Cardiac surgery in patients irradiated for Hodgkin's lymphoma

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Background/Objectives. Therapy for Hodgkin's lymphoma is disease specific and cannot be compared with treatment for other diseases. It often includes more extensive radiotherapy on the mediastinum than for other malignancies. Cardiac morbidity is known to occur in patients previously irradiated. This study describes the postoperative course after cardiac surgery of patients previously irradiated for Hodgkin's lymphoma.

Methods. From January 1990 until June 2008, 12 patients underwent cardiac surgery in the University Medical Center Utrecht after previous irradiation for Hodgkin's lymphoma. Data on radiotherapy, surgery and follow-up were collected retrospectively. The postoperative functional status was assessed by a telephone questionnaire.

Results. Atrial fibrillation (33%) and pleural effusion (25%) were the most common postoperative complications. After a mean follow-up of 2.6 ± 2.9 years four patients had died. The remaining patients were all in a favourable New York Heart Association and Canadian Cardiothoracic Society class. The estimated one-, two- and four-year survival rates were 83, 69 and 46% respectively.

Conclusion. The early postoperative outcome of cardiac surgery in this population is reasonably good. The long-term results may prove to be disappointing, but the cohort is small. (Neth Heart J 2010;18:61-5.)

Keywords: Cardiac Surgical Procedures; Hodgkin Disease; Radiotherapy

Treatment for Hodgkin's lymphoma has improved since the introduction of radiotherapy and chemotherapy. Ten-year survival rates for Hodgkin's lymphoma increased from approximately 68% for patients treated between 1965 and 1972, to 88% for those treated between 1980 and 1988.¹ However, from the 1980s onwards negative long-term side effects of the treatment started to reveal themselves. The effects range from endocrinal disturbances, to second cancers and cardiopulmonary disease.²

The association between cardiac morbidity and mediastinal radiotherapy has often been studied and described.² The most common heart pathology is pericardial disease, conduction disturbance, myocardial fibrosis, coronary heart disease, and valvular heart disease.³ Radiotherapy to the thorax induces damage to the endothelium of the microvasculature, causing hypoperfusion or ischaemia. The cause of valvular fibrosis is still unknown. As to the toxicity of chemotherapy, anthracycline causes damage to the myoepithelium, strongly dependent on the cumulative dose.⁴ The risk of myocardial infarction (MI), angina pectoris, congestive heart failure (CHF) and valvular disorders is increased up to sevenfold in survivors of Hodgkin's lymphoma.⁴

Thoracic irradiation is heterogeneous. Most patients with other thoracic malignancies are irradiated differently and in general cannot be compared with patients treated for Hodgkin's lymphoma.⁵

The 15-year prevalence of Hodgkin's lymphoma in the Netherlands was approximately 4200 patients in the year 2005.⁶ Consequently, cardiothoracic surgeons will encounter patients irradiated for Hodgkin's lymphoma who need to be operated on. Knowledge about the broad range of pathology of radiation-induced cardiovascular disease,⁷ the postoperative morbidity and the long-term follow-up of

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cardiac surgical intervention is therefore of importance. Few studies are available on the outcome of the heart operations and the postoperative course in this specific patient population.

The largest study, performed by Chang and co-workers, included 61 Hodgkin's lymphoma patients.⁵ They concluded that extensive exposure of the heart to radiation increases the perioperative morbidity and decreases short- and long-term survival when compared with limited exposure in patients with breast cancer. Relevant literature on this matter includes only small cohort studies and some case reports.⁸⁻¹⁷

The goal of this study is to describe the postoperative course and complications after cardiac surgery in patients previously irradiated for Hodgkin's lymphoma.

Patients and methods

Patients

From 1 January 1990 until 25 June 2008, 19,663 patients underwent cardiopulmonary surgery at the University Medical Center Utrecht. Twelve of these patients were identified to have undergone cardiac surgery after previous mediastinal irradiation for Hodgkin's lymphoma.

Data were collected by reviewing medical records, including operation reports, anaesthetic notes, laboratory investigations, ultrasound data, cardiac catheterisation data and clinical case histories. Radiotherapy details were collected from separate radiation records. If patients had not been irradiated in the UMC Utrecht, data were collected from radiation records elsewhere. Data were retrospectively reviewed and defined according to the Society of Thoracic Surgeons Adult Cardiac Data Specification,¹⁸ EuroSCORE¹⁹ and recent guidelines for reporting mortality and morbidity after cardiac valve interventions.²⁰

Preoperative patient characteristics are shown in table 1. The patients were relatively young. Most of the patients had advanced functional limitations. The most common preoperative risk factors for cardiovascular disease in this study group are hypertension and hypercholesterolaemia.

Left-sided valvular disease is more common than right-sided disease. Aortic stenosis is the most frequent valvular pathology. As a consequence eight of nine patients with a valvular operation received an aortic valve prosthesis. Only two patients underwent isolated coronary bypass grafting (table 2).

The study group was characterised by an acceptable EuroSCORE¹⁹ prior to surgery.

Table 1. Preoperative patient characteristics.

Patient characteristic	Total (n=12)
Age	51±13
Women	6 (50)
NYHA class III or IV	6 (50)
History of AF	1 (8)
Previous myocardial infarction	2 (17)
History of PPM	1 (8)
Previous stroke	1 (8)
Hypertension	4 (33)
Diabetes mellitus	0 (0)
Hypercholesterolaemia	9 (75)
BMI	26±4.0
Chronic lung disease	0 (0)
Creatinine >200 mmol/l	0 (0)
Dialysis dependency	0 (0)
Euroscore logistic	3.0±1.9
Euroscore standard	3.4±2.3
LVEF	
- Normal ≥50%	8 (67)
- Reduced 30-50%	4 (33)
- Poor ≤30%	0 (0)
Constrictive pericarditis	1 (8)
Valve disease	
- Aortic stenosis	9 (75)
- Aortic regurgitation	7 (58)
- Mitral stenosis	4 (33)
- Mitral regurgitation	6 (50)
- Tricuspid stenosis	1 (8)
- Tricuspid regurgitation	3 (25)
- Pulmonary regurgitation	1 (8)

Data expressed as mean ± standard deviation (SD) or number with percentage in brackets. NYHA=New York Heart Association, AF=atrial fibrillation, PPM=permanent pacemaker, BMI=body mass index, LVEF=left ventricular ejection fraction.

Patients were treated with radiotherapy at an average age of 27 years (range 40 years). The interval between radiation therapy and cardiac surgery was approximately 24 years (range 26 years). Detailed information on radiation therapy could be retrieved in 10 of the 12 patients. Half of the patients had additional chemotherapy, usually the combination of mustine, vincristine, procarbazine, and prednisone (MOPP). The majority of our study patients were treated with radiation therapy in the 1970s. All but one patient received radiotherapy by mantle field.

Data on follow-up were collected retrospectively. Clinically relevant information and the most recent medical notes were obtained from cardiologists, describing hospitalisation and outpatient visits and investigations. To obtain subjective data on

Table 2. Cardiac operations.

Cardiac operation	Total (n=12)
Isolated valvular	7 (58)
Isolated CABG	2 (17)
Valvular and CABG	2 (17)
Pericardiectomy	1(8)
Aortic valve	8 (66)
- Bioprosthesis	1
- Mechanical prosthesis	7
- Plasty	0
Mitral valve	3 (25)
- Bioprosthesis	1
- Mechanical prosthesis	2
- Plasty	0
Tricuspid valve	1 (8)
- Plasty	1
Pulmonary valve	0 (0)

Data expressed as numbers with percentages in brackets.
CABG=coronary artery bypass graft

their cardiac health status, patients were contacted. A questionnaire on cardiac status was performed by telephone. A Dutch translated and slightly amended version of Kubo was used as questionnaire. The structured interview and questionnaire were used to assess the current New York Heart Association (NYHA) and Canadian Cardiothoracic Society (CCS) class. Total follow-up was 32 patient-years with a mean of 2.6 ± 2.9 years and median of 1.4 years.

The study plan was approved by the Medical Ethics Commission and all patients gave informed consent.

Statistical analysis

Data analysis was performed in SPSS 15 for Windows, SPSS Inc. Chicago 2001. Survival was estimated by using the Kaplan-Meier method. Significance of differences between means was calculated non-parametrically by using the Mann-Whitney test.

Results

Clinical data

Half of the patients had a postoperative cardiac complication, as is shown in table 3. Atrial fibrillation and pulmonary complications were the most common complications. One patient had to be re-operated for bleeding. No hospital death, sepsis or stroke occurred in our study population. The median postoperative intensive care unit (ICU) stay was 1.0 day. Two outliers with a total ICU stay of 10 and 19 days account for the high mean of 3.6 days. The median postoperative length of stay in the

Table 3. Postoperative complications.

Complication	Siregar et al. ⁵ (n=12)	Chang et al. ⁵ (n=70)
Myocardial infarction	1 (8)	0 (0)
Atrial fibrillation	4 (33)	
Cardiac decompensation	3 (25)	
Respiratory insufficiency*	1 (8)	17 (24)
Ventilation >24 h	1 (8)	
Pneumonia	1 (8)	
Pleural effusion	3 (25)	
Pneumothorax	1 (8)	
Renal failure [†]	2 (17)	6 (9)
Sepsis	0 (0)	9 (13)
Stroke	0 (0)	4 (6)
Hospital death	0 (0) [‡]	9 (13)
Reoperation for bleeding	1 (8)	4 (6)
Sternal wound infection	0 (0)	3/67 (4)
ICU length of stay (days)		
Mean	3.6	2 (1, 13) [§]
Median	1	
Postoperative hospital stay		
Mean	15.1	8 (5, 36)**
Median	8	

Data expressed as numbers with percentages in brackets, unless otherwise stated. *Combination of reintubation, >72 hours intubated and readmission to intensive care unit for respiratory complications. [†]New onset requiring haemodialysis. [‡]Including operative mortality: 30 days postoperative. [§]15th, 85th percentiles. **15th, 85th percentiles.

hospital is eight days, with one outlier, who stayed in the hospital for 91 days. No cardiac reoperations were performed after initial discharge. The results of this study are contrasted with the only available detailed study on a sizable group of patients with extensive thoracic irradiation therapy.⁵

Follow-up

All patients alive in 2008 were in NYHA class I or II and CCS class 0 or I (mean 2.6 ± 2.9 years). After a total follow-up of 32 years, four patients had died. The cause of death was cardiac decompensation in three and a second malignancy in one patient. The estimated 1, 2 and 4 year survival rates are 83, 69 and 46% respectively. All surviving patients rated their general health above 6 on a scale from 1 to 10. The average score was 8 ± 0.9 .

Discussion

Principal findings

The goal of this study is to describe the postoperative course and complications after cardiac surgery in patients previously irradiated for Hodgkin's

lymphoma. The early postoperative course of our operated patients seems to be favourable. Hospital death rate was nil. Neither the type nor the number of early postoperative complications in the study patients differed from those normally encountered after cardiac surgery. Other studies described rates varying from nil¹⁴ to 13%.^{5,13}

In contrast, the long-term results are less positive. The estimated four-year survival rate in our study group was 43%. Others found four-year survival rates of 64 and 73%.^{5,13} For the surviving patients the level of the quality of life in the years after surgery was high.

Thoracic irradiation

Thoracic irradiation consists of a multitude of regimes. All irradiation protocols have a disease-specific radiation dose, field, fraction and additional chemotherapy agents. Not surprisingly, Chang⁵ showed significant differences in outcome of heart operations among patients with previous irradiation of the chest for Hodgkin's lymphoma and other malignancies. Extensively irradiated patients have a higher risk of developing radiation heart disease, but also an increased risk on perioperative morbidity. Short- and long-term survival of these patients is decreased. Unfortunately large cohort studies by Crestanello²¹ and Handa²² analysed a very heterogeneous group of irradiated patients. Only a few studies have given separate facts and figures for the included Hodgkin's lymphoma patients.^{5,9-17} To the authors' knowledge this is the first study in the Netherlands that describes a cohort of Hodgkin's lymphoma patients from a cardiosurgical perspective.

Several predictors of increased risk for developing cardiac disease after irradiation have been identified. One could hypothesise that preoperative damage to the heart negatively influences the postoperative course. Irradiation for Hodgkin's lymphoma at a young age,^{2,4} radiotherapy with a higher irradiated heart volume,⁵ the addition of anthracycline-containing chemotherapy,⁴ and the presence of hypercholesterolaemia and diabetes⁴ have all been described to increase the risk on cardiovascular disease. None of these factors have shown to be of influence on the postoperative outcome in our group.

Pulmonary complications

Radiation and chemotherapy for Hodgkin's lymphoma causes pulmonary impairment, developing insidiously years after treatment.²³ Where Chang described high rates of postoperative respiratory insufficiency,⁵ we only found one patient to have this complication. Pleural effusion accounts for most of the pulmonary problems in our patients. Hicks noted only one pulmonary complication in seven

Hodgkin's lymphoma patients.¹⁴ The results suggest that the incidence and severity of pulmonary complications are variable.

Cardiac complications

Cardiac complications in our group consisted mainly of atrial fibrillation, with a comparable incidence as normally encountered in cardiac surgery.²⁴ The left internal mammary artery (LIMA) was used in two patients who received bypass grafts. Just as the coronary arteries are damaged in relation to radiation dosimetry,²⁵ the LIMA is subject to radiation injury as well. Graft closures have been described in patients who have been irradiated.^{26,27} In this study group no clinical signs of closed grafts were documented. Pericarditis is a frequently described complication of mediastinal radiation⁷ and is suggested to be related to complications during and after surgery. The single patient presenting with constrictive pericarditis needed drainage of pleural effusion and had a prolonged ICU stay.

Limitations and strengths

The small number of patients in available studies made it impossible to draw quantitative conclusions. This is inevitable considering the low incidence of Hodgkin's lymphoma in single-centre studies.

New radiation strategies combining chemotherapy with involved field radiation therapy have only recently been developed by the European Organisation for Research and Treatment of Cancer (EORTC).²⁸ Trials involving extensive radiation fields were still performed up until 2003²⁹ and the new Involved Nodes Radiation Therapy guidelines from 2006³⁰ will only be applied in an upcoming EORTC – GELA (Group d'Etude de Lymphomes Adultes) randomised trial. As cardiac complications evolve over a period of years to decades, patients treated with extensive radiation fields will still present for cardiac surgery in the coming years. This subject therefore remains highly relevant.

Conclusion

Patients with previously treated Hodgkin's lymphoma who are receiving cardiac surgery should be considered as a specific patient population. This population has a high prevalence of cardiac abnormalities, which are surgically treated decades after irradiation. The early postoperative outcome of cardiac surgery in patients previously treated for Hodgkin's lymphoma is reasonably good, especially when morbidity after extensive radiation therapy and chemotherapy is considered. The long-term results may prove to be less positive; the survival rate four years after surgery is disappointing, but the cohort is small. ■

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