Molecular pathology/classification (MPC)

MPC-01

PROGNOSTIC ROLE OF TERT PROMOTER IMPROVES THE STRATIFICATION OF IDH-MUTATED LOWER GRADE GLIOMA.

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TERT promoter mutation is associated with favorable prognosis and 1p/19q codelletion in IDH-mutated gliomas. The current diagnostic system, however, did not incorporate this change as a diagnostic marker in this entity. We investigated the value of prognostication incorporating TERT using the Japanese original cohort of 560 IDH-mutated adult gliomas. We collected the information of molecular status of IDH, TERT and 1p/19q and patient clinical data including KPS score, age, and sex. TERT codelletion and 1p/19q codelletion were found in 303 and 285 cases, respectively. For the purpose of this study, the patient cohort was divided into four groups by a combination of 1p/19q and TERT status, and the characteristics of 1p/19q intact-TERT mutated group (Astro-TERT group) (n=24) were dissected in light of the differences comparing with 1p/19q intact-TERT wild (Astro-group, n=251) or 1p/19q codelleted-TERT mutated (Oligo-group, n=279) cases. Astro-TERT group with any grade showed intermediate overall survival between the Oligo-group and Astro-group although the survival differences were not statistically significant (median OS: not reached (NR) versus NR, and 106 months, respectively, p<0.05). In grade II-III gliomas, the survival curve of the Astro-TERT group overlapped with that of the Oligo-group while the Astro-TERT group showed short survival as well and TERT codelletion 1p/19q were oncogene driver as a target of drug treatment. In conclusion, TERT promoter mutation provides the additional information for prognostication at least in grade II-III gliomas in the current diagnostic system.

MPC-02

REVIEW OF MEDULLOBLASTOMA FOR THE ASSESSMENT OF CONSENSUS IN PATHOLOGICAL DIAGNOSIS USING JPMMG CASES.

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Medulloblastoma (MB) is now classified by WHO 2016 classification as “genetically defined” and “histologically defined” variants. The aim of this study is to search for consensus on pathological diagnosis and assess the correlation between the central pathological diagnosis and the molecular subgrouping. We performed the pathological and molecular analyses in a total of 176 JPMNG (The Japan Pediatric Molecular Neuro-Oncology Group) cases. The diagnosis of MB was made by three expert neuropathologists (AS, JH, and TH) without knowledge of the molecular data. Subgroup affiliation was determined by expression profiling of 22 medulloblastoma subgroup-specific genes using the nanomodr RNA-Counter system. Histologically, classic MB accounted for approximately 80% of all MB cases. Genetic analyses of 176 cases revealed four distinct molecular subgroups: WNT (14%), SHH (27%), group 3 (16%), and group 4 (43%). The central review reached a diagnosis of ATD in ten cases. Immunohistochemical, WNT MBs showed nuclear accumulation of β-catenin protein, but the immunoreactivity was patchy in approximately one-quarter of WNT cases. GAB1 often exhibited little or no reactivity in the SHH subgroup. No reliable staining was observed for YAP1. All MB (16 cases) or MB-like cases (2 cases) were defined as SHH tumors. All MB (16 cases) in infants (<3 years of age), and genetically subdivided into SHH-TP53 wild-type tumors. Variable degrees of anaplasia, including LCA MB, occur across the genetic subgroups, and the LCA MB WNT type was rare (2/24+8.3%) among WNT subgroups. This study demonstrated that the combination of morphological and molecular analyses can precisely diagnose MB. More robust, surrogate markers should be developed as an ancillary diagnostic testing for subgroup classification. Further exploration of the clinical significance of the variable degree of LCA histology and some subtypes (i.e. LCA, WNT) will be necessary for risk stratification.

MPC-03

IMMUNOHISTOCHEMICAL ANALYSIS OF TUMOR ASSOCIATED MACROPHAGE INDUCED AFTER BIODEGRADABLE CARMUSTINE WAFER IMPLANTATION IN HUMAN GLIOBLASTOMA.

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The carmustine (BCNU) wafer, a biodegradable polymer, is currently the only drug that is able to be placed at the surgical site to treat malignant tumors. Biomaterials to treat cancers holds therapeutic potential; however, how they behave inside the tumor microenvironment requires further study. We previously investigated the tumor microenvironment after BCNU wafer implantation, and found that CD68-positive macrophages was significantly introduced around the wafer (Shihabara et al. J Neurooncol 2018). Recent studies demonstrated the importance of tumor-associated macrophage (TAM). However, we could not clarify whether the increased macrophage around the wafer was pro-tumor or anti-tumor phenotype. In the present study, we immunohistochemically examined expressions of CD68, IBA1, CD163, TMEM119, BIN1, CD31, and VEGF to investigate TAM after the BCNU wafer implantation. Quantitative evaluation revealed that CD68-positive cells were significantly increased (P = 0.0009), whereas TMEM119-positive cells were significantly decreased (P = 0.0081) after wafer implantation compared to tissue from cases without wafer implantation. CD163, a known marker of poor prognosis in glioblastoma, did not differ with and without wafer implantation. Among the other markers, BCNU wafer induced tumor TAM, but reduced microglial marker, TMEM119. In addition to the aspect of chemotherapy, BCNU wafer may have potential to modify the tumor microenvironment such as TAM.

MPC-04

MOLECULAR FEATURES AND CLINICAL OUTCOMES OF ELDERLY GLOBLASTOMA PATIENTS: ANALYSES OF KANSAI NETWORK AND TCGA COHORTS.

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INTRODUCTION: Aging is a negative prognostic factor in glioblastoma (GB) and the genetic background in clinical outcome of elderly GB could exist. This study investigates the difference of elderly patients from younger ones regarding molecular characteristics as well as clinical outcomes in IDH-wildtype GB. METHODS: We collected adult cases diagnosed with IDH-wildtype GB and enrolled in Kansai Molecular Diagnosis Network for CNS Tumors (Kansai Network) (212 cases) and The Cancer Genome Atlas (TCGA) project (359 cases). Clinical and pathological characteristics were analyzed retrospectively and between elderly (≤70 years) and younger ones (≤50 years). Molecular analysis included copy number alterations (CNAs) of eight genes (EGFR, PDGFRA, PTEN, CDKN2A, CDK4, MDM2, TP53, NF1/2). RESULTS: Included in the study were 92 cases.
TUMORRELATED 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 concerned with TRE in gliomas. To examine the relationship between IDH mutations and TRE in our cases.

METHODS: 115 patients who had a supratentorial glioma and were treated in our hospital from February 2009 to November 2018 were retrospectively assessed for IDH mutations and TRE. RESULTS: 54 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.

LRG1 HAS MULTIPLE POTENTIAL FOR CLINICOPATHOLOGICAL BIOMARKER OF GLOBLASTOMA

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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 2009 to 2018 were collected. The expression pattern was evaluated by IHC at cancers of WHO grade II–IV. Immunohistochemical intensity of LRG1 was evaluated by using the H-score. IHC-stained hilar was divided in two groups: score 0–1 was defined as low expression and score 2–3 was defined as high expression. Mutations of IDH1/2 and TERT promoter were analyzed by Sanger method. In glioblastoma, the relationship between LRG1 expression and clinical parameters such as age, preoperative Karnofsky Performance Scale, tumor location, extent of resection, MGMT promoter, and prognosis were examined. RESULTS: LRG1 high expression rate was 41.2% (47/114) in glioblastoma, 2.0% (2/105) in astrocytoma, 20.0% (3/15) in oligodendroglioma, and 0.0% (0/6) in anaplastic astrocytoma. The observed significant high expression level of LRG1 corresponded to lower-grade glioma (p=0.0003). Expression of LRG1 was an independent favorable prognostic factor (HR: 0.41, 95% CI 0.18–0.86, p=0.019) in IDH-wildtype glioblastoma, and correlated with gross total resection (p=0.002) and the tumor location of the non-subventricular zone (SVZ) (p=0.00007). CONCLUSION: LRG1 demonstrated multiple potential as diagnostic, prognostic, and regional biomarker for glioblastoma.

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 in significantly longer overall survival (OS) 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 four 19q-intact IDH-mutated astrocytomas by immunohistochemistry.

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 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 oligodendrogial differentiation.

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

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 (tGCTs). 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 iGCTs 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 Infinnium Human Methylation 450K BeadChip array (Illumina, CA). Idat files were processed using R (Version 3.5.3) and minfi package (1.3.0) to generate copy number variations. Compared with average genome-wide copy number level, 12p gain was determined. Then, we examined 12p gain with clinicopathological information were analyzed for progression-free survival (PFS) and overall survival (OS). Those tumors that consist of only other germ cell and/or mature teratoma components were classified as Favorable Histology (FH) and all the others that contains malignant histological components were classified as Unfavorable Histology (UH). RESULTS: 12p gain was observed in 100% (3/3) of seminoma, 13.6% (3/22) of germinoma, 16.7% (5/30) of yolk sac tumor, 25% (1/4) of embryonal carcinoma, and 25% (5/20) of mixed germ cell tumor. 12p gain was also frequently seen in testicular germ cell tumors (tGCTs). 12p gain is also observed in 100% (3/3) of seminoma, 13.6% (3/22) of germinoma, and 16.7% (5/30) of yolk sac tumor. 12p gain was significantly higher in FH (72%, 18/25) than that in UH (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.