Therapeutic results in children with brain tumors – a single center experience over 18 years

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Abstract

Background and aims. Tumors of the central nervous system represent the main cause of death by cancer in children. The diagnosis and molecular classification of these neoplasms have seen great improvement in the past years, due to ongoing genomic advances. In general, the treatment consists of surgery, radiation therapy and chemotherapy. However, the currently available pharmacological treatment options have limited effectiveness due to the particular characteristics of the blood-brain barrier.

Methods. We decided to study the therapeutic results in children treated for brain tumors in the Cluj-Napoca "Prof. dr. Ion Chiricuta" Oncology Institute, between 2001 and 2018, in order to provide a more accurate understanding of the disease and the available therapeutic options in our center.

Results. Out of the 207 cases included in this study, we recorded 98 deaths (47.3%). This is significantly less than the 5-year survival rate recorded in the US between 2012 and 2018 (74.9%). There are many factors that could explain the low survival rate, such as a very late diagnosis, the inability to implement innovative radiation therapy techniques until 2018, and the fact that between 2001 and 2010 the chemotherapy regimens in our center were not as effective as the more recent ones.

Conclusions. The therapeutic results recorded in this study are similar to those in other middle-income countries, however, the available treatment options for pediatric brain tumors are not as effective as those currently in use for other pediatric and adult malignancies.

Keywords: brain tumors, children, therapeutic outcome, disease prognossis, Romania

Background and aims

Pediatric tumors of the Central Nervous System (CNS) represent the most frequent solid neoplasm and the main cause of death by cancer in children aged 0-15 years. The causes for these tumors are very heterogeneous and can be broadly classified into hereditary and non-hereditary. Non-hereditary brain tumors are caused by environmental carcinogens such as: exposure to ionizing radiation, tobacco smoke, exposure to organic compounds or nitrosamines, but also immunodeficiency [1].

Studies of genetic risk factors have identified germline variants associated with an increased risk for various childhood brain tumors. The most common syndromes associated with the development of childhood brain tumors are neurofibromatosis type 1 and type 2, tuberous sclerosis type 1 and type 2, von Hippel Lindau syndrome, Li Fraumeni syndrome, nevoid basal cell carcinoma syndrome, Turcot's syndrome, ataxia-telangiectasia syndrome and Down syndrome [2].

According to the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System,

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brain tumors are classified into the following categories: gliomas, glioneuronal and neuronal tumors, ependymal tumors, choroid plexus tumors, embryonal tumors, pineal gland tumors, cranial and paraspinal nerve tumors, meningiomas, mesenchymal non-meningothelial tumors, melanocytic tumors, hematolymphoid tumors, germ cell tumors, tumors of the sellar region and metastatic tumors [3].

The better understanding of the molecular alterations involved in these tumors is now leading to the development of targeted treatment options. The evolution from the conventional combination of standard radiation treatment and chemotherapy to molecular therapies will allow for the development of new risk-adapted treatment protocols [4].

Childhood brain tumors have a relatively poor survival rate compared to other childhood malignancies. This comes as a result of multiple factors: the rareness of the disease relative to other childhood illnesses - which often leads to late diagnosis, the large diversity in morphological features, the biological particularities of the blood-brain barrier and nervous tissue, and furthermore, the narrow spectrum of available therapies [5].

Low grade gliomas have a relatively good 10-year progression-free survival, ranging from 85% for completely resected tumors, to 45% for subtotal resections. Medulloblastomas have a variable 5 year survival rate, depending on the molecular pattern: 90% for Wingless-activated (WNT), 70 % for Sonic Hedgehog (SHH)-activated, 50% for the non-WNT/non-SHH groups. Less than two thirds of children diagnosed with ependymoma survive [6].

The aim of the current study was to evaluate the survival rates of children with brain tumors and to underline the differences between literature and real-life settings for the treatment of brain tumors in children, in a middle-income country, over a period of 18 years.

Methods

We have studied all children diagnosed with primary brain tumors at the Cluj-Napoca "Prof. Dr. Ion Chiricuta" Oncology Institute between 2001 - 2018. The inclusion criteria were: patients under the age of 18 diagnosed with primary brain tumors. The exclusion criteria were: lack of compliance to treatment and incomplete medical records. We followed the patients for a minimum of two years.

The informed consent form was signed by the children's parents and the study was approved by the Ethics Committee of the Cluj-Napoca Institute of Oncology.

We retrospectively recorded the following variables for our patients: demographic data (county of birth, date of birth, the age at diagnosis, gender), tumor histology, the presence of genetic syndromes (neurofibromatosis), surgical intervention type (complete/incomplete resection/ biopsy/inoperable), radiation therapy type (curative/ palliative/no radiation therapy), chemotherapy (yes/no), the presence/absence of a ventriculoperitoneal shunt, the date of the response, the date of relapse, the date of death. We also recorded the side effects due to the tumor at the time of diagnosis, after the surgery and at the end of the treatment (intracranial hypertension, ataxia, hemiparesis, sensory deficit, cranial nerve palsy, etc.).

In these patients, we identified 9 histological groups: astrocytomas, medulloblastomas, high grade gliomas, low grade gliomas, germ cell tumors, ependymomas, meningiomas, primitive neuroectodermal tumors and other histological types. The patients who could not benefit from tumor biopsy were included in the "no histology" group.

The rare cases were included in the "other histologies" group (pituitary gland tumors, pineal gland tumors, choroid plexus carcinoma, teratoma, craniopharyngioma, cerebral mesenchymal tumors).

All patients were diagnosed according to the WHO Classification of Primary Brain Tumors (depending on the version that was available at the time). After the end of the treatment, the follow-up evaluations were conducted every 3 months for 1 year, every 6 months up to 5 years, followed by annual examinations. The standardized follow-up protocol allowed early diagnosis of side effects or disease relapse.

In all of the 207 patients the therapeutic response was assessed according to the "Response Evaluation Criteria for Solid Tumors" (RECIST) that was in use at the time of the treatment. Complete remission (CR) was defined as the disappearance of all target lesions. Partial remission (non-CR) was as well defined according to the RECIST criteria in use at the time of treatment.

All operable cases benefited from surgery as the first therapeutic gesture. The extent of the surgical resection was classified as gross total resection and subtotal resection (which consisted of either a tumor biopsy, tumor resection, or tumor reduction). The quality of the surgical resection was evaluated based on the surgical report and post-operative imaging (computed tomography (CT) or magnetic resonance imaging (MRI)).

We recorded the number of patients who received radiation therapy (RT) to the craniospinal axis (i.e., whole brain, posterior fossa, and spinal cord) and those who did not. Children under 3 years of age did not undergo radiation therapy. The radiation therapy groups were divided according to the aim of the treatment (curative radiation and palliative radiation) and according to the extent of the treatment (cranial radiation and cranio-spinal radiation).

If chemotherapy was administered, the children underwent regimens depending on the patients' characteristics (age, underlying diseases, hepatic and renal function, etc.), histopathological diagnosis, the extent of disease. The treatment was administered according to the golden standard protocol at the time of diagnosis.

Results

Out of the 255 children diagnosed with primary brain tumors at the Cluj-Napoca "Prof. Dr. Ion Chiricuta" Oncology Institute between the years 2001-2018, 48 children were not compliant to the treatment and were excluded from the study. Therefore, a total of 207 eligible patients were included in the study.

The median patient age at the time of diagnosis was 8 years (range 0–18). The patients were divided into 3 groups, as follows: 39 (18.8%) patients were younger than 3 years of age, 66 (31.9%) were in the 3–7 years age group, 102 (49.3%) were in the 8–18 years age group. The male/female ratio was 1.5:1.

Among these patients, we identified 9 histological groups: those suffering from astrocytomas- 42 patients, medulloblastomas - 62 patients, high grade gliomas - 14 patients, low grade gliomas - 12 patients, germ cell tumors- 14 patients, ependymomas - 26 patients, meningiomas - 2 patients, primitive neuroectodermal tumors - 11 patients, other histologies - 11 patients. Twelve patients were diagnosed with neurofibromatosis type 1. Thirteen of the patients could not benefit from a tumor biopsy due to the tumor location, therefore the histology in these cases was unknown. The 11 cases included in the "other histologies" group, consisted of: 2 pituitary gland tumors, 3 pineal gland tumors, 1 choroid plexus carcinoma, 1 teratoma, 1 craniopharyngioma and 1 cerebral mesenchymal tumor. Among the 42 astrocytoma patients, we recorded 17 high grade tumors and 25 low grade tumors. The high-grade glioma group consisted of 11 glioblastomas and 3 gliomas. As far as the medulloblastomas were concerned, 57 of them were located in the posterior fossa, while 5 had other sites.

Regarding surgery, 194 patients underwent surgery, while 13 of the cases were inoperable. Of the patients who underwent surgery we registered a complete remission in 78 patients (40.2%), a partial remission in 17 patients (8.8%), the disease was stationary in 11 patients (5.6%) and an unfavorable evolution was noted in 88 patients (45.4%). Of the 194 cases who underwent surgery, we registered 88 deaths due to tumor progression and one death as a result of neuroblastoma. Of the 13 patients who did not undergo surgery, we registered a partial remission in 2 patients (15.4%) and a progression in 11 patients (85.6%).

Out of the study group, 158 patients received radiation to the craniospinal axis (i.e., whole brain, posterior fossa, and spinal cord) and 48 did not receive any radiation at all. We have to keep into consideration that children under 3 years of age did not undergo radiation therapy. Of the 158 children who underwent radiation, 154 received curative radiation, while 4 received palliative radiation. One hundred patients received cranial radiation, while 58 received only cranio-spinal radiation (Table I).

When chemotherapy was administered, the children underwent regimens depending on the patients' characteristics (age, underlying diseases, hepatic and renal function, etc.), as well as the histopathological diagnosis, the extent of disease, as required by the golden standard protocol at the time of the diagnosis. One hundred and seventy-three patients received standard chemotherapy, consisting of various protocols, while 45 the patients did not undergo chemotherapy (Table II).

The chemotherapy regimens consisted of Temozolomide, Carmustine, Lomustine, Cisplatin, Carboplatin, Etoposide, Irinotecan, Methotrexate, Cytosine-arabinoside, Procarbazine, Vincristine, Cyclophosphamide and Ifosfamide (Table II).

Table I. Treatment response (CR-complete response, Non-CR- incomplete response).

		CR	Non-CR	Total
Surgery	Yes	78(40.2%)	116 (59.8%)	194
	No	0 (0%)	13 (100%)	13
Irradiated	Yes	62 (39.2%)	96 (60.8%)	**158**
	No	16 (32.6%)	33 (67.4%)	49
Purpose of RT	Curative	62 (40.3%)	92 (59.7%)	154
	Palliative	0 (0%)	4 (100%)	4
	No	16 (32.7%)	33 (67.3%)	49
Total		78 (37.7%)	129 (62.3%)	**207**

Table II. Chemotherapy response (CR-complete response, Non-CR- non complete response).

Chemotherapy	CR	Non- CR	Total
Yes	64 (37%)	109 (63%)	173
No	14 (41.2%)	20 (58.8%)	34
Total	78 (37.7%)	129 (62.3%)	207

Ependymoma

Of the 26 ependymoma patients, 25 had high grade tumors (WHO grade 2-4), while 1 patient had a WHO grade 1 ependymoma. All these patients underwent surgery, and in a half of the cases the resection was complete, while in the other half it was incomplete. Twenty-two of the children received chemotherapy, while 4 children did not. Twenty-one children received radiation treatment, with doses ranging from 45 Gy to 54 Gy. As stated before, no child under the age of 3 received any radiation treatment (Figure 1).

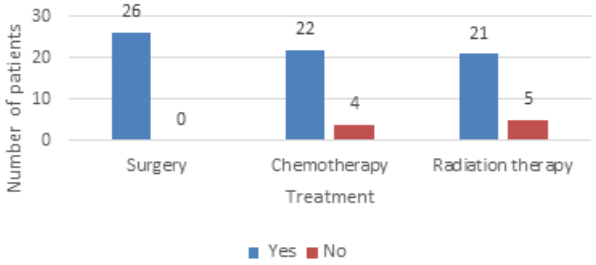

Figure 1. Ependymoma treatment.

Germinoma

The best survival rate was recorded in the 14 patients of the germinoma group (85.7%). All 14 children underwent surgery, 5 of them had complete macroscopic tumor resections, 2 of them had incomplete tumor resections, while 7 of them only underwent tumor biopsies. Eleven children benefited from chemotherapy and radiation therapy, while 3 of them did not receive any of these adjacent treatments. No children under the age of 3 received radiation treatment (Figure 2).

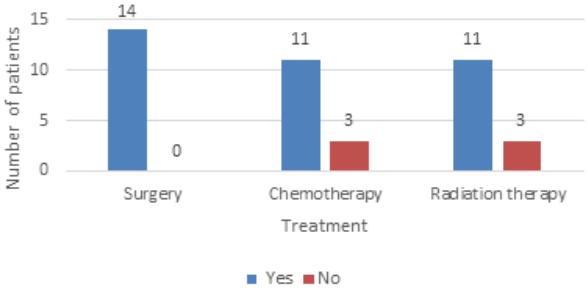

Figure 2. Germinoma treatment.

Astrocytoma

There were 42 astrocytoma patients included in the study. One patient suffered from a type 1 neurofibromatosis. Of these patients, 17 had high grade tumors (WHO grade 2-4), while 25 had WHO grade 1 tumors. Twenty-nine of these patients underwent incomplete tumor resections, 11 of them benefited from complete tumor resections, and 2 of them had tumor biopsies. Twenty-eight patients received chemotherapy and radiation therapy, the other 14 patients did not. No children under the age of 3 received radiation treatment. We identified 15 complete remissions (35.7%) and 27 non-complete remissions (64.3%). We recorded 16 deaths (38.1%), among these patients one of them died as a result of a neuroblastoma while the astrocytoma patient was in complete remission (Figure 3).

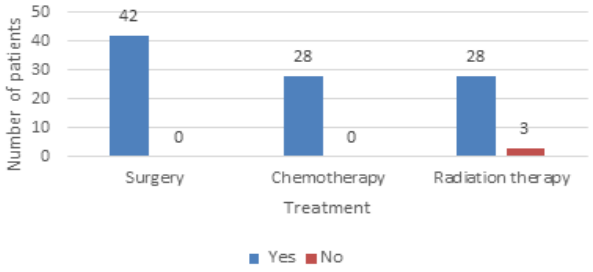

Figure 3. Astrocytoma treatment.

Medulloblastoma

Sixty-two children were diagnosed with a medulloblastoma. In this patient group we identified one child suffering from type 1 neurofibromatosis. All patients underwent surgery, resulting in 41 patients with complete tumor resections and 21 with a subtotal tumor resection. Chemotherapy was administered to 59 patients (95.2%), while 3 patients did not receive chemotherapy. Fifty patients received radiation therapy, with doses ranging from 30 Gy to 68 Gy to the brain and doses ranging from 22.4 Gy to 36 Gy. Forty-one patients received radiation to the craniospinal axis, while 9 patients only received brain radiation. The survival rate was 54.8%, accounting for 34 patients (Figure 4).

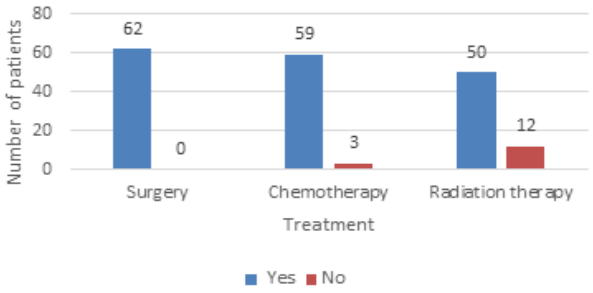

Figure 4. Medulloblastoma treatment.

High grade glioma

In the 15 high grade glioma group, we recorded a survival rate of 26.6%, accounting for 4 patients. All children underwent surgery, in 5 of the cases complete resection was obtained, while in the other 10 cases the resection was subtotal. As far as chemotherapy and radiation therapy was concerned, 12 children underwent both treatments, while 3 of them did not benefit from either (Figure 5).

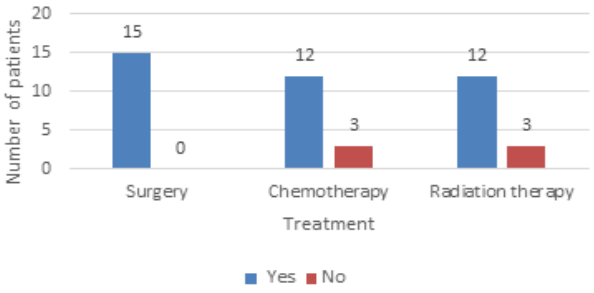

Figure 5. High grade gliomas treatment.

Low grade glioma

There were 11 children diagnosed with a low-grade glioma, with a survival rate of 81.8% (9 patients). Eight children were diagnosed with type 1 neurofibromatosis prior to the brain tumor diagnosis. Four patients had tumor biopsies, 5 patients had subtotal resections and only 2 patients had a complete resection. Nine of the 11 patients received chemotherapy. Seven children received radiation therapy, while 4 of them did not (Figure 6).

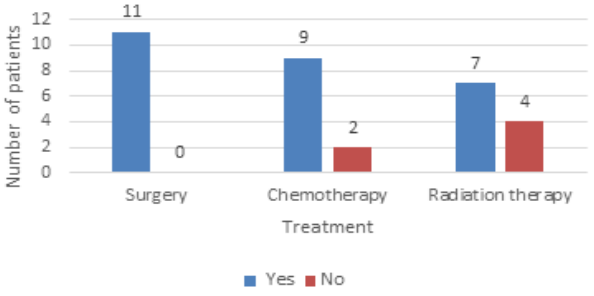

Figure 6. Low grade gliomas treatment.

Meningioma

Two patients were diagnosed with meningiomas. Both children underwent surgery, resulting in complete tumor resections. One of the cases was diagnosed with an anaplastic meningioma and underwent chemotherapy and radiation therapy, but, unfortunately, he died less than 6 months after the diagnosis. The other patient only underwent surgery, resulting in a complete remission. The survival rate in this patient group was 50%.

Primitive neuro-ectodermal tumors (PNETs)

Eleven children were diagnosed with PNETs. All children underwent surgery, radiotherapy and chemotherapy. In seven of the cases the surgical resection was complete, while 4 of the cases only benefited from a subtotal tumor resection. We recorded one complete remission and 10 deaths, thus obtaining a survival rate of 9.1%.

Other histological types

Eleven children were included in the "other histologies" group, consisting of 6 different entities (Table III).

Table III. Other histologies (ATRT - atypical teratoid/rhabdoid tumor).

Histology	Total= 11
Pituitary gland tumor	2
Pineal gland tumor	3
Choroid plexus carcinoma	1
Teratoma	1
Craniopharyngioma	1
Cerebral mesenchymal tumor	1
ATRT	2

All children underwent surgery, resulting in 3 total resections and 8 subtotal resections. Children under the age of 3 did not receive radiation therapy. Seven children received chemotherapy and radiation therapy, while 4 did not. We recorded 4 complete remissions and 7 non-complete remissions. The survival rate in this patient group was 72.7%, accounting for 8 patients (Figure 7).

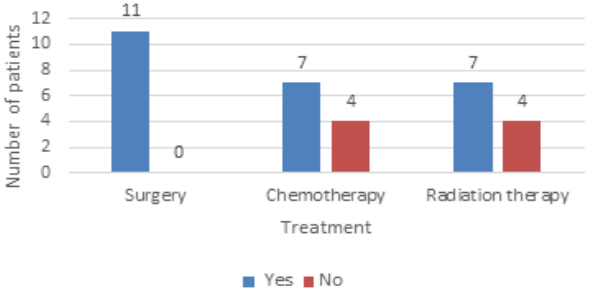

Figure 7. Other histologies treatment.

No histology

Thirteen patients did not undergo surgery due to tumor type and location. All children suffered from diffuse brain-stem tumors. Eleven of the 13 patients underwent radiation therapy. No children under the age of 3 received radiation treatment. All 13 patients received chemotherapy. The survival rate in this patient group was 15.3% (Figure 8).

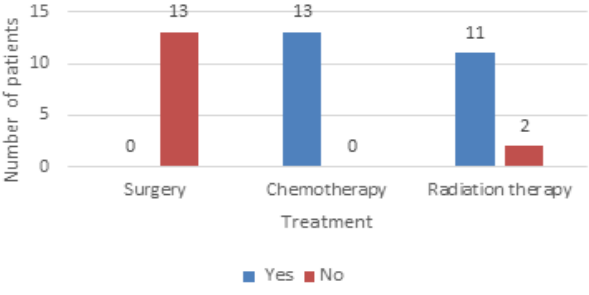

Figure 8. No histology treatment.

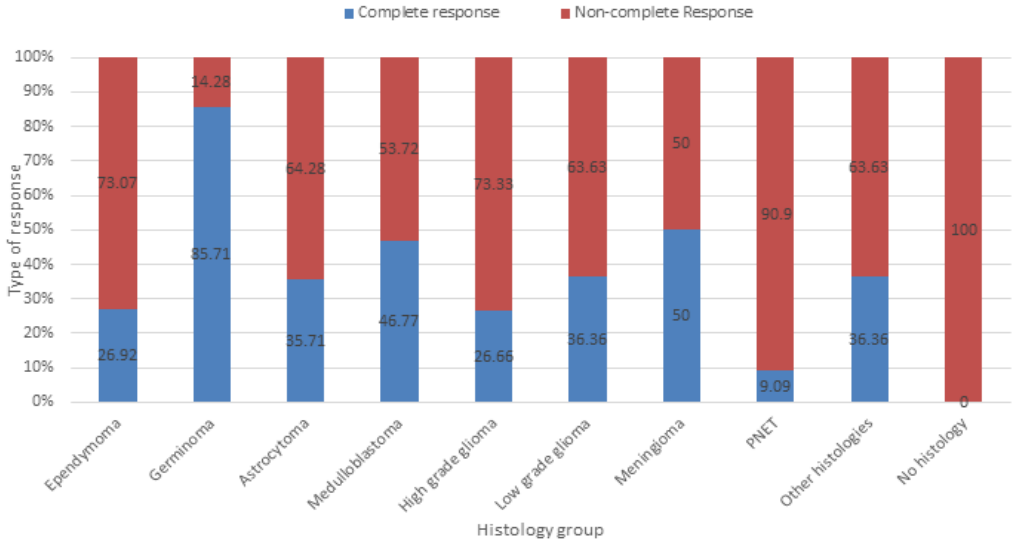

Figure 9. Therapeutic results according to histology.

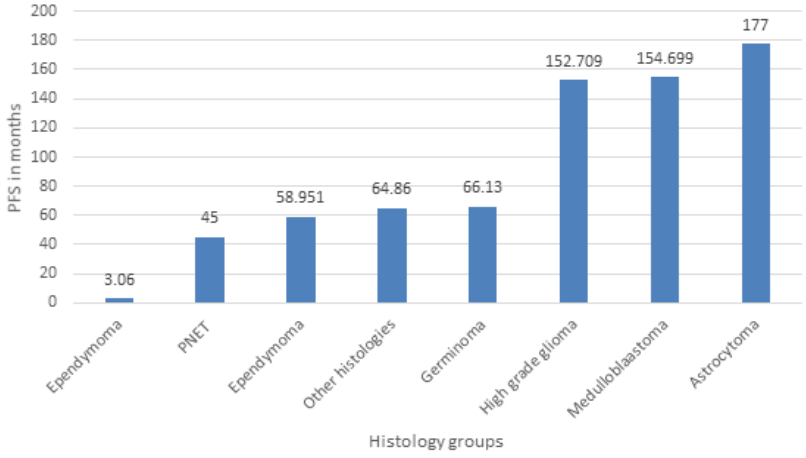

Figure 10. PFS according to histology - expressed in months.

Therapeutic results and survival

The therapeutic results were divided into complete and non-complete response. The non-complete response category encompassed: partial remission, progression and relapse. The germinoma patients had the highest CR rate, while the "no histology" group had the highest non-CR rate (Figure 9).

The progression free survival (PFS) expressed in months according to histology was evaluated. The lowest PFS was recorded for the meningioma group, while the highest PFS rates were recorded in the astrocytoma group (Figure 10).

The overall PFS was 131.3 months. The PFS for boys was higher than the one for girls (144.9 months, vs 104.8 months). We divided the patients into 3 age groups [0-3] years, (3-8] years and (8-18] years and assessed the PFS accordingly (Figure 11).

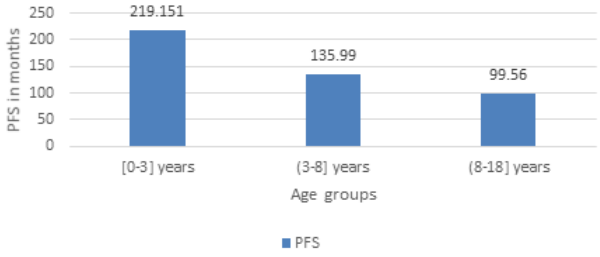

Figure 11. PFS according to age group - expressed in months (PFS - progression free survival).

Discussion

We have presented the experience in brain tumors treatment of a regional pediatric oncology referral center in Romania, over an 18-year period.

Due to the fact that Romania lacked a National Pediatric Cancer Registry until 2009, the data obtained in this study was compared with the information recorded in the same time period in the US, Canada and Europe.

Our study showed a predominance of male patients (the male to female ratio was 1.5:1), which is in accordance with other European studies. A study from Denmark reported a male to female ratio of 1.1:1 [7].

The median patient age at the time of diagnosis was 8 years (range 0–18), while the largest age group was represented by children aged 8–18 years (102 children, accounting for 49.2%). This is similar to the data reported by the Danish study group [7].

We found 12 patients diagnosed with neurofibromatosis type 1. This resembles the data recorded by other study groups [8].

The most common brain tumors in our study were medulloblastomas (29.9%), followed by astrocytomas (20.28%) and ependymomas (12.5%). This is not consistent with other data published in literature, which report low grade gliomas (LGG) and embryonal tumors as the most frequent tumor types. This is because our center only treats patients in need of adjuvant therapy following surgery. This is why the LGG and embryonal tumor patients who only received surgery were not included in this study [7-9].

The survival rates for pediatric brain tumors reported in the specialty literature until 2016 are variable. This is due to the fact that one histology group encompassed multiple molecularly different tumors. This is also the case in the current study.

The uncommonly high PFS rates of the glioblastoma and medulloblastoma patients were due to the fact that they were diagnosed according to the old WHO Classifications of brain tumors. This is one of the areas where the new 2021 WHO Classification of brain tumors will aid clinicians in classifying children with similar histologies into separate prognostic groups [3,9].

Of the patients who underwent surgery, we recorded a 40.2% complete response rate. The complete response rate for the children who did not undergo surgery was 0%. This is consistent with the data reported in literature [10].

The overall PFS in our study was 131.3 months. The highest PFS was recorded for the 0-3 age group (219.1 months). This finding contrasts most data in literature, which show that children aged 12 and older have the best PFS [11]. This may be caused by the fact that younger children develop astrocytomas and medulloblastomas more frequently, compared to older children who develop more LGGs. A large number of patients with LGG undergo surgery alone and need no further adjuvant therapy, therefore they were not included in our study. The survival rate for the meningioma group was uncommonly low compared to the literature data. This was because most low grade meningiomas are not addressed to the pediatric oncology department after surgery. Only two patients were included in this group. One of them had anaplastic histology. He underwent surgery with complete tumor resection, however, he did not respond to chemo- and radiation-therapy, resulting in death. The other patient only underwent surgery, but the follow-up period was only 3 months.

Out of the 207 patients included in this study, we recorded 98 deaths, resulting in a 52.6% survival rate. This is a lot less than the 5-year survival rate recorded in the US between 2012 and 2018 (74.9%). [8] There are many factors to explain this, such as very late diagnosis, the inability to perform innovative radiation therapy techniques until 2018 and the fact that between 2001 and 2010 the chemotherapy regimens were not as effective as the more recent ones. However, the survival rates recorded in our study are similar to those reported by other middle-income countries [12].

The PFS was a lot higher for boys than it was for girls. This is likely due to the fact that the boy-girl ratio in our study was 1.5:1, thus leading to more boys surviving long term than girls. This is consistent with the data found in literature [12].

The 2 year response rate in this study was 59%, compared to 60% reported by a Polish group for all tumor histologies, for the corresponding time period. High grade malignancies had lower survival rates than low grade tumors. The 1 year survival rate for medulloblastomas was 44%, similar to the data reported in literature (48%). Low grade astrocytomas had a 2 year survival rate of 79%, compared to the data reported by the polish group (83%). Medulloblastomas had a 2 year survival rate of 42%. This is consistent with other data found in literature (42%) [13].

Conclusion

The therapeutic results recorded in this study are similar to those in literature, however the available treatment options for pediatric brain tumors are not as effective as those currently used in other pediatric and adult malignancies. The common efforts of the scientific community have led to the development of new molecular strategies of classification that classify patients with similar histologies into different prognostic groups. New molecular targeted therapies are being studied in order to provide better survival and quality of life for children with brain tumors.

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