Table 1 Patient characteristics

Case No	Group	sex	ATC cumulative dose (mg/m^2)	age at test	diagnosis	duration post ATC therapy
1	N	M	0	8y11m	ALL	5y7mos
2	N	F	0	15y9m	ALL	6y7mos
3	N	M	0	12y2m	ALL	5y6mos
4	N	M	0	16y8m	ALL	4y7mos
5	N	M	0	14y6m	ALL	4y8mos
6	N	M	0	13y2m	ALL	7y2mos
7	N	M	0	11y2m	ALL	6y2mos
8	L	F	80 (THP: 80)	13y2m	ALL	5y11mos
9	L	M	100 (THP: 100)	8y11m	ALL	5y7mos
10	L	M	175 (ADM: 75, DXR: 100)	28y3m	ALL	10y2mos
11	L	F	180 (ADM: 180)	17y9m	ALL	13y0mos
12	L	F	140 (ADM: 140)	3y7m	LCH	1y6mos
13	L	M	130 (THP: 100, ACR: 30)	12y10m	ALL	8y11mos
14	L	M	100 (THP: 100)	6y9m	ALL	3y9mos
15	L	M	170 (THP: 120, MIT: 20, ACR:30)	18y0m	ALL	4y8mos
16	M	M	200 (ADM: 200)	9y5m	NHL	2y8mos
17	M	F	220 (THP: 220)	11y0m	ALL	2y4mos
18	M	F	220 (IDAR: 120, THP: 20)	11y0m	ALL	4y3mos
19	M	F	250 (DNR: 50, ADM: 200)	7y5m	ALL	3y6mos
20	M	F	270 (ADM: 270)	3y8m	Ewing sarcoma	1y4mos
21	M	F	300 (ADM: 200, DNR: 100)	7y0m	ALL	4y2mos
22	M	F	300 (ADM: 300)	9y5m	Wilms tumor	5y6mos
23	M	F	300 (ADM: 200, DNR: 100)	8y0m	ALL	4y6mos
24	M	F	305 (THP: 90, MIT: 35, ACR: 180)	15y11m	ANLL	4y9mos
25	M	M	330 (DNR: 180, ACR: 150)	18y4m	ALL	12y7mos
26	M	M	330 (DNR: 180, ACR: 150)	15y5m	ALL	11y10mos
27	M	F	360 (ADM: 360)	8y10m	Ewing sarcoma	3y8mos
28	M	F	220 (THP: 220)	7y0m	ALL	3y2mos
29	M	M	232 (THP: 100, IDAR: 132)	15y0m	ALL	3y6mos
30	M	M	300 (ADM: 200, DNR: 100)	16y9m	ALL	3y5mos
31	M	F	375 (THP: 375)	13y0m	ANLL	9y1mos
32	H	M	420 (ADM: 420)	13y3m	Neuroblastoma	8y4mos
33	H	M	490 (ADM: 50, EPR: 440)	9y6m	NHL	4y2mos
34	H	F	540 (ADM: 360, THP: 180)	18y4m	ANLL	9y2mos
35	H	M	600 (DNR: 60, THP: 360, ACR: 180)	18y0m	ANLL	4y6mos
36	H	M	840 (DNR: 140, THP: 720)	6y8m	NHL	2y3mos
37	H	F	460 (ADM: 360, THP: 100)	16y8m	ANLL	8y10mos

M: male, F: female, ATC: anthracycline, ALL: acute lymphoblastic leukemia, ANLL: acute non-lymphoblastic leukemia, LCH: Langerhans cell histiocytosis, NHL: non-Hodgikin's lymphoma, ADM: doxorubicin, DNR: daunorubicin, IDAR: idarubicin, TPH: pirarubicin, MIT: mitoxantrone, ACR: aclarubicin

Dobutamine Stress Protocol

Dobutamine was infused at an initial rate of 5 μg/kg/min for 3 minutes, and the infusion rate was increased by 5 μg/kg/min every 3 minutes to a maximum of 30 μg/kg/min. Infants and small children were sedated during the dobutamine stress test. Administration of dobutamine was prematurely stopped under the following conditions: if the subject experienced intolerable chest pain, palpitations, headache, nausea, or other symptoms; if the systolic blood pressure rose to >200 mmHg; if frequent episodes of ventricular arrhythmia were observed; or if sustained ventricular tachycardia was observed. Throughout this protocol, continuous ECG monitoring was performed. Heart rate and blood

pressure were recorded at baseline and after each stage of dobutamine infusion, and the double product (DP: defined as heart rate multiplied by systolic pressure) was calculated as an index of stress volume.

ECG and QT Analysis

Standard 12-lead ECGs were recorded at a paper speed of 25 mm/s for each study subject in the supine position with Cardio Multi FDX-4520 (Fukuda Denshi, Tokyo, Japan). Subjects were required to lie supine for 5 minutes for stabilization before ECGs were recorded. All ECGs were sampled at 250 Hz with simultaneous 12-lead recordings, and digitized data were saved to a floppy disk for automated analysis. For each ECG, QT intervals in each lead were automatically calculated without manual modification of the computerized recognition of the T-wave offset. The T-wave offset was detected as the intersect of the T-P isoelectric baseline with the least-squares-fit line around the target to the T-wave downslope. The heart-rate corrected QT (QTc) was calculated using the Bazett formula: $QTc=QT/\sqrt{RR}$ interval. The QT intervals were measured from the QRS complex to the end of the T wave. If a U wave was present, the T wave offset was defined as the nadir between the T and U waves. If the T wave offset could not be identified, the lead was excluded from analysis. The QTd, which is defined as the difference between the maximum and minimum QT intervals, was derived for each recording. The heart-rate corrected QTd (QTcd) was calculated with the Bazett formula.

Echocardiography and Pulsed Doppler Echocardiography

After 5 minutes of rest, systolic and diastolic blood pressures were measured in the upper limb by means of a manual sphygmomanometer with a 5-, 9-, or 14-cm cuff. Echocardiography and pulsed Doppler echocardiography were performed with a Hewlett-Packard SONOS-2500 (Hewlett-Packard, Palo Alto, CA, USA) with a 5- or 3.5-MHz transducer. Phonocardiograms, indirect carotid pulse tracing, and ECGs were simultaneously recorded at a paper speed of 50 mm/s. The 2-dimensional echocardiogram was recorded in the standard left ventricular (LV) short axis view at the level of the chordae tendineae, with the M-mode cursor angled through the center of the LV cavity. We measured the LV end-systolic and end-diastolic dimensions (LVDs and LVDd), and the end-systolic and end-diastolic posterior wall thickness (PWTs, PWTd). We calculated the following indices: 1) LV ejection fraction (EF)=$(LVDd^3 - LVDs^3)/LVDd^3$, as an index of cardiac performance; 2) end-systolic wall stress (ESS)=$P \times LVDs \times 1.35/4 \times PWTs \times (1 + PWTs/LVDs)$[15], where P is the LV end-systolic pressure calculated from the measured upper limb systolic blood pressure (P=0.66 × systolic blood pressure + 13.5[16]), as an index of LV after-load; 3) percentage LV posterior wall thickening (%PWT)=$100 \times (PWTs - PWTd)/PWTd$, as an index of the rate of change of LV wall thickness. Pulsed Doppler echocardiograms were obtained in the left parasternal 4-chamber view. The sample volumes were placed on the mitral valve annulus, and the angle between the Doppler beam and the presumed mitral flow vectors was kept as small as possible. We measured the maximum early filling peak velocity (E) and the atrial contraction peak velocity (A) from the LV transmitral flow wave recordings, and calculated E/A as an index of diastolic function.

The investigators who interpreted the QT dispersion, M-mode echocardiograms, and pulse Doppler echocardiograms were blinded to the clinical data.

Statistical Analysis

Differences among the groups were analyzed at each stage with one-way analysis of variance (Scheffe's method). Differences with a probability value of $p<0.05$ were considered statistically significant.

Results

Clinical Data of the Patients and Control Subjects

There were no significant differences in the levels of hemoglobin or electrolytes between any of the groups (**Table 2**).

Table 2 Hemblobin and electrolytes

	Hb (g/dL)	Na^+ (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mg/dL)
control	13.5 ± 0.8	141.4 ± 4.3	4.3 ± 0.3	9.4 ± 0.2
N	12.6 ± 0.6	139.8 ± 3.6	4.2 ± 0.2	9.6 ± 0.3
L	11.9 ± 0.9	140.2 ± 2.9	4.5 ± 0.3	9.4 ± 0.2
M	12.6 ± 0.8	142.3 ± 4.9	4.2 ± 0.2	9.7 ± 0.4
H	12.1 ± 0.7	140.6 ± 5.2	4.1 ± 0.2	9.5 ± 0.2

Hb: hemoglobin

Hemodynamic Changes before and after Dobutamine Stress

No subjects showed any symptoms or arrhythmias in response to dobutamine administration, and all subjects were a given the full dobutamine dose of 30 μg/kg/min. In each group, the heart rate and systolic blood pressure increased significantly from those at rest to those after administration of dobutamine at 30 μg/kg/min. There were no significant differences between any of the groups at rest or after administration of dobutamine at 30 μg/kg/min. In all groups, DP was greater after administration of dobutamine at 30 μg/kg/min than at rest or after low-dose dobutamine administration. In all groups, the mean DP increased significantly up to 20,000, which is thought to be a practical exercise volume after administration of dobutamine at 30 μg/kg/min **(Table 3)**.

QTd, QTcd Values at Rest, and after Low- and High-dose Dobutamine Stress

We could not identify the T wave offset in 4 patients at high-dose dobutamine stress, which included leads I and aV_L in 2 patients from groups M and H, lead aV_L in 1 patient from group M, and lead V_1 in 1 patient from group L. We examined whether sex affected QTd and found that QTd is not sex-dependent (male QTd: 44.5 ± 3.9, female QTd: 46.3 ± 4.1). At rest, QTd and QTcd were significantly greater in groups M and H (group M: 51.3 ± 4.5, 52.8 ± 3.6, group H: 52.1 ± 4.1, 54.0 ± 3.4) than in the other 3 groups or in healthy control subjects ($p< 0.05$). This finding indicates that inhomogeneity of ventricular repolarization occurred even at rest in patients who received an anthracycline dose of ≥200 mg/m^2. When the cut-off value for normal QTd was set at <50 milliseconds[17,18], 68.8% (11 of 16) of the patients in group M and 83.3% (5 of 6) of patients in group H had an abnormal QTd. After administration of dobutamine at 5 μg/kg/min, the results were the same as those at rest. After administration of dobutamine at 30 μg/kg/min, QTd and QTcd were significantly greater in patients from group L (56.5 ± 4.8, 79.6 ± 8.4), group M (61.2 ± 6.4, 81.3 ± 8.5), or group H (64.3 ± 7.7, 83.0 ± 10.5) than in the other 2 groups or in healthy control subjects ($p<0.05$) **(Table 4)**. With a QTd cut-off value of <50 milliseconds, 5 of the 8 patients (62.5%) in group L, 15 of the 16 patients (93.8%) in group M, and all 6 patients in group H had an abnormal QTd. On the other hand, there were no significant differences in QTd or QTcd between group N and the control subjects at rest or after administration of dobutamine at 5 or 30 μg/kg/min.

Correlation between Cumulative Anthracycline Dose and QTd at Rest and after Dobutamine Stress at 30 μg/kg/min.

We tested the correlation between cumulative anthracycline dose and QTd after dobutamine stress at 30 μg/kg/min, and found a good correlation using the following correlation formula: $y=0.051x + 42.2$ ($r=0.81$, $p<0.001$) **(Fig. 1)**. This correlation suggests that QTd was worse at the highest cumulative anthracycline dose. The cut-off value for detection of abnormal cardiac reserve function was at a cumulative anthracycline dose of 152.9 mg/m^2, which was calculated using the correlation formula between QTd and cumulative anthracycline dose. The sensitivity and specificity for detection of anthracycline cardiotoxicity based on our findings of abnormal QTd (≥50 milliseconds) after high-dose dobutamine stress in patients with a cumulative anthracycline dose of >150 mg/m^2 were 96.0% and 83.3%, respectively. This finding shows that patients receiving a cumulative dose of anthracycline of 150 mg/m^2 or more display subclinical electrophysiological anthracycline cardiotoxicity. Thus, QTd is a reliable predictor of anthracycline cardiotoxicity in patients treated with anthracyclines, and subclinical myocardial

Table 3 Cardiovascular hemodynamic changes before and after dobutamine stress

group	HR rest	HR DOB-5	HR DOB-30	sys BP rest	sys BP DOB-5	sys BP DOB-30	DP rest	DP DOB-5	DP DOB-30
control	71.6 ± 12.2	75.3 ± 16.3	121.7 ± 20.8	109.1 ± 12.3	123.8 ± 11.2	166.3 ± 19.4	7,784 ± 684	9,436 ± 1,679	20,892 ± 1,126
N	65.0 ± 11.2	67.1 ± 10.2	121.3 ± 9.1	107.1 ± 6.7	124.3 ± 10.4	166.2 ± 14.0	7,608 ± 832	9,563 ± 956	21,454 ± 969
L	73.1 ± 16.6	72.0 ± 12.3	120.4 ± 28.9	107.2 ± 12.0	122.5 ± 12.3	163.2 ± 17.1	7,803 ± 766	9,457 ± 887	21,798 ± 945
M	73.4 ± 11.1	72.6 ± 12.6	125.2 ± 19.8	100.9 ± 12.6	125.4 ± 14.7	150.5 ± 18.8	8,021 ± 896	9,138 ± 1,236	22,105 ± 1,203
H	68.8 ± 9.9	83.5 ± 36.4	137.0 ± 15.4	100.5 ± 10.5	123.0 ± 5.3	154.0 ± 18.6	7,996 ± 913	10,166 ± 2,076	21,326 ± 1,026

HR: heart rate, DOB: dobutamine, sys BP: systolic blood pressure, DP: double product

Table 4 QTd and QTcd values at rest, after DOB 5 μg/kg/minute and 30 μg/kg/minute stress

	QTd rest (msec)	QTd DOB-5 (msec)	QTd DOB-30 (msec)	QTcd rest (msec)	QTcd DOB-5 (msec)	QTcd DOB-30 (mseec)
control	37.1 ± 9.0	41.1 ± 7.8	42.6 ± 7.9	44.1 ± 10.9	46.8 ± 13.1	57.8 ± 9.8
N	38.7 ± 3.6	39.2 ± 4.6	41.2 ± 4.6	44.7 ± 7.8	47.2 ± 5.6	58.3 ± 7.9
L	39.1 ± 4.6	41.1 ± 4.2	56.5 ± 4.8*	43.1 ± 6.0	48.3 ± 7.1	79.6 ± 8.4*
M	51.3 ± 4.5*	51.7 ± 5.3*	61.2 ± 6.4*	52.8 ± 3.6*	56.6 ± 6.5*	81.3 ± 8.5*
H	52.1 ± 4.1*	52.2 ± 6.8*	64.3 ± 7.7*	54.0 ± 3.4*	57.3 ± 8.4*	83.0 ± 10.5*

QTd: QT dispersion, QTcd: corrected QT dispersion
*$p<0.05$ vs. other groups

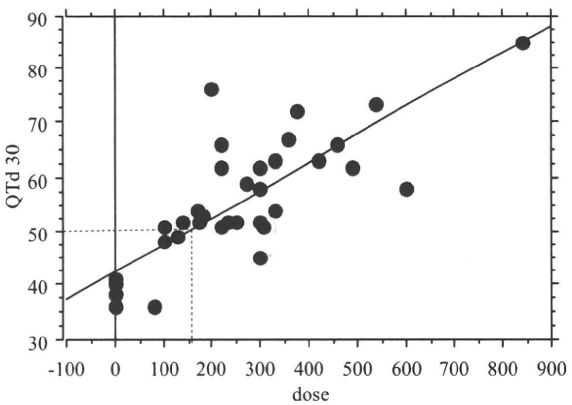

Fig. 1 Correlation between cumulative anthracycline dose and QT dispersion after dobutamine stress at 30 μg/kg/min.
The Y axis shows QT dispersion after dobutamine stress at 30 μg/kg/min, and the X axis shows the cumulative anthracycline dose. There was a good correlation between these indices, with a correlation formula of $y=0.051x + 42.2$ ($r=0.81$, $p<0.001$).

abnormalities can develop in patients receiving a cumulative anthracycline dose of ≥150 mg/m^2. On the other hand, we found a good correlation between anthracycline dose and QTd at rest using the following correlation formula: $y=0.04x + 28.9$ ($r=0.78$, $p<0.001$). When the abnormal value was 50 milliseconds, the cut-off value for detection of cardiotoxicity was a cumulative anthracycline dose of 526.3 mg/m^2, which seems far less sensitive for detecting anthracycline cardiotoxicity.

EF, ESS, E/A, and %PWT at Rest and after Low- and High-dose Dobutamine Stress

We could perform cardiac performance tests for 7 of 10 control subjects, all patients of group N, 7 of 8 patients of group L, 14 of 16 patients of group M, and all patients of group H. At rest and after dobutamine stress at 5 μg/kg/min, E/A and %PWT were significantly lower in group H than in the other 4 groups. After dobutamine stress at 30 μg/kg/min, groups M and H showed ESS, E/A, and %PWT values that were significantly different from those of the other 3 groups. Increases in ESS and decreases in %PWT were due to reduced end-systolic LV wall thickness (data not shown), and decreases in E/A indicated reduced diastolic function. These results suggest that patients with a cumulative m^{2}dose of ≥400 mg/m^2 had subclinical decreases in LV muscle volume and subclinical increases in LV wall stiffness. On the other hand, there were no significant differences in EF among the 5 groups at rest, after dobutamine stress at 5 μg/kg/min, or after dobutamine stress at 30 μg/kg/

Table 5-1 EF and ESS values at rest, after DOB 5 μg/kg/minute and 30 μg/kg/minute stress

	EF rest	EF DOB-5	EF DOB-30	ESS rest	ESS DOB-5	ESS DOB-30
control	64.1 ± 6.0	69.7 ± 9.6	79.0 ± 4.7	55.1 ± 7.0	54.2 ± 3.2	51.1 ± 2.5
N	68.3 ± 3.6	74.9 ± 3.6	80.9 ± 4.8	55.8 ± 6.3	55.3 ± 2.9	52.3 ± 3.1
L	62.5 ± 9.1	70.4 ± 8.7	78.0 ± 7.7	56.6 ± 2.1	56.4 ± 9.1	51.5 ± 2.1
M	61.6 ± 8.3	67.0 ± 8.4	75.8 ± 10.8	54.7 ± 8.7	56.2 ± 8.6	63.9 ± 7.1*
H	58.7 ± 9.5	68.7 ± 4.9	81.0 ± 1.0	58.8 ± 14.8	61.6 ± 17.5	62.2 ± 13.1*

EF: ejection fraction, ESS: end-systolic left ventricular wall stress, *p<0.05 vs. other groups

Table 5-2 E/A and %PWT values at rest, after DOB 5 μg/kg/minute and 30 μg/kg/minute stress

	E/A rest	E/A DOB-5	E/A DOB-30	%PWT rest	%PWT DOB-5	%PWT DOB-30
control	2.0 ± 0.1	2.2 ± 0.1	1.5 ± 0.1	96.2 ± 1.6	115.3 ± 5.6	132.7 ± 5.7
N	2.1 ± 0.2	2.3 ± 0.1	1.4 ± 0.1	94.8 ± 4.3	118.6 ± 7.6	134.8 ± 4.9
L	2.1 ± 0.1	2.3 ± 0.2	1.6 ± 0.2	91.2 ± 4.6	109.1 ± 9.5	135.8 ± 26.3
M	2.0 ± 0.2	2.1 ± 0.3	1.2 ± 0.1*	91.7 ± 3.2	112.4 ± 6.1	96.2 ± 3.8*
H	1.7 ± 0.2*	1.8 ± 0.2*	1.0 ± 0.1*	68.9 ± 6.1*	92.4 ± 11.2*	92.2 ± 5.5*

E/A: ratio of the maximum early filling peak velocity (E) and the atrial contraction peak velocity (A), %PWT: percentage left ventricular posterior wall thickness
*p<0.05 vs. other groups

min. These findings suggest that even the highest cumulative m^2doses in the patients did not reduce LV systolic function (**Table 5-1, 5-2**). These findings using 2-dimensional echocardiography and pulse Doppler echocardiography are similar to the findings we obtained in our previous study[14].

Discussion

Late cardiotoxic effects of anthracycline are an increasing problem for survivors of childhood cancer. Anthracycline-induced congestive heart failure is a dose-dependent phenomenon. Reported incidences of anthracycline-induced congestive heart failure range from >5% (cumulative adriamycin dose, 501 to 550 mg/m^2) to >30% (cumulative adriamycin dose, >601 mg/m^2)[19]. In a long-term follow-up study, patients who had no symptoms of cardiotoxicity at the time of complete remission of cancer after adriamycin therapy had an unusually high incidence of cardiovascular complications typical of adriamycin cardiomyopathy over the subsequent 4 to 20 years[20]. Thus, it is important to find ways to avoid or minimize the cardiotoxic side effects of anthracycline in the treatment of cancer.

Several effects of anthracycline which may play critical roles in the pathogenesis of anthracycline cardiomyopathy have been described. Most studies support the view that an increase in oxidative stress (evidenced by increases in free radicals and lipid peroxidation and decreases in antioxidants and sulfhydryl groups) plays an important role in the pathogenesis of anthracycline cardiomyopathy[21,22]. The unique sensitivity of the myocardium to anthracyclines may be due to the low levels of catalase and superoxide dismutase in cardiac myocytes[23].

The main features of cardiac biopsies from anthracycline-treated patients are cytoplasmic vacuolization due to dilation of the sarcotubules and loss of myofibrils[19,24]. In patients who received a high dose (455–500 mg/m^2) of daunomycin, cardiac biopsies exhibited degenerative, atrophic, and lytic lesions in cardiac muscle cells, and interstitial edema and fibrosis[23]. These histological abnormalities could strongly affect myocardial action potentials and cell-to-cell conduction, and lead to inhomogeneity of ventricular depolarization and repolarization. Previously, we reported that anthracycline-treated patients exhibited abnormal ventricular depolarization, as revealed by signal-averaged electrocardiography[25]. However, there have been no other reports of abnormalities of ventricular repolarization in anthracycline-treated patients. QT

dispersion is defined as the difference between the maximum and minimum QT interval durations on a 12-lead standard ECG and is considered to reflect local differences in repolarization of the myocardium. In the present study, at rest, when the cut-off value for normal QTd was set at <50 milliseconds[17,18], the QTd was abnormal in 68.8% of the patients with a cumulative anthracycline dose of ≥200 mg/m^2 and in 83.3% of the patients with a cumulative anthracycline dose of ≥400 mg/m^2. An abnormal increase in QT dispersion could be caused by inhomogeneity of ventricular repolarization. The QTc was prolonged at rest by more than 450 milliseconds in only 5 of the present cases. The QTc may be less sensitive as an index of anthracycline cardiotoxicity at rest than are the QTd data. On the other hand, in the present study, 2-dimensional echocardiography showed that only patients with a cumulative anthracycline dose of ≥400 mg/m^2 had a significantly reduced LV cardiac muscle volume at rest, which is consistent with our previous findings[25]. It appears likely that decreased numbers of cardiac myocytes and increased interstitial edema and fibrosis leads not only to reduced ventricular cardiac volume but also to abnormal microelectrical findings. Our findings show that for patients with a cumulative anthracycline dose of ≥200 mg/m^2, electrical findings at rest indicates cardiotoxic effects (morphological changes in ventricular myocardium) that require intervention.

Dobutamine is a synthetic catecholamine α1, β1 and β2 with mimetic activity. Dobutamine has inotropic effects at low doses (5–10 μg/kg/min) and causes increased heart rate, blood pressure, and coronary vasodilation at high doses (>20 μg/kg/min). Thease changes lead to increased oxygen consumption in the myocardium and increase the inhomogeneity of ventricular myocytes at moderate doses (>10 μg/kg/min)[26]. These findings suggest that the inhomogeneity of ventricular repolarization can be increased in cardiac myocytes exposed to anthracyclines. In this study, we evaluated myocardial reserve function as an indicator of cardiotoxicity, by performing electrophysiological and morphological evaluations under dobutamine-induced stress. After dobutamine stress at 30 μg/kg/min, patients with a very low cumulative anthracycline dose (anthracycline dose ≥80 mg/m^2) had significantly greater QTd and QTcd than did control subjects or patients who had not received an anthracycline. With the cut-off value of >50 milliseconds, an abnormal QTd was found in 62.5% of patients with a cumulative anthracycline dose of 80 to <200 mg/m^2, 93.8% of patients with a cumulative anthracycline dose of 200 to <400 mg/m^2, and 100% of patients with a cumulative anthracycline dose of ≥400 mg/m^2. We also evaluated cardiotoxicity by examining cardiac muscle performance under dobutamine stress using 2-dimensional echocardiography and pulsed Doppler echocardiography. The values for ESS, E/A, and %PWT that we obtained were consistent with our previous findings[25], yet were much less sensitive than were the QTd and QTcd data that we obtained in the present study. Because these indices are calculated from changes in LV wall motion on echocardiograms, detectable changes in wall motion must require much higher cumulative doses than the electrophysiological changes detected on the basis of QT dispersion. Data from 2-dimensional echocardiography and pulsed Doppler echocardiography is more difficult to evaluate than are data from 12-lead ECG. Moreover, whereas sedation may be needed for infants and small children when they undergo echocardiography, there is no need for sedation to perform 12-lead ECG. Thus, in terms of ease of use, QTd and QTcd have clear advantages over ESS, E/A, and %PWT as indices for detecting anthracycline cardiotoxicity that manifests as abnormal cardiac reserve function.

In the present study, there was little difference between QTd and QTcd. Some earlier studies have found no evidence that QT dispersion requires the same type of heart rate correction as the duration of the QT interval[27,28]. Also, clear criteria have recently been established for detecting abnormal QTd based on electrophysiological findings[17,18], whereas no precise value for detecting abnormal QTcd has been established. Moreover, assessing QTd is much easier than assessing QTcd. Thus, QTd has an advantage over QTcd as an index for detecting abnormal ventricular inhomogeneity.

In the present study, we also assessed the correlation between cumulative anthracycline dose and QTd after dobutamine stress at 30 μg/kg/min. We found a good correlation between those 2 variables when using the correlation formula: $y = 0.051x + 42.2$ ($r=0.81$, $p<0.001$) **(Fig. 1)**. With this formula, we determined that a cumulative anthracycline dose of 152.9 mg/m^2 was the cut-off for detecting abnormal cardiac reserve function. Based on these results, the sensitivity and specificity for detecting anthracycline cardiotoxicity as indicated by abnormal QTd after high-dose dobutamine stress (≥50 milliseconds) in patients with a cumulative anthracycline dose of >150 mg/m^2 were 96.0% and 83.3%, respectively. This finding suggests that the physicians of patients with a cumulative anthracycline dose of >150 mg/m^2 should consider the possibility of decreased cardiac reserve function. QTd appears to be a useful index for detecting cumulative anthracycline cardiotoxicity.

Previously, we reported that anthracycline-treated patients exhibit abnormal ventricular depolarization, as revealed by signal-averaged ECG (SAE). However, the microvolt electrophysiological changes detected with SAE require several criteria that are dependent on method and age. Because measurement of QTd is a convenient and independent of age and sex[29], it is, therefore, a much better method than SAE for detecting anthracycline cardiotoxicity.

Finally, we did not evaluate the reproducibility of QTd in this study. Many papers have reported that the reproducibility of QT dispersion is significantly poorer than the reproducibility of the QT interval itself. Nevertheless, despite this poor reproducibility, our physicians were able to distinguish between healthy subjects and patients with heart disease on the basis of QT dispersion[17,30,31].

Study Limitations

The most important limitation of this study was the measurement of QT dispersion. The end of repolarization can be difficult to define because of flattening of the T wave or the presence of a U wave. In the present study, when the T wave offset could not be identified, the lead was excluded from analysis.

The Bazett formula is commnly used to correct the QT interval for heart rate. Recently, the Fridericia formula has been considered better for correcting the QT interval when the heart rate is high. We would have liked to use the Fridericia formula in the present study, especially for high heart rates during dobutamine stress, however, the Cardio Mulyi FDX-4520 is not formatted for the Friderica formula. Hence, in this study the QT interval was corrected with the Bazett formula.

In the present study, we did not obtain control data from children because we decided that the dobutamine stress test was too invasive and that healthy children should not be subjected to such a stress test. Also, we could not obtain age-matched data. However, there were no significant differences between the control group and any of the 3 patient groups in the basic findings of heart rate and blood pressure, which strongly affect electrophysiological data. Therefore, we felt that the index of age could be ignored in this study.

Conclusions

Dobutamine-stress QT dispersion is a useful method for detectinglate anthracycline cardiotoxicity, especially for patients who cannot tolerate physical exercise. On the basis of these findings we believe that the physicians of patients with a cumulative anthracycline dose of >150 mg/m^2 should be aware of the possibility of subclinical anthracycline cardiotoxicity.

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ORIGINAL ARTICLE

Late effects and quality of life of childhood cancer survivors: Part 2. Impact of radiotherapy

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Abstract To examine the late effects and health-related quality of life of childhood cancer survivors (CCS) after radiotherapy (RT), we performed a cross-sectional survey using self-rating questionnaires. The subjects were divided into 3 groups: CCS treated with or without RT, and a general population matched for age, gender, residential area, and work status. The numbers in each group were 113, 72, and 1,000, respectively. The median ages of CCS at diagnosis and the time of the survey were 8 and 22 years, respectively. The mean final heights of males and females were significantly lower in CCS with RT than in the other 2 groups. Risk factors for a short stature were total body irradiation (TBI) [odds ratio (OR) 17.8, $p < 0.001$], spinal irradiation (OR 8.31, $p = 0.033$), and an age younger than 10 years at diagnosis. Late effects were observed in 68% of CCS with RT compared with 36% of CCS without RT. Multivariate analysis revealed that TBI was significantly associated with endocrine dysfunction (OR 12.3), skull and spinal irradiation with cognitive dysfunction (OR 16.1 and 11.5, respectively), and spinal irradiation with a short stature (OR 14.1), respectively. Physical dysfunction, psychological stress, and problems of social adaptation were observed in >50% of CCS with RT.

Keywords Radiotherapy · Radiation · Late effects · Childhood cancer survivors · Quality of life

1 Introduction

With advances in treatment, the majority of children diagnosed with cancer now survive [1]. In Japan, the estimated number of childhood cancer survivors (CCS) is >50,000, or approximately 1 in 700 adults between 20 and 39 years. Among long-term CCS, chronic adverse health

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conditions such as organ dysfunction, physical disabilities, as well as reproductive problems are common [1–4].

We reported that a short stature (<−2 SD) and being underweight (BMI < 18.5) were observed frequently in CCS treated with stem cell transplantation (SCT), and that late effects were noted in 78% of SCT-treated CCS versus 45% of CCS treated without SCT [5]. In our previous report, multivariate analysis revealed that not only SCT [odds ratio (OR) 3.39, $p = 0.014$] but also radiotherapy (RT) (OR 2.8, $p = 0.009$) were independent significant risk factors for late effects [5]. Many articles have demonstrated that one of the most important risk factors for late effects in CCS is RT [4, 6–9]. The late effects might affect the health-related quality of life (QOL) of long-term CCS. Many comprehensive reviews on the late effects of CCS have been published in Western countries (USA and Europe); however, information on CCS treated with RT in Asian countries, including Japan, is quite limited [10, 11].

In this study, we investigated the late effects and QOL of CCS who were >16 years old at the time of the survey by comparing the outcomes of CCS treated with and without RT with a general population as a control.

2 Materials and methods

2.1 Study design

We performed a cross-sectional survey using self-rating questionnaires on the late effects and QOL among CCS, with a general population as a control group. We simultaneously obtained medical data on the CCS from their attending pediatricians. The study was conducted from 1 August, 2007 to 31 March, 2009.

2.2 Participants and methods

The inclusion and exclusion criteria for participants and the methods were reported previously [5, 12]. Briefly, the subjects were divided into 3 groups: CCS treated with RT, CCS treated without RT, and a general population as a control group. CCS were recruited from participating hospitals listed in Table 1. The control group participants were recruited by a consultancy (Cross Marketing Inc., Tokyo, Japan) performing web-based research, after confirming that neither the participants nor their siblings had a history of childhood cancer. After obtaining appropriate informed consent, the CCS were provided with an anonymous questionnaire by the attending pediatricians, and were asked to return it by post within 1 month. After recruiting the general population from online panels, quantitative research with web-based methods was conducted using the same self-rating questionnaire. The participants were sampled from the research panel by matching with their age, gender, living area, and work status with those of the CCS group.

2.3 Measurement of variables

The patients' clinical records were reviewed to analyze cancer-related variables, including the diagnosis, birth year

Table 1 List of participating hospitals

No.	Institution	Investigators	Number of distributions	CCS (% of response)
01	Kyusyu Cancer Center	Jun Okamura	27	19 (70.4%)
02	Niigata Cancer Center	Keiko Asami	44	28 (63.6%)
03	Nihon Medical School	Miho Maeda	4	3 (75.0%)
04	National Center for Child Health and Development	Naoko Kakee Keniichiro Aritaki	3	1 (33.3%)
05	Ehime University	Yasushi Ishida Misato Honda	51	44 (86.3%)
06	Tohoku University	Masaki Nio Yutaka Hayashi	13	11 (84.6%)
07	Kagawa Children's Hospital	Tsuyako Iwai	10	10 (100%)
08	Nagoya Medical Center	Naoko Maeda Keizo Horibe	39	26 (66.7%)
09	Kurume University	Shuichi Ozono Hiroko Inada	43	30 (69.8%)
10	International Medical Center in Japan	Hideko Uryu Takeji Matsushita	10	3 (30.0%)
11	Juntendo Univeristy	Kouichi Ishimoto Masahiro Saitou	5	5 (100%)
12	St. Luke's Int'l Hospital	Yasushi Ishida	12	9 (75.0%)
Total			261	189 (72.4%)

and month, age at diagnosis, age at therapy completion, time since diagnosis, treatment variables [operational procedure and site, irradiation -site and dose, chemotherapy-anthracyclines, alkylating agents, or etoposide (yes/no), SCT], and the late effects on the CCS observed at the time of the survey. We used an encrypted numbering system for sending data to the principal investigator to maintain the confidentiality of the patients' information. Late effects were defined as adverse events, which were grade 2 (symptomatic or needing some intervention) or higher using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3), originally developed by the National Cancer Institute (Japanese CTCAE v.3.0 by JCOG and JSCO, http://www.jcog.jp/). We classified the late effects into 14 categories: cardiovascular dysfunction, pulmonary dysfunction, endocrine dysfunction, short stature, kidney and bladder dysfunction, bone or muscle problems, skin problems or hair loss, neurocognitive impairment, gastrointestinal dysfunction, liver dysfunction, immunological dysfunction, secondary cancers, chronic infection, and others.

The questionnaire consisted of 220 items with 3 items involving free writing. We evaluated 7 background items (gender, age at survey, diagnosis, age at diagnosis, age at therapy completion, and height and weight at survey) and 4 general health-related problems (physical problems, difficulty in daily life, psychological stress, and difficulty in social adaptation).

2.4 Ethical issues

The study was performed in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the principal investigator's institution (Y. Ishida, Ehime University Graduate School of Medicine and St. Luke's International Hospital). The study was also approved by the local ethics committees of all the participating hospitals before initiation.

2.5 Statistical analysis

We estimated the prevalence of outcomes among CCS and the general population. Three primary outcomes were assessed: (1) anthropometric indicators, (2) the presence of late effects as judged by the attending pediatrician (for the CCS group only), and (3) the general QOL as estimated from the questionnaires. We performed χ^2 tests or Fisher's exact test (for any cells with expected counts <5) within categorical predictors, and the t test or analysis of variance for continuous variables. The adjusted ORs of RT for adverse outcomes were estimated employing logistic regression analysis. As adjusted variables, we selected independent, significant risk factors like SCT, solid tumors, recurrence, and duration after therapy completion, as shown in our previous article [5]. To avoid multi-collinearity, we assessed associations between predictors in a pairwise fashion. Data were analyzed with SPSS software, ver. 17.0 (SPSS Japan Inc., Tokyo, Japan).

The results of the North American Childhood Cancer Survivor Study (CCSS) indicate that approximately half of CCS exhibit some late effects [16]. Data from approximately 180 CCS were required to analyze 9 determinants by multivariate logistic regression methods to identify risk factors for the occurrence of late effects. We planned to survey independent cases and controls with 5 controls per case. Our final target numbers were 200 for CCS and 1,000 for the general population with some margin (cases were excluded on the basis of the exclusion criteria or because of missing data).

3 Results

The demographic data of the participants were reported previously [5, 12]. Table 2 shows the characteristics of CCS with or without RT. The mean heights of both male and female patients at the time of the survey were significantly lower for the CCS with RT than those of CCS without RT and the general population. The mean body mass index (BMI) of CCS treated with RT compared to those without RT was significantly lower for only males. The time period after therapy completion and primary cancer distribution were not significantly different between CCS treated with and without RT. CCS with RT more often received alkylating agents, SCT, and suffered from recurrence more frequently than CCS without RT.

The height distribution at the time of the survey with regard to gender in CCS groups treated with or without RT was compared with that of the general population (Fig. 1). A short stature (<−2 SD) was significantly observed more frequently in the CCS treated with RT group (20% of males and 16% of females) compared to the CCS treated without RT and the general population groups (0–2.6% of males and 1.9–5% of females). The BMI distribution at the time of the survey with regard to gender for CCS treated with or without RT compared to the general population is shown in Fig. 2. The CCS treated with RT were frequently found to be underweight (BMI < 18.5) in only males. There was no large difference in the frequencies of being overweight (BMI > 25) among the 3 groups.

The adjusted ORs for a short stature were estimated using logistic regression analysis. The age at diagnosis (0–5 years of age, OR 42.2, $p = 0.003$; 6–10 years of age, OR 26.0, $p = 0.006$ as reference of more than 10 years of age), skull irradiation (OR 4.71, $p = 0.040$), and total body irradiation (TBI) (OR 39.9, $p = 0.013$) were independent

Table 2 Characteristics of cancer survivors with or without radiotherapy

Continuous variables	With RT ($n = 113$)	Without RT ($n = 72$)	RT versus no RT t test (p value)	General population ($n = 1{,}000$)	RT versus general t test (p value)
Age at diagnosis	8.56 ± 4.8 (8.18)	7.88 ± 4.9 (7.54)	0.350	NA	–
Age at survey	24.0 ± 5.0 (23.0)	21.6 ± 4.5 (21.0)	<0.001	23.9 ± 5.6 (23)	0.233
Height at survey (cm): male	164.3 ± 6.9 (165.0)	170.6 ± 5.0 (170)	<0.001	170.8 ± 5.8 (170.5)	<0.001
Height at survey (cm): female	153.7 ± 6.5 (155.0)	157.7 ± 6.2 (158)	0.002	157.6 ± 5.4 (158)	<0.001
BMI at survey (kg/m^2): male	20.7 ± 3.4 (20.3)	22.6 ± 4.2 (22.0)	0.041	21.8 ± 3.6 (21.0)	0.073
BMI at survey (kg/m^2): female	20.8 ± 4.2 (20.3)	20.4 ± 3.1 (19.8)	0.569	20.7 ± 3.0 (20.1)	0.832
Categorical variables	With RT ($n = 113$)	Without RT ($n = 72$)	χ^2 or Fisher (p value)	General population ($n = 1{,}000$)	χ^2 or Fisher (p value)
Female	68 (60%)	40 (56%)	0.534	584 (58.4%)	0.716
Years after therapy completion				NA	
1–4 years	4 (4%)	1 (1%)	0.255		
5–9 years	28 (25%)	22 (31%)			
10–14 years	31 (27%)	26 (36%)			
15 years or more	50 (44%)	23 (32%)			
Primary cancer				NA	
Hematological	80 (71%)	48 (67%)	0.131		
Brain tumor	9 (8%)	1 (1%)			
Bone or soft tissue sarcoma	9 (8%)	9 (13%)			
Other solid tumor	15 (13%)	14 (19%)			
Anthracycline	93 (82%)	59 (82%)	0.951	NA	
Alkylating agents	101 (89%)	54 (75%)	0.010		
Etoposide	50 (44%)	26 (36%)	0.273		
Stem cell transplantation	39 (35%)	7 (10%)	<0.001	NA	
Operation	40 (35%)	30 (42%)	0.391		
Recurrence	28 (25%)	5 (7%)	0.002		

Age, height, and BMI were expressed as mean value ± standard deviation (median value)

RT radiotherapy, *NA* not available

significant risk factors for short stature (Table 3). Spinal irradiation had marginal effects (OR 6.35, $p = 0.084$) on a short stature.

Late effects were observed by attending physicians in 50% of female and 64% of male patients in the CCS groups. The adjusted ORs of RT for various late effects (adjusted variables were independent significant risk factors like SCT, solid tumors, recurrence, and duration after therapy completion, as shown in the previous article) are shown in Table 4. The adjusted ORs of RT for late effects, 2 or more late effects, endocrine dysfunction, and others were significant. The OR of neurocognitive dysfunction was relatively high but not significant. Of note was the fact that the cases of secondary cancers occurred only in CCS treated with RT.

The adjusted ORs of RT for various late effects according to radiation sites are presented in Table 5. Skull and spinal RT were significantly associated with neurocognitive dysfunction, spinal RT with a short stature, TBI with endocrine dysfunction, and chest and/or abdominal RT with bone/soft tissue damage. The ORs of extremity RT with secondary cancer and chest and/or abdominal RT with gastrointestinal dysfunction and kidney dysfunction were relatively high but not significant.

Figure 3 shows the subjective general QOL (physical dysfunction, difficulty in daily activities, psychological stress, and problems with social adaptation). More than 50% of CCS treated with RT exhibited physical dysfunction, psychological stress, and problems with social adaptation. The domains of both physical dysfunction and psychological stress were significantly affected in the CCS group treated with RT when compared with the CCS group treated without RT and the general population ($p < 0.001$). The adjusted ORs for a poor QOL between the RT and no RT group compared to the general population as a reference are shown in Table 6. The adjusted ORs for a poor

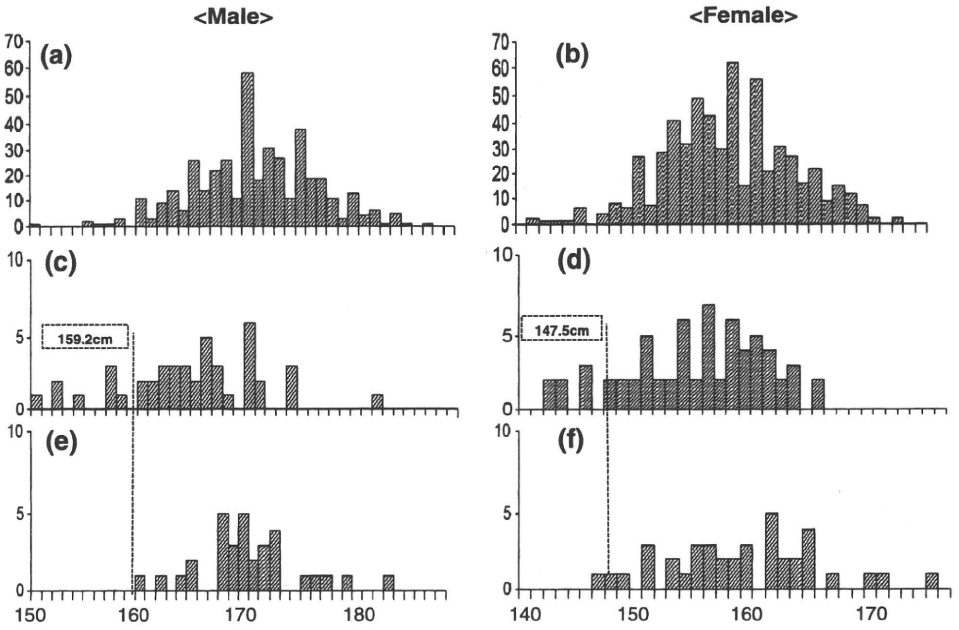

Fig. 1 Height distribution at survey. The height distribution data at survey are presented with respect to gender: **a**, **b** the general population; **c**, **d** CCS treated with RT; **e**, **f** CCS treated without RT. The mean −2 SD height was 159.2 cm for males and 147.5 cm for females in Japanese adults

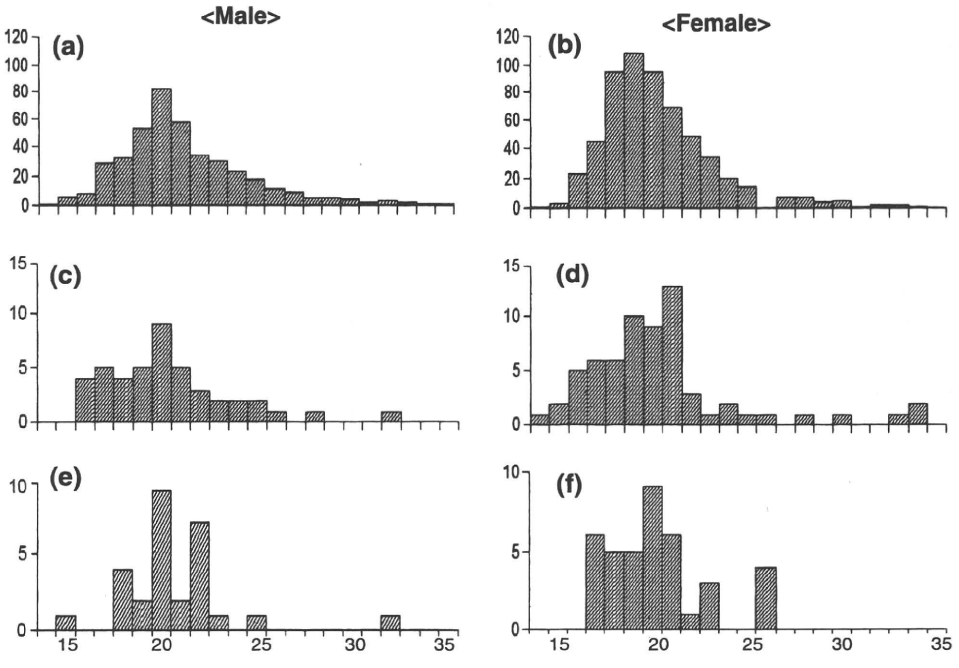

Fig. 2 BMI distribution at survey. The BMI distribution data at survey are presented with respect to gender: **a**, **b** the general population; **c**, **d** CCS treated with RT; **e**, **f** CCS treated without RT. Underweightness (BMI < 18.5) was noted in 27% of males and 26% of females in the CCS with RT group, 9% of males and 26% of females in the CCS without RT group, and 14% of males and 21% of females in the general population group, respectively. Overweightness (BMI > 25) was observed in 11% of both males and females in the CCS with RT group, 22% of males and 8% of females in the CCS without RT group, and 15% of males and 8% of females in the general population group, respectively

QOL in the CCS treated with RT were significantly high for physical dysfunction, difficulty in daily activities, and psychological stress. Each poor QOL factor in the CCS groups was closely associated with the presence of late effects (data not shown).

4 Discussion

We found that late effects and a poor QOL were closely associated with the use of RT in CCS; this finding is important because quality of cure is very critical for CCS because the cure rates have improved markedly. To our knowledge, this report is the first to comprehensively evaluate late effects on CCS after RT in Japan.

In the present survey, a short stature (<−2 SD) and being underweight (BMI < 18.5) were common in the CCS group treated with RT. A short stature was noted in 22 (12%) of 185 CCS participants; it is an important point that 20 (91%) out of 22 CCS with short stature had received RT. Skull irradiation and TBI were closely associated with a short stature, and the adjusted ORs of

Table 3 Risk factors of childhood cancer survivors for short stature

Categories	Factors	Short stature		χ^2 or Fisher (p value)	Logistic regression analysis*	
		Yes ($n = 22$)	No ($n = 161$)		Adjusted odds ratio (95% CI)	p value
Gender	Female	13	93	0.906	1.18 (0.39–3.70)	0.759
	Male	9	68		Ref	
Age at diagnosis (years)	0–5	13	46	<0.001	42.2 (3.69–483)	0.003
	6–10	8	42		26.0 (2.49–271)	0.006
	>10	1	73		Ref	
Years after therapy completion	15 years or more	13	58	0.037	1.68 (0.43–6.52)	0.452
	14 years or less	9	103		Ref	
Primary cancer (1)	Solid tumor	7	49	0.895	2.39 (0.55–10.3)	0.244
	Hematological	15	112		Ref	
Primary cancer (2)	Hematological	15	112	0.693	–	
	Brain tumor	2	8			
	Bone/soft tissue sarcoma	1	17			
	Other solid tumor	4	24			
Radiation sites	Any	20	92	0.002	–	
	Skull	12	55	0.063	4.71 (1.07–20.7)	0.040
	Chest or abdomen	0	12	0.366	–	
	Total body	8	20	0.008	39.9 (2.16–736)	0.013
	Spine	4	4	0.008	6.35 (0.78–51.5)	0.084
	Extremity	0	5	1.000	–	
Stem cell transplantation	Yes	9	37	0.069	0.50 (0.04–6.28)	0.594
Chemotherapy	Anthracycline	18	133	1.000	–	
	Alkylating agents	20	134	0.536		
	Etoposide	9	67	0.950		
Operation	Yes	8	60	0.934	–	
Recurrence	Yes	8	25	0.033	0.72 (0.16–3.31)	0.670

* Hosmer and Lemeshow: $\chi^2 = 66.4$ ($p < 0.001$)

RT for them were significantly high. The adjusted OR of spinal RT was relatively high but not significant because of the small number of CCS with spinal RT in our study. Our results confirmed those of CCSS [13, 14], demonstrating that ORs for a short stature in adulthood among those at 4 years of age or younger at diagnosis, relative to ages of 10–20 years, was 5.67 (95% CI 3.6–8.9) and that hypothalamic-pituitary axis radiation exposure increased the risk of a short stature in adulthood in a dose–response fashion (trend test, $p < 0.0001$). The OR of cranial irradiation with 20 Gy or more was 1.5 (95% CI 0.4–5.1) compared to cranial irradiation with less than 20 Gy; the dose–response was not clear, mostly because of the small number of cases in our study. Growth hormone deficiency due to cranial irradiation is one of the main mechanisms leading to a short stature in CCS; however, the mechanisms behind the association between RT and a short stature remain to be fully elucidated. This study suggests that spinal RT might be one of the independent risk factors for a short stature because the adjusted OR of spinal RT was high, which suggests that direct bone growth failure is one of the mechanisms of a short stature caused by RT in CCS.

In the CCSS study, adjuvant chemotherapy was not an independent risk factor for a short stature in adulthood [13]. In contrast, Noorda et al. [15] reported that all CCS treatment exposure groups (chemotherapy alone, chemotherapy with cranial or craniospinal radiotherapy) showed a decreased adult height and an increased risk of a short stature in adulthood compared with siblings ($p < 0.001$). They also revealed that the risk of a short stature in survivors treated with chemotherapy alone was elevated (OR 3.4, 95% CI 1.9–6.0) compared with siblings [15]. In our study, no chemotherapeutic agents were associated with the prevalence of a short stature (Table 3, multivariate data not shown).

Table 4 Adjusted odds ratios of radiotherapy for various late effects

Categorical variables	Total (n = 183)	With RT (n = 113)	Without RT (n = 72)	Adjusted odds ratio[a] (95% CI)	p value
Number of late effects					
1 or more	104 (56%)	77 (68%)	26 (36%)	2.74 (1.32–5.69)	0.007
2 or more	42 (23%)	37 (33%)	5 (7%)	5.48 (1.84–16.3)	0.002
3 or more	16 (9%)	14 (12%)	2 (3%)	2.82 (0.54–14.7)	0.219
Content of late effects					
Cardiovascular dysfunction	5 (4%)	5 (4%)	3 (4%)	1.19 (0.24–5.89)	0.835
Pulmonary dysfunction	3 (2%)	2 (2%)	1 (1.4%)	–	0.841[#]
Endocrinological dysfunction	34 (19%)	31 (27%)	3 (4%)	7.27 (1.81–29.3)	0.005
Short stature	25 (13%)	22 (20%)	3 (4%)	2.77 (0.74–10.4)	0.132
Kidney dysfunction	9 (5%)	7 (6%)	2 (3%)	2.26 (0.41–12.4)	0.349
Bone or muscle damage	18 (10%)	12 (11%)	6 (8%)	0.62 (0.42–4.18)	0.623
Skin disorder or hair loss	12 (7%)	10 (9%)	2 (3%)	1.18 (0.20–6.82)	0.854
Neurocognitive dysfunction	8 (4%)	7 (6%)	1 (1%)	6.39 (0.72–56.7)	0.096
Gastrointestinal dysfunction	3 (2%)	2 (2%)	1 (1.4%)	1.28 (0.09–17.5)	0.851
Liver dysfunction	16 (9%)	10 (9%)	6 (8%)	0.58 (0.17–1.97)	0.385
Immunological dysfunction	0	0	0	–	
Second cancer	5 (2.7%)	5 (4%)	0	–	0.070[#]
Chronic infection	0	0	0	–	
Others[b]	23 (12.6%)	19 (7%)	5 (7%)	3.16 (1.05–9.48)	0.004

[#] Non-adjusted p value

[a] Adjusted by cell transplantation, solid tumor, recurrence and duration after Tx completion

[b] Scoliosis, obesity, asymmetric face, poor vision, psychosocial problems, hearing loss, school absence, fatty liver, short bowel syndrome, and hypertension

Table 5 Adjusted odds ratios for various late effects according to radiation sites

Radiation sites	Adjusted odds ratio[a] (95% CI)				
	Skull (n = 67)	Spine (n = 8)	Total body (n = 28)	Chest/abdomen (n = 13)	Extremity (n = 5)
Number of late effects					
1 or more	2.40 (1.11–5.18)	3.06 (0.32–29.0)	3.36 (0.72–15.6)	1.15 (0.25–5.32)	0.91 (0.09–9.13)
2 or more	1.36 (0.57–3.28)	2.06 (0.37–11.4)	2.34 (0.65–8.41)	9.65 (2.34–39.8)	0.23 (0.02–2.76)
3 or more	1.66 (0.44–6.23)	6.42 (0.72–57.1)	2.19 (0.45–10.6)	1.56 (0.23–10.7)	
Content of late effects					
Cardiovascular dysfunction	1.16 (0.24–5.59)	–	–	1.18 (0.11–13.1)	5.09 (0.32–61.5)
Endocrine dysfunction	1.85 (0.68–5.04)	1.12 (0.15–8.11)	12.3 (2.63–57.2)	0.36 (0.06–2.25)	0.24 (0.02–3.36)
Short stature	1.63 (0.56–4.77)	14.1 (2.09–95.6)	1.95 (0.45–8.44)	0.39 (0.04–3.79)	–
Kidney dysfunction	0.81 (0.15–4.54)	–	2.71 (0.18–40.1)	4.47 (0.74–23.9)	–
Bone or muscle damage	0.52 (0.13–1.99)	2.14 (0.33–13.7)	1.39 (0.21–9.34)	4.27 (1.08–16.9)	0.74 (0.07–7.73)
Skin disorder or hair loss	2.26 (0.52–9.87)	–	1.04 (0.21–5.28)	3.91 (0.25–61.3)	–
Neurocognitive dysfunction	16.1 (2.28–114)	11.5 (1.24–106)	–	1.07 (0.11–10.6)	–
Gastrointestinal dysfunction	–	–	–	9.65 (0.72–12.8)	–
Liver dysfunction	0.51 (0.14–1.87)	–	0.44 (0.05–4.32)	2.40 (0.19–30.5))	–
Second cancer	0.19 (0.01–5.71)	–	–	1.81 (0.12–26.6)	23.3 (0.87–622)
Others[b]	1.49 (0.57–3.91)	2.20 (0.37–13.2)	2.62 (0.41–16.7)	1.54 (0.36–6.68)	0.96 (0.09–9.79)

[a] Adjusted by stem cell transplantation solid tumors, recurrence and duration after Tx completion

[b] Scoliosis, obesity, asymmetric face, poor vision, psychosocial problems, hearing loss, school absence, fatty liver, short bowel syndrome, and hypertension

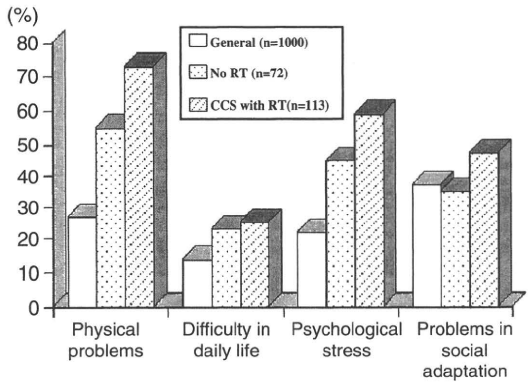

Fig. 3 General QOL of the 3 groups. Physical dysfunction, daily stress, and difficulties with social adaptation were observed in >50% of CCS treated with RT. The general QOL was affected in the CCS treated with compared with the CCS treated without RT and the general population. *Solid bars* the general population; *dotted bars* CCS treated without RT; *hatched bars* CCS treated with RT

Oeffinger et al. [16] reported that 62.3% of CCS exhibit at least 1 late effect and 27.5% exhibit 2 or more late effects. Our results showed similar trends except that late effects were observed in 68% of CCS treated with and 36% of CCS treated without RT. Endocrine system dysfunction is the most frequent complication among the late effects observed in CCS [17–19]. Miyoshi et al. [10] showed that endocrine abnormalities were observed in as many as 67% of 122 CCS in Japan; these data were obtained in cases where endocrinologists were actively involved in the long-term follow-up of CCS. Our results showed that TBI was significantly associated with endocrine dysfunction [11, 18, 20], skull and spinal irradiation with cognitive dysfunction [21], spinal irradiation with a short stature [22], and chest or abdominal irradiation with bone and soft tissue damage [23], respectively.

The multivariate logistic regression analysis in our previous article [5] revealed that independent significant risk factors besides RT and SCT for late effects were >15 years' duration after therapy completion, solid tumors, and one or more episodes of cancer recurrence. A poor subjective QOL was demonstrated in more than 50% of CCS with RT associated with various late effects, and its prevalence was significantly higher considering high adjusted ORs compared with the general population.

The limitations of our study were as follows: (1) a limited number of subjects was analyzed, (2) patients with solid tumors were underrepresented as compared to those with hematological cancers, (3) a selection bias might have been presented because patients were not recruited by random sampling, (4) incidence and time-to-event data were not available because of the cross-sectional design of the study, (5) thorough medical surveys were not conducted for certain complications such as dental problems and gonadal dysfunction, and (6) standardization of the radiation exposure was not conducted regarding the radiation machine source.

Finally, RT is a well known and the most important risk factor for secondary cancers in CCS. In our study, there were only 5 CCS with secondary cancers, but all cases received RT before the incidence of secondary cancer. Kony et al. [24] reported that both genetic factors and exposure to RT have independent effects on the risk of secondary cancers. The CCSS demonstrated that, in multivariate regression models adjusted for therapeutic radiation exposure, secondary cancers were independently associated with a female sex ($p < 0.001$), younger age at

Table 6 Adjusted odds ratios for poor QOL between RT and no RT group

Question	Group	Yes	No	χ^2 (p value)	Adjusted odds ratio[a] (95% CI)	p value
Physical dysfunction	With RT	81	30	<0.001	7.34 (4.67–11.5)	<0.001
	Non-RT	39	32		3.69 (2.21–6.13)	<0.001
	General	270	730		Ref	–
Difficulty in daily activity	With RT	28	85	0.002	1.92 (1.20–3.09)	0.007
	Non-RT	16	55		2.03 (1.10–3.73)	0.024
	General	136	864		Ref	–
Psychological stress	With RT	67	46	<0.001	5.24 (3.47–7.90)	<0.001
	Non-RT	32	39		2.74 (1.65–4.54)	<0.001
	General	217	783		Ref	–
Problems in social adaptation	With RT	53	59	0.106	1.40 (0.94–2.10)	0.103
	Non-RT	25	46		0.86 (0.51–1.48)	0.586
	General	374	626		Ref	–

[a] Adjusted by gender, age at survey, marital status, and student or not student

diagnosis (p for trend < 0.001), Hodgkin's lymphoma or soft-tissue sarcoma ($p < 0.001$ and $p = 0.01$, respectively), and exposure to alkylating agents (p for trend $= 0.02$) [8, 25]. A cohort study with an extended follow-up period is being conducted now by our research team to analyze the cumulative incidence and risk factors for secondary cancers in Japanese CCS.

5 Conclusions

1. A short stature was frequently observed among CCS treated with RT.
2. Late effects were noted in 68% of CCS treated with RT versus 36% of CCS treated without RT.
3. Skull and spinal RT were significantly associated with neurocognitive dysfunction, spinal RT with a short stature, TBI with endocrine dysfunction, and chest and/or abdominal RT with bone/soft tissue damage.
4. The general QOL was the most markedly affected in CCS treated with RT.

On the basis of these findings, we need to promote a further reduction of RT without a decrease in the survival rates. More studies on the long-term health effects in CCS are needed to improve the therapy in the future [26].

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Conflict of interest statement The authors declare no financial interests.

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