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Predicting valvular heart disease in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort (SJLIFE)

Background: Radiotherapy (RT)-related valvular heart disease (VHD) is an understudied late toxicity of childhood cancer therapy. We aimed to define the risk of VHD with clinical data available at 5 and 20 years from cancer diagnosis.

Methods: Mean heart RT doses were estimated for participants of the CCSS and SJLIFE cohorts treated with RT. Two piecewise exponential regression prediction models were developed in the CCSS, from entry into survivorship (5 years post cancer diagnosis) and 20 years post diagnosis (inclusive of age- and lifestyle-acquired risk factors), to assess subsequent risk of developing severe/life-threatening/fatal VHD (≥ grade 3 Common Terminology Criteria for Adverse Events [CTCAE]) by age 50 years. Models were validated among clinically assessed SJLIFE survivors.

Results: Among 18,807 CCSS participants [mean age (±standard deviation) at diagnosis=8.1 (5.8) years and 40 (11.1) at assessment] including 9,998 treated with RT, 164 (0.9%) reported VHD after cohort entry. Of those ≥20 years post diagnosis (n=16,618) [7.9 (5.8) years at diagnosis; 42.5 (9.6) at assessment] 138 (0.8%) reported VHD. In SJLIFE, 44 (1.0%) of 4,388 survivors, including 2,103 treated with RT, and 35 (1.4%) of 2,423 ≥20-year survivors had VHD (mean ages at diagnosis and assessment: 7.8 [5.7] and 32 [12] years; 7.6 (5.5) and 38.7 (9.2) years, respectively). Prediction performance at age 50 years was good for both models [areas under the receiver operating characteristic curves 0.84 (95% CI 0.79-0.89) and 0.87 (95% CI 0.81-0.91)]. For each 10 Gy of heart RT, the rate of VHD increased approximately 2.5-fold (Table). Acquired risk factors, except glucose intolerance, further increased the risk, marginally for hypertension, significantly (p<0.05) for obesity (RR 1.7 95% CI 1.0-2.8) and dyslipidemia (RR 2.3 95% CI 1.3-4.0).

	Rate ratios (RR) of VHD			
	From entry into survivorship		From 20-year post diagnosis	
	RR	(95% CI)	RR	(95% CI)
Mean heart RT dose (per 10 Gy)	2.4	(2.2-2.7)	2.5	(2.2-2.9)
Age at diagnosis (years)				
<5		referent		referent
5-9	1.1	(0.6-2.1)	1.2	(0.6-2.5)
10-15	1.1	(0.6-2.1)	1.3	(0.6-2.6)
≥15	1.1	(0.6-2.1)	1.2	(0.6-2.6)
Female sex	1.1	(0.8-1.5)	1.3	(0.9-1.9)
Race/Ethnicity				
non-Hispanic White		referent		referent
non-Hispanic Black	1.3	(0.5-2.8)	0.8	(0.2-2.3)
Other	1.1	(0.6-1.6)	1.0	(0.6-1.7)

Anthracycline dose (mg/m^2)

None		referent		referent
<100	0.6	0.1-1.6	0.8	(0.2-2.2)
100-249	0.9	0.5-1.4	0.9	(0.5-1.5)
≥250	1.5	1.0-2.2	1.3	(0.8-2.1)
Acquired risk factors[*]				
Glucose intolerance			0.3	(0.02-1.3)
Smoking (Y/N)			1.1	(0.8-1.5)
Hypertension		N/A	1.6	(0.9-2.7)
Obesity			1.7	(1.0-2.8)
Dyslipidemia			2.3	(1.3-4.0)

[*] ≥grade 2 CTCAE

Conclusions: In the first study to develop validated risk prediction models for VHD in survivors of childhood cancer, mean heart RT dose and acquired factors significantly increased the risk, suggesting opportunities for intervention.

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