tients, Grade3:16 patients, Grade 4:47 patients) with recurrent malignant glioma treated with AVAgamma therapy as salvage therapy at the time of relapse after initial treatment. The average age is 55.7 years, with 44 men and 27 women. The tumor volume is 150 ml or less, and KPS is 40% or more as the indication of AVAgamma therapy. When the irradiation volume of the gamma knife was 15 ml or less, the marginal dose was 20 to 26 Gy, and when the irradiation volume was 15 ml or more, the marginal dose was 12 to 15 Gy in two divided doses.The mean therapeutic borderline dose was 24 Gy. Bevacizumab was administered 10 mg / kg or 15 mg / kg 1 to 10 times after GK. Methods: Median progression-free survival (mPFS) from AVAgamma treatment, median survival (mOS), and mOS from initial treatment were examined and compared with mOS in the RPA classification of recurrent glioma. Results: In relapsing glioma RPA classification, NABTT CNC class 2 mOS is 17.2 months, class 3 mOS is 3.8 months, class 5 mOS is 5.6 months, class 6 mOS is 6.4 months, but mOS from AVAgamma therapy is 18 months in class 3, 11 months in class 5, 9 months in class 6. The survival time has been extended in class3, class5, class6. Discussion: By AVAgamma therapy, it was thought that recurrent lesions were locally controlled and life prognosis was prolonged. Conclusion: AVAgamma therapy is thought to prolong the survival of recurrent malignant glioma and play an important role as salvage treatment.

Key words: gamma knife | bevacizumab | recurrent malignant glioma

RT-4

TREATMENT OUTCOME OF PROTON BEAM THERAPY FOR GLIOBLASTOMA

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Introduction: Proton beam therapy enables high dose irradiation for tumors while reducing the dose to surrounding normal tissue due to the sharp energy peak called the Bragg peak. We retrospectively analyzed the efficacy of the high dose radiotherapeutic strategy using proton beam for glioblastoma (GBM) in our institution. Methods: Twenty-nine patients with newly diagnosed GBM who underwent high dose proton beam therapy concomitant with temozolomide were investigated. All patients received hyperfractionated concomitant radiotherapy consisting of X-ray radiotherapy (50.4Gy in 28 fractions) and proton beam therapy (46.2Gy [RBE] in 28 fractions). The survival outcome and adverse events were analyzed. Results: The median overall survival time and progression free survival time for all 29 patients were 31.0 months (95%CI, 25.9–36.1) and 11.0 months (95%CI, 7.8–14.2), respectively. No significant survival difference according to the MGMT methylation status was shown. Failure patterns after proton beam therapy included 17 cases of local recurrence, 3 cases of distant recurrence, and 5 cases of dissemination. Although there was no significant difference in time to recurrence according to the failure pattern, there was a tendency of longer survival in the local recurrence group. Regarding adverse events, radiation necrosis was observed in 8 cases (including 2 asymptomatic cases). The median time to onset of necrosis after radiation was 18.2 months (95%CI, 10.3–26.2). There were 5 cases of long survivor over 5 years out of 29 cases (17.2%). Of these, 4 cases developed radiation necrosis. Conclusions: Our results indicate that high dose proton beam therapy of 96.6Gy (RBE) prolonged survival in selected GBM patients. Particularly in long survivors, special attention and effective treatment to radiation necrosis is a remaining problem.

Key words: glioblastoma | proton beam therapy | high dose radiation

RT-5

BORON NEUTRON CAPTURE THERAPY HAS EXTENDED PROGRESSION-FREE SURVIVAL ABOUT RECURRENT MALIGNANT PERIPHERAL NERVE SHEATH TUMOR - A CASE REPORT

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Introduction: Recurrent malignant peripheral nerve sheath tumor (MPNST) is intractable. Boron neutron capture therapy (BNCT) is a treatment using tumor-selective particle radiation, and is indicated for medical treatment for head and neck cancer, and also used for malignant glioma and malignant meningioma.<Case>20-year-old woman who has MPNST that extends from the subcutaneous tissue of the right neck to the posterior fossa. <Medical History>Chemotherapy and local irradiation(50.4Gy/28fr) for primary embryonal rhabdomyosarcoma of the right ear canal at the age six.<Current medical history>Right cervical tumor developed at 17-year-old, some chemotherapy regimens and tumor resections were performed as recurrence of rhabdomyosarcoma at the previous hospital. After she was diagnosed with MPNST in the pathology consultation at our hospital, she was irradiated with heavy ion beam 70.8Gy(RBE)/16fr and received additional chemotherapies at our department, but her tumor was refractory. Although BNCT for MPNST is not covered by health insurance in Japan, she wanted to try to be treated for BNCT. After confirming boron accumulation in the tumor (SUVmax 4.28) by FBPA-PET, tumor growth and hydrocephalus occurred while waiting for travel to Taiwan due to the spread of COVID-19 infection. She was performed tumor resection(NTR) and irradiated with SRS 20Gy/fr for the residual lesion, but tumor had a rapid recurrence from the margin of the excision cavity. Finally, she could travel about 3 months after the operation and underwent BNCT, that used neutrons and 10B-boronophenylalanine from the Tsinghua University research reactor in Taiwan. No serious adverse events including cerebral edema were observed, and dramatic tumor shrinkage was maintained after treatment. FBPA-PET of 3 months later showed accumulation in the part of the margin of the cavity, the recurrence was observed on MRI after 3 and a half months. Discussion: BNCT for refractory/recurrent MPNST showed acceptable safety and was able to prolong progression-free survival.

Key words: BNCT | MPNST | PFS

MOLECULAR PATHOLOGY/CLASSIFICATION (MPC)

MPC-1

DNA METHYLOME ANALYSIS SUGGESTED THE PRESENCE OF "TRUE" IDH-WILDTYPE LOWER-GRADE GLIOMAS

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Background: There will be significant changes in the diagnosis of IDH-wildtype adult-type gliomas in the upcoming 5th edition of the WHO Classification of Central Nervous System Tumours. IDH-wildtype lower grade gliomas (IDHwt LGGs) that harbor molecular features of glioblastoma (EGFR amplification, the combination of whole chromosome 7 gain and whole chromosome 10 loss (7+/10-), or TERT promoter mutations) will be diagnosed as glioblastomas (GBMs), while IDH-wildtype astrocytomas will not be included as a separate tumor type. However, IDHwt LGGs are a very heterogeneous group of tumors, and further investigation is warranted particularly in those without molecular features of glioblastoma. To elucidate the biology of IDHwt LGGs, we analyzed DNA methylation profile and survival time. Materials and Methods: Of the 724 adult-type diffuse glioma samples from a multi-institutional study, 64 IDHwt LGG, including 54 without any of molecular features of GBM and 10 with PDGFRA amplification or TERT promoter mutation, were examined using Infinium MethylationEPIC BeadChip. The raw data files (IDAT files) were analyzed by the web-based DNA methylation classifier provided by DKFZ (MolecularNeuropathology.org) or by R (Version 4.0.4) using the minfi

(1.34.0) and Rtsne (0.15) packages. [Result] Twenty-three out of 54 IDHwt LGGs matched known methylation classes using the DKFZ methylation classifier. In t-Distributed Stochastic Neighbor Embedding clustering analysis, 20 cases formed a cluster within the methylation class family glioblastoma, IDH-wildtype, mainly subclass RTK I ("GBM" cluster). Another 29 IDHwt LGGs formed an independent cluster ("LGG" cluster) separate from any of the existing reference groups near but not overlapping with several subtypes of pediatric-type lower grade gliomas. The "LGG" cluster cases had significantly longer overall survival than the "GBM" cluster cases. Discussion: Methylation profiling showed that IDHwt LGGs without molecular features of GBM were heterogeneous group of tumors. Our data suggested the presence of "true" IDHwt LGGs with intermediate prognosis.

Key words: glioma | IDH-wildtype | DNA methylome

MPC-2

CLINICAL COURSE AND PROGNOSIS OF LOWER-GRADE GLIOMA, IDH WILDTYPE AND PTERT MUTANT

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Background and Purpose: In the cIMPACT-Now update 3, it was proposed that grade 2 astrocytic gliomas without IDH-mutations and grade 3 astrocytic gliomas with TERT promoter mutations should be designated as diffuse IDH wildtype astrocytic glioma with molecular features of WHO grade IV glioblastoma. Therefore, we investigated whether this group of tumors actually corresponds to grade IV prognostically in cases that we encountered ourselves. Cases and Methods: Among the 65 patients having primary astrocytic glioma who were operated in our hospital from January 2016 to March 2021, the prognostic values of seven patients with lower-grade glioma, IDH wildtype, and pTERT mutant were investigated. Results: Among the seven patients, the median age was 59 years (50–66 years). Four of them had anaplastic astrocytoma, two had diffuse astrocytoma, and no tumor lesion could be identified upon histological examination for one patient. The male-to-female ratio was 1:6. MGMT methylation was observed in two patients (29%). The median survival was 20 months, with a significantly worse prognosis when compared with lower-grade glioma without the TERT promoter mutation (13 patients: median survival 40 months), but a better prognosis when compared with glioblastoma (45 patients: median survival 13 months) (Log-rank p = 0.0051). Conclusion: Although EGFR amplification, combined whole chromosome 7 gain, and whole chromosome 10 loss were not examined, the prognostic value of lower-grade glioma, IDH wildtype, and pTERT mutant was not as poor as that of glioblastoma. Further investigation is required to confirm whether these groups of tumors should be treated in the same way as grade IV glioblastoma.

Key words: lower grade glioma | TERT | prognosis

MPC-4

MALIGNANT TRANSFORMATION OF DIFFUSE LOW-GRADE GLIOMAS: SYSTEMATIC REVIEW AND META-ANALYSIS

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While malignant transformation of diffuse low-grade glioma (LGG) is a critical event affecting the patient survival, the incidence and related factors have been inconsistent in the literature. According to the PRISMA guideline, we systematically reviewed articles from 2009, meta-analyzed the incidence of malignant transformation and clarified factors related to the transformation. Forty-one articles were included in this study (n = 7122). We identified two definitions of malignant transformation: histologically proven (Htrans) and clinically defined (Ctrans). The malignant transformation rate curves in Htrans and Ctrans were almost in parallel when calculated from the results of meta-regression by the mean follow-up time. The true transformation rate was supposed to lie between the two curves, namely about 40% at the 10-year mean follow-up. Risk of malignant transformation was evaluated by the hazard ratio (HR). Pooled HRs were significantly higher in tumors with a larger pre- and postoperative tumor volume, lower degree of resection and notable preoperative contrast enhancement on magnetic resonance imaging than in others. Oligodendroglial histology and IDH mutation (IDHm) with 1p/19q codeletion (Codel) also significantly reduced the HRs. Using Kaplan-Meier curves from 8 studies with molecular data, we extracted data and calculated the 10-year malignant progression free survival (10yMPFS). The 10yMPFS in patients with IDHm without Codel was 30.4% (95% confidence interval (95%CI) [22.2–39.0]) in Htrans and 38.3% (95%CI [32.3–44.3]) in Ctrans, and that with IDHm with Codel was 71.7% (95%CI [61.7–79.5]) in Htrans and 62.5% (95%CI [55.9–68.5]) in Ctrans. The effect of adjuvant radiotherapy or chemotherapy could not be determined.

Key words: low-grade glioma | malignant transformation | 1p19q codeletion

MPC-5

CHARACTERISTICS OF H3 G34-MUTANT GLIOMAS

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Introduction: Diffuse hemispheric gliomas, H3 G34-mutant (DHG H3G34-mutant) are newly recognized infiltrating gliomas of the cerebral hemispheres of pediatric and young adult patients. We experienced 6 DHG H3G34-mutant cases. In this study, we describe the clinical, radiological and pathological characteristics of these cases. Result: Mean age at diagnosis was 16.8 years (range:10–26). Three patients were male. Among six cases, tumors located in cerebral cortex in five cases and multiple sites including basal ganglia and cortex in a case. All tumors showed no or only a faint contrast-enhancement and harbored restriction of diffusion. One patient underwent total resection, four underwent partial resection and one underwent biopsy. Pathological diagnosis were CNS embryonal tumors (n=3/6), glioblastoma, IDH-wildtype (n=2/6) and anaplastic astrocytoma, IDH-wildtype (n=1/5). All cases were negative for Olig2 and positive for GFAP in immunohistochemistry. Mean Ki-67 index was 38% (range: 10–60%). All cases revealed at least one of mitosis, necrosis or microvascular proliferation. Especially, mitosis was the most frequently found (n=5/6). The *H3F3A* mutations were G34R mutations in all cases. One case revealed a characteristic mutation pattern, therefore now we are performing further examination. Adjuvant chemoradiotherapies were performed for all cases. Mean progression free survival was 10.1 months (range: 1.6–33.1). Discussion: As published literatures reported, all cases exhibited restriction of diffusion and negative for Olig2. For a cerebral hemispheric tumor of pediatric or young adult patient which shows restriction of diffusion and no contrast-enhancement, and of which pathological findings is malignant and olig2 is negative, genetic analysis of *H3F3A* gene might be essential.

Key words: Glioma | H3 G34-mutant | Diffuse Hemispheric Glioma

MPC-6

CLINICAL SIGNIFICANCE OF WHOLE CHROMOSOMAL ABERRATION SIGNATURES IN NON-METASTATIC MEDULLOBLASTOMAS TREATED WITH 18GY OF CRANIOSPINAL IRRADIATION

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Background: One of the most significant challenges is a reduction in the dose of craniospinal irradiation (CSI) in patients with medulloblastoma to minimize neurological sequelae. However, a North American clinical trial failed to show the prognostic non-inferiority of lower-dose irradiation compared to that associated with standard-dose radiation therapy for non-metastatic medulloblastomas. A European retrospective study revealed that whole chromosomal aberration signatures (WCASs) are a potential prognostic factor in Group 3/4 medulloblastoma without metastasis, but whether the molecular signature has the same clinical impact in patients treated with lower-dose CSI remains unknown. Methods: We conducted DNA methylation analysis using an Illumina Infinium Human Methylation EPIC BeadChip array