Wspolczesna Onkol 2012; 16 (1): 26–33

DOI: 10.5114/wo.2012.27333

Original paper

# Institutional experience of paediatric high-grade central nervous system tumours: an analysis of 74 patients and review of the literature

**Faruk Guclu Pinarli[1], Aynur Oguz[1], Ceyda Karadeniz[1], Arzu Okur[1], Avni Sarac[1], Kemali Baykaner[2], Huseyin Bora[3], Aylar Poyraz[4]**

[1]Pediatric Oncology, Gazi University Medical Faculty, Ankara, Turkey
[2]Neurosurgery, Gazi University Medical Faculty, Ankara, Turkey
[3]Radiation Oncology, Gazi University Medical Faculty, Ankara, Turkey
[4]Pathology, Gazi University Medical Faculty, Ankara, Turkey

**Aim of the study:** Although the survival for children with certain central nervous system (CNS) tumour types has improved through current surgical and adjuvant treatment modalities, the prognosis of many high-grade tumours remains poor despite aggressive treatment. The aim of this study is to analyse patients with high-grade brain tumours in our institution to determine the histopathology, clinical characteristics, treatment modalities, and survival.

**Material and methods:** A total of 74 patients with a diagnosis of high-grade brain tumour were analysed. There were a total of 31 patients with embryonal tumours, 27 patients with high-grade glial tumours, 12 patients with brain stem gliomas and 4 patients with other high-grade brain tumours.

**Results:** There were 48 (65%) boys and 26 (35%) girls (ratio: 1.85) with a median age of 99.7 months (range = 2-204 months). The median follow-up period was 19 months (range = 1-204 months). Tumour recurrence was observed in 38 patients (51.4%). The overall survival rate and event-free survival rate of our patients were 27% and 19.5%, respectively.

**Conclusions:** Pediatric high-grade CNS tumours have a very aggressive behaviour and a significant number of children eventually succumb to disease despite multimodal treatment. There is a need of more effective therapeutic approaches for these tumours with poor prognosis. The future improvement in childhood high-grade brain tumour management depends on a better understanding of the molecular genetics and biology of brain tumours.

**Key words:** CNS cancers, paediatric oncology, survival, chemotherapy, medulloblastoma, glioma.

## Introduction

Primary central nervous system (CNS) neoplasms are the most common paediatric solid tumours and the leading cause of cancer-related death in children. Although the survival for children with certain CNS tumour types has improved through current surgical and adjuvant treatment modalities, the outcome of many high-grade tumours remains dismal despite aggressive treatment, still representing a challenge for paediatric oncologists [1-3]. The World Health Organization (WHO) initially published a sophisticated classification of CNS tumours in 1979 based on histopathology and three further editions were published thereafter [4, 5]. A simplified but clinically useful categorization is to distinguish embryonal tumours (primitive neuroectodermal tumours, PNETs), glial tumours and others (neural, mesenchymal, lymphomas, germ cell tumours, etc.). The WHO classification also provides a parallel grading system for each type of tumour, which is of critical importance to decide on the management. Low-grade (WHO gra-de I-II) tumours are generally locally aggressive and can be managed with surgery, and radiotherapy (RT) in case of incomplete excision. However, high-grade tumours (WHO grade III-IV) are very aggressive tumours with high metastatic potential. Although a multimodal approach including surgery, RT and chemotherapy (CT) is the usual treatment for high-grade CNS tumours, recurrences are frequent and the prognosis of these malignancies remains poor. The most common paediatric high-grade glial tumours are grade III anaplastic astrocytomas, anaplastic ependymomas and grade IV glioblastoma multiforme (GBM). All embryonal tumours are grade IV malignancies and the most common is medulloblastoma (MB), followed by supratentorial PNET. In this study, we analysed our patients with high-grade brain tumours within an 18-year period to determine the histopathology, clinical characteristics, treatment modalities, and survival.

## Material and methods

A total of 74 patients with a diagnosis of "high-grade brain tumour" between 1992 and 2010 in the Department of Pediatric Oncology, Gazi University Medical Faculty, Ankara, Turkey, were analysed. Beside 62 patients with a pathological diagnosis, 12 patients with diffuse intrinsic pontine gliomas without a biopsy were also included in the study as they were accepted as high-grade glial tumours. The clinical characteristics of the patients at diagnosis are given in Table 1. There were a total of 31 patients with embryonal tumours, 27 patients with high-grade glial tumours (excluding brain stem glioma),

12 patients with brain stem gliomas and 4 patients with other high-grade brain tumours.

The surgical interventions were planned and performed by an experienced senior neurosurgeon (KB). Unfortunately, no CSF examination obtained during surgery was available for the great majority of the patients. The adjuvant CT and RT decisions were made after a detailed discussion of each patient by physicians consisting of paediatric oncologists, neurosurgeons, radiation oncologists, pathologists and radiologists. The same procedure was performed in the case of relapsed or progressive disease as well as changes in the treatment protocols. Cranial and spinal magnetic resonance imaging (MRI) studies were performed in all patients at diagnosis and post-operative computerized tomography or MRI was obtained within 48 h for the detection of the residual mass. The follow-up imaging studies were done every 3 months for the first 2 years, every 6 months until 5 years after the operation, and thereafter yearly. The follow-up period was defined as the period from the date of diagnosis up to the date of the last medical review or the date of death. Statistical analysis was performed with the statistical program SPSS version 13.0. Kaplan-Meier analysis was performed for determination of the survival and the chi-square test was used to identify factors of significance.

## Results

The clinical characteristics of the patients according to tumour localization and the treatment modalities and the final status of the patients according to tumour type are given in Tables 2 and 3, respectively. The outcome of all the patients is given in Table 4. The patients lost to follow-up were included for statistical analysis and were accepted as "events" in the EFS. Of the 5 patients with initial spinal metastasis, the patient with anaplastic ependymoma was still under CT, one of the patients with MB was surprisingly alive with disease after 102 months of diagnosis, and the three other patients were dead of progressive disease. The overall survival rate (OS) and event-free survival rate (EFS) of our patients were 27% and 19.5%, respectively (Figs. 1 and 2). The OS of the patients with embryonal tumours (MBs, PNETs and ependymoblastomas), high-grade glial tumours (anaplastic astrocytomas, anaplastic ependymomas, anaplastic oligodendrogliomas, anaplastic gangliogliomas, glioblastomas multiformes, and undifferentiated high-grade glial tumours, excluding brain stem gliomas), and brain stem gliomas were 33%, 36% and 11%, respectively. Whereas there was no statistically significant difference between glial and embryonal tumours ($p > 0.05$), the OS of both embryonal and glial tumours were longer than brain stem gliomas, as expected ($p = 0.001$ and $p = 0.005$). The EFS of the patients with embryonal tumours, high-grade glial tumours, and brain stem gliomas were 22%, 23% and 9%, respectively. Again there was no statistically significant difference between glial and embryonal tumours ($p > 0.05$) in our series but this result should be cautiously interpreted due to the small number of patients because embryonal tumours were shown to have a better prognosis than high-grade glial tumours with modern treatment methods. The EFS of both embryonal and glial tumours were longer than brain stem gliomas ($p = 0.03$ and $p > 0.05$).

**Table 1.** Clinical characteristics of patients at diagnosis

| | *N* | (%) |
|---|---|---|
| **Sex** | | |
| Male | 48 | 65 |
| Female | 26 | 35 |
| **Age (months)** | | |
| Median (range) | 99.7 (2-204) | |
| **Follow-up (months)** | | |
| Median (range) | 19.0 (1-204) | |
| **Tumour localization** | | |
| Ventricles | 19 | 25.7 |
| Cerebral hemispheres | 18 | 24.3 |
| Cerebellum | 15 | 20.3 |
| Brain stem | 14 | 18.9 |
| Thalamus | 3 | 4.1 |
| Basal ganglia | 2 | 2.7 |
| Medulla spinalis | 2 | 2.7 |
| Suprasellar area | 1 | 1.4 |
| **Spinal metastases** | | |
| Medulloblastoma | 5 | 6.7 |
| Anaplastic ependymoma | 3 | 4.0 |
| Malignant mesenchymal tumour | 1 | 1.35 |
| **Diagnosis** | | |
| Medulloblastoma | 19 | 25.7 |
| Anaplastic ependymoma | 11 | 14.9 |
| Supratentorial PNET | 8 | 10.8 |
| Anaplastic astrocytoma | 7 | 9.5 |
| Ependymoblastoma | 4 | 5.4 |
| Glioblastoma multiforme | 3 | 4.1 |
| High-grade glial tumour | 2 | 2.7 |
| Anaplastic ganglioglioma | 2 | 2.7 |
| Malignant schwannoma | 2 | 2.7 |
| Anaplastic oligodendroglioma | 1 | 1.4 |
| High grade DIA | 1 | 1.4 |
| Malignant meningioma | 1 | 1.4 |
| Malignant mesenchymal tumour | 1 | 1.4 |
| Diffuse intrinsic pontine glioma (clinical and radiological diagnosis) | 12 | 16.2 |

*PNET – primitive neuroectodermal tumour; DIA – desmoplastic infantile astrocytoma*

The OS of the patients with gross total resection, subtotal resection, biopsy only and without surgery (brain stem gliomas) were 36%, 37%, 0%, and 11% respectively. Surprisingly, there was no statistically significant difference between patients with total and subtotal resection ($p > 0.05$). The OS of both gross total resection and subtotal resection groups were significantly longer than biopsy only ($p = 0.01$ and $p < 0.05$, respectively) and inoperable groups ($p = 0.01$ and $p = 0.006$). The EFS of the patients with gross total resection, subtotal resection, biopsy only and without surgery were 29.5%, 22%, 0%, and 9% respectively. Again, there was no statistically significant difference between patients with gross total and subtotal resection ($p > 0.05$). The EFS of the patients with gross total resection were longer than patients with biopsy only ($p < 0.05$), and there was no statistically significant difference between patients with subtotal resection and biopsy only ($p > 0.05$). The EFS of the patients with gross

**Table 2.** Clinical characteristics of patients according to tumour localization

| Tumour localization | *N* | % | Age Dx (med, mo) | Histo E/G/O | N&V (%) | Seiz (%) | Weakn (%) | AT (%) | Symp Dur (med, d) | N. Def (%) | Surgery GT/ST/B (%) | RT (%) | CT (%) | Recur (%) | Status (R/D/AD/L) (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ventricles | 19 | 25.7 | 96 | 8/9/2 | 84 | 5 | 0 | 26 | 5 | 63 | 53/47/0 | 84 | 63 | 42 | 26/42/6/26 |
| Cerebral hemispheres | 18 | 24.3 | 132 | 8/9/1 | 50 | 50 | 11 | 0 | 60 | 61 | 61/28/11 | 88 | 83 | 50 | 33/44/0/23 |
| Cerebellum | 15 | 20.3 | 96 | 13/1/1 | 100 | 0 | 0 | 53 | 20 | 93 | 67//33/0 | 100 | 93 | 67 | 20/53/7/20 |
| Brain stem | 14 | 18.9 | 72 | 1/13/0 | 50 | 14 | 7 | 50 | 15 | 86 | 0/0/2 | 93 | 50 | 71 | 7/57/29/7 |
| Thalamus | 3 | 4.1 | 132 | 0/3/0 | 66 | 33 | 0 | 33 | 60 | 66 | 0/67/33 | 67 | 67 | 67 | 0/100/0/0 |
| Basal ganglia | 2 | 2.7 | 120 | 1/1/0 | 50 | 50 | 0 | 0 | 18 | 100 | 50/50/0 | 100 | 100 | 0 | 0/50/0/50 |
| Medulla spinalis | 2 | 2.7 | 120 | 0/2/0 | 0 | 0 | 0 | 0 | 225 | 100 | 0/50/50 | 100 | 100 | 50 | 50/50/0/0 |
| Suprasellar area | 1 | 1.4 | 156 | 1/0/0 | 0 | 0 | 100 | 0 | 30 | 0 | 0/100/0 | 100 | 0 | 0 | 0/0/100/0 |

*Age Dx – age of diagnosis; med – median; mo – months; Histo – histology; E – embryonal; G – glial; O – others; N&V – nausea and vomiting; Weakn – weakness in the extremities; AT – ataxia; Seizs – seizures; Symp Dur – symptom duration; d – days; N. Def – neurological deficits; GT – gross total; ST – subtotal; B – biopsy only RT – radiotherapy; CT – chemotherapy; Recur – recurrence; R – remission; D – dead of disease; AD – alive with disease; L – lost to follow-up*

**Table 3.** Treatment modalities of patients according to tumour type

| Tumour histopathology | *N* | Surgery | | | Radiotherapy | | | | | Chemotherapy | | | Status | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | G. Total (%) | Subtotal (%) | Biopsy (%) | Post. fossa (%) | CSI (%) | W. Brain (%) | Tm Loc | Dose md (Gy) | VIECC (%) | CVP (%) | T (%) | R (%) | D (%) | AD (%) | L (%) |
| Medulloblastoma | 19 | 79 | 21 | 0 | 5 | 90 | 0 | 0 | 54 | 21 | 69 | 0 | 27 | 53 | 10 | 10 |
| Anaplastic ependymoma | 11 | 45 | 55 | 0 | 36 | 9 | 9 | 28 | 50.4 | 27 | 18 | 9 | 36 | 18 | 10 | 36 |
| Supratentorial PNET | 8 | 75 | 12.5 | 12.5 | 0 | 62.5 | 12.5 | 0 | 52 | 87.5 | 12.5 | 0 | 25 | 62.5 | 12.5 | 0 |
| Anaplastic astrocytoma | 7 | 29 | 42 | 29 | 14 | 0 | 57 | 14 | 53.6 | 0 | 72 | 0 | 14 | 72 | 14 | 0 |
| Ependymoblastoma | 4 | 0 | 100 | 0 | 0 | 25 | 50 | 0 | 55 | 25 | 50 | 0 | 0 | 0 | 25 | 75 |
| Glioblastoma multiforme | 3 | 0 | 67 | 33 | 0 | 0 | 33 | 67 | 54 | 0 | 67 | 33 | 33 | 67 | 0 | 0 |
| Hig-grade glial tumour | 2 | 0 | 0 | 100 | 50 | 0 | 0 | 50 | 50 | 0 | 50 | 0 | 0 | 50 | 0 | 50 |
| Anaplastic ganglioglioma | 2 | 0 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 50 | 50 | 50 | 0 | 0 |
| Malignant schwannoma | 2 | 100 | 0 | 0 | 0 | 0 | 100 | 0 | 54.9 | 50 | 0 | 0 | 50 | 50 | 0 | 0 |
| Anaplastic oligodendroglioma | 1 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 100 |
| High-grade DIA | 1 | 0 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 100 | 0 | 0 | 100 | 0 | 0 | 0 |
| Malignant meningioma | 1 | 100 | 0 | 0 | 0 | 0 | 100 | 0 | 60 | 0 | 0 | 0 | 0 | 100 | 0 | 0 |
| Malignant mesenchymal tumour | 1 | 0 | 100 | 0 | 0 | 100 | 0 | 0 | 39.6 | 0 | 0 | 0 | 0 | 100 | 0 | 0 |
| Diffuse intrinsic pontine glioma (clinical and radiological diagnosis) | 12 | 0 | 0 | 0 | 75 | 0 | 0 | 0 | 50 | 8 | 0 | 33 | 8 | 67 | 0 | 25 |

*G.Total – gross total; CSI – craniospinal irradiation; W.Brain – whole brain; Tm Loc – tumour localisation; md – median; VIECC – VCR/IFO/ETO/CISP/CARBO 6 months; CVP – CCNU/VCR/PRED 6 months; T – temozolomide 6 months; R – remission; D – dead of disease; AD – alive with disease L – lost to follow-up; PNET – primitive neuroectodermal tumour; DIA – desmoplastic infantile astrocytoma*

**Table 4.** Outcome of the 74 patients with high-grade CNS tumour

| | *N* | (%) |
|---|---|---|
| **Recurrent disease** | **38** | **51.4** |
| Primary tumour localization | 15 | 20.3 |
| Primary tumour localization + widespread dissemination | 13 | 17.6 |
| Medulla spinalis | 4 | 5.4 |
| Primary tumour localization + medulla spinalis | 3 | 4.1 |
| Distant regions | 3 | 4.1 |
| Time (mean ± SD): 22.7 ±32.4 months | | |
| **Deceased** | **37** | **50** |
| Tumour progression | 31 | 41.8 |
| Surgery complication | 3 | 4.1 |
| Toxicity of CT/RT | 3 | 4.1 |
| Survival (mean ± SD): 22.7 ±23.9 months | | |
| **Alive in remission** | **16** | **21.6** |
| **Lost to follow-up** | **13** | **17.6** |
| With disease | 12 | 16.2 |
| Without disease | 1 | 1.4 |
| **Alive with disease** | **6** | **8.1** |
| **Transfer to another centre** | **2** | **2.7** |

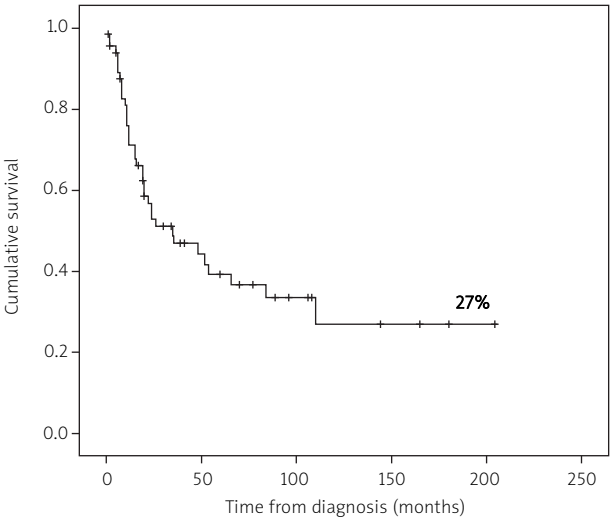


**Fig. 1.** Overall survival rate of patients

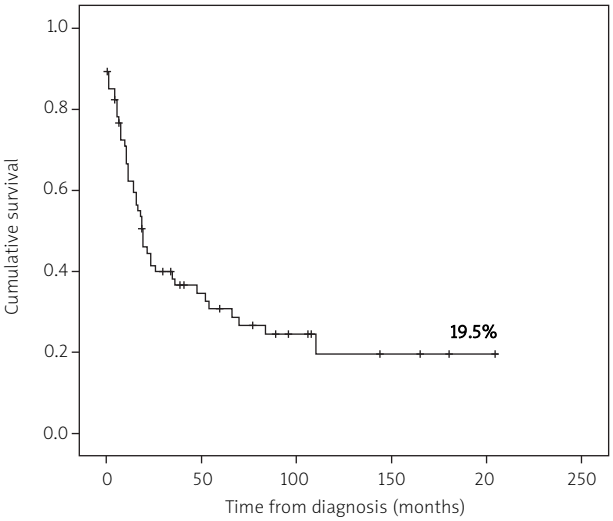


**Fig. 2.** Event-free survival rate of patients

total resection and subtotal resection were significantly longer than patients without surgical intervention ($p = 0.002$ and $p < 0.05$, respectively). The OS of the patients treated with combination CT protocol, CCNU-based CT and without CT were 44%, 31.5%, and 22%, respectively. There was no statistically significant difference between these three groups ($p > 0.05$). All of the 6 patients treated with temozolomide were dead or lost to follow-up with disease. The EFS of the patients treated with combination CT protocol, CCNU-based CT and without CT were 44%, 19%, and 14% respectively. Although there was no statistically significant difference between combination CT and CCNU-based CT groups ($p > 0.05$), the EFS of both the CT groups were significantly longer than the group without CT ($p = 0.006$ and $p = 0.05$). Ten patients (3 PNETs, 3 brain stem gliomas, 2 anaplastic ependymomas, 1 MB and 1 high-grade glial tumour) were less than 3 years of age at the time of diagnosis and only 3 of them had a gross total resection. Five of these patients were dead (all PNETs, 1 brain stem glioma and 1 anaplastic ependymoma), 2 patients were lost to follow-up with disease (brain stem gliomas) and 3 patients were in remission at the time of the study. The OS of the patients < 3 years of age and > 3 years of age at diagnosis were 31% and 26%, respectively ($p > 0.05$).

## Discussion

Paediatric CNS tumours are a heterogeneous group of neoplasms with different origins, pathobiologies, treatments and prognoses. Advances in the management of paediatric brain tumours have been less successful than in other areas of paediatric oncology. Although significant improvement in the outcome of certain brain tumours such as MB and ependymoma were achieved with modern treatment modalities, survival advantages have still not been found for the others [3, 6, 7]. The WHO histopathological classification and grading is a useful but less than adequate method to determine the prognosis of childhood CNS tumours as the genetic characteristics of low-grade and high-grade brain neoplasms in children were found to influence the clinical outcome [8].

While surgery and RT are the mainstay of therapy, complete surgical resection is generally difficult to perform effectively and RT has the potential to damage the child's developing nervous system. Chemotherapy has also played a key role in improving survival in certain paediatric CNS tumours. Medulloblastoma is the first brain tumour to show efficacy of CT in large prospective trials. However, many children with brain tumours remain incurable with current therapies and CT regimens for almost all patients with high-grade gliomas and for most young patients with residual or metastatic disease of any histology are not effective. Modest improvements in outcome may be achieved by further refining treatment schedules, and introducing new chemotherapeutic agents [9, 10]. Overall survival and EFS in our series seems to be inferior compared with most series reported in the literature. The reasons for this result are the inclusion of patients dating nearly two decades ago in the study and, more importantly, the transfer of complicated cases to our centre, especially for surgery. Also, we analysed a heterogeneous group of CNS tumours including brain stem gliomas with a very poor prognosis. Although we apply modern surgery, CT and radiation therapy techniques nowadays, we are still not able to base the management of our patients on molecular genetic studies. The limitation of our study is the small number of patients for each particular tumour type.

The limited number of new drugs against paediatric brain tumours is somewhat disappointing. Temozolomide (TMZ) is an oral alkylating agent with proven antitumoural activity in adults with high-grade glioma (HGG). Although TMZ has shown evidence of activity against paediatric HGGs and MBs, clinical trials conducted in paediatric HGGs and diffuse pontine gliomas have failed to demonstrate a survival advantage with this agent [7, 11, 12]. Our patients treated with TMZ were diagnosed with brain stem glioma, GBM and anaplastic ganglioglioma. They tolerated TMZ treatment well without significant neutropenia, but no response was obtained. Early promising results from a limited single institution phase II study of irinotecan were not confirmed in subsequent, larger studies [7, 13]. Recently, preclinical studies of flavopiridol suggested potential efficacy of this synthetic flavonoid inhibitor of cyclin-dependent kinases against rhabdoid tumour cell lines, and phase II studies are awaited [14]. However, we used neither of these agents in our patients. High-dose chemotherapy (HDCT) followed by haematopoietic stem cell transplantation (HSCT) has been used from many years for high-risk, metastatic or recurrent paediatric CNS tumours, particularly MB and HGG. Leptomeningeal dissemination was one of the most important indications because of the possibility of resistance to standard CT [7, 15-17]. It is suggested that a selected group consisting of young patients treated with CT alone as initial therapy followed by HDCT + HSCT and RT at the time of disease recurrence may be able to achieve durable disease control. Patients with metastatic recurrent disease have a much worse outcome. There is also evidence that HDCT+HSCT might have a role in embryonal tumours of infants and young children, such as rhabdoid tumours, high-risk MB and supratentorial primitive neuro-ectodermal tumours [18-24]. The HDCT for high-risk patients was particularly useful for patients who were in remission before HDCT. Because of these limitations in the patient selection and the physical limitations of our clinical in the early years, we had no candidate patient for HDCT/HSCT. Sequential high-dose CT regimens have recently been piloted with success and the use of this modality is increasing as an alternative to single high-dose regimens [25-27].

Fractionated schedules of drug administration using smaller doses than the maximum tolerated dose (metronomic schedules) might increase the antiangiogenic activity of certain drugs [28]. There are potential advantages of metronomic CT with minimal toxicity in the context of paediatric brain tumours. The most commonly used agents are etoposide, temozolomide, cyclophosphamide and vinblastine given alone or in combination. Phase I or II studies of small molecules that target specific pathways or proteins in the cancer cells such as gefitinib, everolimus, imatinib, cloretazine, tipifarnib and semaxanib revealed no optimistic results, despite occasional observations of stable disease. On the other hand, the mTOR inhibitor rapamycin is found to be useful in tuberous sclerosis patients with subependymal giant cell astrocytomas. There is currently no other proven role for molecular targeted therapy as monotherapy in paediatric neuro-oncology [29, 30].

Despite developments in neurosurgery and new drugs in CT, irradiation is an essential part of the management in most paediatric brain tumours. Conformal RT techniques are performed using multiple treatment fields, allowing for a high homogeneous dose of irradiation to be delivered to the tumour region while minimizing the doses to normal tissue [31, 32]. The development of conformal radiation techniques has also opened the possibility for re-irradiation in the setting of failure after conventional treatment. It is suggested that re-irradiation with curative intent can be considered for patients with recurrent ependymoma after previous focal irradiation and also a subset of children with recurrent MB can be salvaged with multimodal treatment that includes HDCT and re-irradiation [7].

High-grade gliomas represent approximately 8% to 12% of all paediatric CNS tumours and this percentage increases when diffuse intrinsic pontine gliomas are also categorized as high-grade gliomas. Children with HGG carry a little better prognosis than in adults, but outcomes for these patients also remain poor [31, 33]. These tumours are locally invasive and rarely present with signs of leptomeningeal or distant spread. The degree of surgical resection is one of the most

important clinical prognostic factors known in children with supratentorial HGG, independent of location, histology, and age. Histological grade influences outcome whereby patients with WHO grade 3 (anaplastic astrocytomas) tumours have a superior outcome as compared to patients with WHO grade 4 (GBM) tumours. The analysis of 6212 cases of gliomas from the Surveillance, Epidemiology, and End Results Database revealed that tumour grade is the most significant independent prognostic factor in all age groups except the youngest age group, in which the extent of resection was most significant. Surgery other than gross total resection was an adverse prognostic factor and age < 3 years predicted a greater likelihood of survival in patients with HGGs and brainstem tumours [34]. Paediatric HGGs harbour a distinct spectrum of genetic aberrations compared to adults and it was suggested that younger children harbour high-grade tumours with unique molecular and biologic characteristics. Also, overexpression of epidermal growth factor receptor (EGFR) protein and mutation of the TP53 tumour suppressor gene with or without overexpression of the p53 protein are some of the genetic features of paediatric HGGs [35-37]. The standard adjuvant treatment consists of a combination of focal RT and CT in children > 3 years of age and CT alone for younger children. Some new drugs such as TMZ were well tolerated and somewhat effective in children with recurrent high-grade glioma but it is still unclear whether TMZ plus irradiation offers improved survival as compared to irradiation alone [31, 33, 38, 39]. We have a small number of patients treated with TMZ yielding limited information for an objective comment.

Tumours within the brain stem represent 15-20% of all paediatric CNS tumours. The majority of these tumours are diffuse and infiltrating lesions of the pons known as diffuse intrinsic pontine gliomas, and are highly infiltrative and aggressive lesions that are not generally considered amenable to surgical resection. The prognosis for children with diffuse brain stem glioma is still very poor, with an OS less than 10% to 15%, and conventionally fractionated local therapy remains the standard of care. Multiple trials involving various regimens of CT and several studies on new chemotherapeutic agents, small molecules, or radiosensitizers are ongoing. TMZ with RT has not yielded any improvement in the outcome of diffuse intrinsic pons glioma compared with RT alone [40]. Concurrent RMP-7 and carboplatin with radiation therapy can be a feasible option, requiring more studies to prove the efficacy. Very little is known about the genetic and molecular biology of diffuse intrinsic pontine glioma, and if stereotactic biopsies can be performed at diagnosis, biological and molecular data will help to direct future targeted therapies [31, 33, 41-44]. We have used no CT in the majority of our patients with diffuse infiltrating pons glioma and used low dose or metronomic CT in the others.

Medulloblastoma/PNET accounts for approximately 20% of brain tumours occurring in the paediatric age group. Medulloblastoma is one of the few high-grade CNS tumours showing improved outcome. The 5-year progression-free survival rates and OS of 50-60% evolved to survival rates as high as 85% in children with non-disseminated MB and survival rates of 65-70% in higher-risk patients. Adjuvant CT has resulted in a significant improvement in the survival of children with MB. For patients with standard risk MB, good results were obtained with pre-irradiation CT and full dose craniospinal irradiation, or with reduced dose RT and adjuvant CT. Although risk-adapted RT followed by dose-intensive CT improved the outcome of children with high-risk MB, the outcome for patients with metastatic disease still remains poor. Molecular genetic prognostic factors such as high Trk C expression, c-myc mRNA expression, β-catenin mutation and ERBB2 overexpression in MBs have been increasingly well characterized and the next major step in the management of MB is the integration of biological advances to the patient risk characterization and treatment [2, 31, 41, 45, 46]. Supra-tentorial PNETs are histologically the same as MBs, but have a worse prognosis. Chemotherapy is less effective and the results of multi-institutional studies did not support lowering the craniospinal dose for these tumours [47-50]. The results in our patients with embryonal tumours seem to be far from optimal for nowadays, with an OS of 33%, but we expect an improvement with the use of modern approaches in surgery, RT and possibly CT in the last years.

In patients with malignant ependymomas, factors such as extent of surgical resection, tumour location, and degree of anaplasia probably all affect the likelihood of long-term survival. At present the standard treatment is radiation therapy for all patients after gross-total or near-total resection and poorer survival rates were noted for children with subtotally resected tumours. In patients with localized ependymoma, limited volume conformal radiation therapy achieves high rates of disease control and results in stable neurocognitive outcomes. The predominant site of failure is the primary tumour site, and craniospinal irradiation should be omitted in patients with localized disease. Although the utility of CT in the management of ependymomas is questionable, CT coupled with RT might improve survival for high-risk patients with subtotally resected ependymomas [2, 31, 51-53].

In conclusion, paediatric high-grade CNS tumours have a very aggressive behaviour and a significant number of children eventually succumb to disease despite multimodal treatment. There is a need of more effective therapeutic approaches for these tumours with poor prognosis. In the treatment of children with high-grade brain tumours, paediatric oncologists must overcome the poor response rate to adjuvant treatment taking into consideration the fragility of the developing brain that is particularly vulnerable to RT and CT. The major hope for future improvements in childhood high-grade CNS tumour management depends on a better understanding of the molecular genetics and biology of brain tumours, allowing molecularly targeted therapies to be used in the treatment of these tumours.

**References**

1. Reddy AT. Advances in biology and treatment of childhood brain tumors. Curr Neurol Neurosci Rep 2001; 1: 137-43.
2. Packer RJ. Childhood brain tumors. Progress and challenges in childhood brain tumors. J Neurooncol 2005; 75: 239-42.
3. Karajannis M, Allen JC, Newcomb EW. Treatment of Pediatric Brain Tumors. J Cell Physiol 2008; 217: 584-9.
4. Kleihues P, Cavenee WK. World Health Organization classification of tumors: Pathology and genetics of tumors of the nervous system, IARC Press, Lyon, 2000.

5. Cunliffe CH, Fischer I, Parag Y, Fowkes ME. State-of-the-art pathology: new WHO classification, implications, and new developments. Neuroimaging Clin N Am 2010; 20: 259-71.
6. Rutka JT, Kuo JS, Carter M, Ray A, Ueda S, Mainprize TG. Advances in the treatment of pediatric brain tumors. Expert Rev Neurother 2004; 4: 879-93.
7. Bouffet E, Tabori U, Huang A, Bartels U. Possibilities of new therapeutic strategies in brain tumors. Cancer Treat Rev 2010; 36: 335-41.
8. Faria C, Miguéns J, Antunes JL, et al. Pediatric brain tumors: genetics and clinical outcome. J Neurosurg Pediatr 2010; 5: 263-70.
9. Gottardo NG, Gajjar A. Chemotherapy for malignant brain tumors of childhood. J Child Neurol 2008; 23: 1149-59.
10. Grundy RG, Wilne SH, Robinson KJ, Ironside JW, Cox T, Chong WK, Michalski A, Campbell RH, et al. Primary postoperative chemotherapy without radiotherapy for treatment of brain tumours other than ependymoma in children under 3 years: Results of the first UKCCSG/SIOP CNS 9204 trial. Eur J Cancer 2010; 46: 120-33.
11. Koukourakis GV, Kouloulias V, Zacharias G, et al. Temozolomide with radiation therapy in high grade brain gliomas: pharmaceuticals considerations and efficacy; a review article. Molecules 2009; 14: 1561-77.
12. Ridola V, Barone G, Lazzareschi I, Ruggiero A, Rizzo D, Riccardi R. Feasibility study of 21-day-on/7-day-off temozolomide in children with brain tumors. J Neurooncol 2011; 103: 147-53.
13. Turner CD, Gururangan S, Eastwood J, Bottom K, Watral M, Beason R, McLendon RE, Friedman AH. Phase II study of irinotecan (CPT-11) in children with high-risk malignant brain tumors: The Duke experience. Neuro Oncol 2002; 4: 102-8.
14. Smith ME, Cimica V, Chinni S, Challagulla K, Mani S, Kalpana GV. Rhabdoid tumor growth is inhibited by flavopiridol. Clin Cancer Res 2008; 14: 523-32.
15. Pérez-Martínez A, Lassaletta A, González-Vicent M, Sevilla J, Díaz MA, Madero L. High-dose chemotherapy with autologous stem cell rescue for children with high risk and recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors. J Neurooncol 2005; 71: 33-8.
16. Guruangan S, Dunkel IJ, Goldman S, Garvin JH, Rosenblum M, Boyett JM, Gardner S, Merchant TE. Myeloablative chemotherapy with autologous bone marrow rescue in young children with recurrent malignant brain tumors. J Clin Oncol 1998; 16: 2486-93.
17. Finlay JL, Dhall G, Boyett JM, Dunkel IJ, Gardner SL, Goldman S, Yates AJ, Rosenblum MK. Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: outcome compared with conventional chemotherapy: A report from the Children's Oncology Group. Pediatr Blood Cancer 2008; 51: 806-11.
18. Fangusaro J, Finlay J, Sposto R, et al. Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors (sPNETs): report of the Head Start I and II experience. Pediatr Blood Cancer 2008; 50: 312-8.
19. Fangusaro J, Massimino M, Rutkowski S, Gururangan S. Non-Cerebellar Primitive Neuroectodermal Tumors (PNET): Summary of the Milan Consensus and State of the Art Workshop on Marrow Ablative Chemotherapy With Hematopoietic Cell Rescue for Malignant Brain Tumors of Childhood and Adolescents. Pediatr Blood Cancer 2010; 54: 638-40.
20. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, Woo S, Wheeler G, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol 2006; 7: 813-20.
21. Gajjar A. High-dose chemotherapy for recurrent medulloblastoma: time for a reappraisal. Cancer 2008; 112: 1643-5.
22. Butturini AM, Jacob M, Aguajo J, et al. 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 2009; 115: 2956-63.
23. Grill J, Dufour C, Kalifa C. High-dose chemotherapy in children with newly-diagnosed medulloblastoma. Lancet Oncol 2006; 7: 787-8.
24. Ridola V, Grill J, Doz F, et al. High-dose chemotherapy with autologous stem cell rescue followed by posterior fossa irradiation for local medulloblastoma recurrence or progression after conventional chemotherapy. Cancer 2007; 110: 156-63.
25. Aihara Y, Tsuruta T, Kawamata T, et al. Double high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation for primary disseminated medulloblastoma: a report of 3 cases. J Pediatr Hematol Oncol 2010; 32: e70-4.
26. Foreman NK, Schissel D, Le T, Strain J, Fleitz J, Quinones R, Giller R. A study of sequential high dose cyclophosphamide and high dose carboplatin with peripheral stem-cell rescue in resistant or recurrent pediatric brain tumors. J Neurooncol 2005; 71: 181-7.
27. Massimino M, Cohen KJ, Finlay JL. Is there a role for myeloablative chemotherapy with autologous hematopoietic cell rescue in the management of childhood high-grade astrocytomas? Pediatr Blood Cancer 2010; 54: 641-3.
28. Hanahan D, Bergers G, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. J Clin Invest 2000; 105: 1045-7.
29. Herrington B, Kieran MW. Small molecule inhibitors in children with malignant gliomas. Pediatr Blood Cancer 2009; 53: 312-7.
30. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol 2006; 59: 490-8.
31. Skowrońska-Gardas A. A literature review of the recent radiotherapy clinical trials in pediatric brain tumors. Rev Recent Clin Trials 2009; 4: 42-55.
32. Timmermann B. Proton beam therapy for childhood malignancies: status report. Klin Padiatr 2010; 222: 127-33.
33. Fangusaro J. Pediatric high-grade gliomas and diffuse intrinsic pontine gliomas. J Child Neurol 2009; 24: 1409-17.
34. Qaddoumi I, Sultan I, Gajjar A. Outcome and prognostic features in pediatric gliomas. A review of 6212 cases from the surveillance, epidemiology, and end results database. Cancer 2009; 115: 5761-70.
35. Rood BR, MacDonald TJ. Pediatric high-grade glioma: Molecular genetic clues for innovative therapeutic approaches. J Neurooncol 2005; 75: 267-72.
36. Hargrave D. Paediatric high and low grade glioma: the impact of tumour biology on current and future therapy. British J Neurosurg 2009; 23: 351-63.
37. Bax DA, Mackay A, Little SE, et al. A distinct spectrum of copy number aberrations in pediatric high-grade gliomas. Clin Cancer Res 2010; 16: 3368-77.
38. Song KS, Phi JH, Cho BK, et al. Long-term outcomes in children with glioblastoma. J Neurosurg Pediatr 2010; 6: 145-9.
39. Wolff J, Driever PH, Erdlenbruch B, et al. Intensive chemotherapy improves survival in pediatric high-grade glioma after gross total resection: results of the HIT-GBM-C protocol. Cancer 2010; 116: 705-12.
40. Jalali R, Raut N, Arora B, Gupta T, Dutta D, Munshi A, Sarin R, Kurkure P. Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. Int J Radiat Oncol Biol Physics 2010; 77: 113-8.
41. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 2006; 7: 241-8.
42. Packer RJ, Goldwein J, Nicholson HS. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group study. J Clin Oncol 1999; 17: 2127-21.
43. Packer RJ, Krailo M, Mehta M, et al. A Phase I study of concurrent RMP-7 and carboplatin with radiation therapy for children with newly diagnosed brainstem gliomas. Cancer 2005; 104: 1968-74.
44. Roujeau T, Machado G, Garnett MR, et al. Stereotactic biopsy of diffuse pontine lesions in children. J Neurosurg 2007; 107: 1-4.
45. Verlooy J, Mosseri V, Bracard S. Treatment of high risk medulloblastomas in children above the age of 3 years: A SFOP study. Eur J Cancer 2006; 42: 3004-14.
46. Dhall G. Medulloblastoma. J Child Neurol 2009; 24: 1418-30.
47. Bayani J, Zielenska M, Marrano P, Ng YK, Taylor MD, Jay V, Rutka JT, Squire JA. Molecular cytogenetic analysis of medulloblastomas and supratentorial primitive neuroectodermal tumors by using conventional banding, comparative genomic hybridization, and spectral karyotyping. J Neurosurg 2000; 93: 437-48.

48. Johnston DL, Keene Dl, Lafay-Cousin L, et al. Supratentorial primitive neuroectodermal tumors: a Canadian pediatric brain tumor consortium report. J Neurooncol 2008; 86: 101-8.
49. Biswas S, Burke A, Cherian S, et al. Non-pineal supratentorial primitive neuro-ectodermal tumors (sPNET) in teenagers and young adults: Time to reconsider cisplatin based chemotherapy after cranio-spinal irradiation? Pediatr Blood Cancer 2009; 52: 796-803.
50. Behdad A, Perry A. Central nervous system primitive neuroectodermal tumors: a clinicopathologic and genetic study of 33 cases. Brain Pathol 2010; 20: 441-50.
51. Robertson PL, Zeltzer PM, Boyett JM, et al. Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. J Neurosurg 1998; 88: 695-703.
52. Saito R, Kumabe T, Kanamori M, Sonoda Y, Tominaga T. Dissemination limits the survival of patients with anaplastic ependymoma after extensive surgical resection, meticulous follow up, and intensive treatment for recurrence. Neurosurg Rev 2010; 33: 185-91.
53. Massimino M, Buttarelli FR, Antonelli M, Gandola L, Modena P, Giangaspero F. Intracranial ependymoma: factors affecting outcome. Future Oncol 2009; 5: 207-16.

**Address for correspondence**

Faruk Guclu Pinarli MD
Gazi University Faculty of Medicine
Department of Pediatric Oncology
Besevler, 06510, Ankara, Turkey
tel. +90 312 202 60 21
fax +90 312 215 01 43
e-mail: fgpinarli@gazi.edu.tr

**Submitted:** 17.04.2011
**Accepted:** 13.11.2011