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## **ABSTRACT**

### **Background**

Quantification of radiation dose to normal tissue during radiotherapy is critical for assessing risk for radiotherapy-related late adverse effects, such as subsequent neoplasms (SN). The preferred method for case-control studies reconstructs absorbed radiation dose to the specific location of the SN using individual treatment parameters. An alternative to this resource-intensive method estimates the maximum prescribed dose to body regions.

### **Methods**

We compared radiation dose estimates and SN risk estimates obtained from the two dose reconstruction methods using data from case-control studies of brain (64 cases, 244 controls) and breast SN (94 cases, 387 controls) nested within the Childhood Cancer Survivor Study cohort of 5-year survivors of childhood cancer diagnosed in 1970-1986.

### **Results**

Agreement between categorical body-region and tumor location-specific doses was high for brain (weighted kappa statistic = 0.94; 95% confidence interval (CI) 0.90-0.97) and somewhat lower for breast (weighted kappa statistic = 0.75; 95%CI 0.68-0.81). In both studies, the

percentage of patients for whom categorical body-region and location-specific doses agreed was lowest among patients treated with fields that delivered a heterogeneous dose across the tissue of interest (e.g., partial brain field - 57.1% agreement; mantle field - 61.2% agreement) and highest among patients treated with fields that delivered a relatively homogeneous (high or low) dose (e.g., whole brain field - 100% agreement; no chest-directed field - 100%). Estimated excess odds ratios per Gy from conditional logistic regression analyses were 1.16 (95%CI 0.40-4.90) and 0.97 (95%CI 0.34- 3.70) for brain SN and 0.16 (95%CI 0.08-0.34) and 0.09 (95% CI 0.04-0.21) for breast SN, using the location-specific and body-region doses, respectively.

## **Conclusions**

Our results suggest that body-region doses provide a good approximation of location-specific dose when the tissue of interest is clearly in or out of the radiation field whereas it performs less well when there is greater ambiguity of tumor location relative to the treatment field due to heterogeneous dose distribution across the tissue of interest. Body-region doses may provide an efficient basis for preliminary dose-response analyses and inform the decision to invest in the more resource-intensive dose reconstruction.