The risk of reoperative cardiac surgery in radiation-induced valvular disease

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ABSTRACT

Objective: Mediastinal radiation therapy (MRT) increases the risk for adverse outcomes after cardiac surgery and is not incorporated in the Society of Thoracic Surgeons (STS) risk algorithm. We aimed to quantify the surgical risk conferred by MRT in patients undergoing primary and reoperative valvular operations.

Methods: A retrospective analysis of 261 consecutive patients with prior MRT who underwent valvular operations between January 2002 and May 2015. Short- and long-term outcomes were compared for STS predicted risk of mortality, surgery type, gender, year of surgery, and age-matched patients stratified by reoperative status.

Results: Mean age was 62.6 ± 12.1 years and 174 (67%) were women. The majority had received MRT for Hodgkin lymphoma (48.2%) and breast cancer (36%). Overall, 214 (82%) were primary and 47 (18%) were reoperative procedures. Reoperation carried a higher operative mortality than primary cases (17% vs 3.7%; $P = .003$). Compared with the 836 nonradiated matches, operative mortality and observed-to-expected STS mortality ratios were higher in primary (3.8% [1.4] vs 0.8% [0.32]; $P = .004$) and reoperative (17% [3.35] vs 2.3% [0.45]; $P = .001$) patients with prior MRT. Cox proportional hazard modeling revealed that in patients with previous MRT, primary (hazard ratio, 2.24; 95% confidence interval, 1.73-2.91) and reoperative status (hazard ratio, 3.19; 95% confidence interval, 1.95-5.21) adversely affected long-term survival compared with nonradiated matches.

Conclusions: Surgery for radiation-induced valvular heart disease has a higher operative mortality than predicted by STS predicted risk of mortality. Reoperations are associated with increased morbidity and mortality compared with primary cases. Careful patient selection is paramount and expanded indications for transcatheter therapies should be considered, especially in reoperative patients. (J Thorac Cardiovasc Surg 2017;154:1883-95)

Reoperative status was a significant predictor for long term mortality (hazard ratio, 1.92; $P = .013$).

Central Message

Surgery for radiation-induced valvular heart disease has higher mortality than predicted by Society of Thoracic Surgeons score. Reoperations are associated with increased morbidity and mortality compared with primary cases.

Perspective

This analysis of patients undergoing surgery for radiation-induced valvular heart disease shows that the Society of Thoracic Surgeons risk model does not adequately capture their operative mortality. Reoperation for radiation-induced valvular heart disease is associated with a higher operative and long-term mortality compared with primary surgery. This result should prompt careful preoperative risk evaluation and expand the indications for transcatheter valve therapies.

See Editorial Commentary page 1896.

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Mediastinal radiation therapy (MRT) remains an effective treatment for thoracic and chest wall neoplasms, including lymphomas, breast cancer, thymomas, and lung and esophageal cancers. However, MRT carries many delayed cardiovascular adverse effects such as accelerated coronary

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Abbreviations and Acronyms

AVR	= aortic valve replacement
EMR	= electronic medical record
MRT	= mediastinal radiation therapy
NYHA	= New York Heart Association
PROM	= predicted risk of mortality
STS	= Society of Thoracic Surgeons
VHD	= valvular heart disease

artery disease, valvular heart disease (VHD), conduction system abnormalities, pericardial constriction, and restrictive cardiomyopathy.¹⁻⁶ This risk is increased with extended radiation treatment fields and higher radiation doses, such as those used to treat Hodgkin lymphoma, testicular cancer, and thymomas.⁷ VHD is estimated to develop in 6% to 15%⁸ of patients who receive MRT, 11 to 16 years after its completion.^{2,9} Aortic regurgitation, aortic stenosis, and tricuspid regurgitation are present in 60%, 16%, and 4% of these patients, respectively.^{10,11} Aortic stenosis is the most common MRT-induced valvular abnormality requiring surgical intervention.¹⁰

It is known that prior MRT is associated with inferior short-term and long-term outcomes after cardiac surgery.^{5,7,12,13} However, the most commonly used risk prediction algorithm in the United States, the Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM), does not incorporate prior MRT into its calculations.^{14,15} Although there are several reports evaluating operative outcomes for radiation-induced VHD, they are limited by their small numbers and heterogeneous cohorts.^{3,5,13,16} We hypothesized that surgery for radiation-induced VHD is associated with adverse outcomes and that this risk is amplified in patients undergoing reoperative cardiac surgery. Accordingly, we compared the outcomes of patients undergoing primary and reoperative valvular operations for radiation-induced VHD to a matched cohort of primary and reoperative valvular patients without a history of MRT.

METHODS

Study Population

All adult patients aged ≥ 18 years who underwent valvular surgery at Brigham and Women's Hospital between January 2002 and May 2015 were identified from our electronic medical record (EMR). All patients with isolated valvular or concomitant valvular and/or coronary artery bypass graft surgery were included. Those with valvular operations for endocarditis, heart transplantation, or ventricular assist devices were excluded. A total of 261 out of 9659 (2.7%) patients underwent valvular surgery for VHD following MRT for a documented malignancy. Patients were grouped by whether it was a primary cardiac surgery ($n = 214$) or a redo sternotomy (reoperation) ($n = 47$).

The indication for MRT was collected for all patients. However, the dates and doses of MRT were not reliably documented in the available EMR, predominately due to the remoteness of the MRT. The diagnosis

of MRT-induced VHD was based on comprehensive clinical and imaging data as well as the expert opinion of the referring cardiologist. All patients were cleared by oncology before surgery.

Data Collection and Outcomes

Patient characteristics, perioperative data, laboratory test results, and in-hospital outcomes were recorded electronically at the time of presentation. Data were extracted from the EMR and variables were defined and coded according to the STS Adult Cardiac Surgery Database version 2.52 specifications, unless otherwise noted. The presence of meaningful coronary artery disease was defined as a $\geq 70\%$ obstruction in any coronary or $\geq 50\%$ in the left main coronary artery. Right ventricular dysfunction, right ventricular dilation, nonischemic cardiomyopathy, and restrictive cardiomyopathy were deemed positive if present as moderate or severe in the patients' preoperative echocardiogram. Operative mortality was defined as any death occurring in-house during the index admission, or within 30 days of surgery if discharged.

The primary outcomes of interest were operative mortality and long-term survival. Secondary outcomes included valve-related complications, perioperative morbidity, and length of stay.

Longitudinal mortality data was obtained from our internal research repository, routine patient follow-up, and our state Department of Public Health. Survival follow-up was 100% in this cohort. Follow-up time was measured in months from the date of surgery to the date of death or study end (April 30, 2016) if alive.

Partners Healthcare Institutional Review Board approved this study. Informed consent from individual patients was waived.

Statistical Analysis

Normally distributed continuous variables are expressed as mean $\pm$ standard deviation and were compared using Student *t* tests with Levene test for homogeneity of variance. Nonnormally distributed variables are expressed as median and interquartile range and were compared using Mann-Whitney *U* tests. Categorical variables are presented as number and percentage and were compared using χ^2 or Fisher exact tests. Longitudinal survival was estimated by Kaplan-Meier analyses, and groups were compared using log-rank test. A forward-stepwise Cox proportional hazard model was used to evaluate risk factors influencing survival. Continuous variables evaluated included age, creatinine (in milligrams per deciliter), and ejection fraction (as a percentage). Categorical variables included type of cancer, type of surgery, gender, vascular and cerebrovascular disease, renal insufficiency, congestive heart failure, and previous cardiac surgery. Variables selected for inclusion in the Cox model included those that were significantly associated with mortality on univariate analyses, those known to be contributors to all-cause mortality, and those with clinical importance to morbidity and mortality. All analyses were conducted using IBM SPSS Statistics version 22.0 (IBM-SPSS Inc, Armonk, NY) and $P \leq .05$ was the criterion for significance.

Matched Analysis

To better quantify the operative morbidity and mortality risks associated with MRT before reoperative valvular surgery, we sought to compare outcomes with a matched cohort. We thus first derived from our consecutive series of valve patients a pool of potential matches with the same frequency distributions for age, gender, year of surgery, and type of procedure, who had no documented history of cancer. We then selected matches on the basis of nearest STS PROM within a 0.05% caliper, followed by surgery type, gender, year of surgery, and age, stratified by reoperative status. The intended goal was 3 to 4 matches per MRT patient; however, all matches with exact STS PROM (to 4 decimal places), procedure, and gender were retained. A total of 1049 matched patients were identified; 836 primary patients without MRT (3.2 matches per MRT patient) and 213 reoperative patients (5.7 matches per reoperative

TABLE 1. Baseline characteristics of primary and reoperative patients with radiation-induced valvular heart disease

Demographic characteristic	All patients (n = 261)	Reoperative (n = 47)	Primary (n = 214)	P value
Age (y)	62.6 ± 12.1	60.5 ± 13.5	63.1 ± 12.1	.178
Women	174 (66.6)	19 (40.4)	155 (72.4)	.001
Diabetes	47 (18.0)	13 (27.7)	34 (15.9)	.062
Renal insufficiency	15 (5.7)	6 (12.8)	9 (4.2)	.034
Preoperative Cr (mg/dL)	1.15 ± 0.38	1.23 ± 0.57	0.98 ± 0.43	.001
Peripheral vascular disease	33 (12.6)	13 (27.7)	20 (9.3)	.002
Cerebrovascular accident	5 (1.9)	3 (6.4)	2 (0.9)	.042
Endocarditis	9 (3.5)	5 (10.6)	4 (1.9)	.011
Congestive heart failure	133 (51.0)	32 (68.3)	101 (47.2)	.053
NYHA class III or IV	104 (39.8)	27 (57.4)	77 (36.0)	.008
Ejection fraction (%)	60.0 (50-65)	55.0 (45-60)	60.0 (50-65)	.009
Atrial fibrillation	24 (9.2)	19 (8.9)	5 (10.6)	.780
STS PROM	3.01 ± 3.05	5.21 ± 5.37	2.58 ± 2.15	.001
Preoperative cardiac function				
Coronary artery disease	111 (42.5)	85 (39.7)	26 (55.3)	.072
Left coronary artery	86 (32.9)	64 (29.9)	22 (46.8)	.039
Right coronary artery	69 (26.5)	47 (22)	22 (46.8)	.002
Left main disease	31 (11.8)	23 (10.7)	8 (17)	.222
Nonischemic cardiomyopathy	20 (7.7)	16 (7.5)	4 (8.5)	.765
Restrictive cardiomyopathy	4 (1.5)	3 (1.4)	1 (2.1)	.550
Moderate/severe RV dysfunction	6 (2.3)	2 (0.9)	4 (8.6)	.011
Moderate/severe RV dilation	11 (4.2)	6 (2.8)	5 (10.6)	.030
Moderate/severe tricuspid regurgitation	50 (19.1)	36 (16.8)	14 (29.8)	.063

Values are presented as n (%), mean ± standard deviation, or median (IQR). Cr, Creatinine; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; PROM, predicted risk of mortality; RV, right ventricle.

MRT patient). Three MRT patients could not be matched satisfactorily. Conditional models using logistic regression for operative mortality and a Cox proportional hazards for cumulative survival were performed to adjust for remaining differences in the matched cohorts baseline characteristics.

RESULTS

Preoperative Characteristics of Patients With Radiation-Induced VHD

Baseline characteristics and preoperative cardiac function of the overall cohort of primary and reoperative patients with radiation-induced VHD are shown in Table 1. Although age was similar between primary and reoperative patients (63.1 vs 60.5 years, respectively; $P = .18$), there were more women in the primary surgical group (72.4% vs 40.4%; $P = .001$). Reoperative patients had more comorbidities, including renal insufficiency (12.8% vs 4.2%; $P = .034$), peripheral vascular disease (27.7% vs 9.3%; $P = .002$), prior stroke (6.4% vs 0.9%; $P = .042$), and previous history of endocarditis (10.6% vs 1.9%; $P = .011$). The overall prevalence of atrial fibrillation was 9.2% (10% in reoperative and 8.9% in

primary cases; $P = .78$) The mean STS PROM was significantly higher for reoperative patients with those undergoing primary procedures (5.21 vs 2.58; $P = .001$).

The overall prevalence of coronary artery disease was 42%—32.9% on the left and 26.5% on the right coronary artery—with 11.8% having >50% obstruction in the left main coronary artery. Patients undergoing reoperation had a higher burden of both left (46.8% vs 29.9%; $P = .039$) and right (46.8% vs 22%; $P = .002$) coronary disease, compared with primary cases.

Pericarditis was present in 10.7% of patients, 2.7% of which was constrictive. Moderate or severe right ventricular dysfunction was observed in 2.3% of the cohort, but was higher among reoperative cases (8.6% vs 0.9%; $P = .011$). Moderate or severe right ventricular dilation was present in 4.2% of patients and was also higher among reoperative cases (10.6% vs 2.8%; $P = .030$).

The malignancies for which MRT was indicated are shown in Table 2. Hodgkin lymphoma was the most common overall (48.3%), but was more common in the reoperative group (61.7% vs 45.3%; $P = .053$). Breast cancer was the second most common malignancy (36%),

TABLE 2. Previous malignancy for reoperative and primary patients with radiation-induced valvular heart disease

Previous malignancy	All patients (n = 261)	Reoperative (n = 47)	Primary (n = 214)	P value
Breast cancer	94 (36.0)	8 (17.0)	86 (40.2)	.002
Hodgkin lymphoma	126 (48.3)	29 (61.7)	97 (45.3)	.053
Testicular/thymic	6 (2.3)	1 (2.1)	5 (2.3)	1.000
Other	35 (13.4)	9 (19.1)	26 (12.1)	.236
Adenoid carcinoma	1 (0.4)	0 (0.0)	1 (0.5)	
Esophageal	4 (1.5)	2 (4.3)	2 (0.9)	
Germ cell tumor	1 (0.4)	0 (0.0)	1 (0.5)	
Head and neck	1 (0.4)	0 (0.0)	1 (0.5)	
Laryngeal	1 (0.4)	0 (0.0)	1 (0.5)	
Leukemia	1 (0.4)	1 (2.1)	0 (0.0)	
Lung/bronchus	6 (2.3)	1 (2.1)	5 (2.3)	
Neuroblastoma	1 (0.4)	1 (2.1)	0 (0.0)	
Non-Hodgkin lymphoma	11 (4.3)	1 (2.1)	10 (4.8)	
Ovarian	1 (0.4)	0 (0.0)	1 (0.5)	
Prostate, metastatic	1 (0.4)	1 (2.1)	0 (0.0)	
Sarcoma	2 (0.7)	0 (0.0)	2 (0.9)	
Seminoma	2 (0.7)	0 (0.0)	2 (0.9)	
Throat	2 (0.8)	2 (4.3)	0 (0.0)	

Values are presented as n (%).

but was significantly more prevalent in the primary group (40.2% vs 17%; $P = .002$). The remaining 15.7% of patients had a variety of malignancies. None of the patients had a documented recurrence at the time of valvular surgery.

Operative Variables of Patients With Radiation-Induced VHD

The indications for surgery and the types of procedures performed are shown in Table 3. Altogether, 77% (202 out of 261) of patients underwent an aortic valve replacement (AVR) (79% of primary vs 68% of reoperations; $P = .12$). The most common procedure was isolated AVR, constituting 31% of the primary and 27% of the reoperative group, respectively. Most concomitant surgeries were a combination of AVR with coronary artery bypass graft in 20.3% or AVR with a second valve in 8% of all patients. Complex valvular procedures comprised 18.3% of our series and isolated mitral valve surgery was performed in 15% of patients in both groups. There was no difference in the distribution frequencies of all surgical procedures between primary and reoperative cases ($P > .55$).

Reoperations had longer median cardiopulmonary bypass time (248 minutes vs 131 minutes) and crossclamp time (145 minutes vs 92 minutes) compared with the primary group (both P values $\leq .001$). More patients were transfused with packed red blood cells (59% vs 32%; $P = .001$), fresh frozen plasma (53% vs 8.4%; $P = .001$), and platelets (48% vs 7.9%; $P = .001$) among patients undergoing reoperation (Table 3).

Postoperative Outcomes of Patients With Radiation-Induced VHD

Reoperative group was at greater risk of returning to the operating room (8.5% vs 1.9%; $P = .037$) (Table 4). They also had a higher incidence of new onset renal dysfunction and postoperative transfusions. The median time on a ventilator (20.3 hours vs 7 hours), length of stay in the intensive care unit (122 hours vs 51 hours), and overall hospital length of stay (15 days vs 7 days) were significantly longer in the reoperative group (all P values = .001).

Operative mortality for the entire cohort was 6.1% (16 out of 261) and was significantly higher in reoperative cases (17% vs 3.7%; $P = .003$) (Table 4). The observed to expected STS mortality ratio (observed-to-expected STS) was 3.2 (17 out of 5.2) for reoperative and 1.4 (3.7 out of 2.6) for primary patients. There was no difference in operative mortality based on the underlying history of cancer: 8.5% (8 out of 94) for breast cancer versus 6.1% (8 out of 132) for Hodgkin/thymic/testicular cancer ($P = .60$).

Long-term Survival of Patients With Radiation-Induced VHD

Median follow-up was 3.8 years (IQR, 1.8-6.7; range, 0-13.8 years), for a total of 1149 patient-years, and there were 79 deaths during follow-up observation. Estimated overall survival was 55% at 10 years, and observed survival was significantly higher for primary patients (mean, 9.5 years; 95% confidence interval [CI], 8.7-10.4) than for reoperative cases (5.7 years; 95% CI, 4.1-7.6;

TABLE 3. Operative data for reoperative and primary patients with radiation-induced valvular heart disease

Operative data	All patients (n = 261)	Reoperative (n = 47)	Primary (n = 214)	P value
Valve procedures				.552
Isolated aortic valve	80 (30.7)	13 (27.7)	67 (31.3)	
Aortic valve + coronary artery bypass graft	53 (20.3)	6 (12.8)	47 (22.0)	
Aortic valve + other valve	21 (8.0)	3 (6.4)	18 (8.4)	
Isolated mitral valve	39 (15.0)	7 (14.9)	32 (15.0)	
Other isolated valve	5 (1.9)	4 (8.1)	1 (0.5)	
Other valve + coronary artery bypass graft	15 (5.7)	4 (8.5)	11 (5.1)	
Miscellaneous complex valve	48 (18.3)	10 (21.3)	38 (17.7)	
Indication for surgery				
Aortic insufficiency	40 (15.3)	9 (19.1)	31 (14.5)	
Aortic stenosis	41 (15.7)	7 (14.9)	34 (15.9)	
Aortic insufficiency/aortic stenosis	136 (52.1)	16 (34.1)	120 (56.1)	
Other valve indication	44 (16.9)	15 (31.9)	29 (13.6)	
Perfusion time (min)	142 (102-215)	248 (191-390)	131 (98-180)	.001
Crossclamp time (min)	98 (74-141)	145 (94-212)	92 (67-133)	.001
Patients transfused in operating room				
Pack of red blood cells	98 (37.5)	28 (59.6)	70 (32.7)	.001
Fresh frozen plasma	43 (16.5)	25 (53.2)	18 (8.4)	.001
Platelets	40 (15.3)	23 (48.8)	17 (7.9)	.001

Values are presented as n (%) or median (interquartile range).

$P < .001$) (Figure 1). We did not observe a significant difference in postoperative survival between patients with a history of breast cancer (mean, 9.1 years; 95% CI, 7.851-10.378) and those with a history of Hodgkin/thymic/testicular cancer (mean, 8.9 years; 95% CI, 7.9-10.1; $P = .829$).

Matched Analysis of Primary and Reoperative Patients With and Without Prior MRT

The matched cohorts of primary (836 without MRT and 213 with MRT) and reoperative (213 without MRT and 46 with MRT) valve surgery patients were well balanced. Both primary and reoperative matched cohorts had similar baseline characteristics, including STS PROM, left ventricular ejection fraction, New York Heart Association (NYHA) class III or IV, renal insufficiency, and diabetes (Table 5). However, primary matched patients with MRT were younger (63.2 vs 65.3 years; $P = .026$) and had a higher proportion of women (72.3% vs 40.9%; $P = .001$) compared with primary patients without MRT. Conversely, primary matched patients without MRT had more prior strokes (5.5% vs 0.9%; $P = .003$) and endocarditis (5.4 vs 1.9; $P = .029$). Reoperative matched patients with MRT had more peripheral vascular disease than reoperative patients without MRT (28.3% vs 14.6%; $P = .031$).

The operative characteristics of both matched cohorts were not different with respect to the type of procedure ($P = .73$ for primary and $P = .38$ for reoperative patients) (Table 5). Compared with reoperative patients without MRT, reoperative patients with MRT underwent longer perfusion (248 vs 198 minutes; $P = .002$) and crossclamp times (146 vs 114 minutes; $P = .037$).

Postoperative Outcomes of the Matched Primary and Reoperative Patients

Postoperative outcomes for primary and reoperative valve surgery in matched patients with and without MRT are shown in Table 6. Primary patients with a history of MRT had a higher operative mortality compared with nonradiated patients (3.8% vs 0.8%; $P = .004$). For nonradiated primary patients, the observed-to-expected STS mortality ratio was 0.32 compared with 1.48 in patients with previous MRT. Also, primary patients with previous MRT had a higher incidence of deep sternal wound infections (1.9% vs 0.6%; $P = .89$), new onset renal insufficiency (6.1% vs 2.2%; $P = .005$), postoperative red blood cell transfusions (32.4% vs 24.5%; $P = .023$), and longer length of stay in an intensive care unit (51 days vs 47 days; $P = .003$), compared with their nonradiated primary counterparts.

A higher operative mortality was also present in reoperative MRT patients compared with their nonradiated

TABLE 4. Postoperative data and in-hospital outcomes

Outcome	All patients (n = 261)	Reoperative (n = 47)	Primary (n = 214)	P value
Postoperative complications				
Return to OR	8 (3.1)	4 (8.5)	4 (1.9)	.037
Reoperation for bleeding	7 (2.7)	3 (6.4)	4 (1.9)	.118
Reoperation of valve	1 (0.4)	1 (2.1)	0 (0.0)	.180
Permanent stroke	13 (5.0)	4 (8.5)	9 (4.2)	.260
New onset renal insufficiency	23 (8.8)	10 (21.3)	13 (6.1)	.003
In-hospital outcomes				
PO pRBC	98 (37.5)	29 (61.7)	69 (32.2)	.001
PO FFP	43 (16.5)	16 (34.0)	27 (12.6)	.001
PO platelets	24 (9.2)	10 (21.3)	14 (6.5)	.004
Total mechanical ventilation time (h)	7.5 (4-15)	20.3 (6-79)	7.0 (4-12)	.001
Mechanical ventilation ≤ 24 h	43 (16.5)	22 (46.8)	21 (9.8)	.001
ICU stay (h)	63 (28-131)	122 (61-328)	51 (28-107)	.001
Postoperative LOS (d)	8 (6-16)	15 (9-27)	7 (5-14)	.001
Operative mortality	16 (6.1)	8 (17.0)	8 (3.7)	.003

Values are presented as n (%) or median (IQR). OR, Operating room; PO, postoperative; pRBC, pack of red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay.

matches (17.4% vs 2.3%; $P = .001$), which resulted in observed-to-expected STS mortality ratios of 3.35 and 0.45, respectively. Overall, reoperative MRT patients had higher incidence of postoperative adverse events such as

stroke (8.7% vs 2.8%; $P = .081$) and new-onset renal insufficiency (19.6% vs 8.9%; $P = .062$). Reoperative MRT patients were transfused with more fresh frozen plasma (32.6% vs 17.8%; $P = .042$) and platelets

FIGURE 1. Kaplan-Meier survival curves for primary and reoperative patients with mediastinal radiation. Reoperative patients with mediastinal radiation-induced valvular heart disease had significantly shorter survival compared with patients without a previous sternotomy. MRT, Mediastinal radiotherapy.

TABLE 5. Baseline and operative characteristics of matched primary and reoperative patients with and without radiation-induced valvular heart disease

Demographic characteristic	Matched primary		<i>P</i> value	Matched reoperations		<i>P</i> value
	No MRT (n = 836)	MRT (n = 213)		No MRT (n = 213)	MRT (n = 46)	
Age (y)	65.3 ± 13.1	63.2 ± 12.1	.026	63.5 ± 13.6	60.1 ± 13.0	.265
Women	342 (40.9)	154 (72.3)	.001	83 (39.0)	19 (41.3)	.868
Diabetes	153 (18.3)	34 (16.0)	.483	55 (25.8)	13 (28.3)	.715
Renal insufficiency	33 (3.9)	9 (4.2)	.845	23 (10.8)	5 (10.9)	.999
Preoperative creatinine	1.09 ± 0.67	0.98 ± 0.42	.028	1.20 ± 0.67	1.17 ± 0.41	.786
Peripheral vascular disease	74 (8.9)	20 (9.4)	.789	31 (14.6)	13 (28.3)	.031
Cerebrovascular disease	88 (10.5)	11 (5.2)	.017	39 (18.3)	7 (15.2)	.832
Cerebrovascular accident	46 (5.5)	2 (0.9)	.003	17 (8.0)	3 (6.5)	1.000
Endocarditis	45 (5.4)	4 (1.9)	.029	36 (16.9)	5 (10.9)	.379
Congestive heart failure	351 (42.0)	100 (46.9)	.215	135 (63.4)	30 (65.2)	.867
NYHA class III or IV	304 (36.4)	76 (35.7)	.873	112 (52.6)	27 (58.7)	.516
Ejection fraction (%)	60.0 (55-65)	60.0 (50-65)	.269	55.0 (50-65)	55.0 (45-60)	.084
STS PROM	2.51 ± 2.51	2.57 ± 2.15	.337	5.16 ± 5.04	5.20 ± 5.36	.963
Operative data						
Valve procedures			.737			.383
Isolated AV	286 (34.2)	67 (31.4)		66 (31.0)	13 (28.3)	
AV + CABG	146 (17.5)	46 (21.6)		19 (8.9)	6 (12.8)	
AV + other valve	80 (9.6)	18 (8.5)		15 (15)	3 (6.4)	
Isolated MV	125 (15.0)	32 (15.0)		20 (9.4)	7 (14.9)	
Other isolated valve	4 (0.5)	1 (0.5)		15 (7.0)	4 (8.1)	
Other valve + CABG	52 (6.2)	11 (5.2)		24 (11.3)	4 (8.5)	
Miscellaneous complex valve	142 (17.0)	38 (17.7)		54 (25.3)	10 (21.3)	
Perfusion time (min)	125 (93-172)	131 (98-180)	.239	198 (144-293)	248 (191-390)	.002
Crossclamp time (min)	92 (67-133)	92 (67-133)	.746	114 (81-170)	146 (94-214)	.037
Patients transfused in OR						
pRBC	148 (17.7)	69 (32.4)	.001	94 (44.1)	27 (58.7)	.076
FFP	84 (10.0)	18 (8.5)	.520	84 (39.4)	24 (52.2)	.138
Platelets	59 (7.1)	17 (8.0)	.657	66 (31.0)	22 (47.8)	.023

Values are presented as n (%), mean ± standard deviation, or median (interquartile range). *MRT*, Mediastinal radiotherapy; *NYHA*, New York Heart Association; *STS*, Society of Thoracic Surgeons; *PROM*, predicted risk of mortality; *AV*, aortic valve; *CABG*, coronary artery bypass graft; *MV*, mitral valve; *OR*, operating room; *pRBC*, pack of red blood cells; *FFP*, fresh frozen plasma.

(21.7% vs 10.3%; *P* = .46), had longer ventilation time (20.3 hours vs 10 hours; *P* = .003), intensive care unit length of stay (120 hours vs 66 hours; *P* = .003), and overall length of stay (15 days vs 7 days; *P* = .001), compared with nonradiated reoperative patients.

Adjusted Operative Mortality Analysis of the Matched Primary and Reoperative Patients

Adjusted odds for operative mortality were higher in reoperative patients with MRT (odds ratio [OR], 12.96; 95% CI, 4.97-33.78; *P* = .001), followed by primary patients with MRT (OR, 4.87; 95% CI, 1.72-13.78; *P* = .003), reoperative patients without MRT (OR, 1.1; 95% CI, 0.380-3.18; *P* = .851), compared with primary patients without a history of MRT. Additional predictors

of operative mortality in our model were age (OR, 1.06; 95% CI, 1.02-1.10; *P* = .002) and renal insufficiency (OR, 4.92; 95% CI, 1.84-13.15; *P* = .001) (Table 7).

Long-term Survival of the Matched Primary and Reoperative Patients

For all patients included in the primary and reoperative matched cohorts, there were 259 deaths during the study period. Mean survival was significantly lower for primary patients with MRT (9.51; 95% CI, 8.68-10.34) compared with their matched counterparts without MRT (11 years; 95% CI, 10.65-11.35; *P* < .001). Similarly, reoperative patients with MRT had a significantly lower survival (5.7 years; 95% CI, 4.01-7.55) compared with matched reoperative patients without prior MRT (9.46 years; 95%

TABLE 6. Postoperative data and in-hospital outcomes of matched primary and reoperative patients with and without radiation-induced valvular heart disease

Outcome	Matched primary		P value	Matched reoperations		P value
	No MRT (n = 836)	MRT (n = 213)		No MRT (n = 213)	MRT (n = 46)	
Postoperative complications						
Return to OR	16 (1.9)	4 (1.9)	.037	18 (8.5)	4 (8.5)	.037
DSWI	5 (0.6)	4 (1.9)	.089	3 (1.4)	1 (2.2)	.545
Sepsis	11 (1.3)	4 (1.9)	.521	4 (1.9)	1 (2.2)	.999
Permanent stroke	22 (2.6)	4 (1.9)	.630	6 (2.8)	4 (8.7)	.081
New onset renal insufficiency	18 (2.2)	134 (6.1)	.005	19 (8.9)	9 (19.6)	.062
In-hospital outcomes						
Patients transfused postoperatively						
pRBC	205 (24.5)	69 (32.4)	.023	107 (50.2)	28 (60.9)	.198
FFP	110 (13.2)	27 (12.7)	.910	38 (17.8)	15 (32.6)	.042
Platelets	51 (6.1)	14 (6.6)	.720	22 (10.3)	10 (21.7)	.046
Total ventilation time	6.5 (4, 11)	6.9 (4, 12)	.001	10.0 (5, 17)	20.3 (6, 86)	.003
Vent ≤ 24 h	68 (8.1)	21 (9.9)	.611	41 (19.2)	21 (45.7)	.001
ICU stay (h)	47 (24, 75)	51 (28, 107)	.003	66 (38, 133)	120 (57, 332)	.003
Postoperative LOS (d)	7 (5-10)	7 (5-14)	.003	9 (6-14)	15 (9-27)	.001
Operative mortality	7 (0.8)	8 (3.8)	.004	5 (2.3)	8 (17.4)	.001
O/E based on STS PROM	0.32	1.48		0.45	3.35	

Values are presented as n (%) or median (interquartile range). *MRT*, Mediastinal radiotherapy; *OR*, operating room; *DSWI*, deep sternal wound infection; *pRBC*, pack of red blood cells; *FFP*, fresh frozen plasma; *ICU*, intensive care unit; *LOS*, length of stay; *O/E*, observed to expected; *STS*, Society of Thoracic Surgeons; *PROM*, predicted risk of mortality.

CI, 8.59-10.33; $P < .001$). Primary patients with MRT had a similar survival compared with reoperative patients with no history of MRT ($P = .89$) (Figure 2).

Adjusted Survival of the Matched Primary and Reoperative Patients

A conditional Cox proportional hazards model was done to elicit risk factors associated with decreased survival in the matched cohorts (Figure 3 and Table 8). Compared with nonradiated primary patients, primary patients with prior MRT (hazard ratio [HR], 2.24; 95% CI, 1.73-1.91; $P < .001$) and reoperative patients with prior MRT (HR, 3.19; 95% CI, 1.95-5.21; $P < .001$) had a significantly higher risk of decreased survival. Additional predictors of

increased long-term mortality were age (HR, 1.04; 95% CI, 1.03-1.05; $P < .001$), renal insufficiency (HR, 1.56; 95% CI, 1.15-2.11; $P < .004$), congestive heart failure (HR, 1.72; 95% CI, 1.33-2.23; $P < .001$), peripheral vascular disease (HR, 1.33; 95% CI, 1.02-2.72; $P = .030$), diabetes (HR, 1.61; 95% CI 1.23-2.11; $P < .001$), and NYHA class III or IV (HR, 2.81; 95% CI, 1.99-3.97; $P < .001$). The type of cancer, gender, prior history of stroke, infectious endocarditis, and type of procedure were not contributory (all P values $> .17$).

DISCUSSION

To our knowledge, this study represents the largest cohort of surgically treated patients with radiation-induced VHD. In this relatively young group of predominantly Hodgkin lymphoma and breast cancer survivors, aortic valve replacement was performed in more than three-quarters of all patients. Both primary and reoperative procedures for radiation-induced VHD resulted in worse outcomes than those predicted by the STS risk algorithm. Furthermore, in patients with prior MRT, reoperative surgery was associated with a 13% increase in operative mortality compared with primary surgery. These findings were emphasized after matching primary and reoperative patients with radiation-induced VHD to nonradiated counterparts. In matched patients who underwent primary valve procedures, MRT was associated with a higher operative

TABLE 7. Logistic regression analysis for operative mortality

Predictor variable	Odds ratio	<i>P</i> value	95% Confidence interval	
			Low	High
Group (vs primary patients without MRT)		.001		
Reoperative patients without MRT	1.10	.861	0.380	3.180
Primary patients with MRT	4.87	.003	1.724	13.789
Reoperative patients with MRT	12.96	.001	4.977	33.788
Age	1.06	.002	1.021	1.103
Renal insufficiency	4.92	.003	1.842	13.158

MRT, Mediastinal radiation therapy.

FIGURE 2. Kaplan-Meier survival curves for matched primary and reoperative patients with and without prior mediastinal radiation. The lowest cumulative survival was observed in reoperative, followed by primary patients with mediastinal radiotherapy (MRT), compared with their matched counterparts without MRT. Primary patients with MRT had a similar survival compared with reoperative patients with no history of MRT ($P = .89$).

mortality (3.8% vs 0.8%) and a 2.2-fold higher risk of decreased long-term survival (HR, 2.24). Similarly, in the reoperative matched cohort, MRT patients had substantially worse outcomes with respect to operative mortality (2.3% vs 17.4%) and decreased long-term survival (HR, 3.19) compared with primary nonradiated patients. Our results underscore the unfavorable outcomes associated with surgery for radiation-induced VHD and emphasize the underestimation of operative risk in these patients when relying solely on the STS PROM, especially for patients undergoing reoperation. These findings should persuade physicians to carefully evaluate the risks associated with surgical treatment in these patients, with consideration toward less-invasive therapeutic modalities, including transcatheter-based approaches.

Outcomes of Radiation-Induced VHD

Radiation-induced cardiac disease will become progressively more relevant as long-term cancer survival continues to improve.¹⁷ The time interval from radiation to surgery ranges from 10 to 25 years and these patients frequently present at a younger age relative to the general population, especially for radiation-associated aortic valve replacements.^{2,11,18,19} Indeed, the average age of our radiated cohort was 62.6 years compared with 76 years in the STS

Adult Cardiac Surgery Database.²⁰ Our observed pattern for radiation-induced VHD was consistent with the literature,¹¹ with a high prevalence of aortic valve disease (77%), with mixed stenotic and regurgitant lesions, followed by mitral valve disorders. In our study, less than half of surgeries were isolated valve replacements (30% aortic valve replacement and 15% mitral valve replacement), and the majority were a combination of concomitant valve procedures or complex valve surgeries, exemplifying the ubiquitous nature of radiation-induced heart disease.

Total radiation dose is a determinant in the development of radiation-induced VHD.²¹ Chang and colleagues⁷ used type of cancer as a surrogate for radiation field and dose, and showed improved outcomes in patients exposed to tangential compared with extensive radiation. Although the exact radiation dose and the time to development of valvular disease could not be determined in our study, operative mortality was not significantly different when comparing breast cancer to Hodgkin/thymic/testicular cancers, and type of cancer was not found to be contributory on unadjusted survival analyses. Furthermore, multivariate modeling failed to show a significant change in mortality risk based on cancer type. However, the high frequency of subjects who underwent mediastinal radiation for Hodgkin lymphoma (48%) and breast cancer (36%),

FIGURE 3. Conditional Cox proportional hazards modeling survival curves. Primary patients with prior mediastinal radiotherapy (MRT) (hazard ratio, 2.24; 95% confidence interval, 1.73-1.91; $P < .001$) and reoperative patients with prior MRT (hazard ratio, 3.19; 95% confidence interval, 1.95-5.21; $P < .001$) had a significantly lower adjusted survival, compared with nonradiated primary matches. *XRT*, Radiotherapy; *Reop*, reoperation.

emphasizes the contemporary relevance of radiation-induced VHD in this patient population,^{9,22} even with considerable advancements in limiting radiation field and total dose.

Outcomes of Primary Cases

Our overall 6% operative mortality compares favorably with previous reports of cardiac surgery in patients with MRT.^{3,5,6,23} Handa and colleagues⁵ described 60 cases of radiation-induced VHD where aortic valve replacement

was also the most frequent procedure. A smaller series by Crestanello and colleagues³ focused on the surgical experience with atrioventricular valves—14 mitral and 6 tricuspid repairs—in which they observed a high rate of early repair failure. The latter series was composed mainly of complex procedures, with only 5 isolated valve repairs. Early surgical mortality for these studies was 12% to 14% for valve surgery.^{3,5} Chang and colleagues⁷ published the largest series to date, with 230 patients who underwent cardiac surgery from 2000 to 2005 and were exposed to different intensities of chest radiation. Their operative mortality ranged from 2.4% to 13% depending on the radiation field. A recent publication by Wu and colleagues¹⁶ included 173 surgical cases (coronary and valve, both isolated and concomitant) with radiation-associated heart disease that were matched to 305 patients without chest radiation. The radiated group experienced a significantly higher mortality (4%) compared with the comparison group (0.3%). Despite the heterogeneity of these studies, there is consistency in the increased mortality risk conveyed by MRT.

In our study, compared with nonradiated matches, patients who underwent primary valve surgery for radiation-induced VHD had a substantially higher operative mortality (3.8% vs 0.8%) despite a similar STS PROM (2.51 and 2.57, respectively), resulting in a higher observed-to-expected STS mortality ratio (1.48 vs 0.32). These findings we further supported by the observed 4.8-fold increase in the odds of operative mortality in patients with prior MRT compared with nonradiated matches.

The estimated 10-year survival of our cohort was 55%. Previously reported 5-year survival is 66%⁵ and others have published similar long-term results with varying follow-ups.^{7,16} We observed a shorter cumulative survival in patients with MRT who underwent primary valve procedures compared to their nonradiated matches. Similar findings have been reported in other studies, in which patients with radiation-induced heart disease have

TABLE 8. Conditional Cox proportional hazard model for long-term survival

Predictor variable	Hazard ratio	P value	95% Confidence interval	
			Low	High
Group (vs primary patients without MRT)		.001		
Reoperative patients without MRT	1.16	.418	0.806	1.679
Primary patients with MRT	2.24	.001	1.738	2.911
Reoperative patients with MRT	3.19	.001	1.959	5.215
Age	1.04	.001	1.030	1.054
Diabetes	1.61	.001	1.236	2.117
Congestive heart failure	1.72	.001	1.330	2.232
NYHA class III or IV	2.81	.001	1.998	3.971
Renal insufficiency	1.56	.004	1.158	2.115
Peripheral vascular disease	1.33	.030	1.028	1.725

MRT, Mediastinal radiation therapy; NYHA, New York Heart Association.

been consistently marked by decreased survival, relative to both matched population life tables⁷ and matched controls.¹⁶

Outcomes of Reoperative Cases

Reoperative valve surgeries are more technically demanding than primary procedures and are associated with worse outcomes, even in nonradiated patients.²⁴⁻²⁶ Reoperative valve surgery in a radiated chest poses increased complexity from both technical and medical perspectives. Technical difficulties include denser adhesions, smaller valve annulus size, and fibrotic tissues, which result in longer cardiopulmonary bypass and aortic crossclamp times. Further inflammatory insults, due to extensive dissection during the procedure, result in a higher incidence of postoperative pleural effusions and third spacing of fluids, necessitating longer hospital stays.

The reoperative patients with prior MRT were more complex, with a higher burden of comorbidities and a higher mean STS PROM (5.21) compared with primary patients with MRT (2.58). Despite this difference, their STS PROM considerably underestimated the observed mortality by 3.2-fold.¹⁶ Although reoperative-matched patients with and without prior MRT had similar STS PROM (5.20 and 5.16, respectively), operative mortality was substantially higher in the former group (17.4% and 2.3%). This resulted in a high observed to expected STS mortality ratio in reoperative patients with prior MRT, but not in their nonradiated counterparts (3.35 and 0.25, respectively). It is beyond the scope and reach of this article to assess the performance, both calibration and discrimination, of the STS PROM in these patients, but this type of analysis might be possible with the addition of mediastinal radiation to the updated version 2.81 STS data collection form. However, our findings emphasize the underperformance of the STS PROM in patients with radiation-induced VDH, particularly in reoperative cases.

In our study, the shortest cumulative survival was present in patients with a history of mediastinal radiation and a prior sternotomy (5.78 years), which was significantly shorter compared with both nonradiated reoperative matches (9.46 years) and primary patients with prior MRT (9.51 years). Wu and colleagues¹⁶ also described an important difference in longitudinal survival (with a mean follow-up of 7.6 years) between reoperative (71%) and primary (51%) patients with prior MRT.

Factors Influencing Long-term Survival

Primary and reoperative patients with radiation-induced VHD had more than 2 and 3 times the risk of long-term death, respectively, compared with nonradiated matched patients in our conditional adjusted survival model. The increased risk of long-term mortality conferred by reoperation was not present in nonradiated matched

patients. Our results show that mediastinal radiation is a significant risk factor for worse long-term survival and that a concomitant prior sternotomy confers a higher risk that is not observed in nonradiated matched patients. Additional predictors of long-term survival were age, renal insufficiency, congestive heart failure, diabetes, peripheral vascular disease, and NYHA class III or IV. Similar to our findings, previously described factors associated with decreased long-term survival in MRT patients are constrictive pericarditis, left ventricular ejection fraction <50%, NYHA class IV symptoms of heart failure, and prolonged cardiopulmonary bypass time.^{3,5} Wu and colleagues¹⁶ reported previous cardiac surgery and diabetes to be significantly associated with increased mortality. However, previous cardiac surgery was not a significant predictor of increased mortality in their adjusted survival analysis. The updated American College of Cardiology/American Heart Association guidelines include radiation as a procedure-specific impediment for cardiac surgery,²⁷ but with the poor surgical outcomes among reoperative cases we suggest that reoperation in the context of MRT may be a prohibitive risk factor for surgery.

Alternative Treatment Options

Heart transplantation has been previously advocated for patients with prior MRT, especially for those with concomitant radiation-induced pulmonary disease. However, there is continuing concern about the administration of immunosuppressive agents in patients with a positive cancer history. Although the low number of deaths due to cancer¹¹ and low prevalence or recurrence at the time of surgery¹⁷ in these patients might appear encouraging, extrapolating data from patients without immunomodulation therapy to posttransplant patients has serious caveats. Nevertheless, early reports on a small number of heart transplants in patients with prior chest radiation have yielded promising results.²³

Conservative treatment in high-risk surgical patients is a reasonable option and an argument could be made for delaying surgical intervention in reoperative patients with prior mediastinal radiation. However, one can argue that waiting allows for the development of a more significant congestive heart failure, deriving from their underlying cardiomyopathy, which would result in even worse outcomes.

Emerging alternatives such as transcatheter-based therapies may offer viable alternatives to surgery in these patients. Transcatheter aortic valve replacement is a valid option for high-risk patients, and with the high prevalence of aortic stenosis in MRT patients we believe that reoperative patients with radiation-induced VHD may derive particular benefit from this new intervention. In a small series, Bouleti and colleagues²⁸ showed similar short-term mortality (8% for both) and 5-year survival (33% vs 42%; $P = .26$) between 26 transcatheter aortic

valve replacement patients with radiation-induced VHD and 26 nonradiated matched transcatheter aortic valve replacement controls. Despite the lack of large patient series and long-term follow-up data, it is obvious that transcatheter therapies should be included in the armamentarium of valve treatments offered to patients with MRT. Burgeoning technologies such as transcatheter mitral valve replacements and repairs will likely be used for other radiation-induced valvular pathologies in the future.

Limitations

The current study has limitations related to its retrospective, observational design and as a single center study there are inherent disadvantages, especially related to selection bias, that may influence the generalizability of our findings to other populations. We were unable to ascertain the patients' cancer stage, radiation field, and radiation dose or the time interval to the index surgery, all of which might have influenced surgical outcomes. Although the type of cancer was not a contributory factor in unadjusted and multivariable survival analyses, our findings may not apply to other populations of patients with MRT. Because the cause of death data were unavailable for longitudinal survival analyses, we cannot evaluate how cancer recurrence may have contributed to long-term outcomes. Although reoperative cardiac surgery was identified as a significant risk factor associated with reduced postoperative survival, the current study design cannot determine whether this relationship is directly causal, or describe precise mechanisms resulting in our findings. Lastly, due to the inconsistent reporting of preoperative echocardiography findings, especially at the beginning of our observation period, an analysis of preoperative cardiac output and its association with long-term outcomes in patients with radiation-induced VHD was not possible and therefore remains as a potential confounder. Our results should be interpreted with these cautions.

CONCLUSIONS

To our knowledge, this cohort represents the largest experience to date in the surgical management of radiation-induced VHD. Preoperative assessment based only on STS PROM might underestimate these patients' true surgical risk, both with primary and reoperative surgeries. In particular, reoperations are associated with significantly higher operative and long-term mortality. Our results emphasize the need for careful preoperative risk assessment. Further studies are needed to assess the potential benefit of using nonsurgical approaches such as transcatheter aortic valve replacement in these patients.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: mediastinal radiotherapy, valvular heart disease, radiation-induced valvular heart disease, reoperative valve surgery

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