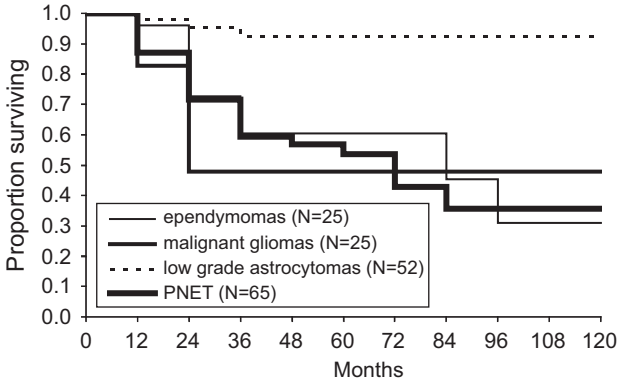

Figure 5. Overall survival of patients with childhood brain tumors according to histological tumor type (p=0.0001).

Survival and histological tumor type

Five-year OS rate for low grade astrocytomas was 92.4%, for malignant gliomas 47.8%, for ependymomas 60.3% and for PNETs 53.5% (Figure 5).

Patients with low-grade astrocytomas had statistically significant better OS compared with malignant gliomas, ependymomas and PNETs (log rank= 27.44, p=0.0001). There were no statistically significant differences among patients with malignant gliomas, ependymomas and PNETs (log rank = 1.37, p=0.503).

Discussion

The long-term OS survival of children with brain tumors has improved considerably in the last 3 decades, approaching 70%, owing to advances in neuroimaging techniques, progress in surgical and radiotherapy techniques, integrations of molecular biology in the decision-making process, introduction of new antineoplastic agents and better knowledge of short- and long-term side effects [10,11].

In a series of 610 children with intracranial tumors under 16 years of age, conducted in the Royal Marsden Hospital, UK, children treated with megavoltage X-ray equipment (1970-1981) had significantly better survival OS than those treated with orthovoltage X-rays (1950-1969) [12]. The actuarial survival OS rate for 579 new cases (31 had recurrent disease) was 53% at 5 years, 46% at 10 years, 40% at 20 years and 39% at 30 years. The 5-year OS survival of the 355 patients treated between 1950 and 1969 was 45% and of the 244 cases treated between 1970 and 1981 was 65% ($p<0.05$).

Medulloblastoma is a good example of improved outcome and evolving management. Less than 25 years ago, multiple series reported 5-year, progression-free survival (PFS) and OS rates of 50-60% for children older than 3 years with medulloblastoma [13,14].

Recent series, many of which are prospective with patients treated over the past decade, are now describing progression-free survival (PFS) rates as high as 85% in children with non-disseminated medulloblastoma, and PFS rates of 65-70% in higher-risk patients [15,16].

The reason for these improved survival rates are multiple and include improved postoperative care, possibly earlier or better detection of disease (especially disseminated disease), more aggressive surgery, improved radiotherapeutic techniques and refinements in the timing and dosing of chemotherapy [17,18].

Similarly, the management of ependymomas has benefited from a better awareness of the role of surgery and the emergence of radiation techniques that allow a better distribution of radiation to the tumor bed [19].

The 5-year OS rate in completely resected ependymomas currently approaches 80% [20].

In their 20-year institutional experience report of treatment of pediatric ependymoma Hui-Kuo Shu et al. the OS rates at 2, 5 and 10 years were 87.5, 66.2 and 56.3%, respectively. Patients who had a favorable prognosis had 5-year OS and PFS rates of 83.1% and 60.6%, respectively [21].

In germinoma, where the outcome is excellent, current questions surrounding management are essentially philosophical and aim to address the respective role of chemotherapy and radiation [22].

For some tumors, such as cerebellar astrocytoma, the 5- and 10-year OS rates approach 100% following surgery only [23].

Although neurosurgical removal of a low grade glioma is usually the optimal treatment, there are several locations in the brain where surgery cannot always be performed safely, such as the optic pathways, hypothalamus, and certain regions of the brain stem. These

tumors often require adjuvant non-surgical treatment, either chemotherapy or radiation. When treatment is needed, either at diagnosis or later in the disease process, the main issue in the management of these unresectable low grade gliomas is the choice of treatment with the best chance of sustained tumor control and the lowest risk of long-term side effects [24].

There are however pediatric brain tumors that still are challenging. The outcome of high grade gliomas and diffuse pontine gliomas is still very poor and no evidence of survival improvement has been seen since the 1980-90s despite numerous cooperative trials [25,26].

Similarly the outcome of young children with embryonal tumors of the central nervous system remains equally poor among all tumor types [27].

Although some subsets of infants, primarily those with non-disseminated localized disease have a relatively better outcome, OS remains disappointing and this group currently represents one of the biggest challenges in the prospect of new treatment strategies for pediatric brain tumors [28].

In our study, which included 212 patients with intracranial tumors, the 5- and 8-year OS rates were 70 and 61.5%, respectively.

Although our results are in accordance with other modern series, it might be noted that from our study were excluded patients with brainstem tumors, those with no histologically proven diagnosis, patients with metastatic disease at the time of diagnosis and patients who were treated only with chemotherapy or had complications after neurosurgery. These are high-risk patients who would have had considerable impact on treatment results.

Also, we chose to present results of treatment until 2004 because in 2005 we introduced in our Institute 3-DCRT which is now commonly used. We hope to analyze results of treatment of this group of patients in the future.

Brain tumors occur more frequently in males than in females. Bloom and associates reported that there was no difference in survival between 328 boys and 251 girls in their study [12]. Also in the group of patients with medulloblastoma (107 boys and 53 girls; 2:1 ratio), there was no difference in survival according to sex.

In our group of patients the male to female ratio was 1.7:1 (133 boys vs. 79 girls). Although the survival was better in females than in males, this difference was not statistically significant.

The recommendation of the SIOP subcommittee for brain tumors in 1995 was to divide patients into 3 groups: the first with children up to 3 years of age (36 months), the second from 3-16 years (36-192 months) and the third with children more than 16 years of age [29].

Most of the literature indicates lower survival rates in children less than 3-4 years old [30,31].

The management of these very young patients remains challenging since the immature brain is particularly susceptible to the toxicity of current treatment options. There is belief that medulloblastomas in the very young child have a more aggressive behavior and a higher incidence of metastasis at the time of diagnosis, although the data is limited. Evans et al. reported that 34% of children under the age of 4 years presented with disseminated disease compared with only 14% of children aged 4 years or older [13].

Similar results were reported separately with 62% of children less than 5 years of age demonstrating metastatic disease vs. 38% in children older than 5 years [28].

The impact of age on prognosis is difficult to assess because younger patients normally receive different treatment modalities than older children. In an attempt to delay or obviate radiation therapy, multiple studies have been performed using different chemotherapy regimens.

One of the largest trials for young children from the CCG (CCG 9921) reported on 92 children younger than 3 years of age, of which 61 had no evidence of metastasis at the time of diagnosis. Children were treated with two different induction schemes followed by 8 cycles of maintenance chemotherapy. Children with no residual tumor after induction therapy and no metastasis at diagnosis did not receive radiation therapy unless they had evidence of recurrence. The event-free survival (EFS) in the nonmetastatic group was 41% in 38 patients with of gross total resection (GTR) and 26% in 23 patients with residual tumor. In 31 patients with metastatic disease the EFS was 25% [32].

Jenkin et al. evaluated survival and functional morbidity for 222 children who were less than 4 years old when they were irradiated. The 10-year OS rate was 40%, not significantly different than the 45% for 776, 4-16 years old children with irradiated brain tumors treated at the some institutions [33].

In our study the majority of patients (n=179) were in the 4-16 years age group, 13 patients were in the 0-3 age group years and 20 patients were older than 16 years. There was no statistically significant difference in survival in these 3 groups of patients (p=0.367).

One of the reasons for this might be the unequal distribution of patients among the groups (13 patients, 179 patients, 20 patients). The relatively better survival rates for the groups less than 3 years and older than 16 years of age can be explained by the distribution of histological tumor types in these groups. Among 13 patients less than 3 years of age, 4 patients were diagnosed with low-grade astrocytomas, 2 with optic nerves low-

grade gliomas, 3 with medulloblastoma and 3 with ependymoma. One patient was lost to follow-up. Also, our attempt to delay radiotherapy whenever possible might contribute to that, too.

The majority of 20 patients older than 16 years had "favorable" histological tumor type. Eight patients were diagnosed with low-grade astocytomas, 1 patient with optic nerves low-grade glioma, 1 with craniopharyngioma, 1 with chordoma, 1 with meningioma, 1 with pineal region germinoma, 3 with malignant gliomas, 3 with medulloblastoma and 1 with ependymoma.

According to Childhood Brain Tumor Consortium data in a study that included 3291 children with brain tumors based on surgical biopsies from 10 north American institutions, 45-50% patients had supratentorial tumors and 50-55% patients had infratentorial tumors [34].

According to Bloom et al. data among 579 new cases with intracranial tumors, 3 were at multiple sites and were excluded, leading 576 cases for analysis; 263 (46%) of the children had supratentorial tumors and 313 (54%) infratentorial lesions. This distribution is in agreement with other reported series. At 5 years 69% of the supratentorial group of patients were alive, compared with only 39% of those with lesions in the posterior fossa. The difference in survival for the two groups was significant [12].

In our study 118 (55.7%) patients had supratentorial and 94 (44.3%) infratentorial tumors. This distribution is in agreement with other reported series, having in mind that from our study patients with brainstem tumors were excluded. Patients with supratentorial tumors had statistically significant better survival (p=0.036). Five and 8-year OS rates for patients with supratentorial tumors were 75 and 71.9% and for patients with infratentorial tumors 63.7 and 49%.

In our study we also analyzed OS according to histologic tumor type. Due to limitations posed by the number of patients in the groups, we decided to analyze patients with low grade astrocytomas in one group (supratentorial 32 and infratentorial 20 patients), ependymomas (supratentorial 7 and infratentorial 18 patients) and PNETs (supratentorial 10 and infratentorial 55 patients). We also analyzed the group of patients with malignant gliomas (n=25), while the number of patients with other histological tumor type was too small to be analyzed in this article.

Our results are in accordance with other published series. Five-year (and 8-year) OS rates were as follows: for low grade astrocytomas 92.4% (and 92.4%), ependymomas 60.3% (and 31.3%), malignant gliomas 47.8% (and 47.8%), and PNET 53.5 (and 35.7%).

Patients with low-grade astrocytomas had statistically significant better survival than malignant gliomas, ependymomas and PNETs (log rank=27.44, p=0.0001). There were no statistically significant differences among patients with malignant gliomas, ependymomas and PNETs (log rank=1.37, p=0.503).

We believe that our study has some limitations. The group of patients was, in a way, "selected", because high-risk patients, as it was mentioned in the discussion, were excluded from the study.

Also, in an attempt to present for the first time the results of treatment for childhood brain tumors in Serbia, we didn't analyze possible treatment parameters (type of surgery, radiotherapy parameters, number or type of different chemotherapy protocols used etc), but focused more on just presenting the results of OS of this group of patients treated in our country during the 10-year period.

Childhood brain tumors remain a challenging oncologic condition. Even though long-term survival for children with a brain tumor approaches 70% there is need for improved treatment approaches. Secondary malignancies, neurocognitive deficits and treatment failure continue to afflict these children and young adults. Therapy for childhood brain tumors requires a delicate balance between the need to intensify therapy for some recalcitrant tumor types and the desire to reduce potentially neurotoxic therapy and risk for other malignancies, so as to have a greater number of survivors with cognitive, psychological and endocrinologic abilities allowing them to live "normal" lives. In our study of patients with childhood brain tumors treated in Serbia, OS rates were concordant with those published in other modern series. Although the survival rates were encouraging, there is still significant room for improvement in the management of this disease.

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