PTCOG Abstract (350 words, limit 350)

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Radiation Oncology Workflow-Integrated Individualized Risk Calculator to Comprehensively Predict Future Cardiac Disease Risk Among Pediatric and Adolescent Cancer Patients

Background/Aims: To develop and validate radiation therapy (RT) workflow-integrated individualized risk prediction models to estimate future risk of coronary artery disease (CAD), heart failure (HF), valvular heart disease (VHD), and any cardiac disease in pediatric and adolescent cancer patients.

Methods: Piecewise exponential regression models were developed in the Childhood Cancer Survivor Study (CCSS) and externally validated in the St. Jude Lifetime Cohort (SJLIFE) to predict severe or life-threatening CAD, CHF, VHD, and any cardiac disease (events/participants:1,076/19,838[CCSS]; 295/4,361[SJLIFE]). For mean cardiac substructure dose (MCSD) models, lasso regression with 10-fold cross-validation (100 repeats) selected radiation predictors from mean doses to the heart, 11 cardiac substructures, and heart V5/V20; variables retained ≥95% of iterations were included. Models were adjusted for attained age, sex, race/ethnicity, age at diagnosis, and anthracyclines, with comparison models using mean heart dose (MHD) alone. An in-silico study predicted risk for 22 patients aged 10-20 years treated with mediastinal intensity-modulated radiotherapy (IMRT) compared with estimated risk from simulated intensity-modulated proton therapy (IMPT) plans having the same planning objectives. A PYTHON script-based risk calculator was developed within the RayStation commercial RT-planning system.

Results

Modeling: For HF, VHD, and any cardiac disease, MHD-models demonstrated strong discrimination (internal/external AUCs:0.730-0.802/0.736-0.845; all $p<0.034$ vs chest-RT dose models), with no improvement from adding MCSDs. For CAD, the MHD-model achieved internal/external AUCs of 0.736/0.686. Using left ventricle and left main coronary artery mean doses improved CAD prediction (internal/external AUC: 7.44/6.94; $p=0.016$ vs MHD).

In-silico Study: Using MCSD-models, median predicted CAD rate (IQR:4.43-7.62) for IMRT was 5.22 per 1,000 person-years, decreasing by 40% to 3.19(IQR:2.75-4.57) with IMPT. For CAD, CHF, VHD, and any cardiac disease, median rates for IMRT predicted with MHD-models were 1.96(IQR:1.13-2.57), 4.99(IQR:2.52-10.70), 2.02(IQR:1.22-2.95), and 9.95(IQR:5.42-17.33) per 1,000 person-years, respectively, with IMPT reducing risk by ~15%. Figures 1&2 summarize in-silico results, including rates, rate ratios versus same-sex siblings without cancer, and the RayStation-integrated calculator (representative patient), which reports the higher of the MHD- and MCSD-based CAD risks for a conservative estimate.

Conclusion: We developed and validated a RT workflow-integrated risk-calculator, enabling real-time estimation of future long-term cardiac disease risk during RT treatment planning, allowing comparison of risk from different modalities**.**

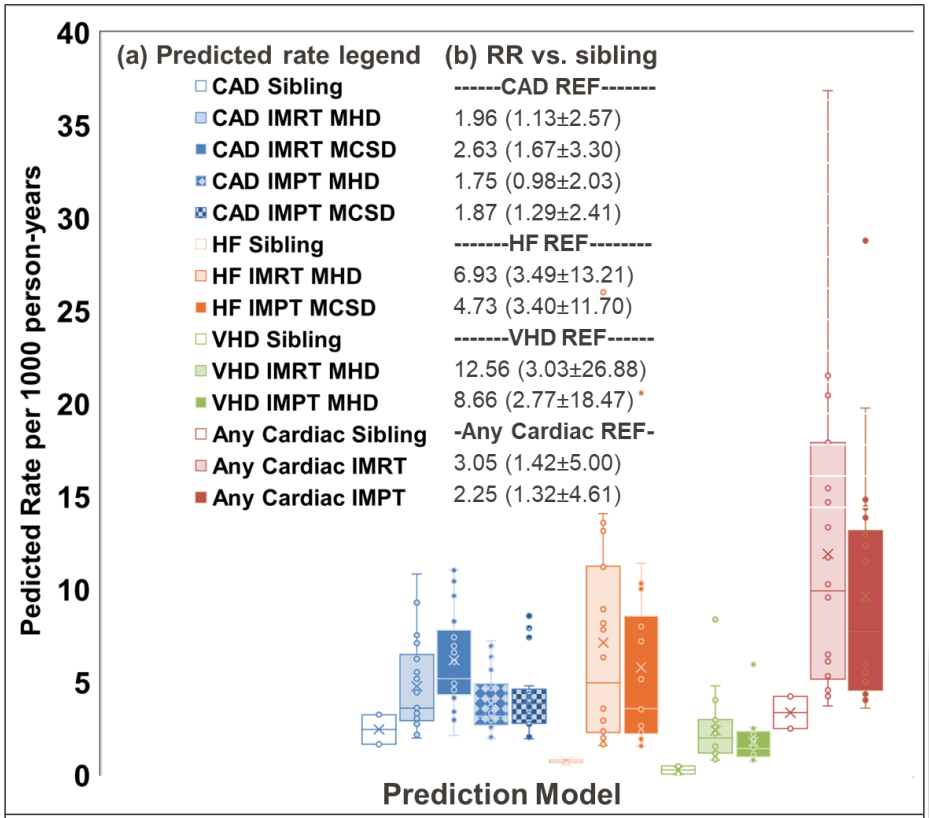

FIGURE 1. **(a)** Box-and-whisker plots of predicted rates of coronary artery disease (CAD), heart failure (HF), valvular heart disease (VHD), and any cardiac disease for 22 patients treated with intensity modulated radiation therapy (IMRT) and anthracyclines, compared with rates for simulated intensity-modulated proton therapy (IMPT) plans prescribed to the same planning target volume and cumulative anthracycline doses. Also shown are median rates with interquartile ranges (IQRs) for each outcome in same-sex siblings from the CCSS sibling cohort without cancer; **(b)** Median rate ratios (RRs) with IQRs for CAD, HF, VHD, and any cardiac disease for each individual in the in-silico study, with rates normalized to the corresponding same-sex sibling.

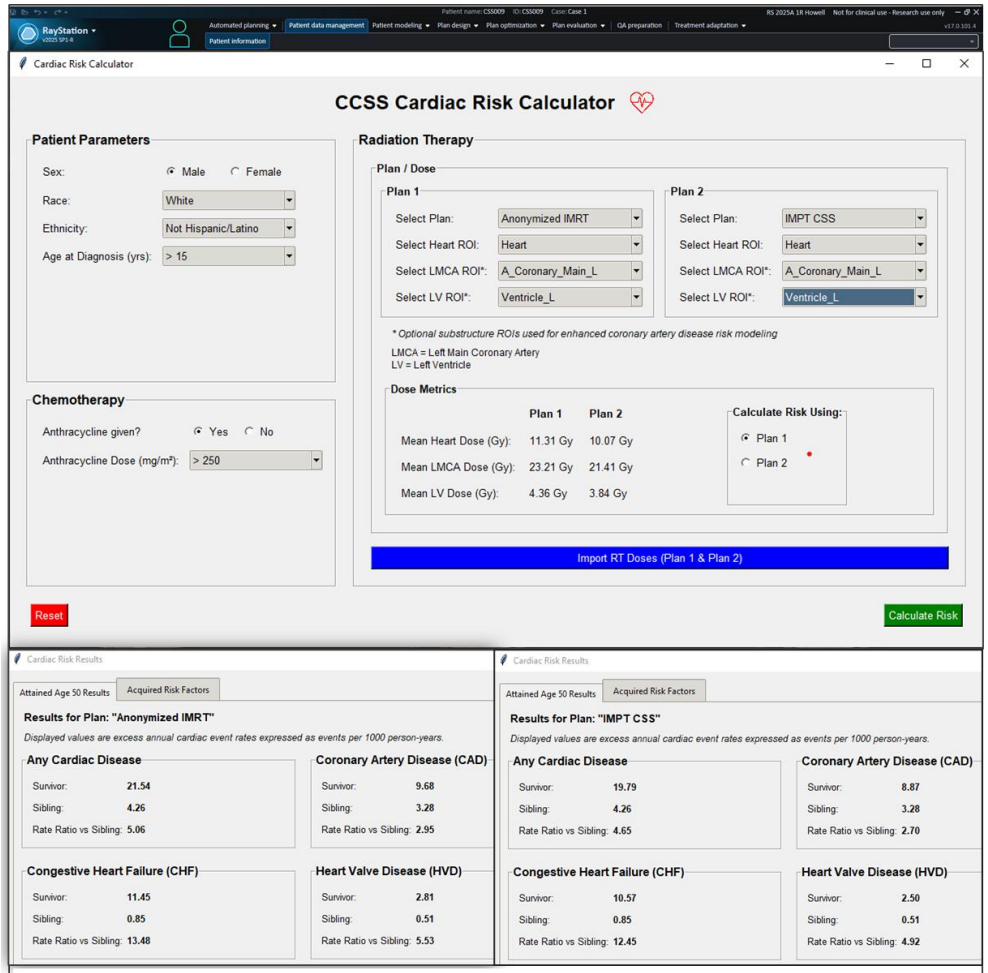

FIGURE 2. Example input and output graphical user interfaces of the CCSS cardiac disease risk calculator implemented in the RayStation commercial treatment planning system (TPS), illustrated for IMRT and IMPT treatment plans from a representative patient in the in-silico study.

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