Research Article

Cardiac Function in Long-Term Survivors of Childhood Lymphoma

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Objectives. We studied long-term effects of therapy for childhood lymphoma on cardiac function. *Design and patients*. We prospectively evaluated 45 survivors of childhood lymphoma, using clinical parameters, electrocardiography and echocardiography. Further comparisons were made between lymphoma subgroups and between males and females. *Results*. Mean age at diagnosis was 9.1 years. Mean followup duration was 10.9 years. The NYHA functional class was I in 43 patients and II in 2 patients. A prolonged QTc interval (>0.44 msec) was found in 8 patients. Left ventricular (LV) systolic function and compliance were normal (LV shortening fraction $40 \pm 5.6\%$; cardiac index 2.84 ± 1.13 L/min/m^2; E/A wave ratio 2.5 ± 1.3; mean $\pm$ S.D.), LV mass was normal (97 ± 40 grams/m^2, mean $\pm$ S.D.). Mitral regurgitation was observed in 7/45 patients (16%). Asymptomatic pericardial effusions were found in 3/45 (7%) patients. *Conclusions*. Long-term follow-up shows that most parameters of cardiac function are normal in survivors of childhood lymphoma. This is likely due to relatively low doses of anthracyclines in modern protocol modalities. Abnormalities in mitral valve flow, QTc prolongation and in a small proportion of survivors, and functional capacity necessitate long-term cardiac follow-up of these patients.

1. Introduction

Increased long-term survival following effective treatment of childhood lymphomas has placed greater emphasis on residual sequelae of therapy for lymphoma and the impact of these sequelae as the cause of further morbidity and mortality. Following treatment of childhood Hodgkin's disease, cardiac pathology is second only to neoplasm as the cause of death in initial survivors [1]. As the number of cancer survivors increases, so does the number of patients exposed to therapies toxic to the heart and lung, including radiation and chemotherapeutic modalities

that employ anthracyclines [2]. The literature is replete regarding effects of anthracyclines and radiation on the heart; however, there is still debate regarding the detection of cardiac sequelae [3], their significance [4], and the relation between different treatment modalities and the development of cardiac sequelae. We hypothesized that protocols employing anthracyclines and radiation would adversely affect long-term cardiac function and that these effects would differ between survivors who received different treatment modalities. We therefore prospectively evaluated long–term cardiac function in 45 survivors of childhood lymphomas, using clinical parameters, electrocardiography,

TABLE 1: Demographic characteristics of survivors by lymphoma subtype.

	HD	BL	NHNB	Total/Average
Males (n)	14	7	5	26
Females (n)	12	5	2	19
Mean age at diagnosis (years)	10.8	7.4	5.5	9.1 (range: 2.1–16.4)
Treatment duration (years)	0.9	0.8	1.7	0.94
Age at follow-up (years)	23.1	19.1	16.7	21 (range: 2.1–16.4)
Followup duration (years)	11.3	10.9	9.5	10.9 (range: 2.1–16.4)

and echocardiography and compared these parameters between lymphoma subtypes.

2. Patients and Methods

The study included survivors of histology-diagnosed childhood lymphomas who had at least 5 years of followup from termination of therapy, and who were less than 18 years of age at treatment initiation. These criteria identified 45 survivors of 108 children treated for lymphoma at the Pediatric Hematology and Oncology department of a tertiary care center during a nineteen-year period. Fifteen additional survivors meeting these inclusion criteria declined complete participation in the protocol. All participants underwent evaluation which included an interview to assess functional class (New York Heart Association), physical examination, 12-lead electrocardiography (ECG), and echocardiography. Data were taken from a single assessment at the last available follow-up.

Informed consent was obtained from all participants or their legal guardians.

2.1. Statistics. Statistical analysis was performed using a commercially available package (Sigmastat 5.0 Jandel Scientific, San Rafael, California). Comparisons between the different lymphoma subgroups were made using one way ANOVA or the Tukey correction of this test where normality failed, and where relevant by the Student's T-test or the Mann-Whitney rank sum test where normality failed. Statistical significance was set at $P < .05$.

2.2. Study Population. Characteristics of the study population including treatment duration and mean follow-up duration are presented in Table 1.

2.3. Treatment Modalities. Tumor characteristics and therapeutic modalities are detailed in Table 2.

The BL subgroup was divided between those treated in earlier years with protocols (COMP) that did not include anthracyclines (7/12 patients), and those that were treated more recently (5/12 patients) with protocols (LMB, NCI) containing anthracyclines. These two subgroups did not differ significantly with regard to age at diagnoses (6.7 ± 3.7; 8.30 ± 5.1 years, resp., $P = .52$) or age at follow-up (21.2 ± 4.2; 16.1 ± 5.8 years, $P = .1$).

The mean dose of doxorubicin (adriamycin), for the group as a whole was 25 mg/m^2 per treatment, leading to a cumulative dose of 150 mg/m^2 or a total cumulative dose of 225–250 mg.

All participants underwent evaluation which included an interview to assess functional class (New York Heart Association (NYHA)), physical examination, 12-lead ECG, and echocardiography. Cardiovascular physical examination, ECG, and echocardiography were performed by 2 senior staff pediatric cardiologists (A. Lorber and Y. Braver). Analyses of ECG and echocardiography images were then undertaken in a blinded manner by different investigators (M. Friedberg and I. Solt). Stroke volume was calculated by multiplying the aortic valve area, measured from the 2-dimensional echocardiographic long axis view of the internal aortic diameter at valvular level, with the velocity time integral (VTI) of aortic flow. Cardiac index (CI) was then calculated by multiplying this value by heart rate, and dividing the product by body surface area. Left ventricular indices were measured by M-mode echocardiography. Left ventricular mass was calculated by the Devereux method [5]. Left ventricular diastolic function was assessed from mitral valve inflow Doppler. Mitral regurgitation was graded according to the routine clinical gradation used in the lab as none, trivial, mild, moderate or severe. Echocardiographic data were compared to well-established normal values [6]. Normal values were defined as being within 2 standard deviations of the mean normal value: for LV ejection fraction 66 ± 4%, and LV fractional shortening 36 ± 4%, LV mass index 70.4 gram/m^2 for males (10–95 percentile 48.5–103 gram/m^2) and 60.7 gram/m^2 for females (10–95 percentile 35.6–81 gram/m^2). Early diastolic mitral inflow velocity (E wave) to late diastolic mitral inflow velocity (A wave) ratio is 1.7 ± 0.4 to 2.5 ± 0.9. Cardiac dimensions were defined as being within 2 standard deviations of the normal mean for body surface area. A QTc > 0.44 seconds was defined as prolonged.

3. Results

3.1. Functional Capacity and History. All patients had normal cardiovascular function prior to initiation of therapy.

The NYHA functional class was class I in 43 patients (96%) and class II in 2 patients (4%). These 2 patients did not have other comorbidities or notable toxic effects on follow-up. No Raynaud's phenomenon was reported. No events of near-syncope, syncope, or sudden death were noted. Clinical features of the cohort as a whole and of the Hodgkin's disease subgroup are shown in Table 3.

TABLE 2: Lymphoma characteristics and treatment data of survivors by lymphoma subtype.

Patient	Staging	Histology	ChemoTx	Irradiation	Total dose (cGy)	Mantle dose (cGy)
HL						
1	3B	NONE	MOPP	MANTLE	1500	1500
2	2B	NS	MOPP	MANTLE	3000	3000
3	2B	NS	MOPP	MANTLE	4000	4000
4	1A	LP	MOPP	MANTLE	2000	2000
5	2B	LP	MOPP	MANTLE	4000	4000
6	3A	MC	MOPP/ABVD	TOT. NODAL	1650	1500
7	1A	NS	MOPP	MANTLE	2600	2800
8	2A	MC	MOPP/ABVD	MANTLE	2000	2000
9	2B	MC	MOPP/ABVD	MANTLE,INV.Y.SPLEEN	5800	4000
10	2A	NS	MOPP/ABVD	MANTLE	1800	1800
11	3B	NS	MOPP/ABVD	MANTLE,PARAAORTIC	8000	4000
12	2B	NS	MOPP/ABVD	MANTLE,INV.Y	4000	4000
13	2B	MC	MOPP/ABVD	MANTLE	3060	3060
14	3B	NS	MOPP	MANTLE,INV.Y,SPLEEN	5100	2500
15	2A	NONE	MOPP	MANTLE,INV.Y	8400	4400
16	2B-BULKY	MC	MOPP/ABVD	MANTLE	2600	2600
17	3A	NS	MOPP/ABVD	MANTLE	2600	2600
18	2A-BULKY	NS	MOPP/ABVD	MANTLE	4000	4000
19	1A	NS	MOPP/ABVD	MINIMANTLE	3600	3600
20	2A	NS	MOPP/ABVD	MANTLE	3000	3000
21	3B	LD	MOPP	MANTLE,INV.Y	8000	4000
22	2A	NS	MOPP	MANTLE	4000	4000
23	1A	LP	NONE	MANTLE	4000	4000
24	2A	NS	MOPP/ABVD	MANTLE	2600	2600
25	2A	NS	NONE	MANTLE,PARAO,SPLEEN	8000	4000
26	2B-BULKY	NS	MOPP/ABVD	MANTLE	3000	3000
Average					3935	3152
BL						
27	NP	6	COMP		0	0
28	ABD	6	NCI		0	0
29	ABD	6	LMB		0	0
30	ABD	6	COMP		0	0
31	ABD	6	COMP		0	0
32	ABD	6	COMP		0	0
33	ABD	6	COM		0	0
34	ABD	6	COMP	WHOLE ABDOMEN	1550	0
35	ABD	6	NCI		0	0
36	ABD	6	LMB		0	0
37	NP	6	ACOMP		0	0
38	ABD	6	NCI		4000	0
Average					462	0
NHNB						
39	0	7	LSAL2		0	0
40	0	7	LSAL2/COM	BRAIN,TOT.LUNG	3600	0
41	0	7	LSAL2	BRAIN,INV.Y	5600	0
42	0	7	COM		0	0
43	0	7	LSAL2	MEDIASTINUM	750	0
44	0	7	LSAL2	MEDIASTINUM	2000	0
45	0	7	COMP	BRAIN	2400	0
Average					2050	0

MOPP: nitrogen mustard, oncovin, prednisone, and procarbazine; COM/P: cyclophosphamide,oncovin, and methotrexate/prednisone; ABVD: adriamycin, bleomycin, vinblastine, and deticen; NCI: national cancer institute; ACOMP: like comp with adriamycine; LSA2L2: norma wollner protocol; LMB: no abbreviation; NS: nodular sclerosis; LP: lymphocyte predominance; MC: mixed cellularity; LD: lymphocyte depletion.

TABLE 3: Electrocardiographic and echocardiographic data of all survivors and the Hodgkins disease subtype.

	All	Hodgkins disease	
Electrocardiography			
Heart rate (bpm) (mean ± SD)	77 ± 11		
PR interval (seconds) (mean ± SD)	0.144 ± 0.024		
QTc interval (seconds) (mean ± SD)	0.411 ± 0.032	0.417 ± 0.034	N.S
Echocardiography			
LV Fractional shortening (%)	40 ± 5.6	39.5 ± 5.6	N.S
Cardiac Index (L/min/m^2)	2.84 ± 1.13	3.4 ± 1.03	N.S
LVED (cm)	4.43 ± 0.057		N.S
Septal thickness (cm)	0.65 ± 0.12	0.65 ± 0.13	N.S
Posterior wall thickness (cm)	0.66 ± 0.1	0.67 ± 0.1	N.S
LV mass (gm/m^2)	97 ± 40	96 ± 38	N.S
E/A wave ratio	2.5 ± 1.3	2.29 ± 1.09	N.S
Mitral regurgitation (n, %)	7/45 (16)	4/26 (15)	N.S

3.2. Electrocardiography. All patients demonstrated normal sinus rhythm with no bradycardias or tachycardias noted. The percentage of survivors with a prolonged QTc interval by lymphoma subgroup is shown in Figure 1(a). A prolonged QTc interval was not associated with sinoatrial or atrioventricular node dysfunction-conduction anomalies.

Incomplete right bundle branch block was recorded in 4 patients (9%, all diagnoses); complete right bundle branch block was recorded in 2 patients. No evidence of ischemia or "strain" was noted on nonstress ECG.

3.3. Echocardiography. Cardiac systolic and diastolic function was normal or low-normal for the group as a whole without significant differences between the subgroups (Table 3).

LV mass and shortening fraction did not correlate with mantle irradiation dose, QTc interval, or length of follow-up. Mean LV mass was within normal limits (97 ± 40 grams/m^2, mean ± S.D.). LV mass was significantly higher for males as compared to females (all subjects, 112 grams versus 76 grams, resp.; $P < .01$). There was no significant difference in shortening fraction between males and females. Left ventricular end diastolic internal dimensions did not increase following relatively smaller shortening fraction values. Cardiac index and mass by lymphoma subgroup are presented in Figures 1(b) and 1(c), respectively.

Mild mitral regurgitation was observed in 7 of the 45 patients (16%). The percentage of survivors with mitral regurgitation by subgroup is shown in Figure 1(d). Mitral valve prolapse was recorded in 1 HD survivor. Pulmonary valve insufficiency, more than the accepted physiological norm, was found in 1 survivor of NHNB.

Asymptomatic small pericardial effusions were found in 3 of the 45 patients (7%). No larger effusions or pericardial thickening was noted in any of the patients. A mitral inflow pattern consistent with constrictive or restrictive physiology (elevated E wave velocity, elevated E/A ratio, and short deceleration time) was not noted in any of the patients.

Selected electrocardiographic and echocardiographic parameters for the subset of BL survivors treated with anthracyclines versus those not treated with anthracyclines are presented in Table 4.

4. Discussion

Cardiac abnormalities described after treatment for childhood lymphomas can involve almost any aspect of cardiac function and include pericarditis, pericardial effusions, pericardial fibrosis, pancarditis, myocardial fibrosis with functional impairment, valvular disease, conduction defects, and coronary artery disease [1]. Although sequelae may develop at variable time intervals following treatment, emphasis is now placed on the long-term sequelae of lymphoma therapy [7, 8], which are caused mainly by anthracyclines and radiation [9].

In our study population, most parameters of cardiac status were within normal limits. This is most likely due to the relatively low dose of anthracyclines used. Previous study has shown that an average cumulative dose of 450 mg/m^2 of doxorubicin causes a 23% abnormality rate in echocardiographic findings during a 7-year follow-up period [10] and that sequelae are rare at doses under 300 mg/m^2 [10, 11]. Our study population received an average of 150 mg/m^2 of doxorubicin, leading to a total dose of 225–250 mg, which is less than the average toxic dose. This is achieved in modern protocols through regimens employing multidrug therapy. The average follow-up duration for our population was 10.9 years, which is longer than that of many other studies, with relatively few cardiac sequelae from anthracyclines. However, these patients still warrant long-term cardiac follow-up, as the risk for cardiomyopathy continues to increase over time [12, 13]. This vigilance is further justified by previous findings that patients may develop cardiac complications from anthracyclines, even when lower doses are used [13].

Studies performed 2 to 3 decades ago identified factors that augment the cardiotoxicity of anthracyclines. These include radiation of the mediastinum [14, 15], previous cardiac abnormalities, including involvement of the heart by the tumor [16, 17], uncontrolled hypertension [11, 12], and exposure to other chemotherapy modalities such as

TABLE 4: Comparison of selected electrocardiographic and echocardiographic characteristics between Burkitt lymphoma survivors who received or did not receive anthracyclines as part of their treatment regimen.

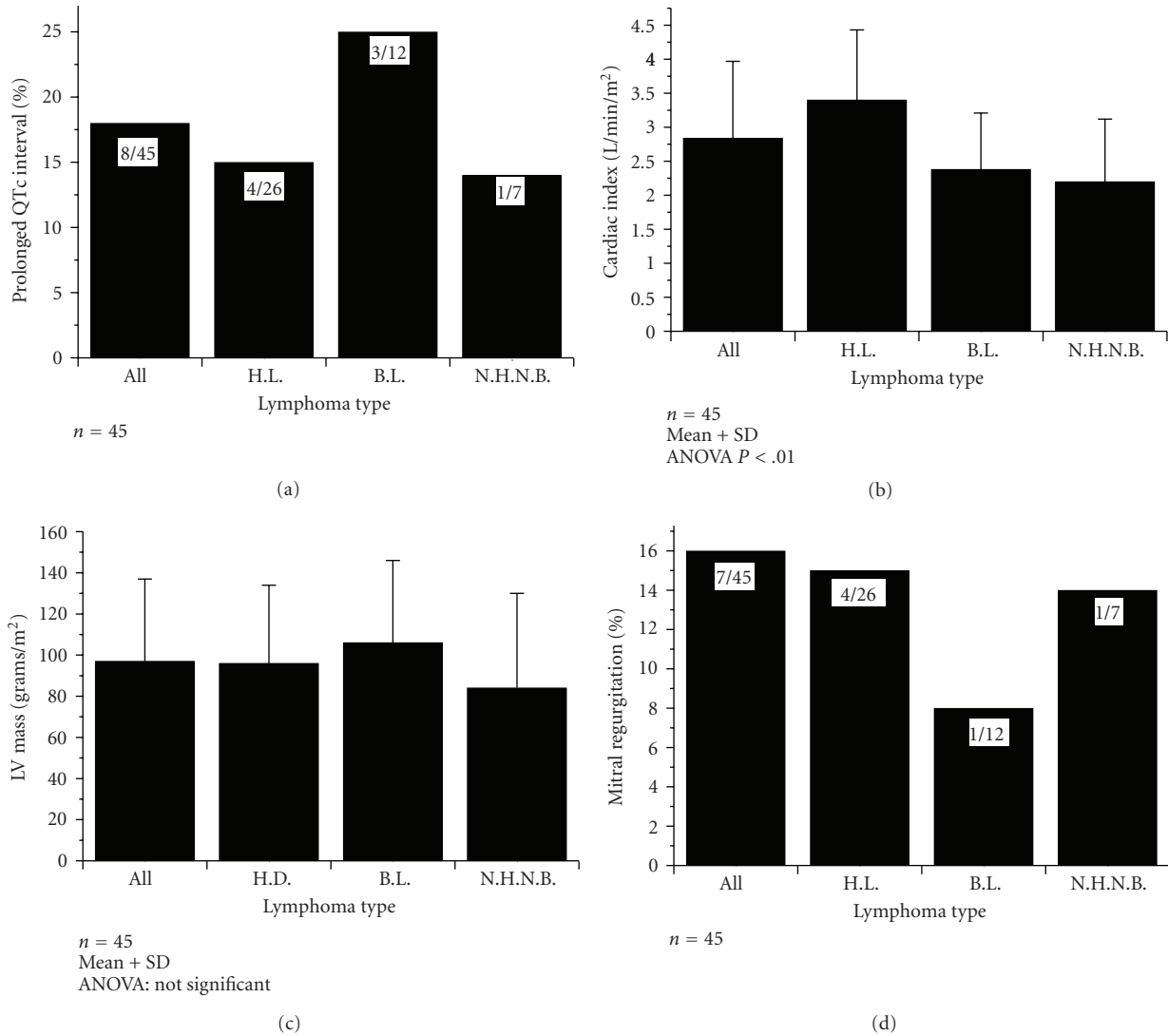|	B.L. patients who received anthracyclines	B.L. patients who did not receive anthracyclines	
LV shortening fraction (%)	41 ± 5	39 ± 3	N.S
QTc	0.416 ± 0.03	0.4 ± 0.02	N.S
LV mass	121 ± 36	85 ± 37	N.S

FIGURE 1: (a) Percentage of survivors with prolonged QTc interval (>0.44 s) among the lymphoma subgroups. (b) Cardiac index among the lymphoma subgroups. $N = 45$, Mean + SD, ANOVA $P < .01$. (c) Left ventricular mass among the lymphoma subgroups. $N = 45$, Mean + SD, ANOVA not significant. (d) Percentage of survivors with mitral regurgitation among the lymphoma subgroups. $N = 45$. H.D.: Hodgkin's Disease, B.L.: Burkitt's Lymphoma, N.H.N.B.: Non Hodgkin Non Burkitt lymphoma.

cyclophosphamide, dactinomycin, mitomycin, vincristine, bleomycin and methotrexate [13, 18, 19]. Demographic factors include young age, female sex, black race and also trisomy 21 [7]. Among these, our study population was exposed to radiation of up to 4400 cGy (but in most instances less than this) and to polychemotherapy, including vincristine and bleomycin, as dictated by the various treatment protocols. More recently a pathophysiological role for the tyrosine kinase receptor, ErbB2, has been implicated in cardiomyocyte susceptibility to anthracyclines [20].

Again, the total dose of doxorubicin was probably the most important factor in preventing significant cardio toxicity among our population. These findings are consistent with other studies that found that modern protocol therapies using MOPP/ABVD and radiation hold low risk for cardiac toxicity [21, 22].

Leandro et al. [9] suggested that cardiac status following anthracyclines is described by a pattern consistent with a thin-walled, compliant left ventricle with reduced muscle mass performing under above-normal levels of wall stress. Our results are consistent with this description and show left ventricular dimensions at the lower level of normal, with good compliance.

It is surprising that no statistical differences in systolic function and left ventricular mass and thickness were found between the lymphoma type subgroups, in the light of the substantial differences in therapy that these groups received. Although differences in left ventricular mass between BL patients who received anthracyclines and those who did not reach statistical significance, our data may correlate with the aforementioned findings that anthracyclines reduce ventricular mass and reduce left ventricular wall thickness. However, no differences were found between the various lymphoma subgroups, among whom HD patients were exposed both to anthracyclines as well as to radiation. Indeed, these patients exhibited increased cardiac output in comparison to the other lymphoma subgroups. We do not have a clear interpretation for this result. More importantly, cardiac index was at the low range of normal, or slightly below normal, for all groups. Differences between males and females were significant regarding LV mass, a factor that contributes to the greater susceptibility of females to anthracyclines [7], and the greater prevalence of prolonged QTc interval among females.

We found an increased prevalence of mitral valve regurgitation in our study population. An earlier study [23] found mitral valve regurgitation in 24% of patients. The significance of mitral valve regurgitation in these patients is not entirely clear. Minimal mitral insufficiency, in the absence of valve deformity, is usually of little clinical significance [24]. However, Allen et al. [25] detected an increase in the prevalence of mitral regurgitation among children who had received anthracyclines, 12% (4 of 34) of whom later developed left ventricular systolic dysfunction, concluding that mitral regurgitation might be an early marker of anthracycline-related cardiac dysfunction.

Seventeen percent of the patients we studied demonstrated a prolonged corrected QT interval. Cardiac dysrhythmias are prevalent in survivors of lymphoma treated with anthracyclines [26]. Our findings correlate with those of previous studies, where both QT and QT dispersion were prolonged following treatment with anthracyclines [27, 28]. A prolonged QT interval may result from myocardial cell damage but does not correlate with decreased contractile function [29, 30]. As dysrhythmias may occur years after termination of treatment and these are potentially life-threatening, patients should be evaluated at regular followup with a 12-lead ECG [8, 31]. Although no sudden death events were observed in our population, following our findings of a prolonged Q-T interval in a substantial percentage of the population, it may be suggested that a 24-hour holter-ECG recording be part of the routine follow-up of these patients.

Coronary artery disease has been reported after radiation therapy to the mediastinum, but not after anthracycline therapy [1, 32]. This pathology led to significantly increased mortality at 7-year follow-up. Our results did not show resting ECG changes, and there was no premature mortality among our study group on a longer follow-up period. In the light of findings from other studies, we would suggest periodic ergometry in the long-term follow-up of patients who have undergone radiation therapy [33].

Additional well-described sequelae of radiation therapy to the mediastinum are pericardial effusion and constrictive pericarditis [34, 35]. We did not note these pathologies to any significant degree in our study population.

The use of possible cardioprotective agents such as dexrazoxane may provide additional protection against long-term cardiac sequelae of anthracyclines, especially in girls [36, 37]. These agents were not used in our study, and we cannot comment further on their effects.

Limitations. This study has certain limitations. This study was performed as a retrospective analysis of data with inherent limitations. The study group is relatively small and the number of patients in subgroups is small. We did not compare the study group with a control group, as our primary objective was definition of cardiac status among survivors. However, we used well-established norms that are commonly and widely used as the basis for this definition. Further comparisons between the different lymphoma subgroups, provided a comparative basis for the different treatment modalities, and specific comparison between Burkitt lymphoma survivors who had been exposed to anthracyclines and those who had not strengthened this comparison. Echocardiographic parameters such as ejection fraction and fractional shortening are limited by load dependency and constitute basic indicators of global ventricular function. Although other echocardiographic methods are available for assessment of cardiac function, each has its specific limitations and in daily clinical practice many oncologists are more familiar with the traditional parameters used in this study. Likewise assessment of left ventricular mass by echocardiography is limited. This study focused on long-term follow-up with data collected at the last available assessment, and we did not collect data on acute or subacute toxicity.

In summary, in this cohort, relatively few long-term cardiac complications were seen in most patients following low-dose anthracycline therapy used in modern treatment protocols for childhood lymphoma. However, anthracycline cardio toxicity has previously been well established and in the current study, abnormalities were found in mitral valve regurgitation abnormalities, QT prolongation, low-normal cardiac index, and in 2 survivors functional capacity reduction leading to a compromised quality of life. The greater frequency of abnormalities in females requires increased vigilance in this group. These findings necessitate comprehensive and long-term cardiac follow-up of these patients.

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