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Radiation Oncology Workflow-Integrated Coronary Artery Disease Risk Calculator for Pediatric and Adolescent Cancer Patients

Hypothesis: Cardiac substructure doses will be significantly ($p < 0.05$) more predictive than whole heart dose in pediatric/adolescent coronary artery disease risk prediction models adjusted for attained age, sex, race/ethnicity, diagnosis age, and anthracycline dose.

Background/Aims: To develop/validate radiation oncology (RO) workflow-integrated personalized pediatric/adolescent cardiac substructure models to predict future risk of coronary artery disease (CAD).

Methods: We developed piecewise exponential models in the Childhood Cancer Survivor Study (CCSS) and externally validated in the St. Jude Lifetime (SJLIFE) to predict severe/life-threatening CAD (events/participants: 549/19,962 CCSS; 129/4,389 SJLIFE). Mean cardiac substructure dose (MCSD) models used lasso regression with 10-fold cross-validation (100 repeats) to select dosimetric predictors from mean doses to coronary arteries, atria, valves, ventricles, and heart V5/V20; we included those retained in $\geq 95\%$ iterations; comparison models used mean heart dose (MHD). Attained age, sex, race/ethnicity, diagnosis age, and anthracycline dose were forced variables. To assess age/lifestyle-acquired cardiovascular risk factors (CVRF: obesity, smoking, hypertension, dyslipidemia, and diabetes), models were refit among those that survived ≥ 20 yrs post-diagnosis. An in-silico study estimated CAD risk for 22 children/adolescents treated with mediastinal IMRT and matched simulated IMPT plans. Risk was also simulated for worst-case scenarios where survivors develop all five CVRF in the decades after treatment. A Python-based calculator was implemented in the RayStation treatment planning system.

Results: MHD models achieved internal/external AUC of 0.736/0.686; CAD rate doubled per 10-Gy MHD (rate ratio (RR): 2.0, 95% CI: 1.87-2.14; $p < 0.001$). MCSD models with left ventricle and left main coronary artery doses statistically significantly improved prediction (internal/external AUC: 0.744/0.694; $p = 0.016$ vs MHD), with RR per 10-Gy of 1.35 (95% CI: 1.11-1.62) and 1.49 (95% CI: 1.32-1.67), respectively ($p < 0.002$). The ≥ 20 -year post-diagnosis MHD models achieved AUC 0.757/0.712; Adding MSDs did not improve fit. Obesity, smoking, hypertension, dyslipidemia, and diabetes increased CAD rates by factors of 1.36, 1.32, 2.80, 1.05, and 2.07, respectively.

In-silico, MCSD models predicted median absolute CAD rates of 5.22 at age 50 per 1,000 person-yr (IQR: 4.43-7.62) for IMRT, reduced by 35% with IMPT (3.89; IQR: 2.87-4.55). MHD models predicted lower rates (IMRT: 3.64; IQR: 3.02-6.31) with $\sim 15\%$ reduction using IMPT (3.15; IQR: 2.75-4.57). The calculator reports the higher of MHD- or MCSD-risk to support conservative decision making. For reference, the predicted CAD rate is 2.49 (IQR: 1.69-3.28) among a same sex matched control group (CCSS siblings without cancer). Among ≥ 20 -year survivors, if five CVRF were to develop versus none,

predicted CAD rates would increase ~5-fold (IMRT RR:4.66, IQR:2.89-6.25); IMPT RR: 4.67, IQR:2.90-6.26).

Conclusion: We developed/validated RO workflow-integrated CAD risk calculators enabling patient-specific, real-time estimates of late CAD risk based on MCSD/MSD, anthracycline dose, demographics, and age/lifestyle-acquired CVRF.

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