Heart, Lung and Circulation (2019) **28,** 334–341
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2017.11.008

ORIGINAL ARTICLE

Early and Late Survival of On-Pump Cardiac Surgery Patients Formerly Affected by Lymphoma

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Received 10 September 2017; received in revised form 24 October 2017; accepted 20 November 2017; online published-ahead-of-print 28 November 2017

Background Survival after cardiac surgery of patients formerly affected by lymphoma has not been well defined.

Methods Forty-five consecutive patients having prior Hodgkin's (HL patients, n = 26) or non-Hodgkin's lymphoma (non-HL patients, n = 19) underwent on-pump cardiac surgery at the authors' institution (2001-2016). Ischaemic, valvular, and ischaemic plus valvular heart disease were present in 14, 13, and 18 patients, respectively. Concomitant aortic disease was treated in three cases. The expected operative risk was calculated by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II. The 10-year survival was estimated by the Kaplan-Meier method and the Charlson Comorbidity Index (CCI). The Cox proportional-hazards regression was used to evaluate the effect of some risk factors on survival.

Results With respect to non-HL patients, HL patients were younger (mean age, 52.5 vs. 64.7 years, p = 0.0017) and underwent cardiac surgery later after lymphoma occurrence (median gap, 21.5 vs. 9.6 years, p = 0.0079). No other intergroup differences as baseline characteristics, risk profiles (median EuroSCORE II, 2.3% vs. 3%, p = 0.78), and in-hospital mortality (7.7% vs. 10.5%, p = 0.99) were found. Older age, severe left ventricular dysfunction, and HL history were predictors of cardiac or cerebrovascular death ($p < 0.1$). The 10-year, crude (40.4%) and adjusted (39.1%) nonparametric estimates of survival were lower than the expected survival by CCI (77.5%, $p < 0.0001$). The 10-year nonparametric estimate of freedom from malignancy was 66.3%.

Conclusions Immediate and long-term survival after on-pump cardiac surgery of patients formerly affected by lymphoma were worse than expected, according to universally used predictive scoring systems. There was an increased risk of malignant tumour.

Keywords Cardiac surgery • Hodgkin's lymphoma • Lymphoma • Survival • Tumour

Introduction

The past use of cardiotoxic chemotherapies and aggressive radiation therapy protocols are both called into question given an increased risk of heart diseases needing surgery in patients formerly affected by lymphoma [1–3]. For these patients [4,5] as well as for all patients formerly affected by other malignant diseases [6,7], there is a generic perception

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among clinicians of frailty and vulnerability to any stress, including surgical [5,8–11]. However, the real impact of cardiac operations on the survival of patients formerly affected by lymphoma has not been explored in depth and specificity.

In the present study, immediate and late outcomes after cardiac surgery of a limited series of consecutive patients formerly affected by Hodgkin's (HL) or non-Hodgkin's lymphoma (non-HL) were reviewed retrospectively. The primary endpoints were in-hospital and long-term survival.

Patients and Methods

Study Patients

Between 2001 and 2016, a total of 472 patients having a history of solid tumour underwent cardiac surgery at the Cardiovascular Department of the Trieste University Hospital, Trieste, Italy. Forty-five (9.5%) of these patients (mean age, 57.7 ± 13.5 years) had a prior HL (n = 26, 57.8%) or non-HL (n = 19, 42.2%); they were enrolled into the present retrospective study.

Baseline characteristics, operative data and surgical features were prospectively recorded for every patient in a computerised data registry. These data are summarised in Tables 1 and 2. The risk profile of each patient was established preoperatively according to the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) [12]. Unless otherwise stated, definitions and cut-off values of the preoperative variables were those employed for EuroSCORE II [12]. Definitions of postoperative complications were in accordance with the internationally agreed definitions of complications after cardiac surgery [13,14].

Surgery

For every patient, surgery was carried out through a median sternotomy with cardiopulmonary bypass. Myocardial protection was achieved with multidose cold blood cardioplegia. Since July 2009, a single-dose crystalloid solution, the Custodiol®-histidine-tryptophan-ketoglutarate solution (Essential Pharma, Newtown, PA, USA), was chosen when mitral valve or aortic surgery were scheduled [15]. Both cardioplegic solutions were delivered in antegrade and retrograde modes.

Coronary, valvular, and combined, coronary plus valvular, surgery were carried out in 14 (31.1%), 13 (28.9%), and 18 (40%) patients, respectively. Concomitant surgery of the ascending aorta was performed in three (6.7%) cases. Native valve (active) infective endocarditis was an indication for surgery in two (4.4%) patients (Table 2).

Follow-Up

An up-to-date clinical follow-up was obtained by a telephonic interview with the patients or their family. The occurrence of death during the follow-up period and the cause of death were both recorded. For this study, follow-up was closed on 18 April 2017.

Approval to conduct the study was acquired from the hospital ethics committee based on retrospective data retrieval; the need for patients to provide individual's written consent was waived.

Statistical Methods

Continuous variables with normal distribution were expressed as mean ± standard deviation and those without normal distribution as median and the range between the first and the third quartile. Discrete variables were expressed as frequencies and percentages. Statistical comparison of baseline characteristics and operative data was performed using the Chi-square, the Fisher's exact, or the McNemar test for categorical variables, and the Student's *t*-test or the Mann-Whitney *U*-test for continuous variables. The 1-, 5-, and 10-year freedom from all-cause death, cardiac or cerebrovascular death, death due to malignancy, major adverse cardiac and cerebrovascular events (MACCEs), and malignancy were estimated with the Kaplan-Meier method. The in-hospital deaths were also included. The 10-year freedom from all-cause death was estimated with the Charlson Comorbidity Index (CCI) as well. Comparisons between survival curves were made by the log-rank test. Independent predictors of all-cause death, cardiac or cerebrovascular death and MACCEs during the follow-up period were found with the Cox proportional-hazards regression analysis. Covariates adjusted survival was estimated. Statistical analysis was performed by the SPSS program for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Early (In-Hospital) Outcome

There were four (8.9%) in-hospital deaths (three of which occurred within 30 days from operation). Causes of death were: multiorgan failure (n = 2), low cardiac output (n = 1), and pneumonia (n = 1). Forty per cent of patients had at least one major complication early after surgery. Prolonged invasive ventilation, low cardiac output, acute kidney injury, multiple blood transfusion, and mediastinal re-entry for bleeding or tamponade were the most frequent major postoperative complications. No perioperative myocardial infarction arose (Table 3).

Late Outcome

The follow-up rate was 100%. A total of 208 cumulative patient-years were reviewed. The mean follow-up had a duration of 4.6 years (median, 2.8 years). Twenty-one (51.2%) patients died after hospital discharge. Eight (19.5%) cardiac or cerebrovascular deaths and 13 (31.7%) non-cardiac non-cerebrovascular deaths occurred. Causes of deaths were: congestive heart failure (n = 5), myocardial infarction (n = 1), stroke (n = 2), malignancy (n = 8), pneumonia (n = 2), liver cirrhosis (n = 1), autoimmune haemolytic anaemia (n = 1), and car accident (n = 1) (Figure 1). Twenty-

Table 1 Baseline characteristics of patients.[a]

Characteristic	Total n = 45	HL patients n = 26 (57.8)	Non-HL patients n = 19 (42.2)	p-Value
Period				0.88
2001–2004	10 (22.2)	6 (23.1)	4 (21.1)	
2005–2008	6 (13.3)	4 (15.4)	2 (10.5)	
2009–2012	16 (35.5)	8 (30.8)	8 (42.1)	
2013–2016	13 (28.9)	8 (30.8)	5 (26.3)	
Time between lymphoma onset and cardiac operation, years	18.1 (9–25)	21.5 (14.8–25.5)	9.6 (6.8–18.2)	0.0079
Age, years	57.7 ± 13.5	52.5 ± 11	64.7 ± 13.5	0.0017
20–40	5 (11.1)	4 (15.4)	1 (5.3)	
40–50	7 (15.5)	6 (23.1)	1 (5.3)	
50–60	10 (22.2)	8 (30.8)	2 (10.5)	
60–70	12 (26.7)	6 (23.1)	6 (31.6)	
≥70	11 (24.4)	2 (7.7)	9 (47.4)	
Female	14 (31.1)	6 (23.1)	8 (42.1)	0.3
Former smoking	3 (6.7)	2 (7.7)	1 (5.3)	0.78
Body mass index, kg/m^2	26.2 ± 5.12	26.1 ± 3.9	26.4 ± 6.6	0.85
<18.5	2 (4.4)	1 (3.8)	1 (5.3)	
>30	7 (15.5)	3 (11.5)	4 (21.1)	
Diabetes				0.55
No history	35 (77.8)	19 (73.1)	16 (84.2)	
Insulin-dependent diabetes	5 (11.1)	4 (15.4)	1 (5.3)	
Non-insulin-dependent diabetes	5 (11.1)	3 (11.5)	2 (10.5)	
Low level of haemoglobin, g/dl				0.82
<12 (women)	9 (20)	4 (15.4)	5 (26.3)	
<13 (men)	15 (33.3)	9 (34.6)	6 (31.6)	
Chronic lung disease[b]	10 (22.2)	6 (23.1)	4 (21.1)	0.84
eGFR (ml/min)[c]	87.7 ± 35.6	96 ± 37.4	76.7 ± 30.5	0.075
>85[b]	18 (40)	14 (53.8)	4 (21.1)	
50–85[b]	20 (44.4)	8 (30.8)	12 (63.2)	
≤50[b]	6 (13.3)	3 (11.5)	3 (15.8)	
Extracardiac arteriopathy[b]	9 (20)	5 (19.2)	4 (21.1)	0.82
Previous cardiac operation (CABG)	3 (6.7)	3 (11.5)	0	0.35
NYHA functional class				0.91
I	17 (37.8)	9 (34.6)	8 (42.1)	
II	11 (24.4)	6 (23.1)	5 (26.3)	
III	11 (24.4)	7 (26.9)	4 (21.1)	
IV	6 (13.3)	4 (15.4)	2 (10.5)	
CCS angina class 4	11 (24.4)	5 (19.2)	6 (31.6)	0.55
Recent myocardial infarction[b]	6 (13.3)	2 (7.7)	4 (21.1)	0.39
Heart disease				0.92
Ischaemic (isolated)	14 (31.1)	8 (30.8)	6 (31.6)	
Valvular (isolated)	13 (28.9)	7 (26.9)	6 (31.6)	
Combined	18 (40)	11 (42.3)	7 (36.8)	
Disease of the thoracic aorta	3 (6.7)	2 (7.7)	1 (5.3)	0.78
Coronary artery disease				0.17
One-vessel	6 (13.3)	5 (19.2)	1 (5.3)	
Two-vessel	5 (11.1)	4 (15.4)	1 (5.3)	
Three-vessel	21 (46.7)	10 (38.5)	11 (57.9)	

Table 1. (continued).

Characteristic	Total n = 45	HL patients n = 26 (57.8)	Non-HL patients n = 19 (42.2)	p-Value
Left main disease	4 (8.9)	3 (11.5)	1 (5.3)	0.84
Aortic valve disease				0.33
None	25 (55.5)	12 (46.2)	13 (68.4)	
Stenosis	17 (37.8)	12 (46.2)	5 (26.3)	
Regurgitation	3 (6.7)	2 (7.7)	1 (5.3)	
Mitral valve disease				0.12
None	35 (77.8)	18 (69.2)	17 (89.5)	
Stenosis	5 (11.1)	3 (11.5)	2 (10.5)	
Regurgitation	5 (11.1)	5 (19.2)	0	
Tricuspid valve disease	3 (6.7)	1 (3.8)	2 (10.5)	0.78
Permanent AF	5 (11.1)	3 (11.5)	2 (10.5)	0.71
Left ventricular ejection fraction, %	54.8 ± 12.2	54.6 ± 10.1	54.9 ± 14.7	0.93
>50[b]	33 (73.3)	19 (73.1)	14 (73.7)	
30–50[b]	9 (20)	6 (23.1)	3 (15.8)	
20–30[b]	2 (4.4)	1 (3.8)	1 (5.3)	
≤20[b]	1 (2.2)	0	1 (5.3)	
Pulmonary hypertension (PAP systolic >55 mmHg)[b]	2 (4.4)	1 (3.8)	1 (5.3)	0.61
Critical state[b]	3 (6.7)	2 (7.7)	1 (5.3)	0.78
Active infective endocarditis[b]	2 (4.4)	2 (7.7)	0	0.61
Surgical priority[b]				0.19
Elective	19 (42.2)	12 (46.2)	7 (36.8)	
Urgent	23 (51.1)	11 (42.3)	12 (63.2)	
Emergency	3 (6.7)	3 (11.5)	0	
Expected operative risk (by EuroSCORE II[d]), %	2.7 (1.5–5.5)[e]	2.3 (1.3–7.5)[e]	3 (1.8–5.1)[e]	0.78
10-Year expected survival (by CCI[f]), %	77.5 (77.5–90.1)[e]	77.5 (77.5–90.1)[e]	77.5 (49.4–95.9)[e]	0.93

Abbreviations: AF = atrial fibrillation; CABG = coronary artery bypass grafting; CCI = Charlson Comorbidity Index; CCS = Canadian Cardiovascular Society; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HL = Hodgkin's lymphoma; NYHA = New York Heart Association; PAP = pulmonary artery pressure.

[a]Unless otherwise stated, the values are the mean ± standard deviation, or the number of patients with the percentage in brackets.

[b]The definitions and the cut-off values are those employed for EuroSCORE II (*Ref.* [12]).

[c]The creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR.

[d]*Ref.* [12].

[e]The values are the median with the range between the first and the third quartile in brackets.

[f]*Ref.* [10].

one (51.2%) patients had at least one MACCE (Figure 2A) that was: stroke (n = 2), transitory ischaemic attack (n = 2), myocardial infarction (n = 2), New York Heart Association functional class III–IV (n = 3), pericarditis (n = 2), need of pacemaker/implantable cardioverter-defibrillator (n = 4), aortic valve/prosthetic replacement (n = 2), transcatheter mitral valve repair (n = 1), and peripheral embolism (n = 1). Older age, left ventricular ejection fraction ≤30%, and HL history were independent predictors of cardiac or cerebrovascular death ($p < 0.1$); chronic lung disease and estimated glomerular filtration rate ≤50 ml/min were independent predictors of MACCEs ($p < 0.05$) (Table 4). Although patients with isolated ischaemic heart disease had higher survival, the difference was not significant ($p = 0.54$). Nine (20%) patients experienced at least one malignant tumour, specifically (non-Hodgkin's) lymphoma in 7.3% of cases (Table 5, Figure 2B).

HL Versus Non-HL Patients

With respect to non-HL patients, HL patients were younger (mean age, 52.5 vs. 64.7 years, $p = 0.0017$) and underwent cardiac surgery later after lymphoma occurrence (median gap, 21.5 vs. 9.6 years, $p = 0.0079$). There were no other intergroup differences as baseline characteristics, risk

Table 2 Operative data.[a]

Data	Total n = 45	HL patients n = 26 (57.8)	Non-HL patients n = 19 (42.2)	p-Value
Coronary surgery	32 (71.1)	19 (73.1)	13 (68.4)	0.99
Grafts				0.2
One ITA	20	11	9	
Two ITAs	8	4	4	
SVGs alone	4	4	0	
No. of coronary anastomoses	3.2 ± 1.6	2.7 ± 1.4	4 ± 1.5	0.018
Aortic valve surgery	20 (44.4)	14 (53.8)	6 (31.6)	0.81
Replacement	20	14	6	
Mechanical	8	7	1	
Biological	12	7	5	
Mitral valve surgery	10 (22.2)	8 (30.8)	2 (10.5)	0.21
Replacement	5	3	2	
Mechanical	2	2	0	
Biological	3	1	2	
Repair	5	5	0	
Tricuspid valve repair	3 (6.7)	1 (3.8)	2 (10.5)	0.78
Surgery of the thoracic aorta	3 (6.7)	2 (7.7)	1 (5.3)	0.78
Other	3 (6.7)	2 (7.7)	1 (5.3)	0.78
Cryoablation for AF	1	0	1	
Pacemaker implantation	2	2	0	
Aortic cross-clamp time, min	109 ± 46.1	118.8 ± 52.5	95.8 ± 32.8	0.11
Cardiopulmonary bypass time, min	141.7 ± 61.7	157.9 ± 68.1	120.3 ± 45.4	0.043
Duration of operation, min	303.9 ± 90.1	319.9 ± 102.5	282.4 ± 67.8	0.17

Abbreviations: AF = atrial fibrillation; HL = Hodgkin's lymphoma; ITA = internal thoracic artery; SVGs = saphenous vein grafts.

[a]The values are the mean ± standard deviation, or the number of patients with the percentage in brackets.

profiles (median EuroSCORE II, 2.3% vs. 3%, p = 0.78), and in-hospital mortality (7.7% vs. 10.5%, p = 0.84). In non-HL patients, a higher number of coronary anastomoses (p = 0.018) and blood transfusions (p = 0.0002) was observed. Cardiopulmonary bypass time was longer in HL-patients (p = 0.043). (Tables 1–3). A history of HL was an independent predictor of all-cause death (p = 0.11) and, as stated above, cardiac or cerebrovascular death (p = 0.062; Table 4).

Discussion

In the present study, the authors retrospectively reviewed early and late outcomes of a consecutive series of 45 patients formerly affected by HL or non-HL who underwent cardiac surgery at an Italian university hospital. The analysis derived from the authors' need to know, at least approximately, the postoperative survival of this particular subset of patients whose risk evaluation is important, not only for the surgeon for decision-making, but also for patient counselling and comparative assessment of quality of care. Actually, to date there are only a few studies that report specific outcomes after cardiac surgery of patients having prior malignant disease [5,8,9,11,12,16–18]. Generally, these clinical reports support surgery, being perioperative results in patients formerly affected by tumour similar to patients having no history of tumour; yet long-term outcomes are slightly worse. These single-centre studies usually arise from limited series of patients undergoing cardiac surgery, primarily coronary, are comparative analyses between off-pump and on-pump technique, and include various types of malignant diseases, which are almost invariably solid tumours. Actually, there are very few studies specifically investigating outcomes after cardiac operations of patients formerly affected by lymphoma [5,11].

At the authors' institution, while in-hospital mortality was lower than expected by EuroSCORE II for all types of cardiac diseases/operations during the same period of the study, in-hospital (or 30-day) mortality for patients formerly affected by lymphoma was high and greater than the 75th percentile of the expected operative risk. Forty per cent of patients had at least one major complication early after surgery. Prolonged invasive ventilation, low cardiac output, acute kidney injury, multiple blood transfusion,

Table 3 In-hospital mortality, postoperative complications, and hospital course of patients.[a,b]

Complication	Total n = 45	HL patients n = 26 (57.8)	Non-HL patients n = 19 (42.2)	p-Value
In-hospital death	4 (8.9)	2 (7.7)	2 (10.5)	0.99
30-Day death	3 (6.7)	2 (7.7)	1 (5.3)	0.99
Stroke	1 (2.2)	0	2 (10.5)	0.17
Prolonged (>48 h) invasive ventilation	10 (22.2)	6 (23.1)	4 (21.1)	0.99
Lower airway infection	4 (8.9)	2 (7.7)	2 (10.5)	0.99
Atrial fibrillation, new-onset	14/40 (35)	7/23 (30.4)	7/17 (41.2)	0.48
Low cardiac output	8 (17.8)	5 (19.2)	3 (15.8)	0.99
Use of inotropic agents	28 (62.2)	17 (65.4)	11 (57.9)	0.61
Intra and postoperative use of IABP	2 (4.4)	2 (7.7)	0	0.5
Acute kidney injury	8 (17.8)	6 (23.1)	2 (10.5)	0.44
Renal replacement therapy	3 (6.7)	3 (11.5)	0	0.25
Mesenteric ischaemia	1 (2.2)	0	1 (5.3)	0.42
48-h Chest tube output/BSA, ml/m^2	515 (366–948)[c]	533 (402–1043)[c]	515 (356–775)[c]	0.14
Blood transfusion	30 (66.7)	11 (42.3)	19 (100)	<0.0001
Multiple blood transfusion (>2 RBCs)	24 (53.3)	8 (30.8)	16 (84.2)	0.0004
Mediastinal re-entry for bleeding or tamponade	7 (15.5)	4 (15.4)	3 (15.8)	0.99
Multiorgan failure	3 (6.7)	1 (3.8)	2 (10.5)	0.56
Deep sternal wound infection	1 (2.2)	0	1 (5.3)	0.42
Leg wound complication	1/22 (4.5)	0/12 (0)	1/10 (10)	0.45
Any major postoperative complication[d]	18 (40)	10 (38.5)	8 (42.1)	0.81
Length of the hospital stay, days	11 (8–18.5)[c]	9 (7–20)[c]	12 (8–19)[c]	0.45
Intensive care unit stay, days	3 (2–6)[c]	3 (2–6.5)[c]	3 (2–6)[c]	0.81

Abbreviations: BSA = body surface area; HL = Hodgkin's lymphoma; IABP = intra-aortic balloon pump; RBCs = red blood cell.

[a]Unless otherwise stated, the values are the number of patients with the percentage in brackets.

[b]The definitions were in accordance with the internationally agreed definitions of complications after cardiac surgery (*Ref.* [13,14]).

[c]The values are the median with the range between the first and the third quartile in brackets.

[d]Stroke, prolonged invasive ventilation, lower airway infection, low cardiac output, acute kidney injury, mesenteric ischaemia, multiple blood transfusion, mediastinal re-entry, multiorgan failure, and deep sternal wound infection were major postoperative complications.

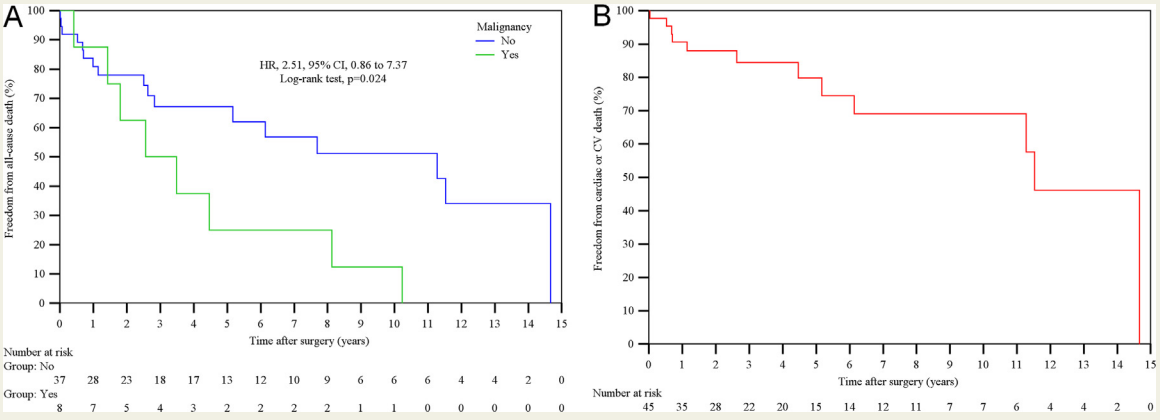

Figure 1 The non-parametric curves and estimates of freedom from (A) all-cause death and (B) cardiac or CV death. The 1-, 5-, and 10-year non-parametric estimates of freedom from all-cause death in people who developed malignancy were 87.5% (95% CI, 75.8%–99.2%), 25% (95% CI, 9.7%–40.3%), and 12.5% (95% CI, 0.8%–24.2%), respectively. The 1-, 5-, and 10-year non-parametric estimates of freedom from all-cause death in people without malignancy were 80.9% (95% CI, 74.4%–87.4%), 67.2% (95% CI, 58.9%–75.5%), and 51.2% (95% CI, 40.9%–61.5%), respectively. The 1-, 5-, and 10-year non-parametric estimates of freedom from cardiac or CV death were 90.6% (95% CI, 86.1%–95.1%), 79.8% (95% CI, 72.6%–87%), and 69.1% (95% CI, 59.7%–78.5%), respectively.
Abbreviations: HR = hazard ratio; CI = confidence interval; CV = cerebrovascular.

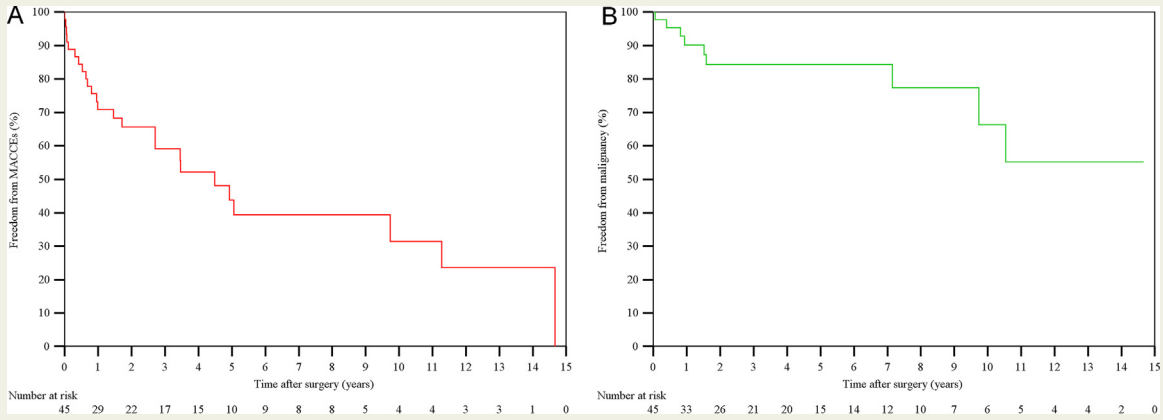

Figure 2 The non-parametric curves and estimates of freedom from (A) MACCEs and (B) malignancy. The 1-, 5-, and 10-year estimates of freedom from MACCEs were 70.8% (95% CI, 64%–77.6%), 43.8% (95% CI, 34.9%–52.7%), and 31.5% (95% CI, 21.4%–41.6%), respectively. The 1-, 5-, and 10-year estimates of freedom from malignancy were 90.2% (95% CI, 85.5%–94.9%), 84.4% (95% CI, 78.5%–90.3%), and 66.3% (95% CI, 53.7%–78.9%), respectively.
Abbreviations: CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular event.

and mediastinal re-entry for bleeding or tamponade occurred in over 15% of cases each one. Over 50% of patients died during follow-up period, and the 10-year, crude and adjusted nonparametric estimates of survival were about half of the expected survival by CCI. Finally, over 50% of patients had at least one MACCE. Consequently, poor, early and late outcomes were highlighted. In the present authors' opinion, these disappointing results were due to increased rates of preoperative anaemia, of comorbidities such as chronic lung disease and renal impairment, as well as of concomitant heart diseases. In addition, high-risk patients such as those having previous cardiac operation, recent myocardial infarction, disease of the thoracic aorta, critical state, active infective endocarditis, and emergency surgical priority were all included in the analysis. Actually, these results were totally unexpected, though prior chemotherapies and radiation-induced systemic injury could explain them, at least partially. Chronic lung disease and severe renal impairment, which may be the consequence of toxic chemotherapies and aggressive radiation therapy protocols, were indeed independent predictors of MACCEs. Between HL and non-HL patients, no substantial differences were found as early outcomes, whereas a history of HL was predictor of all-cause death ($p = 0.11$) and cardiac or cerebrovascular death during the follow-up period ($p = 0.062$).

Table 4 **Cox proportional-hazards regression for all-cause death, cardiac or cerebrovascular death, and MACCEs (N = 45).**

Characteristic	Freedom from all-cause death			Freedom from cardiac or cerebrovascular death			Freedom from MACCEs		
	HR	95% CI	p-Value	HR	95% CI	p-Value	HR	95% CI	p-Value
Age	1.05	1.0–1.1	0.052	1.07	0.99–1.16	0.096	–	–	–
Diabetes	–	–	–	–	–	–	–	–	–
Chronic lung disease[a]	1.89	0.76–4.73	0.17	2.89	0.72–11.5	0.14	2.79	1.17–6.68	0.022
eGFR ≤50 ml/min[a,b]	–	–	–	–	–	–	3.13	1.17–8.37	0.023
Extracardiac arteriopathy[a]	–	–	–	–	–	–	–	–	–
Left ventricular ejection fraction ≤30%[a]	–	–	–	5.26	0.92–30.1	0.063	–	–	–
Hodgkin's lymphoma	2.61	0.81–8.41	0.11	7.32	0.92–58.5	0.062	–	–	–
Time between lymphoma onset and cardiac operation ≤5 years	–	–	–	–	–	–	–	–	–

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HR = hazard ratio; MACCEs = major adverse cardiac and cerebrovascular events.

[c]*Ref.* [12].

[a]The definitions and the cut-off values are those employed for EuroSCORE II (*Ref.* [12]).

[b]The creatinine clearance rate, calculated according to the Cockcroft-Gault formula, was used for approximating the GFR.

Table 5 Malignant tumours occurred during the follow-up period.

Histological type	n = 41
Non-Hodgkin's lymphoma	3 (7.3)
Progression	2
Recurrence	1
Breast cancer	2
Lung adenocarcinoma	2
Oesophagus carcinoma	1
Pancreatic cancer	1
Colon carcinoma	1
Thyroid cancer	1
Melanoma	1

[a]The values are the number of patients with the percentage in brackets.

Nine out of 41 hospital discharged patients developed a total of 12 malignant tumours during the follow-up period, and eight of them died due to tumour. In three cases a lymphoproliferative disease arose, which was invariably non-HL; cardiac operation has been performed within 5 years from tumour remission in one patient and after 5 years in two patients. All of the above data seem to substantiate the hypothesis of a pro-tumoural role of heart surgery using cardiopulmonary bypass [4,9,11]. Besides, since brief (<5 years) time between lymphoma onset and cardiac operation was not a predictor of death during follow-up period, this hypothetical pro-tumoural role would be for a new malignant tumour.

The primary limitation of the present study lies in the retrospective nature of the analysis and in the fact that patients were evaluated at different times after surgery. Because of the limited number of patients and events during the follow-up period, only a few variables were considered for analysis of predictors of death and MACCEs. No comparison was made between different chemotherapy and radiotherapy protocols. Because every operation was carried out with on-pump technique, no comparison between on-pump and off-pump surgery was drawn. In addition, data on late outcomes extended to 5 years only for ~30% of patients, while it is usually beyond this time point that a new malignant disease may occur. Finally, neither lymphocyte typing nor fine laboratory investigation was carried out. Consequently, the results obtained can in no way be considered conclusive and should be verified in a larger patient population by means of prospective controlled trials.

Conclusions

On the basis of the results of this study, immediate and long-term survival after on-pump cardiac surgery of patients formerly affected by lymphoma were worse than expected, according to universally used predictive scoring systems. In addition, an increased risk of malignant tumours was observed. More in depth investigation should be carried out.

Conflict of Interest

None declared.

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