Circulation

RESEARCH LETTER

Long-Term Outcomes of Patients With Mediastinal Radiation–Associated Coronary Artery Disease Undergoing Coronary Revascularization With Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting

Aaron N. Dunn, BA
Eoin Donnellan, MD
Douglas R. Johnston, MD
Alaa Alashi, MD
Grant W. Reed, MD
Christine Jellis, MD, PhD
Amar Krishnaswamy, MD
A. Marc Gillinov, MD
Lars G. Svensson, MD, PhD
Stephen Ellis, MD
Brian P. Griffin, MD
Samir R. Kapadia, MD
Gosta B. Pettersson, MD, PhD
Milind Y. Desai, MD

Patients with prior mediastinal radiation exposure experience an increased risk of coronary artery disease (CAD) and worse outcomes from coronary revascularization compared with patients without prior radiation.[1–4] In addition, 60% to 80% of patients with radiation-associated cardiac disease have valvular disease requiring intervention.[1,3,5] Because of the paucity of literature comparing outcomes of various coronary revascularization strategies for radiation-associated CAD, we sought to study the association of various coronary revascularization strategies with longer-term mortality in such patients.

This observational cohort study included 333 consecutive unique patients with previous mediastinal radiation exposure (190 [57%] for Hodgkin lymphoma, 72 [22%] for breast cancer, 32 [10%] for non-Hodgkin lymphoma, and 39 [11%] others) ≈2 decades before who subsequently developed CAD and underwent coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at a high-volume center between January 2000 and May 2019 (follow-up through September 2019). The Institutional Review Board approved the study with waiver of individual informed consent. All patients were free of recurrent tumor at coronary revascularization. The primary outcome was all-cause mortality. Secondary outcomes were major adverse cardiac events, defined as cardiac death, unplanned revascularization, and nonfatal myocardial infarction. Cox proportional hazards survival analysis was performed (after testing Schoenfeld residuals), and variables with a value of $P<0.1$ on univariable analyses were considered in the multivariable model. Kaplan-Meier analysis was used to generate event curves and compared with the generalized Wilcoxon statistic.

One hundred thirty-three patients (40%) underwent PCI, and 200 (60%) underwent CABG. Clinical and demographic data of the 2 groups are shown in Figure (A). Despite similar baseline SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores (13.8 versus 11.7; $P=0.20$), left main disease and multivessel disease were more prevalent in the CABG group ($P<0.001$). At 106±78 months, death occurred in 158 patients (47%), and 146 patients (44.0%) experienced major adverse cardiac events. There was no significant difference in longer-term mortality among patients undergoing PCI versus those undergoing CABG (generalized Wilcoxon $P=0.61$; Figure [B]), although patients undergoing CABG (versus PCI) experienced lower longer-term major adverse cardiac events (36.0% versus 56.0%; generalized Wilcoxon $P<0.001$), repeat revascularization (29.0% versus 50.0%; generalized Wilcoxon $P<0.001$), and myocardial infarction (12.0% versus 19.0%; generalized Wilcoxon $P=0.01$). After stratification based on concurrent valvular intervention, patients undergoing isolated CABG had better long-term survival compared with patients undergoing isolated PCI, PCI+transcatheter aortic valve replacement, or CABG+multivalve surgery (generalized Wilcoxon statistic $P<0.001$; Figure [C]). On multivariable analysis, concomitant valve intervention (hazard ratio, 3.89 [95% CI, 2.26–6.71]; $P<0.001$) and involvement of the left anterior descending

Key Words: coronary artery bypass ■ coronary artery disease ■ percutaneous coronary intervention ■ radiation ■ radiation injuries

https://www.ahajournals.org/journal/circ

A

Variables	PCI (n=133) N (%)	CABG (n=200) N (%)	p-value
Age (years)	58±13	57±12	0.61
Male gender	65 (49)	112 (56)	0.22
Malignancy history			0.20
Hodgkin's lymphoma	75 (56)	115 (58)	
Breast cancer	26 (20)	46 (23)	
Non-Hodgkin's lymphoma	12 (9)	20 (10)	
Other	20 (15)	19 (9)	
Comorbidities			
Hypertension	90 (68)	133 (67)	0.81
Hyperlipidemia	101 (76)	135 (68)	0.08
Diabetes mellitus	32 (24)	49 (25)	0.97
Smoking History	53 (40)	74 (37)	0.65
Medication use			
Aspirin	114 (86)	150 (75)	0.02
Statin	109 (82)	153 (77)	0.21
Beta blocker	93 (70)	143 (72)	0.80
ACE inhibitor	33 (25)	36 (18)	0.17
ARB	17 (13)	17 (9)	0.27
SYNTAX Score	13±8	11±7	0.20
Echocardiographic data			
≥Moderate MR	50 (38)	78 (39)	0.82
≥Moderate TR	46 (35)	82 (41)	0.24
RVSP (mmHg)	41.7±14.6	42.2±13.7	0.79
LVEF (%)	51.7±12.5	52.8±11.2	0.41
Laboratory data			
Creatinine (mg/dL)	1.14±0.45	1.09±0.6	0.38
Pulmonary function testing			
FEV1/FVC (%)	92±14	92±13	0.81
DLCO (%)	63±18	62±19	0.74
Left main disease	13 (10)	54 (27)	<0.001
Multivessel disease	26 (20)	153 (77)	<0.001
Number of target vessels	1.2±0.6	2.4±1.1	<0.001

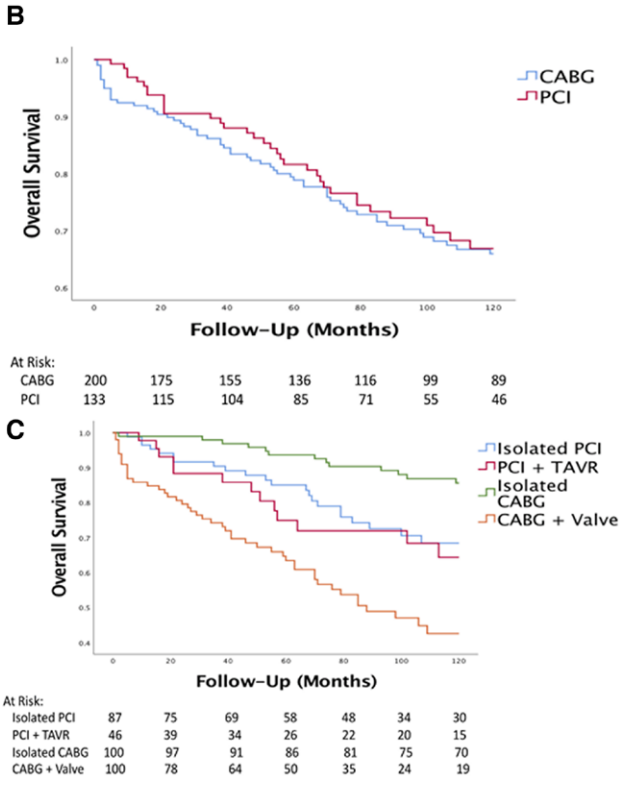

Figure. Cohort description and primary study outcomes.
A, Characteristics of study population. Kaplan-Meier curves divided into 2 subgroups: (**B**) percutaneous coronary intervention (PCI) vs coronary artery bypass grafting (CABG) and (**C**) 4 subgroups (isolated PCI, PCI+transcatheter aortic valve replacement (TAVR), isolated CABG, CABG+valves). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DLCO, diffusion lung capacity; FEV1, forced expiratory volume at 1 minute; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RVSP, right ventricular systolic pressure; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; and TR, tricuspid regurgitation.

artery (hazard ratio, 1.97 [95% CI, 0.51–1.44]; *P*=0.02) were independently associated with mortality.

The optimal strategy for management of CAD in radiation-associated cardiac disease remains understudied. Although the SYNTAX scores tend to be lower in radiation-associated cardiac disease because of discrete lesions that are more proximal rather than bi/trifurcation,[2] an additional challenge is concomitant valvular disease, requiring more complex procedures.[1,3,5] In this study, we identified no difference in mortality between those treated with PCI and patients treated with CABG. However, patients with isolated CABG had much better longer-term survival compared with other groups, including those with isolated PCI. CABG had several favorable long-term outcomes (versus PCI), including lower rates of major adverse cardiac events, revascularization, and myocardial infarction despite comparable baseline SYNTAX scores and demographics. A plausible explanation is that mediastinal radiation exposure is associated with proximal vessel involvement, a factor associated with poorer outcomes in patients after PCI compared with those without proximal disease or those with proximal disease undergoing CABG.[1–4] Our study also provides additional evidence for a high burden of valvular disease in patients with radiation-associated cardiac disease, with 44% of patients with CAD requiring concurrent valvular intervention. Such patients were nearly 4-fold as likely to experience long-term mortality. Given the high rate of comorbid valvular disease among patients with radiation-associated CAD and the poor outcomes among this cohort undergoing reoperations,[3] there is need for further investigation into comprehensive heart team–led management strategies.[1]

ARTICLE INFORMATION

The authors will not make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure.

This manuscript was sent to Marc Ruel, Cardiovascular Surgery Issue Editor, for review by expert referees, editorial decision, and final disposition.

Correspondence

Milind Desai, MD, Heart and Vascular Institute, Mail Code J1-5, 9500 Euclid Ave, Cleveland, OH 44195. Email desaim2@ccf.org

Affiliations

Cleveland Clinic Lerner College of Medicine, OH (A.N.D.). Departments of Cardiovascular Medicine (E.D., A.A., G.W.R., C.J., A.K.., S.E., B.P.G., S.R.K., G.B.P., M.Y.D.) and Cardiothoracic Surgery (D.R.J., A.M.G., L.G.S.), Heart and Vascular Institute, Cleveland Clinic, OH.

Acknowledgments

Dr Desai acknowledges the Haslam Family Endowed Chair in Cardiovascular Medicine and Khouri family philanthropic gift for research in premature CAD.

Disclosures

None.

REFERENCES

1. Desai MY, Windecker S, Lancellotti P, Bax JJ, Griffin BP, Cahlon O, Johnston DR. Prevention, diagnosis, and management of radiation-associated cardiac disease: *JACC* Scientific Expert Panel. *J Am Coll Cardiol.* 2019;74:905–927. doi: 10.1016/j.jacc.2019.07.006
2. Reed GW, Masri A, Griffin BP, Kapadia SR, Ellis SG, Desai MY. Long-term mortality in patients with radiation-associated coronary artery disease treated with percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2016;9:e003483. doi: 10.1161/CIRCINTERVENTIONS.115.003483
3. Wu W, Masri A, Popovic ZB, Smedira NG, Lytle BW, Marwick TH, Griffin BP, Desai MY. Long-term survival of patients with radiation heart disease undergoing cardiac surgery: a cohort study. *Circulation.* 2013;127:1476–1485. doi: 10.1161/CIRCULATIONAHA.113.001435
4. Fender EA, Liang JJ, Sio TT, Stulak JM, Lennon RJ, Slusser JP, Ashman JB, Miller RC, Herrmann J, Prasad A, et al. Percutaneous revascularization in patients treated with thoracic radiation for cancer. *Am Heart J.* 2017;187:98–103. doi: 10.1016/j.ahj.2017.02.014
5. Donnellan E, Krishnaswamy A, Hutt-Centeno E, Johnston DR, Aguilera J, Kapadia SR, Mick S, Svensson LG, Griffin BP, Desai MY. Outcomes of patients with mediastinal radiation-associated severe aortic stenosis undergoing transcatheter aortic valve replacement. *Circulation.* 2018;138:1752–1754. doi: 10.1161/CIRCULATIONAHA.118.035514