Cardiac Transplantation for Radiation-Induced Cardiomyopathy: The Mayo Clinic Experience

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Background. High-dose radiotherapy to the mediastinum for the treatment of malignancies causes injury to the intrathoracic organs. Coronary artery disease, valvular dysfunction, cardiomyopathy, and chronic constrictive pericarditis are common cardiovascular sequelae during long-term follow-up. Cardiac transplantation is indicated for the surgical treatment of heart failure due to radiation-induced end-stage cardiac disease.

Methods. A retrospective study of radiation-induced cardiomyopathy requiring cardiac transplantation was undertaken from December 1992 to August 2010.

Results. Twelve patients (7 men, 5 women), with a mean age of 47.4 years, underwent orthotopic cardiac transplantation. Redo cardiac operations were performed in 9 patients. Lymphoma was the primary malignancy in all patients. Adjuvant chemotherapy was used in 9 patients, and splenectomy was performed in 7. Restrictive cardiomyopathy (n = 8) was the predominant diagnosis. Restrictive lung disease was present in 10 patients (83%). Postoperative chronic kidney injury developed in 3 patients (25%). Hospital mortality was 8.3%. Survival at 1, 5, and 10 years was 91.7%, 75%, and 46.7%, respectively. The overall mean follow-up was 7.7 years (median, 6.1; range, 1.8 to 16.4 years). Late respiratory failure accounted for 3 deaths.

Conclusions. Cardiac transplantation provides satisfactory medium-term to long-term outcome in patients with radiation-induced cardiomyopathy. Secondary malignancies, kidney injury, and respiratory failure contribute to significant postoperative morbidity and death.

Material and Methods
This retrospective study was approved by the Mayo Clinic Institutional Review Board (Reference No. 13-005275).

Patient Population
Twelve patients underwent cardiac transplantation at Mayo Clinic from December 1992 to August 2010 for radiation-induced cardiomyopathy. This represents 4% of patients who underwent isolated cardiac transplant during the period of study (N = 297). All demographic and perioperative details, results of endomyocardial biopsies, and follow-up data were obtained from the institutional transplant database and from patients’ medical records. Details of the primary malignancy needing RT and with late development of restrictive lung disease. Conventional cardiac operations may not be an option for some patients because of the extent of injury after RT, and cardiac transplantation becomes a consideration. There is limited experience with the role of cardiac transplantation for the treatment of radiation-induced cardiac disease. We undertook a retrospective study at the Mayo Clinic, Rochester, Minnesota, to update our experience on the outcomes of cardiac transplantation in patients with radiation-induced cardiomyopathy [5].
chemotherapy and the development of any subsequent malignancies were recorded.

**Immunosuppression Protocol**

A standard 3-drug immunosuppression protocol has been used at the Mayo Clinic for the management of postcardiac transplant patients, including induction therapy and Thymoglobulin (Genzyme Transplant, Cambridge, MA) or OKT3. Postoperative immunosuppression is maintained with mycophenolate or azathioprine, tacrolimus or cyclosporine, and prednisolone. More recently, some patients have been transitioned from calcineurin inhibitor therapy to sirolimus at 3 to 12 months after transplantation. Prednisolone is gradually weaned off after 6 months in patients without any evidence of rejection.

**Rejection Assessment**

Rejection was monitored with surveillance endomyocardial biopsies performed weekly for 4 weeks, twice monthly for 2 months, monthly for 3 to 6 months, eventually quarterly, and after this, annually for the years 3 to 5. Additional biopsies are performed as clinically indicated. Echocardiography was performed at the time of endomyocardial biopsies for the first 3 years after transplant and annually thereafter. Surveillance coronary angiography was performed annually. The institutional protocol for posttransplant immunosuppression and for the rejection surveillance was periodically modified during the study period.

**Operative Procedure**

Donor retrieval and myocardial protection were performed using standard surgical techniques. Orthotopic cardiac transplantation was performed through a median sternotomy. Central or peripheral cannulation was used to establish cardiopulmonary bypass and systemic hypothermia.

**Statistical Analysis**

Descriptive statistics for categoric variables are reported as frequency and percentage, and continuous variables are reported as mean ± standard deviation. The Kaplan-Meier method was used to draw survival curves and calculate survival statistics at 1, 5, and 10 years. The log-rank test was used to test the survival difference between the RT and non-RT groups. The \( \alpha \) level was set at 0.05 for statistical significance.

**Results**

**Baseline Clinical Characteristics**

The study included 12 patients, 7 men and 5 women, who were a mean age at transplantation 47.4 years (median, 49 years; range 29 to 62 years; Table 1). The mean time interval from listing to transplantation was 10 months (median, 5.7 months; range, 0.3 to 44.7 months). Primary malignancy requiring RT was Hodgkin lymphoma in 8 patients and non-Hodgkin lymphoma in 4.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline Hemodynamics/After Administration of Nitroprusside</th>
<th>RAP (mm Hg)</th>
<th>PAP (mean) (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>TPG (mm Hg)</th>
<th>CO (L/min)</th>
<th>CI (L/min/m²)</th>
<th>PVR (WU)</th>
<th>PVRI (WU/m²)</th>
<th>AOP (mean) (mm Hg)</th>
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<td>Mean ± SD</td>
<td>Baseline</td>
<td>15.3 ± 8.7</td>
<td>33.6 ± 13.2 (mean)</td>
<td>21.8 ± 8.9</td>
<td>12.4 ± 6.4</td>
<td>3.0 ± 0.9</td>
<td>5.1 ± 1.6</td>
<td>86.1 ± 20.6</td>
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<td>Nitroprusside</td>
<td>31.8 ± 11 (mean)</td>
<td>21 ± 9.1</td>
<td>10.8 ± 3.2</td>
<td>2.4 ± 0.8</td>
<td>4.1 ± 1.2</td>
<td>74.9 ± 16.2</td>
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</table>

AOP = aortic pressure; CI = cardiac index; CO = cardiac output; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; SD = standard deviation; TPG = transpulmonary pressure gradient; WU = Woods units.
Splenectomy had been performed in 7 patients (58.3%) and adjuvant chemotherapy was used in 9 (75%) as part of the treatment of lymphoma. The mean interval between treatments with RT to cardiac transplantation was 23.2 years (median, 25.1 years; range, 13.4 to 31.3 years). Nine patients (75%) had undergone prior cardiac operations and underwent redo sternotomy at the time of cardiac transplantation. The interval between the exposure to RT and the first cardiac operation was 18 ± 5.4 years (range, 10.9 to 24.7 years). The interval between RT and the second cardiac operation was 14.3 years (range, 13.4 to 15.3 years).

Three patients had secondary malignancies before cardiac transplant. Patient 3 required surgical resection for osteosarcoma of the scapula 15 years after RT. Patient 6 underwent treatment of thyroid carcinoma with radioiodine and thyroidectomy 21 years after RT. Patient 7 needed local surgical resection of carcinoma of the cervix 11 years after mediastinal RT.

All patients referred for cardiac transplantation presented with end-stage cardiac disease due to systolic, diastolic, or a combination of systolic and diastolic heart failure. Restrictive cardiomyopathy was the predominant diagnosis in 8 patients (66%), and features more compatible with dilated cardiomyopathy were present in 4. In addition, coronary artery disease was present in 6 patients, and 9 had associated valvular cardiac disease involving the mitral, aortic, or tricuspid valve to a varying degree. Pulmonary hypertension was present in 9 patients, with a variable response to pulmonary vasodilators (Table 2). Pretransplant pulmonary function studies revealed pattern of restrictive lung disease in 7 and obstructive lung disease in 5 (Table 3).

### Perioperative Details

Among the 12 patients undergoing orthotopic cardiac transplantation, 9 had redo sternotomy, including 2 who had third sternotomy (Table 1). The mean interval between the first cardiac operation and transplantation was 3.9 years (range, 0.9 to 6.8 years) and between the second cardiac operation and cardiac transplant was 3.2 years. All patients had intrapericardial adhesions that needed extensive surgical dissection. Peripheral cannulation was performed in 1 patient through the femoral artery. Bicaval anastomotic techniques were used in 3 patients, whereas the traditional atrial cuff technique was used in the rest of the patients.

The postoperative course of patient 1 was complicated by right heart failure requiring supportive management. This patient had severe restrictive lung disease and nearly systemic pulmonary artery pressures. He died 8 years after the transplant of respiratory and renal failure. Patient 12 required deep hypothermic circulatory arrest (circulatory arrest time, 38 minutes) to perform the operation. Intraoperative bleeding occurred due to coagulopathy, multiorgan failure, and diffuse cerebral injury, and the patient died on postoperative day 4 (hospital mortality, 8.3%).

### Long-Term Follow-Up

Eleven of 12 patients were discharged from hospital (Table 4). Mean follow-up was 7.7 years. Survival at 1, 5, and 10 years was 91.7%, 75%, and 46.7%, respectively (Fig. 1). Chronic kidney injury developed postoperatively in 3 patients due to immunosuppressive therapy and required renal replacement with dialysis. Two of these patients subsequently required a renal transplant. During the first year of follow-up, infection or rejection was diagnosed in 5 patients (41.6%). Only 1 of 5 survivors at the time of latest follow-up was receiving prednisone.

Patient 4, a 34-year-old man, died 5.5 years after his cardiac transplantation of acute myocardial infarction complicated by cardiac failure and aspiration pneumonia. A coronary angiography performed 5 months before his death showed only minor coronary artery disease of the

### Table 3. Preoperative Pulmonary Function Tests

<table>
<thead>
<tr>
<th>Patient</th>
<th>FEV1 (L)</th>
<th>% Predicted FEV1</th>
<th>FVC (L)</th>
<th>% Predicted FVC</th>
<th>FEV1/FVC</th>
<th>DLCO (mL CO/min mm Hg)</th>
<th>% Predicted DLCO</th>
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<tbody>
<tr>
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<td>1.51</td>
<td>35</td>
<td>2.07</td>
<td>38</td>
<td>75</td>
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<td>63</td>
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<tr>
<td>2</td>
<td>2.08</td>
<td>65</td>
<td>3</td>
<td>75</td>
<td>69</td>
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<td>29</td>
<td>88.5</td>
<td>5.9</td>
<td>21</td>
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### Notes

- DLCO = diffusion capacity of the lung for carbon monoxide
- FEV1 = forced expiratory volume in 1 second
- FVC = forced vital capacity
- SD = standard deviation
Severe left main and triple-vessel coronary artery disease was found on autopsy. Secondary malignancies developed in 3 patients (Table 4). B-cell lymphoma developed in patient 2 at 15 years after the transplant, and vulvar and non-small cell lung cancer was diagnosed in patient 7 at 5 years postoperatively; however, both patients died of nonmalignant causes. Inoperable cholangiocarcinoma developed in a 63-year-old man (patient 3) 14 years after the transplant operation, and he was alive at the time of this review.

Comment

Radiation-induced injury leads to delayed onset of tissue fibrosis, necrosis, and vascular injury [6]. Specific effects of RT on the cardiovascular system include coronary artery disease, valvular cardiac dysfunction, cardiomyopathy, aortopathy, and chronic constrictive pericarditis [1, 7]. These patients present with complex cardiovascular disease. Overall, success with conventional cardiac operations using CABG, valve repair or replacement, and pericardectomy has been limited to high mid-term to long-term morbidity and mortality [2, 8–10]. Cardiac surgical interventions also do not always seem to provide good palliation to post-RT cardiac conditions. The interval between the first cardiac operation and transplantation in 9 patients was only 3.9 years.

Preoperative pulmonary hypertension seems to be a common problem in these patients. Severe left main and triple-vessel coronary artery disease was found on autopsy. Secondary malignancies developed in 3 patients (Table 4). B-cell lymphoma developed in patient 2 at 15 years after the transplant, and vulvar and non-small cell lung cancer was diagnosed in patient 7 at 5 years postoperatively; however, both patients died of nonmalignant causes. Inoperable cholangiocarcinoma developed in a 63-year-old man (patient 3) 14 years after the transplant operation, and he was alive at the time of this review.

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Comment

Radiation-induced injury leads to delayed onset of tissue fibrosis, necrosis, and vascular injury [6]. Specific effects of RT on the cardiovascular system include coronary artery disease, valvular cardiac dysfunction, cardiomyopathy, aortopathy, and chronic constrictive pericarditis [1, 7]. These patients present with complex cardiovascular disease. Overall, success with conventional cardiac operations using CABG, valve repair or replacement, and pericardectomy has been limited to high mid-term to long-term morbidity and mortality [2, 8–10]. Cardiac surgical interventions also do not always seem to provide good palliation to post-RT cardiac conditions. The interval between the first cardiac operation and transplantation in 9 patients was only 3.9 years.

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Overall, patients with RT-induced cardiomyopathy represent a difficult treatment dilemma with a paucity of organs for transplantation. A number of these patients have presented with failed medical and surgical therapy due to end-stage cardiac disease. Cardiac transplantation has been used in the management of radiation-induced cardiomyopathy with variable results [5, 11].

There are several important considerations in the treatment of these patients. Technical problems during cardiac operations include dense scarring of the mediastinum from radiation-induced pericarditis and impaired wound healing due to skin changes [2]. Dense intrapericardial adhesions were encountered in all of our patients. Patient 12 required deep hypothermic circulatory arrest intraoperatively to explant a left ventricular assist device.

Cardiac allograft vasculopathy (CAV) represents a complex postoperative complication that can be difficult to diagnose. The incidence of vasculopathy is 8%, 50%, and 90% at 1, 5, and 10 years, respectively [12]. Standard investigations, such as coronary angiography, have low sensitivity for the detection of coronary artery disease. Six of our patients have had mild coronary artery disease, whereas 1 patient had obstructive CAV involving the right coronary artery system. Myocardial infarction caused 2 deaths in our experience. There are no data to suggest whether CAV in the post-RT transplant group behaves differently from the CAV encountered in patients without any prior radiation exposure. Further clinical work will be needed to understand the behavior of CAV after cardiac transplant in RT patients and to define the role of newer imaging modalities such as optical computed tomography [13].

These patients are prone to the development of recurrent or new primary malignancies [2, 8, 14]. This is possibly related to prior exposure to radiotherapy and chemotherapy. The risk of malignancy is further increased by immunosuppressive therapy. Secondary malignancies were encountered in both pretransplant and posttransplant periods in our series. Careful pretransplant evaluation of these patients is mandatory to assess freedom from primary or secondary malignancies.

However, despite the difficulties encountered in the clinical treatment of post-RT transplant patients in our study, we did not find any statistically significant survival difference between the RT and non-RT group, with 1-year, 5-year, and 10-year survival of 91.7%, 75%, and 46.7% compared with 92.6%, 81.8%, and 66.5%, respectively ($p = 0.17$). Overall, the data available on the outcome of this subgroup of patients undergoing cardiac transplant is limited (Table 5).

This study has some limitations. The number of patients in our study is small, and the study was a retrospective analysis. A multiinstitutional study will be powered to identify the factors that affect the outcome after cardiac transplantation in this subgroup.

To conclude, cardiac transplantation provides an excellent treatment option for highly selected patients who manifest cardiac failure after RT. The operation is technically difficult due to associated mediastinal fibrosis. End-stage renal disease due to immunosuppressive drugs and the development of secondary malignancies account for significant late morbidity. Late respiratory failure due to radiation-induced lung disease is responsible for delayed death in a significant proportion of patients.

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References


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Notice From the American Board of Thoracic Surgery

The 2015 Part I (written) examination will be held on Monday, November 16, 2015, at multiple sites throughout the United States using an electronic format. The closing date for registration is August 15, 2015. Those wishing to be considered for examination must apply online at www.abts.org. To be admissible to the Part II (oral) examination, a candidate must have successfully completed the Part I (written) examination. A candidate applying for admission to the certifying examination must fulfill all the requirements of the Board in force at the time the application is received.

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