



NEW APPROACHES IN THE TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM TUMORS

Ph.D. Thesis

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List of full papers that served as the basis of the Ph.D. thesis

- I. **Moze P**, Dittmar JO, Habermehl D, Tonndorf-Martini E, Hideghety K, Dittmar A, Debus J, Combs SE.
Volumetric response of intracranial meningioma after photon or particle irradiation.
Acta Oncol. 2017 Mar;56(3):431-437.
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- II. Daróczy B, Szántó E, Tóth J, Barzó P, Bognár L, Bakó G, Szántó J, **Mózes P**, Hideghéty K.
Post-operative management of primary glioblastoma multiforme in patients over 60 years of age.
Ideggyogy Sz. 2013 Nov 30;66(11-12):391-8.
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- III. **Moze P**, Hauser P, Hortobágyi T, Benyó G, Peták I, Garami M, Cserhádi A, Bartyik K, Bognár L, Nagy Z, Turányi E, Hideghéty K.
Evaluation of the good tumor response of embryonal tumor with abundant neuropil and true rosettes (ETANTR).
J Neurooncol. 2016 Jan;126(1):99-105.
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- IV. **Moze P**, Szanto E, Tizslavicz L, Barzo P, Cserhati A, Fodor E, Hideghety K.
Clinical course of central neurocytoma with malignant transformation-an indication for craniospinal irradiation.
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1. Introduction

Primary brain tumors are a diverse group of neoplasms arising from different cell types of the central nervous system (CNS). The most common primary brain tumors are (anaplastic) astrocytomas, glioblastomas, meningiomas and other mesenchymal tumors.

The treatment of primary brain tumors requires an interdisciplinary team-work. Complete or near-complete tumor resection without serious sequelae could be provided in many cases. External beam radiation therapy plays a central role in the primary or adjuvant treatment of primary brain tumors independently from histology. It has shown its effect in increasing the local tumor control (LC) and in overall survival (OS). Different techniques aim to provide the best available selectivity in dose delivery e.g. 3D-conformal radiotherapy (RT), intensity-modulated radiotherapy (IMRT), fractionated stereotactic radiotherapy (FSRT), or radiosurgery. Charged particle therapy with protons or carbon ions shows benefits over the best photon techniques due to its unique physical and biological properties. Dose deposition with its maximum occurs at the end of the track in the so called Bragg peak. The range of the peaks is shifted to generate an appropriately sized treatment field, the so called spread-out Bragg peak. The normal tissue thereafter can be spared with its steep dose fall-off behind the target volume. Particles with high linear energy transfer provide a higher relative biological effectiveness (RBE) because they cause a dense ionization in the target volume.

Chemotherapy (ChT) as radiosensitizing agent can be combined with RT (simultaneously or adjuvant) aiming to increase LC and OS rates. For example, concomitant to RT and adjuvant temozolomide (TMZ) became a part of the standard therapy in primary high grade glial brain tumors.

However no clinical evidence could be drawn for rare CNS tumor entities, for special age groups such as elderly or young patients, and for the emerging radiation modalities, which require a clinical establishment in the frame of randomized clinical investigations.

Meningiomas are the most common primary non-glial brain tumors in adults and account for 15–30% of all intracranial neoplasms. Despite their generally benign character, they are often neighboring or infiltrating critical neurovascular structures and their growth can cause neurological or neurocognitive deficits leading to a significant worsening in quality of life. Gross total resection (GTR) provides long-term recurrence-free survival in many cases. If only subtotal resection (STR) can be achieved and for recurrent meningiomas, or in cases of grade II tumors, adjuvant RT should be considered. In cases of anaplastic meningiomas RT should be

always a part of the therapy. Due to improvements in treatment planning and technical application of high precision photon RT, FSRT and IMRT have been well established. These techniques showed convincing LC (75–100%) and very low side effect rates.

Glioblastoma multiforme (GBM) is a malignant primary glial brain tumor and it accounts 12-15% of all intracranial neoplasms in adults. GBM is associated with a median OS of only 15 months among patients treated with at least surgical resection and radiotherapy. Age is a significant risk factor for GBM, and the incidence of GBM is increasing along with the aging of the general population. Although survival rates have been improving in the recent years, likely a result of the increased use of TMZ concomitant to post-operative RT and/or as adjuvant therapy.

Embryonal tumor with abundant neuropils and true rosettes (ETANTR) (according to the new world health organization (WHO) classification of primary CNS tumor reclassified as embryonal tumor with multilayered rosettes [ETMR]) is characterized histologically with the presence of undifferentiated neuroepithelial cells, broad bands of well-differentiated neuropil islands, ependymoblastic rosettes and C19MC gene amplification. It is a rare and highly malignant variant of embryonal brain tumors. It usually affects infants and young children under the age of 4 years and exhibits a very aggressive course with a dismal prognosis.

Neurocytoma (NC) accounts for only 0.1–0.5 % of all brain neoplasms, displays a slow and benign clinical course with a low recurrence rate and a low tendency to spread. It has the properties of bipotential precursor cells, which can exhibit both glial and neuronal differentiation. It develops mainly in young adults around the third decade of life. GTR ensures high progression-free survival (PFS) and OS rates without recurrence. On the basis of the histological findings, such as nuclear atypia, anaplasia, vascular endothelial proliferation, focal necrosis, and/or an increased mitotic index a subgroup of this tumor entity is defined as atypical NC. An MIB-1 labeling index (MIB-1 LI) of ≥ 2 % or > 3 % has been claimed to be associated with a significantly poorer survival and to correlate with a higher risk of relapse; moreover an MIB-1 LI of > 4 % correlates significantly with an unfavorable clinical course. Such a high proliferation index is quite uncommon and is extremely rare at the time of the diagnosis.

2. Aims

The aim of this thesis was to seek for strategies resulting in improved therapeutic index for different types of primary CNS tumors.

2.1. The purpose of the assessment of volumetric changes of different grade of meningiomas after treatment with different RBE irradiation was to evaluate the dynamics of tumor response due to different radiation qualities and techniques. We compared the tumor volume (TV) reduction effect of the different radiation qualities, i.e.: photons, protons and carbon ions retrospectively, assessed by the analysis of serial follow-up magnetic resonance imaging (MRI) on patients diagnosed with different grade of meningioma.

2.2. We aimed to evaluate the tolerance and effectivity of the combined treatment approach in elderly patients to define the clinical benefit and the applicability of the Stupp protocol in this special group of patients with GBM. We conducted a retrospective analysis of patients, over 60 years of age diagnosed with GBM who completed a complex treatment of neurosurgery, adjuvant radio(chemo)therapy (RChT) and adjuvant ChT in order to define how this combined treatment is tolerated, and whether it is beneficial in this ageing group, and to search for prognostic factors for quality of life and overall survival.

2.3. In the lack of evidence based approach, we performed a wide literature search on two tumor rarities in the CNS (i.e. ETMR and NC) in order to provide the best treatment options.

2.3.1. Our aim was to introduce a novel complex therapeutic approach for childhood ETMR to improve the therapeutic index using novel technical possibilities. We applied with long-term success in case of recurrence STR, RT of the craniospinal axis (CSI) followed with tumor bed boost with concomitant ChT followed by modified metronomic ChT.

2.3.2. We evaluated different treatment options derived from the literature evaluation in the course of aggressive NC with the purpose to provide useful suggestions on effective management of this rare disease. We investigated the role of CSI, repeated irradiation in the case of recurrence and combination of RT with ChT in the management of atypical central NC.

3. Patients and methods

3.1. Volumetric response of intracranial meningioma after photon or particle irradiation.

The data of two groups of 77 patients were analyzed and compared retrospectively who were suffering from inoperable (even biopsy was not feasible; grade of meningioma is unknown), residual or recurrent meningioma, treated in two time periods with different RT modalities. Group A consists of 38 patients who were treated at the Heidelberg Ion-Beam Therapy Center (HIT) between September 2010 and January 2012 due to inoperable (10/38), residual (6/38) or recurrent (22/38) meningiomas. Histological WHO grade was unknown in 10/38, grade I in 17/38, grade II in 10/38 and grade III in 1/38 patients. Median age at the time of RT was 52.5 years (range: 32.1–76.8 years). Male to female ratio was 9:29. The tumors were located at the skull base in 31/38, attached to the olfactory tract in 4/38, at the falx in 2/38 or in the orbit in 1/38 patients. Proton RT was delivered to the macroscopic tumor with a safety margin in benign cases (unknown and grade I 27/38) with a median dose of 56 GyE (range 54–58 Gy) in 1.8 or 2 GyE daily fractions. For high grade meningiomas (grade II and III 11/38) a mixed photon/carbon ion scheme according to the MARCIE protocol was used: 50 Gy in 2 Gy daily fractions with IMRT and 18 GyE in 3 GyE daily dose carbon ion boost to the macroscopic tumor.

For Group B, 39 patients were selected who had been treated between November 2000 and July 2009 and matched best regarding the clinical parameters (age, gender, tumor volume, etc.). They were irradiated because of inoperable (12/39), residual (10/39) or recurrent (17/39) meningiomas. Histological grade was unknown in 12/39, grade I in 16/39, grade II in 7/39 and grade III in 4/39 patients. Median age at the time of RT was 55.2 years (range 20.6–80.8 years). Male to female ratio was 11:28. Meningiomas were located at the skull base in 25/39, at the convexity in 5/39, in the cavernous sinus in 4/39, at the falx in 2/39, on the optic nerve in 2/39 or at the craniocervical junction in 1/39 patients. IMRT or FSRT was applied with a median dose of 56 Gy (range 39.6–60 Gy) in 1.8 or 2 Gy daily fractions. Patients were individually affixed with special head masks. For delineation of organs at risk and gross tumor volume (GTV) a trimodal image fusion of a contrast-enhanced computed tomography (CT) scan with 3mm slices, a T1 weighted, contrast-enhanced MRI and a DOTATOC-positron emission tomography was used. For photon and proton RT the clinical target volume (CTV) included the GTV as well and a safety margin depending on histology was added (1–3mm in cases of low grade pathology and 10–20mm in atypical and anaplastic tumors). Anatomical borders were

respected. According to the MARCIE trial, a 5mm safety margin was given to the GTV for the carbon ion boost RT. For all patients the planning target volume (PTV) was calculated with an additional margin of 2–3mm in Thermoplast- or 1–2mm in Scotch Cast masks-setup.

The first- and second-year follow-up MRIs were compared with the pre-therapeutic one in each patient to evaluate the volumetric tumor response for this study. Therefore, the GTV was delineated on the initial pre-therapeutic MRI as well as on the first- and second-year follow-up MRIs using Siemens Dosimetrist (Siemens Medical Solutions, Concord, CA). Afterwards, these three GTVs (pretherapeutic, first- and second-year follow-up) were compared and TV were calculated in cm³ (Masterplan Oncentra, Nucletron, Columbia, MD). The statistical analysis was performed with SPSS 20. Paired and two samples t-tests as well as ANOVA tests were done.

3.2. Post-operative management of primary glioblastoma multiforme in patients over 60 years of age.

Records of 75 patients (male:female=34:41) with newly diagnosed and histologically proven GBM who were treated at the University of Debrecen and at the University of Szeged in the period from February 2001 to December 2010 were reviewed retrospectively. Eligible patients were at least 60 years old (median 65.1 years, range: 60-80 years) and they were required to have adequate renal, liver, and hematologic functions. All patients underwent neurosurgery, which was classified by the surgeons as GTR in 29 (38.7%), STR in 32 (42.7 %), and biopsy in 10 (13.3%) patients. The extent of resection could not be determined for 4 patients. Seventy-one patients received standard RT (60 Gy in 30 fractions), three patients received reduced doses of irradiation (48 Gy or 30-33 Gy), and one patient did not receive any RT. Ten of 74 patients who underwent RT received no ChT. Of the remaining patients, 62 received concomitant and/or adjuvant TMZ therapy, and two patients received adjuvant 1,3-bis(2- chloroethyl)-1-nitrosourea (BCNU) but not TMZ. The patients were divided into three age groups: 60–64, 65–69, and ≥ 70 years. The study end points were OS and PFS. OS time was defined as the time between the date of neurosurgery and the date of death or final follow-up. PFS was defined as the time from the date of neurosurgery to the appearance of recurrent or progressive tumor, or neurologic deterioration. Progressive disease was defined as a $\geq 20\%$ increase in the size of the tumor (assessed according to Response Evaluation Criteria In Solid Tumors [RECIST]) or by the appearance of a new tumor. Patients with newly diagnosed GBM received surgery followed by RT with or without concomitant and/or adjuvant TMZ. RT was administered as a conventionally fractionated regimen: once daily at 2 Gy per fraction, five days a week, for a

total of 60 Gy. Concomitant TMZ was administered at a daily dose of 75 mg/m² for 42 consecutive days. Following a four-week rest period, TMZ was administered daily for five consecutive days at a dose of 150–200 mg/m² every 28 days. It was delivered at a dose of 150 mg/m² during the first cycle. Two patients required dose reductions to 100 mg/m² after the first cycle and, in another four patients, the dose was kept at 150 mg/m² during all cycles. All other patients receiving adjuvant TMZ were treated with a dose of 200 mg/m² after the first cycle. Before 2005, patients underwent various treatment modalities. After 2005, either the Stupp protocol was followed (i.e., patients received six cycles of adjuvant TMZ after concurrent RChT) or adjuvant TMZ therapy was continued until complete response or unequivocal progression was observed. Neuroradiologic imaging was performed every three months, and clinical performance was assessed every four weeks or whenever clinical deterioration occurred. The Kaplan-Meier method was used for survival analysis. Differences between survival curves were assessed by a log-rank test. The following baseline variables were considered for survival analysis: age, gender, post-operative Karnofsky performance score (KPS), type of surgery, tumor burden, reoperation, re-irradiation, and tumor localization. For all statistical tests, a value of $p \leq 0.05$ was considered significant. The significance of putative prognostic factors was assessed by univariate and multivariate analyses using the Cox proportional hazards model. Only variables associated with a p value of < 0.1 in the univariate model were included in the multivariate analysis. All analyses were conducted using SPSS 15.0 for Windows (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 5, version 5.0 for Windows (GraphPad Software Inc, La Jolla, CA, USA).

3.3.1. The role of chemoradiotherapy in the good tumor response of embryonal tumor with abundant neuropil and true rosettes (ETANTR).

A 2-year-old girl was operated on a lesion with a diameter of 6 cm in the left cerebellum and left occipital lobe, GTR was performed. Histopathological examination of the tumor sample revealed the diagnosis of ETMR. There was no evidence of spreading via the cerebrospinal fluid (CSF). She received adjuvant ChT according to the Medulloblastoma 2008 high-risk protocol (vincristine, cyclophosphamide, etoposide, carboplatin intravenously and intrathecal) which was followed with an autologous stem cell transplantation (SCT). 2.5 year later a local recurrence occurred and a reoperation with STR was carried out. Thereafter, she received CSI, with 32 Gy in 1.6 Gy daily fractions followed by RChT comprising tumor bed boost with 24 Gy in 1.6 Gy daily fractions and a residual tumor boost with 6 Gy in 1.5 Gy daily fraction

supplemented with 75 mg/m² TMZ daily. Modified adjuvant systemic therapy was continued according to the Kieran schema (thalidomide, celecoxib, fenofibrate, etoposid and cyclophosphamid was changed to TMZ) for 1.5 year. She is still tumor-free 6 years after the tumor recurrence without major neurocognitive deficits. This individual approach was evaluated in a broad literature review and with long follow-up, to give advice for optimal treatment strategy in this rare primary brain tumor.

3.3.2. An indication for craniospinal irradiation - clinical course of central neurocytoma with malignant transformation.

A 40-year-old man was operated on a mass at the bottom and in the posterior third of the third ventricle, which constricted the aqueduct and caused an occlusive hydrocephalus. The cytopathological analysis resulted the diagnosis of a WHO II° central CN with a MIB-1 LI of 25-30%. In the CSF there was no evidence of tumor cells. First postoperative CSI was planned, but after interdisciplinary discussion and literature review an adjuvant focal 3D-RT was performed with a cumulative dose of 59.4 Gy in 1.8 Gy daily fractions. 3 years later a tumor spread was observed via the CSF along the spinal cord in different locations. Via hemilaminectomy a tumor mass from the thoracic spinal cord was removed. Postoperative, conformal irradiation of the whole spinal cord was performed in a total dose of 36 Gy in 1.8 Gy daily fractions, and a 10 Gy boost with 2 Gy daily dose was delivered to the tumor bed in the thoracic IV–VI region. 6 months later the tumor progressed in the cervical spinal cord. At that time the patient underwent simultaneous RChT with 200 mg/m² TMZ five times per week in 28-days cycles and received a reirradiation with a dose of 22.5 Gy in 1.5 Gy daily fractions to the cervical spinal region. The treatment was well tolerated and released a symptom relief and partial remission on MRI. He was then placed on 200 mg/m² TMZ monotherapy. 1 year later multiple intracranial tumor recurrence occurred in the left frontal lobe, in the occipital lobes, and in the left cerebellum. Reirradiation was carried out to the whole brain in a cumulative dose of 27 Gy in 1.8 Gy daily fractions, with initial tumor bed avoidance, and an additional boost dose of 8 Gy in 1 Gy daily fractions to the macroscopic manifestations. 5 months later the patient died, 62 months after the initial diagnosis.

With a comprehensive literature review we identified cases of atypical NCs with high MIB-1 LI and we drew attention on the importance and necessity of aggressive combined therapy from the diagnosis of the disease.

4. Results

4.1. Volumetric response of intracranial meningioma after photon or particle irradiation.

In Group A, 27 patients were treated by proton RT. The mean initial TV was $V_{\text{mean}}=26.1 \pm 22.2 \text{ cm}^3$. There was a significant absolute TV shrinkage after one year ($V_{\text{mean}}=23.5 \pm 19.8 \text{ cm}^3$; $V_{\text{change mean}}=3.7 \pm 4.6 \text{ cm}^3$, $p=0.001$). At the two-year follow-up a steady state could be observed compared to the volumes after one year ($V_{\text{mean}}=24.3 \pm 20.7 \text{ cm}^3$). Eleven patients were treated by carbon ion boost combined with IMRT. The mean initial TV was $V_{\text{mean}}=26.5 \pm 15.4 \text{ cm}^3$. There was a significant absolute TV shrinkage at one-year follow-up ($V_{\text{mean}}=20.9 \pm 14.4 \text{ cm}^3$; $V_{\text{change mean}}=5.7 \pm 5.6 \text{ cm}^3$, $p=0.011$). At two-year follow-up the contrast enhancing volume had decreased ($V_{\text{mean}}=12.9 \pm 10.0 \text{ cm}^3$), however, this shrinkage was not significant ($p=0.083$). There was no significant difference in TV changes between combined IMRT plus carbon ion boost and proton-treated patients.

In Group B, 16 patients were treated by IMRT. The mean initial TV was $V_{\text{mean}}=37.3 \pm 29.5 \text{ cm}^3$. There was a significant absolute TV shrinkage both after one year ($V_{\text{mean}}=34.6 \pm 28.0 \text{ cm}^3$; $V_{\text{change mean}}=4.3 \pm 4.1 \text{ cm}^3$, $p=0.003$) and at the two-year follow-up ($V_{\text{mean}}=23.5 \pm 17.5 \text{ cm}^3$; $V_{\text{change mean}}=9.0 \pm 5.2 \text{ cm}^3$, $p=0.017$). There was a significant absolute shrinkage after two years compared to the one-year follow-up as well ($V_{\text{change mean}}=3.4 \pm 1.5 \text{ cm}^3$, $p=0.020$). Twenty-three patients were treated by FSRT. The mean initial TV was $V_{\text{mean}}=26.7 \pm 23.1 \text{ cm}^3$. There was a significant absolute TV shrinkage both after one year ($V_{\text{mean}}=20.5 \pm 14.3 \text{ cm}^3$; $V_{\text{change mean}}=7.0 \pm 14.7 \text{ cm}^3$, $p=0.042$) and at the two-year follow-up ($V_{\text{mean}}=13.9 \pm 10.0 \text{ cm}^3$; $V_{\text{change mean}}=4.7 \pm 3.9 \text{ cm}^3$, $p=0.001$). There was a significant absolute shrinkage at two-year compared to one-year follow-up as well ($V_{\text{change mean}}=1.3 \pm 1.8 \text{ cm}^3$, $p=0.038$). There was no significant difference in TV changes between IMRT and FSRT treated patients.

A significant absolute TV shrinkage was found in male as well as in female patients. In men (20/77) the mean initial TV was $V_{\text{mean}}=40.6 \pm 31.4 \text{ cm}^3$, after one year $V_{\text{mean}}=34.0 \pm 27.4 \text{ cm}^3$ ($p=0.018$) and after two years $V_{\text{mean}}=19.5 \pm 13.2 \text{ cm}^3$ ($p<0.0001$). In women (57/77) the mean initial TV was $V_{\text{mean}}=24.5 \pm 18.4 \text{ cm}^3$, at one-year follow-up $V_{\text{mean}}=21.6 \pm 16.4 \text{ cm}^3$ ($p<0.001$) and two-year follow-up $V_{\text{mean}}=17.5 \pm 16.2 \text{ cm}^3$ ($p<0.0001$). Men showed a significant higher shrinkage after irradiation over every modalities and at both follow-up examinations. In male patients the $V_{\text{change mean}}$ was $10.1 \pm 15.8 \text{ cm}^3$ and $7.8 \pm 4.6 \text{ cm}^3$ after one and two years, respectively. In women it was $V_{\text{change mean}}=3.5 \pm 4.3 \text{ cm}^3$ and $3.9 \pm 3.3 \text{ cm}^3$ (Mann-Whitney U-test $p=0.028$, $p=0.022$). Therefore, gender was found to be an independent predictive factor for TV change.

In patients with grade III meningioma (5/77, initial $V_{\text{mean}}=31.4 \pm 21.5 \text{ cm}^3$) we observed significantly higher relative TV shrinkage in comparison to patients with unknown histology (22/77, initial $V_{\text{mean}}=22.2 \pm 15.1 \text{ cm}^3$) as well as to patients with grade I meningiomas (33/77, initial $V_{\text{mean}}=30.0 \pm 25.1 \text{ cm}^3$), both at one-year ($p=0.045$ and $p=0.038$) and two-year follow-up ($p=0.010$ and $p=0.012$). The mean relative size of the residual, contrast enhancing TV was $58.0 \pm 22.9\%$ and $52.1 \pm 13.5\%$ in the grade III cases after one and two years. In patients with unknown histology the residual TV was $89.6 \pm 19.9\%$ and $81.7 \pm 6.6\%$ as well as $89.3 \pm 17.3\%$ and $83.0 \pm 13.6\%$ in grade I meningiomas, respectively. Patients with grade II meningioma showed a higher tumor shrinkage at one- and two-year follow-up than patients with unknown or with grade I meningioma, but less tumor volume reduction than grade III. No significance could be detected between the group of grade II meningioma in comparison with the unknown or grade I and grade III tumors.

Neither age, radiation modality (photon vs. charged particle), initial TV, nor operability were found to be significant independent predictive factors for volumetric response at the two-year follow-up.

4.2. Post-operative management of primary glioblastoma multiforme in patients over 60 years of age.

After a median follow-up of 10.3 months (range: 2.2–56.2 months), four patients were alive and 71 had died of tumor progression. Treatment-related toxicity led to permanent discontinuation of ChT in five patients; two patients discontinued concomitant and three discontinued adjuvant TMZ. Concomitant ChT was delivered in 82.7% of patients and no dose reductions were necessary. Of the 75 study participants, 21 underwent some form of salvage therapy because of disease progression after initial treatment. Salvage therapy consisted of surgery ($n=13$), RT ($n=3$), surgery plus RT ($n=3$), or surgery plus adjuvant BCNU after progression on TMZ ($n=2$). Most patients with progressive disease received best supportive care only.

For the total study population ($n=75$), mean OS was 12.9 months and median OS was 10.3 months [95% confidence interval (CI), 8.9–11.7]. Median PFS was 4.1 months (95% CI, 3.9–9.3). The 6-month and 12-month OS rates were 73.3% and 42.6%, respectively, with a 2-year OS rate of 6.7%. Median OS was 4.2 months among patients who received concomitant ChT only and 13.8 months among those who received both concomitant and adjuvant ChT. The use and duration of adjuvant TMZ were highly significant prognostic factors of longer OS. Median

OS times were significantly longer among patients who received adjuvant TMZ versus the median OS time (4.2 months) associated with concomitant therapy only. Median OS after RT was 6.5 months. Biopsy only compared with GTR and KPS <70 were significant negative prognostic factors of OS in both univariate and multivariate analyses. Patients who underwent biopsy with no subsequent partial or total resection had a median OS (4.5 months) that was more than 50% shorter than that of the total study population (10.3 months). Univariate analysis further suggested that additional surgery in patients who experienced disease progression was a significant predictor of longer OS (median OS, 17 vs. 9.2 months for those without salvage surgery, $p=0.049$). Survival analyses by age suggested no major differences in OS between age groups. The median OS was 10.5 months for patients aged <70 years and 7.7 months for those aged ≥ 70 years; however, this difference was not statistically significant in univariate analysis ($p=0.467$). In contrast, age ≥ 70 years was a negative prognostic factor of PFS in univariate analysis ($p=0.0008$). The only other negative prognostic factor for PFS was the type of surgery. As for OS, biopsy only (versus total resection) was a negative prognostic factor for PFS in univariate analysis ($p<0.0001$). Other factors, including gender, KPS, and tumor size, were not found to be prognostic of PFS.

RChT was well tolerated and could be completed without interruption in most patients. TMZ was generally well tolerated. The most common adverse events among patients who received adjuvant TMZ were fatigue and nausea. Grade III/IV adverse events consisted of grade III thrombocytopenia in 1 patient and grade III fatigue in two patients. Adjuvant TMZ treatment of three patients was discontinued because of thrombocytopenia ($n=1$), traumatic bone fractures ($n=1$), or voluntary withdrawal ($n=1$). Notably, none of the patients who received more than six cycles of adjuvant TMZ showed any toxicity at all.

4.3.1. The role of chemoradiotherapy in the good tumor response of embryonal tumor with abundant neuropil and true rosettes (ETANTR).

The patient treated with ETMR is still tumor free 6 years after tumor recurrence without major neurocognitive deficits. A substitutional hormone therapy is necessary to ensure mental and physical development.

Our literature review in 2016 indicated 69 reported cases of ETMR, including our case. The mean age at the time of diagnosis was 25.4 months (range: 3- 57 months). Survival data were available for 48 children (including our case): the median OS was 13.0 months. Patients who underwent STR or GTR had a significant survival benefit in comparison with patients on whom

only biopsy could be performed (14 vs. 6 months, $p = 0.006$) but there were no major differences between the STR and GTR groups. The children who were irradiated had a significant survival benefit relative to non-irradiated children (16 vs. 11 months, $p = 0.029$). Our literature search revealed 6 (including our case) unusually long survivors (at least 30 months after diagnosis) with ETMR. The mean age at diagnosis among long survivals was 31.2 months (range 7–48 months). At the time of the report each of the 6 children was free of disease. They were all operated: 2/6 STR and 4/6 GTR. 1 child who did not receive adjuvant therapy was reoperated 11 months after the first surgery because of tumor recurrence and then received combined ChT followed by SCT. The other 5 children received high-dose ChT in various combinations. RT was applied in 4 cases: hyperfractionated CSI with 36 Gy and a 30 Gy tumor bed boost followed by 8 cycles of carboplatin, vincristine and lomustine; CSI with 36 Gy and a 19.8 Gy tumor bed boost supplemented with concurrent carboplatin and vincristine followed by cisplatin, vincristine, and cyclophosphamide (to date of the literature review he is the longest survivor); in our case, CSI with 32 Gy and a 30 Gy tumor bed boost RChT supplemented with concomitant TMZ in 75mg/m² daily dose, and thereafter 150 mg/m² TMZ monthly up to 1.5 years combined with a modified adjuvant systemic therapy according to the Kieran-Schema (thalidomide, celecoxib, fenofibrate, and etoposid); for one case data about RT were not available. The similarities of these cases are that all 6 children were operated after diagnosis, at least STR was performed and combined high-dose ChT was administered for a certain amount of time.

4.3.2. An indication for craniospinal irradiation - clinical course of central neurocytoma with malignant transformation.

Our case presented a high MIB-LI with 25-30% at the time of the initial diagnosis and 3 years after GTR and adjuvant RT with 60 Gy a tumor recurrence occurred. Salvage surgery, repeated RT courses and application of TMZ resulted in symptom control and prolonged the survival of the patient with a good quality of life. Our literature review resulted in 19 cases, including our case, with unfavorable clinical course and rapid progression: high rates of local recurrence and craniospinal dissemination prior to the diagnosis or following surgical resection. 11 of the 13 patients for whom data were accessible had an initial MIB-1 LI >2 %. For the group of patients in whom the first tumor recurrence or dissemination occurred within 12 months, a higher mean MIB-1 LI was observed (mean 17.82 %, range 4.4–37.3 %). There was a non-significant tendency toward an unfavorable clinical course if the MIB-1 LI was initially elevated. The same phenomenon was observed for the patients who developed spinal metastases, who exhibited an initial mean MIB-1 LI of 13.4 %. 16 patients received adjuvant treatment, i.e. RT ± ChT. A

huge variety of RT techniques (stereotactic radiosurgery=3, conformal RT=12), doses (25–66 Gy) and ChT combinations were used (etoposide, carboplatin, cyclophosphamide, cisplatin, vincristine, cytarabine, ifosfamide, imatinib, TMZ, topotecan, thioTEPA, and nimustine). Four patients received only ChT and two patients did not get any postoperative treatment. The whole craniospinal axis was treated only in the cases with proven manifestation in the spinal cord (n =2). The mean follow-up period was 32.4 months (range 7–72 months). The estimated mean survival was 27.9 months (range 5–46 months). 7 patients died because of tumor dissemination and disease progression. 7 patients were in a stable condition at the time of their last follow-up examination. 2 patients were in disease progression at their last follow-up 15 and 7 months after the first operation. 2 patients were disease-free 9 and 132 months after the first tumor removal. The estimated mean PFS was 15.3 months (range 2-36 months). CSF spreading was detected in 16/18 cases.

5. Conclusions

5.1. Evaluation of contrast enhancing tumor size after RT of meningiomas using MRI-based volumetric measurements is a precise method to detect tumor regression. We observed significant TV shrinkage independently of the applied radiation modality one and two years after RT.

5.2. Our results demonstrate that RChT after neurosurgery was safe and effective in patients diagnosed with GBM aged ≥ 60 years. In particular, a significant survival benefit was seen with the administration of maintenance TMZ after surgery and RT. Overall, more aggressive antitumor therapy in selected patients with GBM over 60 years of age was associated with longer survival. Our findings suggest that aggressive treatment for GBM should not be withheld from patients solely because of their advanced age.

5.3.1. ETMR exhibits a highly malignant course, but some case reports provide evidence that long-term disease free survival can be achieved through radical tumor resection, ChT, SCT and RT. CSI is strongly recommended because ETMR shows a high potential of spreading via the CSF. The application of RChT using advanced RT delivery technique can result in a survival benefit, and TMZ might be effective in embryonal brain malignancies and well tolerated by young children.

5.3.2. The conclusions drawn from meta-analyses of reports on benign NC cannot be applied in cases with aggressive behavior. NC patients with potential malignant transformation should be differentiated, and treated accordingly. Apart from histopathological malignant features the correct evaluation of the MIB-1 LI can help in the identification of these patients. In that cases multimodal treatment including CSI should be considered.

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