therapy (PBT) compared to photon radiotherapy (XRT). However, there are concerns regarding secondary neutron production and possible associated excess SMN with passive scatter proton therapy (PSPT) compared to pencil beam proton therapy. We reviewed our multi-institutional experience treating pediatric medulloblastoma (MB) patients with craniospinal irradiation (CSI) using either XRT or PBT. We hypothesized that excess SMN would not be observed among patients treated with PBT.

Materials/Methods: From 1996 to 2014, 166 patients with MB received CSI followed by tumor bed boost using either PSPT (n = 103) or XRT (n = 63). For the proton cohort, all patients received PSPT for the CSI portion and 93.9% received PSPT for the boost. For XRT patients, all received 3-D conformal RT CSI followed by an IMRT tumor bed boost. Median age was 8.0 years at time of radiotherapy (RT), (8.0 years PBT, 8.1 years XRT). A majority of patients were male (112/166, 67.5%) and a majority had standard-risk MB (102/166, 61.4%). Median follow-up was 78.5 months for the PBT cohort and 153.2 months for the XRT cohort ($p < 0.001$).

Results: The 5- and 10-year overall survival rates were 82.6% and 81.2% for standard-risk and 69.8% and 64.0% for high-risk patients, respectively. No OS difference was identified by RT modality ($p=0.49$). The 5- and 10-year actuarial SMN rate was 2.3% and 8.1% for the entire study population (N=166). By modality, 5- and 10-year SMN rates were 2.6% and 6.0% for PBT patients, and 0.0% and 8.0% for XRT patients ($p=0.71$). There was no difference in incidence of SMN according to age ($p=0.99$), gender ($p=0.50$) or CSI dose ($p=0.61$). There were a total of 8 SMN identified in total (4 in each cohort by RT modality), with a median time from RT completion to SMN diagnosis of 71.2 months (range: 5.8 - 145.6 months). Breaking down SMNs by histology, there were 3 sarcomas, 2 malignant gliomas, 1 papillary thyroid cancer, 1 parotid mucoepidermoid carcinoma, and 1 cerebellar malignant glioneuronal tumor. All 4 SMNs in the PBT cohort occurred either within the previously-irradiated target (n=2), or in the entrance dose region (n=2). For XRT patients, 3 SMN occurred in regions receiving exit dose while 1 was within the target.

Conclusion: Our preliminary analysis demonstrates no difference in the rate of SMN between PBT-treated and XRT-treated patients up to 10 years following RT. Given the shorter follow-up time for PBT patients, longer-term follow-up remains necessary to understand differential SMN patterns across RT modalities better. It is notable that XRT-treated patients developed a higher rate of SMNs in regions of exit dose than in the target volume.

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Incidence, Risk Factors and Screening for Vasculopathy in Children Treated with Proton Radiation for BRAIN Tumors

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Purpose/Objective(s): The aim of our study was to determine the incidence, timing and risk factors for large vessel cerebral vasculopathy after proton radiation for pediatric brain tumors, to better inform screening for this complication off-therapy.

Materials/Methods: We performed a retrospective review of a cohort of children treated with proton radiation for brain tumors, at a single institution. Details abstracted from patient charts included demographics, diagnosis, treatment details (planning target volume, total dose, dose to the optic chiasm), signs of cerebral ischemia/stroke on clinical evaluation and in radiology reports. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) images were reviewed by a single study radiologist, for evidence of vasculopathy and cerebral infarcts. Degree of vasculopathy was determined by the ratio of the diameter of the narrowed vessel to the normal proximal segment (mild: > 0.75; moderate: 0.25 – 0.75; severe: < 0.25/moya-moya disease).

Results: Eighty three patients were treated with proton radiation (22 craniospinal, 56 involved-field, 5 whole ventricle) for brain tumors, at a median age of 8 years (range 0.7 – 20.6 years). No patient had neurofibromatosis type I. Tumors were supratentorial for 53 patients (23 suprasellar; 30 non-suprasellar) and infratentorial for 30 patients. Median follow-up from end of radiation to the last MRI/MRA was 3 years (range 0.1 – 8.3 years). Overall, 5/83 (6%) patients developed vasculopathy, a median of 2.1 years (range 1.3 – 3.7 years) after radiation therapy, all with dose to the optic chiasm greater than 52 Gray (Gy) (median age during radiation 8.4 years). Severe vasculopathy was identified in 4/83 (~5%) patients, all with suprasellar tumors (3 craniopharyngioma, 1 optic pathway glioma). One of these patients had an ischemic infarct. Of 23 patients with suprasellar tumors (median dose to optic chiasm 52 Gy; range 32 – 56 Gy), 4 (17%) were diagnosed with a severe vasculopathy, a median of 1.8 years (range 1.3 – 2.3 years) after radiation. One patient with a non-suprasellar, supratentorial tumor developed a mild vasculopathy, 3.7 years off-therapy. For 4/5 (80%) patients with vasculopathy, the diagnosis was made with MRA, while their MRIs showed normal flow voids, suggesting arterial patency.

Conclusion: Children who receive cranial proton radiation, are at risk for vasculopathy and stroke, especially with a dose greater than 52 Gy to the optic chiasm, a median duration of 2 years after radiation. For a majority of patients in our cohort, vasculopathy was only detected on MRA, and not MRI. Our findings suggest a need for screening children who receive a higher radiation dose to the optic chiasm, with MRA imaging off-therapy. Prospective studies are needed to better define at-risk patients, and timing of screening for vasculopathy. Longer follow-up is needed to assess the long-term incidence of vasculopathy and consequent patient outcomes, after cranial proton radiation.

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Hafnium Oxide Nanoparticles Activated by SBRT for the Treatment of Hepatocellular Carcinoma and Liver Metastasis: A Phase I/II Trial

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Purpose/Objective(s): The medical community faces important challenges to treat liver cancer because of underlying disease. Reduction of healthy tissue irradiation while at the same time increasing energy dose deposit within tumor cells still constitutes a challenge in radiation oncology. NBTXR3, hafnium oxide nanoparticles, increase energy deposit

inside tumor cells only when activated by ionizing radiation such as stereotactic body radiotherapy (SBRT) and thus increase tumor cell death compared to radiation alone. Patients (pts) with hepatocellular carcinoma (HCC) or liver metastasis (mets) may benefit from the physical mode of action of NBTXR3, which does not engage liver and renal functions. A phase I/II clinical trial was conducted to evaluate NBTXR3 activated by SBRT in these pts [NCT02721056].

Materials/Methods: The Phase I part follows a 3+3 dose escalation design with dose levels of NBTXR3 corresponding to 10, 15, 22, and 33% of the baseline tumor volume. Pts were treated with a single NBTXR3 intralesional injection (ILI) followed by SBRT (45 Gy / 3 fractions / 5 to 7 days). Primary endpoints included identification of the recommended phase II dose(s) and early DLTs. Secondary endpoints included assessment of global safety profile, liver function evaluated by Child-Pugh score (CPS), AST to Platelet Ratio Index (APRI), and response rate (mRECIST/RECIST 1.1).

Results: Four levels of the dose escalation part are finalized (n = 17): 6 pts at 10% (2 SBRT doses tested due to organs constraints), 4 pts at 15 and 22% (due to fiducial displacement and ILI shift) and 3 pts at 33%. No NBTXR3 related early DLT or SAE were observed. Indeed only one NBTXR3 related AE (G1 fatigue at 33%) was reported. There were no significant changes in CPS or APRI post-treatment. CT-scan assessment demonstrated absence of NBTXR3 leakage in surrounding tissues. Among 7 evaluable HCC pts, best mRECIST target lesion responses were: 3 CR, 4 PR. Among 5 evaluable mets pts, best target lesion responses were: 2 PR, 1 SD, 2 PD.

Conclusion: NBTXR3 was well tolerated up to the 33% dose level and demonstrated a very good safety profile. The very good tolerance and preliminary anti-tumor effects have supported a protocol amendment to study an additional higher NBTXR3 dose level (42%). Indeed recent data reinforces this further escalation as OS and local control seem to depend on RT dose and tumor volume. Liver dysfunction is the limiting factor for treatment in these pts, hence, this innovative physics based approach may constitute a valuable solution for pts with unresectable liver tumors. NBTXR3 showed statistically superior efficacy over RT alone in a phase II/III trial in soft tissue sarcoma [NCT02379845] and is currently being evaluated in phase I/II trials: head and neck [NCT01946867; NCT02901483], prostate [NCT02805894] and rectal cancers [NCT02465593].

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Multicenter Phase II Study of Stereotactic Ablative Radiotherapy for Hepatocellular Carcinoma ≤ 5 cm (KROG 12-02)

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Purpose/Objective(s): To evaluate the efficacy of stereotactic ablative radiotherapy (SABR) for hepatocellular carcinoma (HCC) ≤ 5 cm.

Materials/Methods: A total of 54 patients with unresectable HCC showing an incomplete response after 1-5 sessions of transarterial chemoembolization were enrolled in a phase II clinical trial of SABR from 6 institutions between July 2012 and June 2015. SABR was delivered with a total dose of 60 Gy in 3 fractions within 14 days, with ≥ 48 hour-intervals between each fraction. The treatment response was evaluated using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Radiation-induced liver disease (RILD) was analyzed at 2 months. Survival outcomes were analyzed with the Kaplan-Meier method. This trial is registered with Clinical Trials.gov, number NCT01825824.

Results: Forty-eight patients were evaluable with a median follow-up of 41 months (range, 2-61 months). The median tumor size was 2.0 cm (range, 1.0?4.5 cm) and most patients (89.6%) had a single lesion. Thirty-six patients (75%) received TACE ≤ 2 times. Local control rate at 2 and 5 years were 97.4% and 94.7%, respectively. Overall survival rate at 2 and 3 years were 90.9% and 78.3%, respectively. Progression-free survival rate at 2 and 3 years were 50.3% and 27.0%, respectively. One patient experienced non-classic RILD with acute toxicity at 2 month after SABR.

Conclusion: The high-dose SABR for HCC ≤ 5 cm is and effective as evidenced by the high rates of tumor control, overall survival, and acceptable treatment-related toxicity.

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Determining and Incorporating the Optimal Predictive Biomarkers in Hepatocellular Carcinoma Patients Treated with Radiotherapy

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Purpose/Objective(s): Radiotherapy (RT) is one of the treatment options for treating hepatocellular carcinoma (HCC) patients. However, treatment responses to RT are heterogeneous and no robust predictive biomarker has been found. Previously, our institution reported the possibility of soluble programmed cell death ligand-1 (sPD-L1), plasma cell-free DNA (cfDNA), inter-alpha inhibitor H4 (ITIH4), interleukin (IL)-6, and IL-10 as predictive biomarkers after RT. However, using a single biomarker to predict treatment outcomes has limitations since the heterogeneity of the tumor and the host-immune system both affect tumor response and oncologic outcomes. Thus, we investigated the optimal biomarkers and incorporated them to predict treatment outcomes in HCC patients treated with RT.

Materials/Methods: Hundred-four HCC patients treated with RT between July 2016 and October 2018 were prospectively enrolled. Conventional RT was performed in all patients, with a median RT dose of 100 Gy (range, 60−100 Gy) for GTV and a median RT dose of 60 Gy (range, 45−60 Gy) for PTV. Peripheral blood was collected at baseline and after RT. A total of six biomarkers, sPD-L1, IL-10, IL-6, cfDNA, ITIH4 and IFN-γ, were analyzed.

Results: Median follow up period was 14.7 months (range, 2.3−28.9 months). Median age was 61 (range, 33−80), 44 patients (44.4%) had single tumor and the median tumor size was 6.5 cm (range, 1.3−21.0 cm). Nine patients had node-positive disease and 52 patients had portal vein tumor thrombosis or invasion. One-year overall survival rates and progression-free rates were 85.1% and 38.6%, respectively. The most common first pattern of failure was regional only failure, followed by distant only failure. Recursive partitioning analysis revealed four prognostic groups for regional failure based on sPD-L1, IL-10, and number of hepatic lesions: group 1, sPD-L1 < 8.17 pg/mL; group 2, sPD-L1 ≥ 8.17 pg/mL, single tumor; group 3, sPD-L1 ≥ 8.17 pg/mL, multiple tumors, IL-10 < 3.64 pg/mL; group 4, sPD-L1 ≥