Pulmonary fibrosis on multidetector computed tomography and mortality in patients with radiation-associated cardiac disease undergoing cardiac surgery

Milind Y. Desai, MD,[a,b] Karuppasamy Karunakaravel, MD,[b] Willis Wu, MD,[a] Shikhar Agarwal, MD,[a] Nicholas G. Smedira, MD,[a] Bruce W. Lytle, MD,[a] and Brian P. Griffin, MD[a]

Objective: In the long-term, malignancy-associated thoracic radiation leads to varying degrees of pulmonary fibrosis and radiation-associated cardiac disease, often requiring cardiothoracic surgery. We sought to determine whether pulmonary fibrosis affects mortality in patients with radiation-associated cardiac disease undergoing cardiothoracic surgery.

Methods: We studied 117 patients (aged 63 ± 15 years, 71% were women) with radiation-associated cardiac disease receiving multimodality imaging who underwent cardiothoracic surgery (21% redo) between 2000 and 2003. Some 50% of patients had breast cancer, 28% of patients had Hodgkin's lymphoma, 9% of patients had lung cancer, and 13% of patients had other cancers. Time from radiation was 18 ± 12 years. Clinical, pulmonary function, angiographic, and echocardiographic parameters were recorded. On multidetector chest computed tomography, ascending aortic calcification and degree of pulmonary fibrosis (in 5 lobes for a score of 15: 0 = none, 1 = linear streaks, 2 = moderate fibrosis, and 3 = severe fibrosis with traction bronchiectasis) were recorded.

Results: Mean European System for Cardiac Operative Risk Evaluation was 7.9 ± 3, and forced expiratory volume at 1 minute/forced vital capacity ratio was 0.75 ± 0.2. Mean left ventricular ejection fraction was 49% ± 12%, and right systolic ventricular pressure was 42 ± 5 mm Hg. Some 27% of patients had severe aortic stenosis, and 46% of patients had II+ or greater mitral regurgitation. On multidetector chest computed tomography, mean pulmonary fibrosis score was 3.5 ± 3, and 59% of patients had ascending aortic calcification. Isolated coronary artery bypass was performed in 17% of patients; the rest were combination surgeries. At 6.3 ± 0.4 years, there were 59 deaths (50%) (3% died 1 month postoperatively). Forty-five patients (39%) had pulmonary complications in follow-up. Increasing pulmonary fibrosis score (hazard ratio, 1.11; 95% confidence interval, 1.02-1.20; $P = .02$), worse European System for Cardiac Operative Risk Evaluation (hazard ratio, 1.10; 95% confidence interval, 1.01-1.21; $P = .04$), and lack of beta-blocker (hazard ratio, 0.54; 95% confidence interval, 0.31-0.94, $P = .008$) and aspirin (hazard ratio, 0.54; 95% confidence interval, 0.31-0.94; $P = .03$) independently predicted mortality.

Conclusions: In patients with radiation-associated cardiac disease undergoing cardiothoracic surgery, worsening pulmonary fibrosis is associated with increased mortality. (J Thorac Cardiovasc Surg 2014;148:475-81)

Supplemental material is available online.

Thoracic radiation is an effective treatment for mediastinal and thoracic cancers; however, cardiac disease is frequently observed as a major cause of morbidity and mortality in long-term survivors.[1-6] Although the exact prevalence of radiation-associated cardiac disease (RACD) is difficult to ascertain, studies have suggested that up to 42% of patients will have significant asymptomatic valvular disease and 14% of patients will have myocardial ischemia[1-3,7-11] in the next couple of decades after radiation.[6] The prevalence of RACD is increasing because of maturation of the latent period from the initial administration of chest radiotherapy, which began in the late 1960s. The long-term cardiac effects of radiation seem to be fairly heterogeneous with aggressive coronary artery disease (especially ostial/proximal), valvular disease (including significant, especially anterior mitral annular thickening), pericardial disease (including diffuse calcific constriction), advanced diastolic dysfunction, and conduction disease developing in patients.[7-11] These patients often require cardiothoracic surgery (CTS), and it is increasingly being recognized that such patients

From the Heart and Vascular Institute[a] and Imaging Institute,[b] Cleveland Clinic, Cleveland, Ohio.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication June 17, 2013; revisions received Aug 12, 2013; accepted for publication Aug 29, 2013; available ahead of print Nov 18, 2013.

Address for reprints: Milind Y. Desai, MD, Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Ave, Desk J1-5, Cleveland, OH 44195 (E-mail: desaim2@ccf.org).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2013.08.087

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CI	= confidence interval
CTS	= cardiothoracic surgery
euroSCORE	= European System for Cardiac Operative Risk Evaluation
FEV1	= forced expiratory volume at 1 minute
FVC	= forced vital capacity
HR	= hazard ratio
LV	= left ventricular
MDCT	= multidetector chest computed tomography
PF	= pulmonary fibrosis
RACD	= radiation-associated cardiac disease
VTI	= velocity time integral

have a high degree of morbidity and mortality.[2,3,5,12-15] In a recent large cohort study, we have demonstrated that patients with RACD have a significantly higher mortality compared with a similarly matched control population undergoing cardiac surgery.[16] Furthermore, the primary cause of mortality in that study was cardiopulmonary failure during long-term follow-up.

In addition to peculiar echocardiographic features,[16] a characteristic pattern of pulmonary fibrosis (PF) also may develop in patients with prior thoracic radiation,[17] ranging from linear fibrotic streaks to severe fibrosis and traction bronchiectasis, especially in the regions that are exposed to the radiation port (Figure E1). We sought to determine the impact of the severity of PF on long-term mortality in patients with RACD who underwent CTS.

MATERIALS AND METHODS

Study Design

This was an observational study of 117 consecutive patients with RACD who underwent CTS at the Heart and Vascular Institute and Imaging Institute between 2000 and 2003 and had a multidetector chest computed tomography (MDCT) scan and a resting echocardiogram performed in close temporal association with the cardiac surgery (typically within 1 month preoperatively). All patients had a history of malignancy requiring chest irradiation and as a result had subsequently developed coronary/valvular disease requiring CTS. The diagnosis of RACD was made after a thorough clinical and echocardiographic evaluation by experienced cardiologists, based on characteristic findings, as described previously.[16] In this group, type of prior malignancy and area of radiation were ascertained. Where available, year of last radiation dose was recorded. Also, the radiation dosages for various malignancies were recorded on the basis of historic data. All patients were cancer-free at the time of cardiac surgery.

Clinical Data

Data were assembled after appropriate approval by the institutional review board. Demographics and clinical data were recorded prospectively in the electronic health record. History and type of prior cardiac surgery were recorded. Use of medications at the time of initial presentation and whether they were initiated in the postoperative period were recorded. Presence of permanent atrial fibrillation (defined according to guidelines[18]) was ascertained at baseline and at the time of discharge. Presence of an automated implantable cardioverter defibrillator and need for permanent pacemaker were recorded. From spirometry and pulmonary function testing, we recorded forced vital capacity (FVC) and forced expiratory volume at 1 minute (FEV1) data. We calculated FEV1/FVC ratio. We also recorded the extent of any pulmonary complications during follow-up, dividing them as follows: simple (recurrent pleurocentesis, home oxygen use) and major (prolonged intubation with resultant tracheostomy and pleurodesis/decortication).

The details of cardiac surgery were recorded and categorized as follows: (1) coronary artery bypass grafting (CABG); (2) CABG + 1-valve repair/replacement; (3) CABG + $\geq$2-valve repair/replacement; (4) 1-valve repair/replacement; (5) $\geq$2-valve repair/replacement; and (6) others, including pericardiectomy, transplantation, left ventricular (LV) assist device, aortic surgery, and myectomy. In patients who underwent CABG, the number of bypassed vessels was recorded. On the basis of the available preoperative data, additive euroSCORE was calculated to predict the risk of postoperative mortality.[19]

Follow-up

The beginning of follow-up was considered as the date of cardiac surgery at our institution. Death notification was obtained from the medical record or the US Social Security Death Index database, and survival was ascertained during follow-up (last query was in March 2011). Where available, cause of death was ascertained. Postoperative stroke was defined as transient or permanent neurologic impairment and disability due to vascular causes, including episodes lasting less than 24 hours, which were regarded as transient ischemic attacks.

Echocardiography

All patients underwent a comprehensive transthoracic echocardiogram using commercial instruments (Philips Medical Systems, NA, Bothell, Wash; General Electric Medical Systems, Milwaukee, Wis; and Siemens Medical Solutions USA, Inc, Malvern, Pa) as part of standard clinical diagnostic and pre-open surgery workup. Standard parameters were assessed according to standard guidelines and recorded prospectively.[20-23] Degree of mitral, aortic, and tricuspid regurgitation were assessed on a scale of 0 to 4+ (0 = none, 1 + = mild, 2+ = moderate, 3+ = moderately severe, and 4+ = severe). Right ventricular systolic pressure was recorded from tricuspid regurgitation velocity and estimated right atrial pressure. Peak/mean transvalvular gradients, velocity time integrals (VTIs) across valves/LV outflow tract, and diameter of LV outflow tract were recorded. Aortic valve area was calculated using continuity equation, and aortic stenosis was graded in a standard fashion. Dimensionless index (LV outflow tract VTI/aortic VTI) was calculated. Postoperative transthoracic echocardiography was performed as described earlier.

Chest Multidetector Computed Tomography

Cardiothoracic MDCT angiographic studies were performed using standard scanners available at the time (Siemens Medical Systems, Erlangen, Germany) using the following parameters: nongated spiral imaging, 750 to 850 mAs, 120 kV, and 1-mm slice thickness. In 72 patients, at the discretion of the referring physicians, no iodinated contrast was administered. In the remaining 45 patients, 90 mL isosmolar contrast was administered, with use of peak enhancement in the aortic root for timing of the scan. Over the years, the scan parameters generally remained similar despite scanner upgrades. All images were acquired during an inspiratory breath hold of 10 to 20 seconds.

Two independent readers with experience in interpretation of chest computed tomography (MD and KK) scored the degree of PF, on a