

Risk of Subsequent Neoplasms (SNs) after a primary tumor in patients with NF1

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Background: Radiation therapy (RT) is generally avoided for treating primary tumors in NF1 patients due to concerns about increased SN risk, despite the fact that RT results in improved tumor control (c/w chemotherapy [CT]) for low grade glioma (LGG) and provides superior nerve-sparing (c/w surgery) for malignant peripheral nerve sheath tumors (MPNSTs). Further, alkylator CT is used sparingly in NF1 patients, due to concerns about increased risk of therapy-related leukemia, limiting treatment options for optic pathway glioma. However, gaps in knowledge exist regarding: **A)** SN risk in childhood cancer survivors with and without NF1 patients; **B)** SN risk in NF1 patients with a primary tumor treated with RT or alkylator CT.

Methods: Cumulative incidence of SN used death as competing risk. Proportional subdistribution hazards regression was used for multivariable analyses, adjusting for primary tumor type, age at dx of primary tumor, race/ethnicity, CT (anthracycline, alkylator, platinum) and RT.

Results: (A) We used the Childhood Cancer Survivor Study cohort of 5+y survivors with NF1 (n=176) and without NF1 (n=24,181). Excluding basal cell carcinoma from the SNs, a significantly higher 20y cumulative incidence of SNs was observed in the NF1 cohort (10% vs. 4.1%, p=0.0003). Multivariable analysis, found the NF1 cohort at a 3.1-fold higher risk of SN (95%CI, 1.8-4.9, p<0.0001) than the non-NF1 cohort. **(B)** We constructed a retrospective cohort of 169 NF1 patients treated at 2 centers with dedicated NF clinics (UAB, CHOP), to capture events from primary tumor diagnosis to SN, death or date of last contact. Mean age at diagnosis of primary tumor was 5±5.02y; 71% had a primary brain tumor; CT exposure included: anthracyclines (5.9%), alkylators (63.3%), RT (14.2%). Twenty-eight SNs (glioma: n=14; MPNST: n=8; other: n=7) were observed at a median of Xy (range X-X) from primary tumor dx. Multivariable analysis found that exposure to RT was associated with a 2.39-fold increased risk of SNs (95%CI, XX-XX, p=0.048). In contrast, exposure to alkylator RT was not associated with increased risk of SNs (HR=0.9, 95%CI XX-XX, p=0.9).

Conclusions: NF1 patients with a primary tumor were at a significantly higher risk of developing SNs as c/w non-NF1 cancer patients. Among NF1 patients, exposure to RT, but not alkylator CT was associated with increased SN risk. These findings provide evidence for refining management of primary tumors in NF1 patients.