

To inform management, second look surgery was performed. Pathology showed fibrous tissue only, no malignant cells. The child continues to be treated as per HIT2000. CASE 2: 5 month old girl, metastatic lesions in the cerebellum. Germline SUFU mutation. 2 months after end of treatment, MRI demonstrated progression of cerebellar lesion. Surgical resection was performed, pathology showed differentiated mature neuronal tissue. No further treatment; remains in remission 1 year after suspected progression. CASE 3: 27 month old boy, metastatic lesions in cerebellum. Germline SUFU mutation. 1 month post-completion of treatment progressive prominent nodules along the cerebellum and cerebellar leptomeningeal enhancement. Biopsy not feasible so close MRI surveillance was initiated. MRI remains stable 1 year after suspected progression. CASE 4: 30 months old boy, non-metastatic disease. Complete resection. No germline mutation. End-of-treatment MRI showed subtle new intraspinal leptomeningeal deposits and a suspicious left optic tract nodule, subsequent MRI 8 weeks later showed clear progressive disease. Unfortunately, the child died before radiotherapy could be delivered. CONCLUSION: Salvage radiotherapy for infants with medulloblastoma who progress following chemotherapy treatment can be life-saving but risk significant cognitive impairment. Differentiation of medulloblastoma following radio/chemotherapy has been reported. We recommend considering tissue confirmation prior to embarking on further treatment for suspected relapse.

MEDB-49. RELAPSED SHH MEDULLOBLASTOMAS IN YOUNG CHILDREN. ARE THERE ALTERNATIVES TO FULL-DOSE CRANIOSPINAL IRRADIATION?

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BACKGROUND/RATIONAL: Following initial irradiation sparing therapy, many young children with relapsed medulloblastoma can be salvaged with craniospinal irradiation (CSI). However, the interval to relapse is short and neurocognitive sequelae remain a major concern. The contribution of molecular subgrouping may help refine indications and modalities of salvage strategies in this population. **METHOD:** From a cohort of 151 young children with molecularly characterized relapsed medulloblastoma, subset analysis of the SHH medulloblastoma was conducted to describe the practice of salvage radiotherapy and associated post-relapse survival

(PRS). **RESULTS:** Sixty-seven SHH medulloblastoma patients (46 M0; 54 GTR; 11 non-ND/MBEN) received salvage therapy with curative intent. Before relapse, 54 (80.6%) received conventional chemotherapy (CC), 13 (19.4%) high-dose chemotherapy (HDC), while seven had additional focal radiotherapy (fRT). Median time to relapse was 11.1 months (range 3.8-41.0) and 43.3% were localized. Thirty patients (16 localized relapse) underwent surgery. Forty-seven (71.2%) received salvage radiotherapy (20 with CC; 10 with HDC; 15 alone, two unknown). CSI and fRT accounted for 82% and 18% respectively. CSI median dose was 36Gy (range 18-39Gy). Ten patients (eight with localized relapse) received CSI doses ≤ 23.4 Gy. Nineteen patients (28.8%) did not receive any radiotherapy (nine HDC; 10 CC only). Radiotherapy was associated with better 3-year PRS (73.0% versus 36.1%; $p=0.001$). All patients treated with CSI ≤ 23.4 Gy were alive at median follow-up of 69 months(24-142). Six of nine patients treated with HDC without irradiation were alive at last follow-up. Sixty-three percent of patients received reduced dose CSI (≤ 23.4 Gy), fRT, or no radiotherapy, and their PRS did not significantly differ from those who received CSI ≥ 30.6 Gy ($p = 0.54$). **CONCLUSION:** While salvage CSI provided PRS benefit in this SHH medulloblastoma cohort, we report the use of reduced salvage radiotherapy and irradiation avoidance in 63% of the patients, with 60% alive at last follow-up.

MEDB-50. ASSESSMENT OF CELLULAR RADIOSENSITIVITY AND DNA REPAIR IN MEDULLOBLASTOMA CELL LINES AND PATIENT-DERIVED XENOGRFT SLICE CULTURES

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Medulloblastoma (WHO grade 4) is the most common malignant brain tumor of childhood. Despite the high importance of radiotherapy for disease control, the mechanisms underlying response and resistance to radiotherapy are incompletely understood. Therefore, we assessed the radiosensitivity and DNA repair capacity of medulloblastoma cell lines in-vitro and of patient-derived xenograft (PDX) models ex-vivo. Cell survival after irradiation of seven medulloblastoma cell lines displaying different subgroups was assessed via colony formation assay (DAOY, UW228, UW473, SJMM4, ONS-76, HDMB-03, D283). The ONS-76 and the mouse SJMM4 cell line were the most radioresistant strains (surviving fraction after 6 Gy (SF₆): 0.33 and 0.31, respectively), followed by UW473, UW 228 and DAOY cells (SF₆ 0.16-0.21). The non-WNT/non-SHH-activated cell lines HDMB-03 and D283 cells demonstrated profoundly higher cellular radiosensitivity (SF₆ <0.05). Analysis of residual (24h after irradiation) DNA double-strand breaks (DSB) as assessed by co-localized γ H2AX/53BP1-foci demonstrated a significant correlation between DSB repair capacity and cellular survival. To use a more reliable pre-clinical model for medulloblastoma, we further examined DNA repair foci in ex-vivo irradiated slice cultures of PDX models MED-113 (SHH) and NCH2194 & HT028 (Gr. 3). Immunofluorescence analyses of frozen sections demonstrated non-hypoxic (pimonidazole-negative) and proliferating (EdU-positive) cells at the outer rim of the tumor slices. Two hours after irradiation all three PDX models showed a strong increase in 53BP1-foci, clearly indicating DNA damage induction. Most radiation-induced DSB were repaired after 24h. In a first radiosensitization approach, we treated the HT028 model with the PARP inhibitor olaparib (1 μ M \pm 2Gy irradiation). Twenty-four hours after treatment the sample displayed a strong increase in the amount and size of 53BP1-foci, indicating compromised DNA repair. Further in-vitro and ex-vivo investigations with the aim to predict individual radiosensitivity and effective radiosensitization strategies are ongoing.