AND METHODS: We retrospectively evaluated 42 patients with histological diagnosis of MB, known molecular subgroup, and diagnostic MRI scan performed in our Institution on a 3 Tesla magnet. For each patient, FLAIR, ADC, T2 and contrast-enhanced MPRAGE sequences were analysed. Solid tumor volumes were segmented semiautomatically. 107 features were extracted for each sequence (Pyradiomics, Python). Features were tested for stability against labelling variations, selecting those presenting Intraclass Correlation Coefficient (ICC)>0.9 across all labelling variations and all sequences. Among the remaining features, relevant features were selected with an all-relevant wrapper algorithm (Boruta, R). Remaining features were used to predict MB subgroup with a Random Forest algorithm(R). The most relevant features were ranked based on Gini index (R). RESULTS: 83/107 features presented ICC >0.9 for all sequences. Boruta selected 10 features. Classification analysis yielded an out-of-bag (OOB) error rate of 0.6%, (99.4% accuracy). The most relevant features for classification were "simple" first-order features such as volume, major axis or shape. CONCLUSION: This radiomic study yielded robust features, which showed high accuracy in predicting the molecular MB subgroups. Random forest algorithms are ideal for multiclass classification (eg. MB subgroups) and are intrinsically suited against overfitting. The most relevant for molecular classification were first-order features.

IMG-20. RADIOMIC FEATURES IMPROVE PROGNOSTICATION OVER CONVENTIONAL MR DERIVED QUALITATIVE DESCRIPTORS IN PEDIATRIC SUPRATENTORIAL HIGH GRADE GLIOMA: COMPARISON OF MACHINE LEARNING TECHNIQUES

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PURPOSE/OBJECTIVES: Pediatric supratentorial high-grade glioma (stHGG) is a biologically heterogeneous disease defined by unique mutations, natural history and prognosis. Prior work by our group outlined a role for qualitative imaging features in aiding prognostication. We build on that work by evaluating the prognostic utility of radiomic features (RM) when paired with clinical factors. MATERIALS/METHODS: Ninety-one patients age < 21 years with stHGG treated between 1980–2007 were retrospectively reviewed. Prognostic clinical, qualitative imaging (Visually AcceSAble Rembrandt Images, VASARI), and treatment characteristics were evaluated in concert with manual and automatically segmented (DeepMedic), tumor-derived semi-quantitative radiomic features (Pyradiomics) extracted from MR images. Prognostic RM were limited to stable imaging features which were subsequently selected using bootstrapped least absolute shrinkage and selection operator (LASSO). Nonparametric descriptive statistics and prognostication model evaluation, incorporating RM and clinical variables, were developed using random forest (RF), Cox proportional hazards (CPH), and deep learning (deepsurv) algorithms and assessed for goodness of fit using (c-index). RESULTS: A subset (N=80) of 386 intensity, shape, and texture derived RM were stable between pre-treatment MR. 28 RM features were independently predictive of survival when compared to models utilizing combinations of clinical, VASARI and had comparable model fit statistics. CPH, RF and deepsurv showed comparable utility in modelling RM features. Combined modelling of clinical, VASARI and RM features using CPH, RF, and deepsurv resulted in c-indices of 0.68, 0.67, 0.68, respectively. CONCLUSION: RM features are stable and independently prognostic. Combined modelling of clinical, VASARI, and RM features improves prognostication in stHGG.

IMG-21. PROSPECTIVE PREOPERATIVE DETERMINATION OF ISOCITRATE DEHYDROGENASE MUTATION IN GLIOMAS USING SPECTRAL EDITING MAGNETIC RESONANCE SPECTROSCOPY

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BACKGROUND: Gliomas are the most common malignant brain tumors in children and adults. A subset of these tumors harbour mutations in the enzyme isocitrate dehydrogenase (IDH) which produces the novel oncometabolite *2-hydroxyglutarate* (2HG). In general, patients with an IDH mutant glioma have a longer survival—often necessitating more re-treatment sessions over the span of a patient's life and surveillance monitoring for tumor recurrence. The need to non-invasively detect early evidence of tumor recurrence is therefore heightened in this unique subset of patients with extended survival. As magnetic resonance spectroscopy (MRS) has been demonstrated to measure biochemical components of intracranial tumors using MRI, we conducted a study in 58 pre-operative adult patients to determine if a diagnosis of IDH mutant glioma could be made confidently using imaging data. METHODS: Patients underwent neuroimaging for diagnosis or preoperative planning on a 3 tesla MR scanner. A MEGA-PRESS spectral editing technique was employed. Imaging findings were directly compared to post-operative histopathologic diagnosis. RESUTLS: For all patients with gliomas from grade II to IV, detection of 2-HG with MEGA-PRESS sequence had a sensitivity between 48% and 81%, specificity between 60% and 100%, PPV between 53% and 100% and NPV between 77% and 85% depending on the CRLB threshold. Among the different metabolite ratios, a 2-HG/NAA ratio >0.034 had the highest sensitivity and specificity, 86% and 73% respectively. DISCUSSION: Magnetic resonance spectroscopy (MRS) is an underused advanced MR technique that deserves consideration in pediatric neuro-oncology given its utility in non-invasively detecting malignant gliomas.

IMG-22. A DEEP LEARNING MODEL FOR AUTOMATIC POSTERIOR FOSSA PEDIATRIC BRAIN TUMOR SEGMENTATION: A MULTI-INSTITUTIONAL STUDY

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BACKGROUND: Brain tumors are the most common solid malignancies in childhood, many of which develop in the posterior fossa (PF). Manual tumor measurements are frequently required to optimize registration into surgical navigation systems or for surveillance of nonresectable tumors after therapy. With recent advances in artificial intelligence (AI), automated MRI-based tumor segmentation is now feasible without requiring manual measurements. Our goal was to create a deep learning model for automated PF tumor segmentation that can register into navigation systems and provide volume output. METHODS: 720 pre-surgical MRI scans from five pediatric centers were divided into training, validation, and testing datasets. The study cohort comprised of four PF tumor types: medulloblastoma, diffuse midline glioma, ependymoma, and brainstem or cerebellar pilocytic astrocytoma. Manual segmentation of the tumors by an attending neuroradiologist served as "ground truth" labels for model training and evaluation. We used 2D Unet, an encoder-decoder convolutional neural network architecture, with a pre-trained ResNet50 encoder. We assessed ventricle segmentation accuracy on a held-out test set using Dice similarity coefficient (0–1) and compared ventricular volume calculation between manual and model-derived segmentations using linear regression. RESULTS: Compared to the ground truth expert human segmentation, overall Dice score for model performance accuracy was 0.83 for automatic delineation of the 4 tumor types. CONCLUSIONS: In this multi-institutional study, we present a deep learning algorithm that automatically delineates PF tumors and outputs volumetric information. Our results demonstrate applied AI that is clinically applicable, potentially augmenting radiologists, neuro-oncologists, and neurosurgeons for tumor evaluation, surveillance, and surgical planning.

IMMUNOTHERAPY

IMMU-01. IMMUNE CHECKPOINT INHIBITION FOR PEDIATRIC CNS TUMORS: A SINGLE INSTITUTION EXPERIENCE

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INTRODUCTION: Immune checkpoint inhibition through PD-1 and CTLA-4 blockade has shown efficacy in some adult malignancies and is being investigated in pediatrics. We describe our institutional experience with immune checkpoint inhibition in pediatric CNS tumors. METHODS: We performed a retrospective chart review of patients with recurrent, progressive, or refractory pediatric CNS tumors treated with immunotherapy at Dana-Farber/Boston Children's Hospital between 2018–2019. RESULTS: Eleven patients were identified, with median age of 11 years (range:3–9). Diagnoses included DIPG (n=3), HGG (n=4), ependymoma (n=1), craniopharyngioma (n=1), HGNET (n=1) and NGGCT (n=1). Eight patients had recurrent disease (5 local; 3 disseminated); three had refractory disease (non-recurrent). Nine patients were treated with combination

therapy (ipilimumab/nivolumab); two patients received monotherapy with either nivolumab or pembrolizumab. Median time from initial diagnosis-to-treatment was 8 months (range 0.8–156). Ten patients received radiation therapy (RT) prior to immunotherapy, with one receiving concurrent RT. Median duration of treatment was 6.1 months (range:1–19). Therapy was discontinued in nine patients: seven due to disease progression and two due to adverse events (colitis, transaminitis). Other pertinent toxicities included type 1 diabetes, hypothyroidism and skin toxicity. Based on iRANO criteria, best responses included partial (n=4), stable (n=6) and progressive disease (n=1). Durable response (>12months) was noted in two patients (HGG and progressive NGGCT). CONCLUSION: Immune checkpoint inhibition appears to have clinical benefit and is relatively well tolerated in this cohort of patients. Results from recently completed prospective clinical trials will be critical to inform clinical decisions.

IMMU-02. CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL NEUROTOXICITY CORRELATES WITH PRETREATMENT AND ACUTE CSF NEUROFILAMENT LIGHT CHAIN (NFL) LEVELS

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OBJECTIVE: Immunotherapy for hematologic malignancies with CD19-directed CAR T cells is complicated by neurotoxicity in approximately 40% of patients. We have previously reported evidence of glial injury in pediatric patients with CAR T neurotoxicity by elevated CSF levels of GFAP and S100b. We now hypothesize that NFL is also a useful biomarker of neuronal injury related to abnormal blood-brain-barrier and glial function. METHODS: We used the Mesoscale Discovery platform to measure CSF and serum NFL levels in a consecutive cohort of 43 pediatric patients with B cell ALL who received CD19-directed CAR T cells. In addition, we will present expansion cohort measurements of NFL and GFAP (N=95). RESULTS: CSF NFL levels prior to CAR T cell infusion positively correlated with the risk of subsequently developing severe neurotoxicity (no neurotoxicity, median 275pg/mL, mild 378pg/mL, severe 951pg/mL, P=0.0182 for severe vs none, P=0.0458 for severe vs mild). During neurotoxicity, mean CSF NFL levels increased to 1179pg/mL (mild neurotoxicity, P=0.0338) and 1345 pg/mL (severe neurotoxicity, P=0.0148), respectively. In serum, pretreatment NFL levels were highly abnormal in many patients (median 368pg/mL, range 10–56,321pg/mL; healthy control median 4pg/mL, range 1–7.5pg/mL). However, there was no correlation with neurotoxicity, history of CNS radiation, peripheral neuropathy, stem cell transplant, or number of prior chemotherapies. Day 7 serum NFL levels did not change significantly (median 439pg/mL, range 5–17,439pg/mL, P=0.3254). CONCLUSION: We conclude that CSF NFL is promising biomarker of CAR T neurotoxicity risk and severity. The abnormal baseline serum NFL concentrations remain unexplained and require further study.

IMMU-03. UPDATES ON BRAINCHILD-01, -02, AND -03: PHASE 1 LOCOREGIONAL CAR T CELL TRIALS TARGETING HER2, EGFR, AND B7-H3 FOR CHILDREN WITH RECURRENT CNS TUMORS AND DIPG

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We report preliminary results of three Phase 1 trials of repetitively dosed locoregional CAR T cells for children with recurrent/refractory CNS tumors, targeting HER2 (BrainChild-01), EGFR (BrainChild-02), and B7-H3 (BrainChild-03). Cells are delivered into the tumor cavity (Arm A) or ventricular system (Arm B and BrainChild-03's DIPG-specific Arm C). Primary endpoints are feasibility and safety. Successful CAR T cell manufacture occurred in 2/2 subjects (BrainChild-01) and 2/3 (BrainChild-02). All subjects tolerated intra-patient dose escalation from $1x10^7$ to $2.5x10^7$ cells/dose without DLTs. Two subjects were evaluable on BrainChild-01 (S-001: glioblastoma, Arm A, survival 173 days post-first infusion, received 6 infusions; S-002: ependymoma, Arm B, survival 111 days, 9 infusions). One subject was evaluable on BrainChild-02 (glioblastoma, Arm A, withdrew from trial at 49 days, 5 infusions). One enrolled patient on BrainChild-03 has not begun treatment. None of the subjects developed new neurologic toxicities, although transient worsening of baseline tumor-related signs and symptoms were seen. Secondary endpoints are efficacy and disease response. No objective radiographic responses have been observed. Both BrainChild-01 subjects had transient systemic CRP elevations following infusions (S-001: peak of 3.9 post Course 1 Week 1; S-002: peak of 2.3 post Course 2 Week 1), possibly indicating an inflammatory response. Both subjects had post-infusion CSF cytokine elevations (CXCL10, GCSF, GM-CSF, IFNa2, IFNg, IL-10, IL12-p40, IL12-p70, IL-15, IL-1a, IL-3, IL-6, IL-7, TNFa, VEGF) without concurrent systemic changes. In summary, we provide preliminary evidence of safety and feasibility of intracranial delivery of CAR T cells for pediatric CNS tumors.

IMMU-05. B7-H3-SPECIFIC CAR T CELLS HAVE POTENT ANTI-TUMOR ACTIVITY IN THE GL261 IMMUNE-COMPETENT MURINE BRAIN TUMOR MODEL

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BACKGROUND: We and others have identified B7-H3 (CD276) as a promising target for CAR-based immunotherapies for pediatric brain tumors. So far, B7-H3-CAR T cells have only been studied in xenograft models for brain tumors, which do not recapitulate the immunosuppressive tumor microenvironment (TME). To overcome this obstacle, we decided to adapt the immune-competent GL261 murine glioma model which mimics human disease and host immune barriers. METHODS: To evaluate the safety and efficacy of antigen-specific CAR T cells, murine B7-H3-CAR T cells were generated using retroviral particles encoding 2nd generation B7-H3-specific CD28.z CAR. Expansion, persistence, and anti-tumor activity were evaluated *in vitro* and *in vivo*. Components of the brain TME were then evaluated using flow cytometry and immunostaining. RESULTS: B7-H3-CAR T cells only killed B7-H3+ tumor cells, secreted significant levels of IFNγ and IL-2 in an antigen-dependent manner and expanded an average of 33-fold in repeat stimulation assay with B7-H3+ tumor cells in contrast to control CAR T cells. *In vivo*, intratumoral injection of B7-H3-CAR T cells into orthotopic GL261 glioma induced complete regression in 60% of treated mice. Preliminary studies show numerous infiltration of suppressive tumor-associated macrophages within the tumor and its periphery. CONCLUSIONS: In summary, we successfully generated murine B7-H3-CAR T cells and have demonstrated that these cells have potent anti-tumor activity in the immune-competent GL261 glioma model. However, it is likely that the tumor-associated macrophages are mediating immunosuppressive effects on B7-H3-CAR T cells. Therefore, studies focusing on TME/CAR T cell interactions are in progress.

IMMU-06. T-CELL IMMUNOTHERAPY FOR PEDIATRIC BRAIN TUMORS: DIVERSITY IN CELL SURFACE ANTIGEN AND HLA EXPRESSION NECESSITATES A MULTI-PRONGED APPROACH

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Cell surface or intracellular antigens expressed in pediatric brain tumors are potential targets for chimeric antigen receptor (CAR) or ab (T-cell receptor) TCR T-cell immunotherapy. At present it remains unknown what cell surface antigens are suitable CAR targets for pediatric brain tumors; in addition, cell surface expression of HLA class I, a molecule critical for ab TCR T-cell recognition, has not been systemically studied in these tumors. Therefore, we set out to assess expression of five CAR targets (IL13Ra2, HER2, EphA2, B7-H3, GD2) and HLA class I. We established and validated a flow cytometry-based method to profile CAR targets and HLA class I expression from pediatric patient-derived xenograft (PDX) samples. To date, we profiled 53 PDX samples, including medulloblastoma, HGG, DIPG, ATRT, and ependymoma. We found that antigen expression has high intra- and inter-PDX sample variability with B7-H3 and IL13Ra2 being most consistently expressed. We confirmed these findings using conventional IHC for B7-H3 with PDX samples and patient tissue microarrays. HLA class I was present on the cell surface of HGGs and DIPGs, however significantly down-regulated in 26 out of 36 other brain tumor types. Finally, matched fresh tissue and PDX sample analysis revealed that cells derived from PDX models are indeed representative of fresh tissue. Our results indicate that more than one antigen needs to be targeted to achieve a more complete tumor clearance. In addition, variable expression