Outcomes of Pericardiectomy for Constrictive Pericarditis following Mediastinal Irradiation

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Abstract

Background Pericardiectomy for post-radiation constrictive pericarditis has been reported to generally have unfavorable outcomes. This study sought to evaluate surgical outcomes in a large cohort of patients undergoing pericardiectomy for radiation-associated pericardial constriction. Methods A retrospective analysis of all patients ([?]18years) who underwent pericardiectomy for a diagnosis of constrictive pericarditis with a prior history of mediastinal irradiation from June 2002 to June 2019 was conducted. There were 100 patients (mean age 57.2±10.1 years, 49% females) who met the inclusion criteria. Records were reviewed to look at surgical approach, extent of resection, early mortality and late survival. Results The overall operative mortality was 10.1% (n=10). The rate of operative mortality decreased over the study period; however, the test of trend was not statistically significant (P=0.062). Hodgkin's disease was the most common malignancy (64%) for which mediastinal radiation had been received. Only 27% patients had an isolated pericardiectomy, and concomitant pericardiectomy and valve surgery was performed in 46% patients. Radical resection was performed in 50% patients, whereas 47% patients underwent a subtotal resection. Prolonged ventilation (26%), atrial fibrillation (21%) and pleural effusion (16%) were the most common post-operative complications. The overall 1,5- and 10-years survival was 73.6%, 53.4% and 32.1% respectively. Increasing age (HR 1.044, 95%CI 1.017-1.073) appeared to have a significant negative effect on overall survival in the univariate model. Conclusion Pericardiectomy performed for radiation associated constrictive pericarditis has poor long-term outcomes. The early mortality, though high (˜10%), has been showing a decreasing trend in the test of time.

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Methods

A retrospective analysis of all patients ([?]18years) who underwent pericardiectomy for a diagnosis of constrictive pericarditis with a prior history of mediastinal irradiation from June 2002 to June 2019 was conducted. There were 100 patients (mean age 57.2±10.1 years, 49% females) who met the inclusion criteria. Records were reviewed to look at surgical approach, extent of resection, early mortality and late survival.

Results

The overall operative mortality was 10.1% (n=10). The rate of operative mortality decreased over the study period; however, the test of trend was not statistically significant (P=0.062). Hodgkin's disease was the most common malignancy (64%) for which mediastinal radiation had been received. Only 27% patients had an isolated pericardiectomy, and concomitant pericardiectomy and valve surgery was performed in 46% patients. Radical resection was performed in 50% patients, whereas 47% patients underwent a subtotal resection. Prolonged ventilation (26%), atrial fibrillation (21%) and pleural effusion (16%) were the most common post-operative complications. The overall 1,5- and 10-years survival was 73.6%, 53.4% and 32.1% respectively. Increasing age (HR 1.044, 95%CI 1.017-1.073) appeared to have a significant negative effect on overall survival in the univariate model.

Conclusion

Pericardiectomy performed for radiation associated constrictive pericarditis has poor long-term outcomes. The early mortality, though high (˜10%), has been showing a decreasing trend in the test of time.

Keywords – mediastinal irradiation, pericardiectomy, operative mortality

Abbreviations

RACD	Radiation-associated cardiac disease
NYHA	New York Heart Association
CPB	Cardio-pulmonary bypass

Introduction

Mediastinal radiotherapy has been widely used over the years and has evolved to become one of the cornerstones of treatment for various types of thoracic cancers.[1] However, the proximity of the radiation field to the heart can result in a sustained dose to cardiovascular structures, leading to radiation-associated cardiac disease (RACD).[2] The cardiovascular complications of radiation include myocardial fibrosis, valvular abnormalities, coronary artery disease, pericarditis and conduction system dysfunction.[3] While acute pericarditis

has now become less common with modern radiation protocols, chronic pericarditis may manifest decades after treatment completion, often with resultant constriction.[4]

Constrictive pericarditis leads to a loss of pericardial compliance, with resultant diastolic heart failure.[5]Pericardiectomy has been the treatment of choice for constrictive pericarditis, resulting in symptomatic relief and improvement in functional status.[6-11] Pericardiectomy performed for post-radiation constriction has been reported to generally have unfavorable outcomes but data are limited to small-sized studies[7, 11-13]. We sought to evaluate outcomes in a large cohort of patients undergoing pericardiectomy for constriction after mediastinal irradiation, and to analyze surgical approach, extent of resection, early mortality, and late survival.

Methods

We retrospectively reviewed 130 adult patients (age [?] 18 years) who underwent pericardiectomy with a prior history of mediastinal irradiation, from June 2002 to June 2019 at the Mayo Clinic in Rochester, Minnesota. Both primary and re-operative procedures were included. The study was approved by the Institutional Review Board at Mayo Clinic, Rochester, Minnesota (Date 2/8/2019, IRB no - 19-000542). Individual patient consent requirement was waived as the study was deemed a minimal-risk retrospective study; 2 patients without research authorization were excluded. Patient characteristics were obtained from the prospectively collected database based on definitions set forth by the Society of Thoracic Surgeons (STS) Adult Cardiac Database with additional review of patient records for supplementing missing information.[14]

Patients who underwent pericardiectomy for an indication other than a pre-operative diagnosis of constriction (N=28) were excluded, leaving 100 patients for study inclusion. Our surgical approach and operative techniques for pericardiectomy have been previously reported.[7, 10, 15-17] A radical resection was defined as removal of anterior, inferior (diaphragmatic) and lateral pericardium posterior to the phrenic nerves. Any pericardial resection that did not meet the criteria for radical resection was defined as subtotal resection. Operative mortality was defined as any death, regardless of cause, occurring within 30 days after surgery, or during the same hospitalization as the index surgery, regardless of time.

Statistical analysis

Continuous variables are reported as median (interquartile range [IQR]), and categorical variables are reported as number (percentage). The temporal trend in operative mortality over the study period was visualized with a Loess smoothing estimator and was formally tested with a Wilcoxon rank sum test. Long-term mortality was depicted graphically using the Kaplan-Meier estimator, and the reverse Kaplan-Meier method was used to summarize follow-up time. The unadjusted association between select baseline factors and mortality was assessed in univariable Cox proportional hazards models. Because few of the patients (3 patients) underwent completion pericardiectomy, this group was combined with the radical pericardiectomy group. These analyses were done in SAS version 9.4 (SAS Institute, Cary NC).

Results

The study included a total of 100 adult patients with a history of prior mediastinal irradiation who underwent pericardiectomy for constriction (median (IQR) age 56.8 (50.9, 65.9) years, 49% females). Demographic characteristics are shown in Table 1. Hodgkin's disease was the most common malignancy (64%) for which mediastinal radiation had been received, followed by breast cancer (15%). Most of the patients (75%) had New York Heart Association (NYHA) class III/IV symptoms at presentation. Pericardiectomy was the first cardiovascular surgical procedure in 66% of patients. The median (IQR) duration between mediastinal irradiation and surgery was 28.5 (20, 34) years.

The operative characteristics are outlined in Table 2. The surgical approach was by a full midline sternotomy in 95% of patients, and cardio-pulmonary bypass was used in 96%. Only 27% of patients had an isolated pericardiectomy. A radical resection was performed in 50% of patients, whereas 47% underwent a subtotal resection.

Early outcomes

Overall, the rate of operative mortality was 10.1%. This rate appeared to show a decreasing trend over the study period, although the test for trend was not statistically significant (P=0.06) (Figure 1). Prolonged ventilation (26%), atrial fibrillation (21%) and pleural effusion (16%) were the most common post-operative complications (Table 3). Post-operative dialysis was needed in 13 (13%) patients.

Late outcomes

A total of 52 deaths (early or late) were observed over a median (IQR) follow-up period of 6.01 (3.56, 9.47) years. The overall 1-, 5- and 10-year survival was 73.6%, 53.4% and 32.1% respectively (Figure 2). The prespecified factors assessed for an unadjusted association with overall survival are presented in Table 4. Only older age was univariably associated with increased risk of mortality (per 10-year increase: HR 1.55, 95% CI 1.18-2.02; p=0.002). There was no association between ejection fraction, coronary artery disease, previous cardiac surgery, concomitant surgical procedures, or pre-operative renal failure with mortality. There was no survival advantage of performing a radical resection in this population (HR 1.35, 95% CI 0.77-2.36, p=0.295). There was also no difference in survival between patients that underwent pericardiectomy with concomitant cardiac procedures and patients that underwent isolated pericardiectomy (HR 0.70, 95% CI 0.39-1.27, p=0.246).

Discussion

This study shows that pericardiectomy for constriction in patients with prior mediastinal irradiation is associated with poor long-term survival. The 1, 5- and 10-year survival was 74%, 53% and 32% respectively. Early mortality, though high (˜10%) for the entire period, showed a modest, yet statistically nonsignificant, decreasing trend over time, with mortality rates over the second half of the period (approximately 4%; 2 deaths in 51 surgeries) being more comparable to those with non-radiation related constriction.

Radiation induced pericardial disease is one of the most common manifestations of RACD. This typically manifests itself several years after mediastinal irradiation. In the present study, the median duration from radiation to pericardiectomy was 28.5 years (IQR 20-34 years). This was a mean of 53 months as reported by Siefert and colleagues[18], and a median of 11 years (range 2 to 30 years) as reported by Bertog and colleagues.[11] Ling et al reported a median range of 13 years[7], and McCaughan et al reported a range of 15 months to 44 years.[19]This may also reflect improved cancer cure rates, which have resulted in greater longevity and thus the likelihood of developing delayed cardiovascular sequelae.[7] In previous studies, lymphomas have been the most common malignancy for which mediastinal radiation was received, followed by breast cancer.[7, 11, 18, 19] Our experience has been similar, with lymphomas constituting 69% of the patients and breast cancer a further 15%.

Clinical manifestation of pericardial disease may vary in severity from asymptomatic pericardial effusion to debilitating constrictive pericarditis.[3, 4, 20] Fibrosis is a common sequela of radiotherapy and leads to fibrous thickening of the pericardium. In addition to pericardial fibrosis, there is myocardial fibrosis with possible endocardial fibrosis as well.[21] Brosius and colleagues found interstitial myocardial fibrosis in patients who had received prior irradiation.[21] The pathogenesis of this myocardial fibrosis has been related to capillary endothelial cell injury, leading to a quantitative loss of capillaries, leading to ischemia.[22] It is perceived that the increased filling pressures in these patients may be in part due to increased myocardial stiffness, which may not be relieved even with an adequate pericardial resection.

Pericardiectomy is also technically challenging in this subset of patients. The plane of dissection may not be easily accessible due to the dense mediastinal fibrosis. In the present study, a radical resection could be performed in only 50% of the patients, whereas 47% patients received a subtotal resection. This contrasts with previous reports from this institution where radical pericardiectomy was performed on 77% of patients presenting with constriction for causes other than radiation.[10] Another indicator of the technical difficulty could be the use of cardiopulmonary bypass (CPB) in 96% of these patients. A previous report from this institution documented the use of CPB to be 51% in pericardiectomies performed for constriction for

causes other than radiation.[10] This maybe a reflection of the surgeon deeming it unsafe to perform a radical resection in some patients due to the degree of difficulty of the procedure and having a low threshold of going on CPB. Our experience was corroborated by the findings of Ni and colleagues, who concluded that a complete pericardiectomy may not be achieved in all patients with post-radiation constrictive pericarditis.[13]

Mediastinal irradiation damages the vascular endothelium and leads to radiation-induced vascular disease of peripheral, coronary and carotid arteries.[23] When the coronary vasculature is involved, these patients may present with the classical features of coronary artery disease; however, some may also remain asymptomatic.[24, 25] Valvular disease is frequently seen in this subset of patients as well. The aortic and mitral valves are more commonly involved, and the affected valves are typically fibrotic with focal dystrophic calcification and marked thickening.[21, 26, 27] In the present study too, isolated pericardiectomy was performed in only 27% of the patients, with most of the patients having concomitant valve surgery (46%), coronary artery bypass grafting (4%), or a combination of both procedures (23%). This further illustrates the pan-cardiac involvement in these patients, further adding to the degree of complexity and justifies the higher need for CPB in this population.

Pericardiectomy for post-irradiation constrictive pericarditis has been reported to have high operative mortality with poor late results. Ni and colleagues collected data from a series of 46 patients across literature and reported an operative mortality of 22%.[13] Bertog and colleagues also reported an operative mortality of 21% in this subset of patients in their large series on pericardiectomy for constriction.[11] The general belief is that the effects of radiation on other cardiac structures, including coronary vasculature, valvular abnormalities and the associated myocardial fibrosis all contributes to the increased peri-operative mortality seen in this subset. In the present study, the operative mortality was 10%, which is higher than the 2.5% operative mortality reported by the same institution for pericardiectomy for constriction performed for etiologies other than mediastinal irradiation.[10]However, our data suggest an improvement over time, based on a decreasing rate in operative mortality that trended toward significance and an observed rate of 4% over the second half of the study. This maybe attributed to improved surgical and perfusion techniques, post-operative care, and better patient selection. Noteworthy, pericardiectomy was still associated with significant morbidity, with 13% of patients requiring post-operative dialysis.

The long-term outcomes of this patient population remain poor, with a 1, 5- and 10-year survival of 73%, 53% and 32% respectively. Previous reports from this institution have shown a 1, 5- and 10- year survival of approximately 87%, 77% and 58% respectively, for pericardiectomy performed for all other etiologies of constriction.[10]The only risk factor associated with increased mortality was advanced age which may reflect to medical complexities with high prevalence of comorbidities (coronary artery disease, valvular disorders, renal dysfunction). Despite the poor long-term outcomes, whether pericardiectomy in this population of patients is associated with significant improvements in functional capacity and quality of life requires further investigation.

Conclusion

Patients with prior mediastinal irradiation undergoing pericardiectomy for constrictive pericarditis in the current era have acceptable early mortality, albeit still higher than in other etiologies of constriction; however, the long-term prognosis in this population remains poor.

Limitations

There are several limitations to this study. First, it is a retrospective single-institution study limited by its inherent selection bias. Second, this retrospective study was conducted over a span of 18 years. The surgical techniques and definitions of post-operative complications have continued to evolve and may have contributed to variability of data over time. Lack of functional data, and a comparison group of patients who had mediastinal irradiation induced constriction but did not undergo pericardiectomy are other important limitations.

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Figure 1 – Operative mortality. Test of trend over the study period

Figure 2 – Late mortality at 1-, 5- and 10 years

Table 1 – Patient demographics

Variable	**N=100**
Age (years), median (IQR)	56.8 (20.9, 65.9)
Female Sex, N (%)	49 (49%)
BMI (kg/m^2), median (IQR)	26.1 (23.3, 29.0)
BSA (m^2), median (IQR)	1.9 (1.7, 2.1)
Diabetes Mellitus, N (%)	13 (13%)
Dyslipidemia, N (%)	69 (69%)
Hypertension, N (%)	43 (43%)
NYHA, N (%)	
I	3 (3%)
II	22 (22%)
III	57 (57%)
IV	18 (18%)
Type of Malignancy, N (%)	
Hodgkin's disease	64 (64%)
Breast cancer	15 (5%)
Non-Hodgkin's disease	5 (5%)
Esophageal cancer	5 (5%)
Thymic cancer	3 (3%)
Lung cancer	4 (4%)
Metastasis	4 (4%)
Chronic Lung Disease type, N (%)	
None	62 (63%)
Interstitial fibrosis	19 (19%)
Obstructive	13 (13%)
Other	3 (3%)
Multiple	2 (2%)
Incidence of Cardiovascular Surgery, N (%)	
First surgery	66 (66%)
First redo	31 (31%)
Second/higher redo	3 (3%)
Previous CABG, N (%)	20 (20%)
Previous Valve Surgery, N (%)	15 (15%)
Previous PCI, N (%)	18 (18%)
Heart rhythm, N (%)	
Sinus	80 (80%)
Atrial fibrillation/flutter	5 (5%)
1st degree AV block	15 (15%)

Data was missing in 1 patient.

IQR – Inter-quartile Range, BMI – Body Mass Index, BSA – Body Surface Area, NYHA – New York Heart Association, CABG – Coronary Artery Bypass Grafting, PCI – Percutaneous Coronary Intervention, AV – Atrio-ventricular

Table 2 – Operative characteristics

Variable, N (%)	**N=100**
Operative approach	
Full sternotomy	95 (95%)
Partial sternotomy	2 (2%)
Right thoracotomy	1 (1%)
Left thoracotomy	1 (1%)
Postero-lateral thoracotomy	1 (1%)
Cardio-pulmonary bypass used	96 (96%)
Operative Status	
Elective	80 (80%)
Urgent	20 (20%)
Operative category	
Isolated pericardiectomy	27 (27%)
Pericardiectomy + CABG	4 (4%)
Pericardiectomy + Valve surgery	46 (46%)
Pericardiectomy + CABG + Valve surgery	23 (23%)
Pericardiectomy type	
Radical	50 (50%)
Subtotal	47 (47%)
Completion	3 (3%)
Pericardiectomy indication	
Constrictive	99 (99%)
Effusive-constrictive	1 (1%)
Use of intra-operative blood products	69 (72%)
Use of IABP	11 (11%)
ECMO used during hospitalization	4 (4%)

Data was missing in 4 patients.

CABG – Coronary Artery Bypass Grafting, IABP – Intra-aortic Balloon Pump, ECMO – Extra-corporeal Membrane Oxygenation

Table 3 – Post-operative complications

Variable, N (%)	**N=100**
Operative mortality	10 (10%)
Prolonged Ventilation	26 (26%)
Atrial fibrillation	21 (21%)
Pleural Effusion	16 (16%)
Dialysis required	13 (13%)
Permanent Pacemaker Required	6 (6%)
Sternal Infection	6 (6%)
GI Event	5 (5%)
Re-operation for Bleeding	4 (4%)
Sepsis	4 (4%)
Stroke	1 (1%)
TIA	1 (1%)

Data was missing in 1 patient.

GI – Gastro-intestinal, TIA – Transient Ischemic Attack

Table 4 – Univariate association of factors with overall survival

Variable	**Comparison**	**P Value**	**Hazard Ratio (95% CI)**
Age	per 10-year increase	0.002	1.55 (1.18-2.02)
Gender	Female vs Male	0.736	0.91 (0.52-1.58)
NYHA Class	III/IV vs I/II	0.791	1.09 (0.57-2.09)
Preoperative Renal Failure	Yes vs No	0.747	1.26 (0.31-5.23)
Previous CVS	Yes vs No	0.502	1.21 (0.70-2.10)
Coronary Artery Disease	Yes vs No	0.585	1.17 (0.66-2.09)
EF $< 50\%$	Yes vs No	0.835	0.92 (0.41-2.04)
Pericardiectomy type	Radical/Completion vs Subtotal	0.295	1.35 (0.77-2.36)
Operative category	Concomitant vs isolated pericardiectomy	0.246	0.70 (0.39-1.27)

CI – Confidence Interval, NYHA – New York Heart Association, CVS – Cardiovascular Surgery, EF – Ejection Fraction

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