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Editorial

Radiation-Associated Cardiac Disease: More Complicated Than Just Transcatheter Replacement of the Aortic Valve☆

Milind Y. Desai, Douglas R. Johnston, Lars G. Svensson*
From the Center of Radiation Heart Disease and the Valve Center, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH
*Corresponding author: Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue / Desk J4-1, Cleveland, OH 44195.
E-mail address: svenssl@ccf.org

Mediastinal radiotherapy (XRT), which is frequently used to treat thoracic malignancies and lymphomas, is associated with significantly improved survival for cancer patients. However, in many instances, there is unavoidable irradiation of healthy surrounding tissues, which can cause long-term side effects. Among the myriad potential side effects, radiation-associated cardiac disease (RACD) can develop gradually over several years following XRT. While newer XRT-delivery techniques have reduced doses and cardiac involvement, a major current issue remains the development of RACD in patients exposed to XRT decades ago [1]. As a result, appropriate recognition of RACD is warranted in day-to-day clinical practice. RACD is a spectrum of deleterious effects ranging from pre-clinical findings to symptomatic clinical disease and includes myocardial fibrosis/dysfunction; valvular heart disease (regurgitation and/or stenosis); vasculopathy, including coronary artery disease; pericardial disease; and conduction abnormalities [1].

Radiation-associated valvular disease usually manifests as progressive valve thickening and calcification resulting in valve restriction presenting as stenosis or regurgitation. Usually, patients become symptomatic later than they do with coronary disease. Awareness of this latency is important, given that asymptomatic cancer survivors treated more than 20 years ago remain at significantly increased risk of aortic regurgitation (60% vs. 4%), tricuspid regurgitation (4% vs. 0%), and aortic stenosis (AS; 16% vs. 0%) compared to those treated within the last 10 years [2]. Radiation-associated valvular thickening and calcification is more extensive and often involves surrounding structures, such as the annulus, subvalvular apparatus, and aorto-mitral curtain (intervalvular fibrosa). Occurrence of significant valvular abnormalities ranges from 7% to 39% at 10 years and 12% to 60% at 20 years, with the mitral and aortic valves being the most affected [3]. However, many patients present with multiple overlapping cardiac lesions leading to important management challenges, especially as many patients also have radiation damage to their lung parenchyma, adding to the symptomatology and further impacting cardiac surgical risk.

Multiple studies have suggested that while operative mortality for RACD patients in experienced centers may approach that for matched non-RACD patients, long-term outcomes are demonstrably worse, despite similar preoperative risk scores, with XRT exposure emerging as an independent risk factor [4,5]. Cardiac reoperation in RACD patients is especially associated with higher longer-term mortality. In a recent study of patients with severe AS undergoing surgical aortic valve replacement (SAVR), patients with prior mediastinal XRT had significantly higher longer-term mortality than did a matched cohort (48% vs. 7% over a 5.7-year period) [5]. Also, in patients with moderate AS, despite similar progression of AS in RACD versus a comparison group, RACD patients had significantly higher longer-term mortality, with prior XRT a major risk factor for longer-term mortality [6].

Thus, there is obviously increased enthusiasm about the use of transcatheter aortic valve replacement (TAVR) in high-risk patients with severe AS in the setting of documented RACD. Among patients included in the PARTNER 1B trial and continued-access registry, 85 of 369 patients (23%) were considered inoperable for SAVR because of technical ineligibility [7]. The most common criteria for surgical inoperability in these patients were porcelain aorta (42%) and previous radiation therapy to the chest (25%). At 2-year follow-up, mortality was lower among patients considered technically inoperable than in those given conservative treatment (23.3% vs. 67.4%, $p<0.001$) [7]. A recent study reported outcomes of 98 patients with radiation-associated symptomatic, severe AS undergoing TAVR. At a mean of 2.3 years, annualized mortality was 8% per year [8]. Post-procedural permanent pacemaker was required in 15% of patients, and moderate to severe aortic regurgitation was recorded in 8% of patients.

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* Corresponding author at: Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue / Desk J4-1, Cleveland, OH 44195.
E-mail address: svenssl@ccf.org (L.G. Svensson).

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In their paper published in this issue of *Cardiovascular Revascularization Medicine*, Gajanana and colleagues [9] report outcomes in 44 patients with RACD versus 1106 patients without RACD, all of whom underwent TAVR. As expected, patients with XRT were younger and had similar Society of Thoracic Surgeons risk scores. There was no significant difference between the 2 groups with regard to permanent pacemaker implantation. However, 30-day and 1-year mortality in the RACD group were fairly high at 7% and 25%, respectively, albeit similar to the non-RACD group. The 1-year mortality in this cohort of RACD patients was significantly higher than has been reported in previously published data [8]. The reasons for this are unclear, but it might suggest that these patients were sicker and perhaps had more cardiac lesions than isolated severe AS accounting for their symptomatology. For example, approximately 50% of patients had severe mitral annular calcification, possibly suggesting that they had significant concomitant mitral stenosis/regurgitation, which would not be addressed by TAVR alone.

Given the fact that many of these patients do not just have isolated severe AS, but rather have multivalve disease, concomitant coronary disease, and myocardial dysfunction, careful attention to these additional processes is crucial before addressing one isolated process (i.e., severe AS). Unfortunately, we simply do not understand enough about the variation in myocardial fibrosis and pulmonary disease, and the impact of radiation-induced vasculopathy on outcomes to make meaningful predictions about who is truly high risk for an intervention. As a result, this complex disease process demands the close attention of a multidisciplinary team of experienced providers at an experienced center, with careful application of less invasive technologies when appropriate from a surgical-risk perspective. For those patients in whom the disease has progressed to the point that surgery is appropriate and deemed safe, consideration should be given to performing the most complete operation on all the affected valves and coronary arteries, along with fibrous skeleton reconstruction and aortic reconstruction as necessary, rather than succumbing to the temptation of an isolated TAVR.

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