AT-10. ATYPICAL TERATOID RHABDOID TUMORS AND POORLY DIFFERENTIATED CHORDOMAS: DISTINCT MOLECULAR ENTITIES WITH SMARCB1/INI1 LOSS AND DISMAL PROGNOSIS

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Chordomas are tumors of the skull base and spine thought to arise from remnants of the notochord. Pediatric chordomas showing atypia, increased mitotic activity, unstructured growth pattern and loss of SMARCB1/INI1 expression have been designated as “poorly differentiated chordomas”. It remains uncertain, however, if poorly differentiated chordoma represents a distinct entity or part of the AT/RT spectrum. Therefore, seven poorly differentiated chordomas, 14 conventional chordomas as well as 10 AT/RT of each of three molecular subgroups (i.e. TYR, MYC and SHH) were molecularly characterized including Illumina Infinium Human Methylation 450k Bead Chip profiling. Median age of the four boys and three girls harboring poorly differentiated chordomas was 7 years (range 1-11 years); median overall survival accounted for only 9 months (95% confidence interval 6-12 months). On histopathological examination, all poorly differentiated chordomas lacked SMARCB1/INI1 expression but showed nuclear brachyury expression. Brachyury expression was also observed in 2/30 AT/RT. Unsupervised cluster analysis identified five methylation groups, including two distinct chordoma clusters, representing the poorly differentiated chordomas and the conventional chordomas, respectively, both clustering apart from the AT/RT subgroups. Losses of 22q affecting the SMARCB1 region were the only recurrent alteration in poorly differentiated chordomas and the vast majority of AT/RT. Heterozygous or homozygous deletions affecting the SMARCB1 region could be confirmed on FISH and/or MLPA, while SMARCB1 point mutations were absent on sequencing. In conclusion, poorly differentiated chordoma represents a molecularly distinct entity with dismal prognosis, which can be reliably separated from conventional chordoma and AT/RT by a distinct methylation profile.

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