Pediatric treatment-induced high-grade gliomas are enriched for a specific methylation subgroup and recurrent genomic abnormalities

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BACKGROUND: Pediatric treatment-induced high-grade gliomas (TIHGGs) are an incurable late complication of cranial radiotherapy or combined radiation/chemotherapy. The molecular features of TIHGGs are largely unknown, and there are currently no means of pretreatment risk stratification.

METHODS: TIHGGs (n= 34) from a multi-institutional cohort and the Childhood Cancer Survivors Study Group was evaluated by multimodal molecular analysis. Whole Genome (WGS) or Whole Exome Sequencing (WES) (n= 25) and Illumina Infinium 450/850K methylation profiling (n= 28) was performed on TIHGG. WGS/WES was performed on matched germline DNA from 15 TIHGGs. Genome-wide copy number profiles were derived from the methylation data.

RESULTS: By methylation profiling, 20/28 TIHGGs clustered into a subclass of IDH-wild type midline high-grade glioma. Recurrent copy number alterations included 1p loss (13/28), 1q gain (13/28), Ch.13 loss (14/28), PDGFRA gain/amplification (18/28), and CDKN2A loss (14/28). WGS identified a mean germline mutation load of 1.50 mut/Mb. There was no difference in the number of coding and noncoding mutations in TIHGG compared to a matched cohort of non-TIHGG tumors. Noncoding and coding region mutational spectrums seemed to be biased toward A to G and C to T transitions, respectively. TIHGG cases showed enrichment for pathogenic germline alterations in DNA repair genes including BARD1, BRCA1, BRCA2, ATR, and PMS1.

CONCLUSIONS: The majority of TIHGGs group into an IDH-wild type midline high grade glioma methylation subgroup and are characterized by recurrent copy number abnormalities including amplification of PDGFRA and CDKN2A deletion. Enrichment in TIHGGs for germline mutations in DNA repair pathway genes suggest that pre-radiotherapy testing may be important when considering risk for secondary malignancy.