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 THIGGs for germline mutations in DNA repair pathway genes suggest that pre-radiotherapy testing may be important when considering risk for secondary malignancy.