Title

PATH-30. CLINICAL AND GENETIC CHARACTERISTICS OF HISTONE H3 K27M-MUTANT DIFFUSE MIDLINE GLIOMAS IN ADULTS

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8 others. Glioblastoma (n=115) predominated, followed by grade II-III astrocytoma (n=31), pleomorphic xanthoastrocytoma (n=18), pilocytic astrocytoma (n=12), oligodendroglioma (n=7), or other glioma (n=15). Class I mutations (*BRAFV600E*) comprised 49% (n=97), class II mutations 4.5% (n=9) and class III mutations 4.5% (n=9). Rearrangements occurred in 9.6% (n=19), of which canonical fusions comprised 4% (n=8), occurring primarily in pilocytic astrocytomas; copy number gains affected 13% (n=26), and other alterations 19% (n=38). All pleomorphic xanthoastrocytomas and 43.5% of glioblastoma harbored *BRAFV600E*. Mutation of *NF1*, an inhibitor of RAS/ERK signaling, was significantly associated with class II/III *BRAF* mutations (64.3%) and not observed in *BRAFV600E*-altered glioma (0%, n=62; p< 0.0001). *BRAFV600E* was the sole alteration in a subset of glioma with class I mutations, while others harbored multiple genomic alterations. Among 45 patients with glioblastoma and detailed clinicopathologic data, 7 received RAF-targeted therapy, with variable clinical response. Overall survival was 26 months with *BRAFV600E*, 21 months with class II/III mutation, and 33 months with other *BRAF*-alteration. CONCLUSIONS: This large cohort of *BRAF*-altered adult glioma demonstrates a broad range of alterations, with implications for treatment sensitivity and patient survival.

PATH-27. CLINICAL, RADIOLOGIC AND PROGNOSTIC PROFILE OF IDH WILD TYPE DIFFUSE ASTROCYTOMA WITH MOLECULAR FEATURES OF GLIOBLASTOMA

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BACKGROUND: cIMPACT-NOW-3 recommends that IDH-wildtype diffuse astrocytic glioma Grade II or III with EGFR amplification, or combined whole chromosome 7 gain and whole chromosome 10 loss, or TERT promoter mutation should receive an integrated classification: Diffuse astrocytic glioma, IDH-wildtype with molecular features of glioblastoma, WHO grade IV. The aims of this study were: Outline the features of a cohort of patients with molecular glioblastoma according to the above criteria; Assess clinical and molecular factors that may inform prognosis; Determine if cIMPACT-NOW-3 recommendation changed clinical practice and clinical trial enrolment. METHODS: 61 patients diagnosed with IDH-wildtype diffuse astrocytic glioma Grade II or III and EGFR amp or mTERT or chromosome (+7/-10) between 2011 and 2019 at MGH were included in this single center retrospective cohort study. Data collected: sex, age, extent of surgery, functional status, histological grade, molecular diagnostics and treatment. Progression was defined using RANO criteria, progression was quantified in terms of months from the initial surgery. Survival was defined in terms of months from initial surgery to date of death or last known visit. RESULTS: mOS was 16 months, mPFS was 9 months. 14 patients (23%) survived > 24 months, 7 ≥ 36 months (mOS 32 months; 9 deceased). The probability of survival in patients with markedly enhancing tumors was 0.5 at 3 months versus 0.5 at 11 months in non-enhancing tumors. The probability of survival in patients who underwent biopsy only was 0.5 at 5 months compared to 0.5 at 12 months in patients with maximally resected tumors. 1 patient was enrolled in a clinical trial at diagnosis. 6 were enrolled at time of recurrence. CONCLUSIONS: mOS and pFS in the deceased patients was comparable to historical data on survival in IDH wildtype glioblastomas. Inclusion criteria in clinical trials have not reflected the cIMPACT-NOW-3 recommendation so far.

PATH-28. EXTENT AND PROGNOSTIC VALUE OF MGMT PROMOTOR METHYLATION DEPEND ON IDH MUTATION AND 1P19Q CO-DELETION IN GLIOMA WHO GRADE II

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INTRODUCTION: Methylation of the promotor region of the O6-methylguanin-DNA-methyltransferase (MGMT) gene is associated with increased survival in low- and high-grade glioma. It is unknown whether this association also applies to the 2016 WHO categories of glioma WHO grade II. MATERIAL AND METHODS: We retrospectively searched the institutional database of the Center for Neuro-Oncology for patients with glioma WHO grade II. Patients were assigned to one of three groups according to the 2016 WHO classification system: 1. 1p19q co-deleted oligodendroglioma, IDH mutant; 2. 1p19q non-codeleted astrocytoma, IDH mutant; 3. 1p19q non-codeleted astrocytoma, IDH wild-type. MGMT methylation status was analysed using Sanger sequencing of the CpG sites 74-98 within the MGMT promotor region. The total number of methylated CpG sites was calculated for each patient. RESULTS: 155 patients with glioma WHO grade II were encountered, including 81 1p19q co-deleted, IDH mutant oligodendrogliomas; 54 IDH mutant astrocytomas; and 20 IDH wild-type astrocytomas. The mean number of methylated CpG sites among oligodendrogliomas was significantly higher when compared to IDH mutant astrocytomas (18.9 ± 0.4 vs. 16.3 ± 0.6; p = 0.001). In turn, the number of methylated CpG sites among IDH mutant astrocytomas was higher when compared to IDH wild-type astrocytomas (16.3 ± 0.6 vs. 12.3 ± 1.9; p = 0.007). Median follow-up was estimated at 35 months. Median time to malignant progression was 87 months for all patients, and median overall survival was not reached. In the entire cohort, a larger number of methylated CpG sites was prognostic of overall survival and time to malignant progression. When analysed separately for the three WHO subgroups, a similar association was only retained in IDH wild-type astrocytoma. CONCLUSION: In our series of WHO II gliomas, MGMT promotor methylation appeared strongly associated with 1p19q codeletion and IDH mutations. MGMT promotor methylation was only prognostic in IDH wild-type astrocytoma.

PATH-29. COMPARATIVE ANALYSIS OF DNA METHYLATION PROFILES ASSOCIATED WITH IDH-WILDTYPE GLIOMA AND GLIONEURONAL TUMOR SUBTYPES

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DNA Methylation profiles are highly robust and reproducible as a classification tool. Less is understood regarding the methylation differences that exist among gliomas and glioneuronal tumors. To address this, we analyzed differentially methylated probes (DMPs) of gliomas and glioneuronal tumors compared to normal brain white matter controls. After filtering (Δbeta >0.3, logFC >±1) of significant probes we observed that low grade glioma/glioneuronal tumors (LGGs) had significantly fewer DMPs (Hyper/Hypo) as compared to GBMs. For example, posterior fossa pilocytic astrocytomas (PA's) showed 2861 DMPs (1916 hypo/945 hyper) versus 9653 for GBM-RTKI ((6563/3090) respectively, while tumors such as PXA and anaplastic PA showed intermediate changes between LGG's and GBMs. Hypomethylated and hypermethylated probes were analyzed for gene ontology and KEGG pathway enrichment, with LGG subtypes showing hypomethylated probes/genes associated with cell adhesion, blood vessel development and viral infection (P-value = 10^{-7}). In contrast, hypomethylated probes in GBM subtypes were enriched for plasma membrane and cell periphery gene ontologies (P-value = 10^{-52}). With respect to hypermethylated probes, LGG subtypes showed enrichment for myelination, glial cell differentiation and sphingolipid metabolism (P-value = 10^{-5}) while DNA-binding transcription factor activity was seen in GBM subtypes (P-value=10^{-35}). Examples of the most significantly hypermethylated genes in GBM included the transcription factors, GATA3 and PAX9. Intermediate-grade gliomas such as anaplastic PA and PXA showed enrichment of hypermethylated genes similar to GBM, but of lower significance (P-values = 10^{-6} and 10^{-4}). Overall, understanding of cancer-associated DNA methylation changes in glioma subtypes suggests a hierarchy of biological changes that may underlie the pathogenesis of these tumors and interestingly, highlight tumor types such as PXA and anaplastic PA as having intermediate methylation changes, between benign LGG and GBM. Hypermethylation of transcription-factor genes will be investigated in GBM and compared with changes in gene expression to understand possible roles in the pathogenesis.

PATH-30. CLINICAL AND GENETIC CHARACTERISTICS OF HISTONE H3 K27M-MUTANT DIFFUSE MIDLINE GLIOMAS IN ADULTS

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BACKGROUND: "Diffuse midline glioma, H3 K27M-mutant" is a new tumor entity established in the 2016 WHO Classification of Tumors of the CNS that comprises a set of diffuse gliomas arising in midline structures that is molecularly defined by a recurrent K27M mutation in genes encoding the histone 3 variants H3.3 or H3.1. While this tumor entity is associated with poor prognosis in children, clinical experience in adults re-

mains limited. Given the more frequent origin in the thalamus or spinal cord in adults versus the brainstem in children, gliomas with this mutation may encompass a heterogeneous population of tumor subtypes that vary based on patient age, anatomic site of origin, and concurrent genetic alterations. METHODS: The 60 patients included were 18 years or older at initial diagnosis, during the period of 2014-2019 at UCSF. Cases were identified using immunohistochemistry with a H3 K27M-mutant specific antibody and/or next-generation sequencing of histone 3 genes *H3F3A*, *HIST1H3B* and *HIST1H3C*. Targeted NGS was performed on tumors from 21 patients, utilizing an UCSF institutional panel or a variety of commercial sources. RESULTS: Patients presented primarily in the 3rd decade of life, and 57% of tumors were located in the thalamus. Genomic profiling revealed p.K27M mutations exclusively in *H3F3A* and an absence of mutations in *HIST1H3B* or *HIST1H3C*, which are present in approximately one-third of pediatric diffuse midline gliomas. Additionally, these adult H3 K27M-mutant diffuse midline gliomas are universally IDH-wildtype, and have frequent mutations in *TP53*, *PPM1D*, *FGFR1*, *NF1*, and *ATRX*. The overall survival of this adult cohort is longer than historical averages for both H3 K27M-mutant diffuse midline glioma in children and IDH-wildtype glioblastomas in adults. CONCLUSIONS: Together, these findings indicate that H3 K27M-mutant diffuse midline glioma represents a heterogeneous disease with regard to outcomes, sites of origin, and molecular pathogenesis in children versus adults.

PATH-31. ARTIFICIAL INTELLIGENCE IN GLIOMA PATHOLOGY IMAGE ANALYSIS FOR RISK PREDICTION

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Pathological evaluation of tumor tissue images stained with hematoxylin and eosin (H&E) is pivotal in diagnosis and predictive of outcome, yet only a small fraction of the rich phenotypic information on the slide is currently used for clinical care. In this study, we developed a computational approach based on deep learning to predict overall survival within distinct molecular subtypes of glioma patients and to extract prognostic biomarkers from microscopic images of tissue biopsies. Whole-slide images from 766 unique patients [IDH: 336 IDH-wildtype, 364 IDH-mutant, 1p/19q: 142 1p/19q-codeleted, 620 1p/19q-non-codeleted] were obtained from The Cancer Genome Atlas (TCGA). Sub-images that were free of artifacts and that contained viable tumor with descriptive histologic characteristics were extracted, which were used for training and testing the deep neural-network. Our unified survival deep learning framework (SDL) uses a residual CNN network integrated with a traditional survival model to predict patient risk from digitized whole-slide images. We employed statistical sampling techniques and randomized transformation of images to address challenges in learning from histology images. Univariable and multivariable Cox proportional-hazards regression models were used to evaluate the significance of predicted patient risk with and without controlling for known prognostic factors. The integrated SDL framework showed substantial prognostic power achieving a median c-index of 0.79 [95 % CI 0.77 - 0.81]. In multivariable Cox regression analysis, SDL risk was significantly associated with overall survival (hazard ratio of 1.65, 95% CI 1.49-1.83, $p < 0.001$) after adjusting for age, grade, IDH status, ATRX status, 1p19q codeletion and CDKN2A/2B status. Only IDH-status and age were also significant in the multivariable model. Preliminary findings highlight the emerging role of AI in precision medicine and suggest the utility for computational analysis of tumor tissue images for objective and accurate prediction of outcome for glioma patients and also for risk stratification for targeted clinical therapy.

PATH-32. CLINICAL AND MUTATIONAL PROFILES OF ADULT MEDULLOBLASTOMA GROUPS

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INTRODUCTION: Adult medulloblastomas are clinically and molecularly understudied due to their rarity. METHODS: We studied a cohort of 101 adult medulloblastomas grouped by Nanostring assay. We performed targeted sequencing on exonic regions of 69 genes implicated in medulloblastoma, and Sanger sequencing for TERT promoter hotspot mutations. RESULTS: Median age was 27 (range 19-63), and 9.5% were metastatic at diagnosis. SHH accounted for 50% of cases. Unlike previous studies, Group 3 comprised a significant proportion (14%) of adult medulloblastomas, comparable to WNT (19%) and Group 4 (18%). Median follow-up was 51.1 months. Median OS and PFS were 102 and 99 months respectively. In contrast to paediatric medulloblastomas, molecular groups had no prognostic impact in adults, for both OS (p=0.956) and PFS (p=0.162). Most frequently mutated genes were TERT (including promoter, mutated in 35% cases), chromatin modifiers KMT2C (32%) and KMT2D (31%), TCF4 (31%), PTCH1 (26%) and DDX3X (24%). Adult WNT patients showed enrichment of TP53 mutations (6/15 WNT cases), and 3/6 TP53-mutant WNT tumours were of large cell/anaplastic histology. 5 WNT cases harboured concurrent CTNNB1 and PTCH1 mutations. Adult SHH medulloblastomas had frequent upstream pathway alterations (PTCH1 and SMO mutations) and seldom downstream alterations (SUFU mutations, MYCN amplifications). TERT promoter mutations were found in 71% of adult SHH patients, and were restricted to this group. Adult Group 3 patients lacked hallmark MYC amplifications, but had recurrent mutations in KBTBD4 and NOTCH1. Adult Group 4 patients had recurrent mutations in TCF4 and chromatin modifier genes. Overall, amplifications of MYC and MYCN were rare (3%) in adult medulloblastomas. CONCLUSIONS: We identified distinct clinical and mutational characteristics of adult medulloblastomas that will inform their treatment and risk stratification. Importantly, molecular groups were not prognostic in adult medulloblastoma, TP53 mutations were enriched in adult WNT, and MYC amplifications were absent in adult Group 3.

PATH-33. EPIGENOMIC ANALYSIS OF SPINAL EPENDYMOMA

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BACKGROUND: Ependymomas commonly occur in the fourth ventricle and the spinal cord. Gross total resection, age and WHO grade are known prognostic factors. Ependymomas are currently classified into 9 distinct subgroups by DNA methylation profile analysis. Spinal cord ependymoma is distinct from other subgroups. To investigate heterogeneity within spinal cord ependymoma, we examined DNA methylation profiles. MATERIALS AND METHODS: We used Infinium MethylationEPIC array (illumina) to obtain DNA methylation data from frozen specimens of spinal ependymoma resected at the University of Tokyo, Osaka City University, and Tokyo Metropolitan Neurological Hospital. Japan Pediatric Molecular Neuro-Oncology Group provided methylation data for 11 reported cases. Cluster analysis was performed using Cluster3.0. RESULTS: We analyzed 34 patients, 21 male and 13 female, aged from 18 to 76 years (median 50.5 years), including 2 cases with neurofibromatosis type 2. WHO grade was grade_3 in 2 cases and grade_2 in others. Clustering of the DNA methylation data showed that WHO grade_3 cases tended to be classified into a subgroup distinct from other cases. CONCLUSION: This is the largest DNA methylation profiling study on spinal cord ependymoma to date. The study may suggest a new subgroup correlated with higher WHO grade.

PATH-34. GENETIC PROFILING OF AGGRESSIVE MENINGIOMAS REVEAL DIVERSE SPECTRUM OF ACCOMPANYING ALTERATIONS BEYOND NF2 INACTIVATION

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BACKGROUND: Meningiomas are the most common primary central nervous system tumor in adults. The majority are clinically indolent and WHO grade I. However, 20-30% are WHO grade II and 1-3% are WHO grade III, which have shorter progression-free (PFS) and overall survival. A subset of grade I meningiomas also follow an aggressive course, requiring serial resection and/or radiotherapy, similar to high-grade meningiomas. The objective of this study was to characterize the genetic alterations in meningiomas with an aggressive clinical course. METHODS: Targeted