MPC-05
TUMOR RELATED EPILEPSY AND IDH MUTATIONS IN GLIOMAS
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OBJECTIVE: Tumor related epilepsy (TRE) is an important complication in the treatment of brain tumors. In recent studies, it is assumed that isocitrate dehydrogenase (IDH) mutations are a risk factor with TRE. In the present study, we examined the association between IDH mutations and TRE in our cases.

METHODS: 115 patients who had a supratentorial glioma were treated in our hospital from February 2009 to November 2018 were retrospec-tively assessed for IDH mutations and TRE. RESULTS: 31 patients were the IDH mutant group (16 females, mean age 43.7±12.9 years, mean follow-up time 44.0 months). 77 patients were the IDH wild group (35 females, mean age 61.6±16.6 years, mean follow-up time 18.1 months).

Compared to the IDH wild group, the IDH mutant group was significantly younger and mean follow-up time was longer. There was no difference in the postoperative radiation and chemotherapy in both groups. The incidence of seizures as presenting symptom was 20 patients (32.6%) in the IDH mutant group and 16 patients (20.8%) in the IDH wild group, and was significantly higher in the IDH mutant group (p=0.03). 27 patients (71.1%) in the IDH mutant group had TRE at least once during follow-up time and 39 patients (50.0%) in the IDH wild group (p=0.06). In addition, the median OS for the group with seizure onset (36 patients) was 69.2 months and the group with the other onset forms (79 patients) was 22.4 months. The seizure onset group had a significantly better prognosis (p<0.05).

CONCLUSION: Gliomas with IDH mutations have a higher incidence of TRE. Although IDH mutations are considered to be a risk factor for TRE, which is consistent with previous studies, but it is suggested that differences in survival may have an effect on the incidence of TRE.

MPC-06
LRG1 HAS MULTIPLE POTENTIAL FOR CLINICOPATHOLOGICAL BIOMARKER OF GlioBLASTOMA
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BACKGROUND AND AIM: Leucine-rich α-2 glycoprotein 1 (LRG1) is one of the candidate proteins as a diagnostic marker for glioblastoma. Although association with angiogenesis has been reported, it has been suggested that the role as a biomarker differs depending on the tumor types. The role of LRG1 as a biomarker in glioblastoma was examined clinicopathologically. METHODS: Tumors of 156 cases diagnosed as diffuse glioma (27 astrocytomas, 15 oligodendrogliomas, 114 glioblastomas) according to WHO 2016 classification at Kurume University from January 2001 to April 2019 were used. The immunohistochemical intensity was classified into 4 categories (0: no expression, 1: very weak, 2: weak, 3: moderate, 4: strong). RESULTS: 114 patients showed high expression of LRG1. Patients with high expression had significantly lower median OS (20.1 months) than those with low expression (25.7 months, p=0.01). CONCLUSION: LRG1 demonstrated multiple potential as diagnostic, prognostic, and regional biomarker for glioblastoma.

MPC-07
MECHANISMS OF BETTER PROGNOSIS IN IDH-MUTATED ASTROCYTOMA WITH 19Q-LOSS
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We previously reported that there was a subgroup of IDH-mutated astrocytomas harboring only 19q-loss showing oligodendroglioma-like morphology and survival advantage compared with 19q-intact astrocytomas (Otani et al. Cancer Sci 2018). The purpose of the present study was to reveal how 19q-loss contributed to better prognosis and the morphology in the subgroup. We compared expression pattern between five 19q-loss and five 19q-intact IDH-mutant astrocytomas by mRNA sequencing.

136 up-regulated genes and 203 down-regulated genes were extracted in 19q-loss astrocytomas compared with 19q-intact astrocytomas. Significantly changed genes distributed throughout all chromosomes, but more down-regulated genes were on 19q and 4p, and more up-regulated genes were on 4q.

Genes associated with apoptosis, cell adhesion, and antigen presentation were up-regulated, and genes associated with Ras signaling pathway were down-regulated. These changes could result in better prognosis. By contrast, there was no expression change related gene associated with oligodendroglioma-like morphology although up-regulation of genes associated with axon guidance and down-regulation of genes associated with cell shape might result in the morphology or neuronal differentiation. Expression pattern of 19q-loss astrocytomas indicated no tendency of oligodendroglional differentiation.

Better prognosis of 19q-loss astrocytomas was derived from expression changes associated with tumor proliferation and tumor immunity.

MPC-08
CLINICOPATHOLOGICAL ANALYSIS OF 12p GAIN IN INTRACRANIAL GERM CELL TUMORS
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BACKGROUND: Gain of short arm of chromosome 12 (12p) is commonly observed in testicular germ cell tumors (gCTs). 12p gain is frequently seen in intracranial GCTs (iGCTs). However, little is known about the clinical significance of 12p gain in iGCTs. MATERIALS AND METHODS: We have collected over 200 fresh frozen tissue samples of GCTs through the Intracranial Germ Cell Tumor Genome Analysis Consortium in Japan. Firstly, we analyzed DNA methylation status in 83 iGCTs, 3 seminomas and 6 normal control samples using Infinium Human Methylation 450K BeadChip array (Illumina, CA). Idat files were processed using R (Version 3.5.3) and minfi package (1.30.0) to generate copy number variations. Compared with average genome-wide copy number level, 12p gain was determined. Then, we analyzed clinicalopathological information were analyzed for progression-free survival (PFS) and overall survival (OS). Those tumors that consist of only either germinoma or mature teratoma components were classified as Favorable Histology (FH) and all the others that contain malignant histological components were classified as Unfavorable Histology (UH). RESULT: 12p gain was observed in 100% (3/3) of seminoma, 13.6% (3/22) of germinomas, 16.7% (16/97) of immature teratoma, 25% (1/4) of immature teratoma, 55% (11/20) of mixed germ cell tumor, 100% (4/4) of yolk sac tumor, 100% (1/1) of embryonal carcinoma, and 100% (1/1) of chorioncarcinoma. In total, 44.6% (37/83) of 6CT showed 12p gain. Regarding histological classification, the 12p gain rate in UH (72%, 18/25) was significantly higher than that in FH (12.1%, 4/33, P=0.01). Both PFS and OS were significantly worse in iGCTs with 12p gain (PFS: P=0.027, OS: P=0.0012). DISCUSSION: 12p gain can be a molecular marker to predict prognosis and histological malignancy in iGCTs.

MPC-09
THE OPTIMIZATION OF TREATMENTS FOR SO-CALLED PRIMITIVE NEUROECTODERMAL TUMORS WITH MOLECULAR ANALYSIS
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INTRODUCTION: In the previous WHO classification of central nervous tumors, the supratentorial tumors comprise small round blue cells with aggressive clinical features had been defined as primitive neuroectodermal tumor (PNET). Recent molecular analysis revealed that they do not belong to a single entity, but they are re-classified as the tumors of other well-defined subtypes and newly defined tumor groups were referred to the new classifications. While, there are few studies those showed the
Abstracts

re-consideration of treatments for tumors diagnosed as so-called PNET. In this study, we propose the optimization of treatments for tumors diagnosed by the new classification to clarify which treatments were effective for the tumors those were diagnosed as PNET. MATERIALS AND METHODS: The tumor samples diagnosed as so-called PNETs were analyzed. The molecular information was extracted from tumor specimens. We used high throughput analysis with microarray, FISH, and immunohistochemistry. They all had treated in our institution in last 6 years and their clinical courses were followed by medical records. Informed parental consent was obtained from their guardians and this study was approved by the institutional review board of Juntendo University. RESULTS: Nine tumor samples were able to be analyzed and they were re-classified into high-grade gliomas, anaplastic astrocytomas, sarcoma, embryonal tumors with multilayered rosettes, C19MC altered (ETMR). They resembled each other closely in morphology, and therefore, it was not able to be classified by histopathological findings. There was a case of pineoblastoma, whose molecular background suggested that the tumor was re-classified into neuroblastoma. In terms of treatments, we have succeeded in neuroblastoma cases so far, ETMRs were required multiple surgeries and radiations to maintain remissions. CONCLUSIONS: Re-classification of diagnosis based on the molecular background is necessary to clarify the optimization of treatments for pediatric brain tumors, and the comprehensive methods is required. We present our methods for molecular diagnosis in clinical field and future plans.

MPC-11

IDH1/2 MUTATION ASSOCIATED WITH SEIZURE ONSET AND VETEY IMAGING IN PATIENTS WITH DIFFUSE GLIOMA VISUALIZING 2-HYDROXYGLUTARATE BY MASS SPECTRUM
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BACKGROUND: Mutations in isocitrate dehydrogenase 1 or 2 genes (IDH1/2) frequently occur in lower-grade gliomas. Mutant IDH1/2 proteins gain a new ability to produce 2-hydroxyglutarate (2HG). IDH1/2 mutation has been related to be related with seizure through the structural similarity of 2HG to glutamate. We, therefore, sought to investigate the relationship between seizure and IDH1/2 mutations and to visualize tissue 2HG distribution in patients with diffuse gliomas. METHODS: We assessed 149 patients with diffuse glioma, and measured tissue 2HG concentrations in 104 patients by using liquid chromatography-tandem mass spectrometry. The matrix-assisted laser desorption/ionization high resolution mass spectrometry imaging (MALDI-HR MSI) was used to visualize tissue 2HG distribution for 12 tissue samples. RESULTS: Seizure onset was observed in 34 among 56 (60.7%) patients with IDH1/2 mutant tumor, whereas in 18 among 93 (19.4%) patients with IDH1/2 wild-type tumor (<0.0001). The tissue 2HG concentration was significantly higher in IDH1/2 mutant tumor than in IDH1/2 wild-type tumor (median: 4862 ng/mg vs 73 ng/mg p<0.0001). Multivariate analysis, including tissue 2HG concentration, IDH1/2 status, histology, grade, and location, showed that IDH1/2 mutations were significantly correlated with seizure onset. The MALDI-HR MSI showed that 2HG spread in various concentration independent of cellularity and it also was spread in cancerous tissue in IDH1/2 mutant tumor tissues. CONCLUSIONS: We demonstrated the association between IDH1/2 mutations and seizure, and the heterogeneous 2HG distribution not only in cellular area but also in extracellular space. These findings suggest the potential role of 2HG as an intercellular mediator to tumor environment, resulting in epileptogenesis formation.

MPC-12

ACCURACY OF INTRAOPERATIVE SIMPLE FLOW CYTOMETER FOR HIGH GRADE GLIOMA OPERATION COMPARED WITH INTRAOPERATIVE FROZEN DIAGNOSIS.
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INTRODUCTION: Intraoperative simple flow cytometer (iFC) was developed in recently, we examined the correlation intraoperative frozen diagnosis (IOFD) and iFC. METHOD AND MATERIAL: Total 33 cases of high grade glioma patients underwent operation in April 2017 ~ May 2019, and IOFD and iFC were compared to iFC. Sample of iFC were retrieved just same patients were underwent operation in April 2017 ~ May 2019, and IOFD to iFC. METHOD AND MATERIAL: Total 33 cases of high grade glioma patients underwent operation in April 2017 ~ May 2019, and IOFD to iFC. RESULTS: Accuracy rate of iFC and IOFD was high grade glioma was 84% and 85%, and the concordance rate of grading was17.2%. Correlation coefficients between MB1 and iFC of IOFD was r=0.5019 P=0.0065. Accuracy rate of IOFD was 46.8%, and concordance rate of grading was 35.5%. Correlation coefficients between MB1 and iFC of IOFD was r=0.5899 P=0.0001. CONCLUSIONS: Although iFC accuracy rates abnormality of IOFD and IOFM were high, iFC concordance rates and grade were low. Correlation between MB1 and iFC of IOFM was better than that of IOFD. Probably, iFC of IOFD was a little difficult because of sample heterozygosity.

MPC-14

BRAF V600E MUTANT OLIGODENDROGLIOMA-LIKE TUMORS WITH CHROMOSOMAL INSTABILITY IN ADOLESCENTS AND YOUNG ADULTS.
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We performed genome-wide methylation analysis on 136 pediatric low grade glioma cases, identifying a unique molecular signature of oligodendroglialike BRAF V600E mutant tumors with Recurrent gain of Chromosome 7 and loss of Chromosome 10 (OLIVER). Hierarchical clustering and stochastic neighbor embedding analyses cluster them with previously described pediatric-type low grade gliomas, separate from adult gliomas. OLIVERS exhibit distinct clinical behavior as temporal lobe lesions in adolescents and young adults, prolonged history of seizures and all are alive with no recurrence (follow-up 3.2 to 13.2 years). Morphologically, all showed oligodendrogloma-like features, including round nuclei, hypercellular halos, a chicken-wire pattern of branching capillaries and microcalcification. None showed astrocytic features or characteristics suggestive of high-grade tumors including necrosis or mitotic figures. All tumors harbored multiple chromosomal copy number abnormalities (more than 10 chromosomes per OLIVER), but none showed 1p/19q co-deletion or IDH1 mutation. Interestingly, one tumor showed a TERT promoter mutation. Although the series is small, OLIVER may represent a new category of IDH wild-type low grade glioma which may be confused with molecular GBM. Further, they highlight the heterogeneity of IDH wild-type gliomas and the relatively indolent behavior of pediatric-type gliomas.

MPC-15

FEASIBILITY OF GLIOMA SPECIFIC ONCOPANEL IN THE DIAGNOSIS OF GLIOMA
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AIM: Molecular classification of glioma is a mandatory in the diagnosis of glioma according to the WHO 2016 classification of tumors of the central nervous system. However, WHO does not indicate the molecular methodology to be integrated, and the versatility and cost-effectiveness of molecular diagnosis is a concern. In this study, we evaluate the feasibility of a glioma specific tailored NGS panel where driver gene mutation and copy number alterations can be precisely characterized, thus 1p/19q co-deletion can also be evaluated. We have analyzed 106 glioma patients (Grade II: 19 cases, Grade III: 23 cases, Grade IV: 64 cases) using this system.

RESULTS: From these 106 cases, IDH1 and TERT promoter mutations were detected in 33 cases (28%) and 55 cases (52%), respectively. 1p/19q co-deletion was detected in 19 cases (18%), with IDH1 mutations in all cases. In 57 Grade IV cases, TP53, PTEN, RB1, NF1, PDGFRA mutations were detected in 25 cases (43%), 24 cases (41%), 10 cases (17%), 8 cases (14%) and 6 cases (10%). Although EGFR mutation frequency was low (3%), amplification was detected in 14 cases (24%). As for deletion, PTEN and CDKN2A loci were deleted in 36 cases (62%) and 30 cases (52%), respectively. To note, MET alterations were detected in 2 cases. The cases in which histopathological diagnosis is difficult to make have a tendency to show atypical genetic alterations.

CONCLUSION: Diagnosis of glioma patients with this glioma-specific tailored NGS panel is feasible.

MPC-16

RAPID PROGRESSIVE SPINAL DIFFUSE MIDDLE LINE GLIOMA, A CASE REPORT
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INTRODUCTION: Intraoperative simple flow cytometer (iFC) was developed in recently, we examined the correlation intraoperative frozen diagnosis (IOFD) and iFC. METHOD AND MATERIAL: Total 33 cases of high grade glioma patients underwent operation in April 2017 ~ May 2019, and IOFD and iFC were compared to iFC. Sample of iFC were retrieved just same patients were underwent operation in April 2017 ~ May 2019, and IOFD to iFC. RESULTS: Accuracy rate of iFC and IOFD was high grade glioma was 84% and 85%, and the concordance rate of grading was17.2%. Correlation coefficients between MB1 and iFC of IOFD was r=0.5019 P=0.0065. Accuracy rate of IOFD was 46.8%, and concordance rate of grading was 35.5%. Correlation coefficients between MB1 and iFC of IOFD was r=0.5899 P=0.0001. CONCLUSIONS: Although iFC accuracy rates abnormality of IOFD and IOFM were high, iFC concordance rates and grade were low. Correlation between MB1 and iFC of IOFM was better than that of IOFD. Probably, iFC of IOFD was a little difficult because of sample heterozygosity.