Radiation Dose and Volume to the Pancreas and Subsequent Risk of Diabetes Mellitus: A Report from the Childhood Cancer Survivor Study

Danielle Novetsky Friedman, MD, MS, Patrick Hilden, MS, Chaya S. Moskowitz, PhD, Rebecca M. Howell, PhD, Rita E. Weathers, MS, Susan A. Smith, MS, Suzanne L. Wolden, MD, Emily S. Tonorezos MD MPH, Sogol Mostoufi-Moab, MD, MSCE, Eric J. Chow, MD, MPH, Lillian R. Meacham, MD, John A. Whitton, MSc, Wendy M. Leisenring, ScD, Leslie L. Robison, PhD, Gregory T. Armstrong, MD, MSCE, Kevin C. Oeffinger, MD, Charles A. Sklar, MD

Purpose: Childhood cancer survivors exposed to abdominal radiotherapy (abdRT) are at increased risk for diabetes mellitus (DM). We examined the association between DM risk and pancreatic radiation dose and dose-volume metrics.

Methods: Participants included 4,527 5-year survivors (median age 35 years, range 10–58; median follow-up 21 years, range 2–34) diagnosed 1970–1999 and treated with abdRT, excluding total body irradiation. We estimated maximum radiation dose to the abdomen, whole pancreas, pancreatic head, body and tail, as well as volume of the pancreas absorbing ≥10, 20, and 30 Gy (V10, V20, V30). Prevalence of DM, defined by DM medication use, was compared to 4,853 siblings and 15,944 survivors without a history of abdRT using a GEE model with a Poisson distribution adjusted for attained age.

Results: Survivors exposed to abdRT were 2.9 times more likely than siblings (95% confidence interval [CI] 2.0–4.3) and 1.6 times more likely than survivors not exposed to abdRT (95% CI 1.3–2.1) to have DM. Among those treated with abdRT, the prevalence of DM was 2.9% for survivors aged 31–40 years and 4.7% for those over 40. In multivariable analysis of survivors treated with abdRT, attained age (RR = 1.09, 95% CI 1.06–1.11, p<0.001); body mass index (<18.5: RR = 1.1, 95% CI 0.4–2.7; 18.5–24.9: reference; 25–29.9: RR = 2.7, 95% CI 1.6–4.6; ≥30, RR = 7.7, 95% CI 4.8–12.4, p<0.001); and pancreatic tail dose (0.1–9.9 Gy: reference; 10–19.9 Gy: RR = 6.3, 95% CI 2.1–18.8; 20–29.9 Gy: RR = 4.7, 95% CI 1.4–16.3; ≥ 30 Gy: RR = 11.4, 95% CI 3.6–36.3, p<0.001) were associated with increased DM risk. An interaction was noted between age at diagnosis and pancreatic tail dose (p<0.001), with the largest differences between tail doses found among those diagnosed at age <10. Radiation to other regions of the pancreas, by dose or volume, as well as exposure to cranial irradiation, alkylating agents, and corticosteroids, were not associated with DM risk.

Conclusion: Among survivors treated with abdRT, DM risk is associated with higher pancreatic tail dose, but not with other dosimetric or volumetric factors. Research is needed to identify interventions to decrease cardiometabolic risk in survivors treated with abdRT.