

## Long-term cardiac follow-up in survivors of a malignant bone tumour

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**Background:** Longitudinal studies of cardiac function in long-term childhood cancer survivors are scarce and frequently concern a median follow-up shorter than 13 years.

**Patients and methods:** Cardiac assessment was performed in 22 doxorubicin-treated long-term survivors of a malignant bone tumour at median 22 years (range 15–27.5) post-treatment. Age at follow-up was 39 years (range 27–59) and cumulative dose of doxorubicin was 360 mg/m<sup>2</sup> (range 225–550). Cardiac function was assessed by echocardiography and (24-h) ECG. The results were compared with those of earlier assessments at 9 years (1992) and 14 years (1997) post-treatment.

**Results:** Systolic dysfunction was found in 27% (9% in 1997;  $P = 0.02$ ) and diastolic dysfunction in 45% (18% in 1997;  $P = 0.02$ ). Heart rate variability showed further deterioration compared with earlier results.

**Conclusions:** Twenty-two years after doxorubicin-treatment, bone tumour survivors showed progressive cardiac dysfunction.

**Key words:** anthracyclines, bone tumour, cardiac toxicity, late effects, longitudinal

### introduction

The incidence of overt heart failure in anthracycline-treated cancer survivors has been found up to 5% [1, 2]. However, subclinical abnormalities in systolic and diastolic function and autonomic dysfunction may be even more frequent [3–10]. The natural course of these subclinical cardiac abnormalities remains largely unknown and it is still unclear whether or not progressive cardiac deterioration has to be anticipated.

So far only a limited number of studies on prospective longitudinal cardiac evaluation have been published, all at medium follow-up (up to 17 years) [3–6, 11]. Earlier, we reported the results of longitudinal cardiac assessments in long-term doxorubicin-treated bone tumour survivors 9 and 14 years post-treatment. In this study we found no deterioration of systolic dysfunction, but a progressive reduction of heart rate variability (HRV) [12]. The aim of the current study was to re-evaluate cardiac status in the same cohort of survivors, up to 27 years post-treatment.

### patients and methods

#### patients

The original cohort of long-term doxorubicin-treated survivors of a malignant bone tumour (osteogenic sarcoma and malignant fibrous histiocytoma), treated at the University Medical Centre Groningen, consisted of 31 patients. All patients were treated between 1977 and 1990 with combination chemotherapy according to Rosen's T5 or T10 protocol, both including doxorubicin [13, 14]. Details of treatment were described earlier [12, 15]. Patients had assessment of cardiac function at median 9 years post-treatment in 1992 ( $n = 31$ ), at 14 years post-treatment in 1997 ( $n = 29$ ) and at 22 years post-treatment in 2004 ( $n = 22$ ). Reasons for non-participation in 1992 or 1997 were death from congestive heart failure ( $n = 1$ ), death from second malignancy ( $n = 1$ ), thoracic irradiation for second malignancy and hence exclusion ( $n = 2$ ; both patients were also known with cardiomyopathy), terminal neurodegenerative disease ( $n = 1$ ) and refusal ( $n = 4$ ). Characteristics of the 22 remaining patients are summarised in Table 1.

The study protocol was approved by the Ethics Committee of the University Medical Centre Groningen. Written informed consent was obtained from all patients and controls.

#### measurements

The evaluation consisted of a medical history, physical examination, Doppler echocardiography, fasting blood sample, 12-lead electrocardiograph (ECG) and 24-h ambulatory ECG.

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**Table 1.** Characteristics of the 22 participants in 2004

Male/female	17/5
Age (years) at start of chemotherapy	
Median	17
Range	10–38
Age (years) at follow-up	
Median	39
Range	27–59
Follow-up period (years)	
Median	22
Range	15.0–27.5
Doxorubicin cumulative dose (mg/m <sup>2</sup> )	
Median	360
Range	225–550

Blood pressure was measured twice on both arms in supine position in a quiet room after a minimal rest period of 10 min and compared with age- and sex matched controls (40 males, 12 females; median age 40 years, range 26–55). Criteria for hypertension were systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg and/or treatment with antihypertensiva.

Echocardiography was performed by a single skilled technician on a General Electric VIVID 7 system with a 2.5 MHz probe and consisted of two-dimensional echocardiography, colour flow mapping and 2D-guided M-mode, blood pool and tissue Doppler echocardiography [16]. Systolic function was measured by shortening fraction (SF) and wall motion score index (WMSI). Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD) and end-diastolic left ventricular posterior wall thickness (LVPWed) were measured on M-mode recordings obtained in the standard left ventricular parasternal long axis view. SF was calculated with the formula:  $(LVEDD-LVESD)/LVEDD \times 100\%$ . A SF  $< 29\%$  was considered abnormal. The normal range for LVEDD is 36–54 mm, for LVESD 23–40 mm and for LVPWed 7–11 mm.

For the regional analysis of left ventricle systolic function, the left ventricle was divided into 16 segments. Each segment was visually scored between 0 and 4 (1 = normokinesia; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia). WMSI was derived by adding the scores assigned to each segment and dividing the total score with the number of analysed segments. WMSI of 1.00 was considered normal and to correlate with a left ventricular ejection fraction  $> 60\%$ . WMSI  $> 1.50$  indicates a significant systolic dysfunction.

Diastolic function measurements included mitral valve inflow velocities in early (E) and late (A) diastole and diastolic tissue velocity at the mitral valve annulus [Tissue Velocity Imaging of early diastole (TVI Et)]. E/A ratio  $< 1.00$  was considered abnormal and may represent diastolic dysfunction. A mean TVI Et  $< 8.0$  cm/s was considered diastolic dysfunction [17].

A standard 12-lead ECG was recorded and analysed by a single observer for flattened T-waves, pathological Q-waves or a prolonged QTc. T-waves were characterised as abnormal flattened if three or more precordial leads and three or more standard leads had an amplitude less than  $+2$  or  $-2$  mm. In males QTc  $> 0.44$  s was considered abnormal and in females QTc  $> 0.46$  s.

The 24-h ambulatory ECG was analysed on a GE Marquette Holter system by an experienced Holteranalyst. All Holters were analysed for rhythm and conduction disturbances. Ventricular arrhythmias were classified according to the Lown's criteria [18]. Lown 4 or higher was considered abnormal.

For analysis of HRV, data were transformed to a PC and custom made software (COHWIN) was used to analyse HRV [19]. Both time domain, as well as frequency domain parameters, were calculated in accordance with the recommendations for analysis of HRV [20]. For frequency domain parameters 5 min segments were used. Segments containing more than 10% ectopics as well as non-stationary segments were excluded from the analysis. We determined the spectral power over three frequency regions of interest: LF, low frequency power (0.04–0.15 Hz); HF, high frequency power (0.15–0.4 Hz); and TP, total power (0.01–1.00 Hz). In particular the parameters rMSSD (root mean square of successive difference) and HF reflect parasympathetic activity. HRV is heart rate- and, therefore, gender- and age-dependent [19]. Therefore, we compared all measurements with sex- and age-matched controls, recruited from a group of 419 healthy subjects, who were investigated previously [19]. For comparison of HRV parameters measured in 1997 and 2004, we used two separate control groups. The first control group was matched with the age of the survivors in 1997 and the second control group with the age of the survivors in 2004. Furthermore, the HRV parameters measured in 1997 were reanalysed by the same software used in 2004 and compared with the HRV measurements in 2004.

### statistical analysis

Statistical analyses were performed in SPSS inc. version 12 by the non-parametric Mann–Whitney, Friedman, Wilcoxon's and chi-square tests. Because of the small sample size and the non-Gaussian distribution of the different parameters non-parametric tests were used. Data were reported as median (range). Two-sided *P* values  $\leq 0.05$  were considered significant.

## results

### clinical parameters

One patient complained of dyspnoea on effort. She had medication for left ventricular dysfunction (ACE inhibitor, Captopril®), which was initiated 7 years earlier at 17 years post-treatment. None of the other patients had cardiac symptoms.

### blood pressure

Eight out of 22 patients (36%) had hypertension: five had systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg and three were on antihypertensive medication. Hypertension was equally frequent in controls [14/52 (27%)]. Systolic blood pressure was 121 (range 102–178) mmHg versus 126 (range 96–150) mmHg in controls (not significant, NS). Diastolic blood pressure was 80 (range 70–120) mmHg versus 80 (range 59–106) mmHg in controls (NS).

### echocardiography

The results of echocardiography are summarised in Tables 2 and 3. Six out of 22 patients (27%) had decreased SF, compared with two out of 22 in 1997 (*P* = 0.015). All six patients with decreased SF also had an abnormal WMSI: four of six had a diffuse wall motion abnormality and two of six had a regional wall motion abnormality. One of these six patients was already known with left ventricular dilatation and systolic dysfunction diagnosed earlier. In the other five patients, systolic dysfunction was a novel finding.

Ten of 22 patients had abnormal E/A ratio compared with four of 22 in 1997 (*P* = 0.02). Median E/A ratio decreased significantly (1.05 in 2004 versus 1.31 in 1997, *P*  $< 0.001$ ). TVI Et

**Table 2.** Cardiac dysfunction and hypertension in long-term survivors of a malignant bone tumour ( $n = 22$ )

Patient	Sex	Age	Systolic dysfunction (SF <29%)			Diastolic dysfunction (E/A <1.00 and/or TVI Et <8.0 cm/s)			Hypertension in 2004
			1992 <sup>a</sup>	1997 <sup>a</sup>	2004	1997 E/A <sup>a</sup>	2004 E/A	2004 TVI Et	
1	M	56	—	—	—	+	+	+	—
2	M	39	—	—	—	—	+	—	—
3	F	37	—	—	—	—	—	—	—
4	M	44	—	—	+	+	+	+	+
5	F	42	—	—	—	—	—	—	—
6	M	42	+	—	—	—	—	—	—
7	F	48	+	+	+	—	+	+	+
8	M	58	—	—	—	—	—	+	—
9	M	38	—	—	—	—	+	+	—
10	M	47	—	—	—	—	+	—	—
11	M	33	+	—	—	—	—	—	—
12	M	39	—	—	—	—	—	+	—
13	M	44	—	—	+	+	+	+	+
14	M	30	—	—	—	—	—	—	—
15	F	59	—	+	+	+	+	+	—
16	M	38	+	—	—	—	—	—	—
17	M	37	—	—	—	—	—	—	+
18	M	42	—	—	—	—	—	—	+
19	M	27	—	—	+	—	—	+	—
20	M	34	—	—	—	—	+	+	—
21	F	30	—	—	—	—	—	—	—
22	M	36	—	—	+	—	+	+	+
Total			4	2	6	4	10	11	6

M, male; F, female; E, peak early phase velocity; A, peak atrial phase velocity; TVI Et, tissue velocity imaging; SF, shortening fractioning; +, yes; —, no.

<sup>a</sup>Data from earlier studies [12, 15].

**Table 3.** Summary of the cardiac abnormalities in six patients with systolic dysfunction

Patient	Sex	Age in 2004 (years)	FU (years)	Cumulative	SF (%)	WMSI	Local or diffuse WMA	E/A	Abnormal Q-waves at ECG?
1	M	44	17	300	23.2	1.25	Local	0.77	Yes
2	F	48	21	240	24.5	1.68	Diffuse	0.74	Yes
3	M	44	26	550	25.0	1.13	Diffuse	0.53	Yes
4	F	59	25	360	26.4	2.00	Diffuse	0.70	No
5	M	27	18	360	28.8	1.12	Local	1.15	No
6	M	36	19	450	25.9	1.81	Diffuse	0.61	No

M, male; F, female; FUP, follow-up period; SF, shortening fractioning; WMSI, wall motion score index; WMA, wall motion abnormality; E, peak early phase velocity; A, peak atrial phase velocity; ECG, electrocardiograph.

(not measured in the earlier studies) was abnormal in 11/22 patients (50%). Taking E/A ratio as well as TVI Et into account, 13/22 patients (59%) had diastolic dysfunction (E/A ratio <1.00 and/or TVI Et <8.0 cm/s), including all six patients with systolic dysfunction (Table 2).

Median LVEDD was 49.5 (range 41–56) mm versus 52 (43–58) mm in 1997 ( $P = 0.007$ ). Median LVESD was 33 (23–43) mm versus 35 (31–41) mm in 1997 ( $P = 0.004$ ). Median LVPWed was 9 (6–12) mm versus 8 (7–10) in 1997 ( $P = 0.02$ ). LVEDD was enlarged in two of 22 patients and LVESD was enlarged in one of 22 patients. LVPWed was abnormally thick in two of 22 patients and too thin in one of 22 patients.

We found no correlation between SF, WMSI or E/A ratio and cumulative dose of doxorubicin, age at diagnosis, current age or follow-up.

### ECG

Twelve-lead ECG was performed in 21 of the 22 patients. One patient had a prolonged QTc (0.46 s), although his previous ECG recordings were normal. Four of the 21 patients had abnormal Q-waves: three of them also had systolic dysfunction measured as SF <29% (Table 3). Nine of 21 patients (43%) had T-wave flattening versus five of 22 in 1997 ( $P = 0.003$ ).

In the current study 21/22 patients received 24-h ECG. One patient, who was already known with ventricular couplets

(Lown 4) and non-sustained supraventricular tachycardia (SVT), refused the registration. Median heart rate of the 21 patients was 85 (62–99)/min. One patient, who was already known with second-degree Wenckebach atrio-ventricular (AV) block at night, had a third-degree AV-block at night at the current 24-h ECG. Five of 21 patients had sporadic (less than 100/24 h) premature ventricular contractions (PVCs) (Lown 1), seven of 21 had multiform PVCs (Lown 3) and one of 21 had ventricular couplets (Lown 4). None of the patients showed (non-) sustained (supra) ventricular tachycardia [18].

HRV was evaluable in 19/22 patients. HRV results were compared with age-matched controls and also with the individual earlier HRV analysis of 1997. Compared with age-matched controls, patients showed lower values of HRV parameters, except for LF/HF and LFNU (normalised unit of LF). LnTP (natural logarithm of TP) was significantly lower in patients compared with controls ( $P = 0.041$ ). Therefore, HRV measurements indicate sympathetic dominance in the patient group. Almost all HRV parameters decreased compared with the measurements in 1997, some of them significantly. Low frequency parameters, as LF/HF and LFNU, increased (Figure 1–2).

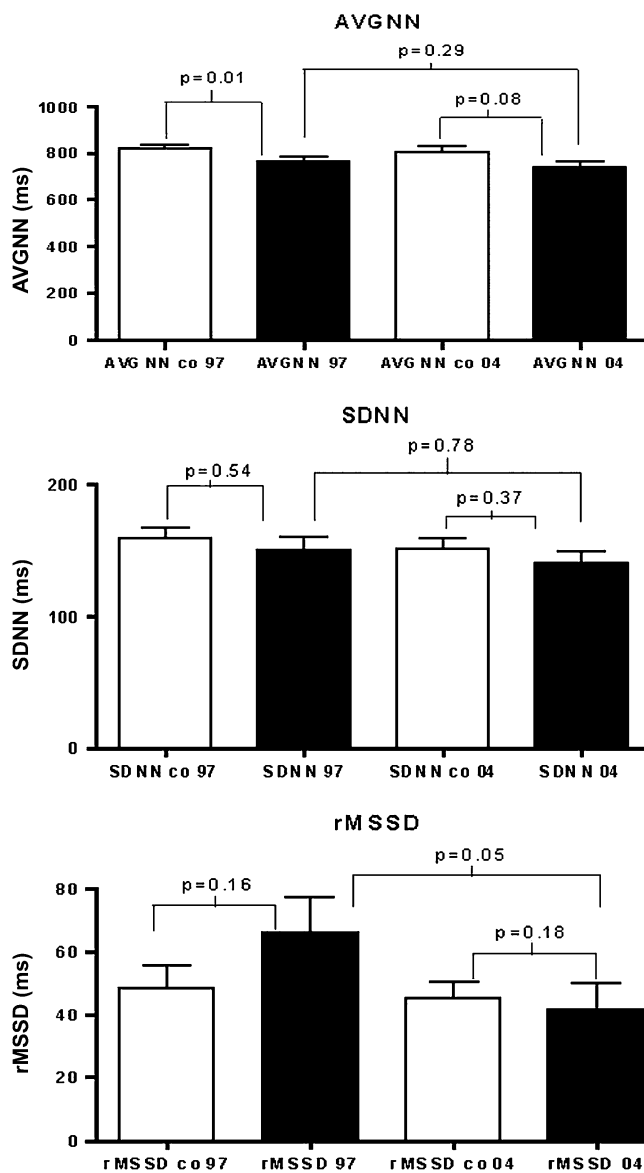
## discussion

In this longitudinal study we found progressive impairment of systolic and diastolic function and of HRV in doxorubicin-treated bone tumour survivors after a very long follow-up period (up to 27 years). Forty-five per cent of the 22 long-term survivors (median age 39 years) had diastolic dysfunction and 27% had systolic dysfunction. Furthermore, three of the nine patients who did not participate in the current evaluation were already known with cardiac dysfunction.

Although in our previous study systolic dysfunction, measured as SF, did not progressively decrease in 9–14 years follow-up, the number of patients with abnormal SF increased significantly in this extended follow-up study. All six patients with impaired SF at the current assessment also had an elevated WMSI. Four of them had diffuse wall motion abnormalities and two had regional wall motion abnormalities, suggesting ischaemic heart disease (confirmed in one of them by positron emission tomography).

The results of longitudinal echocardiography in moderate term anthracycline-treated cancer survivors have been somewhat conflicting: some studies showing ongoing progression of abnormalities, others showing no further deterioration [3–6, 11]. Lipshultz et al. [6] showed a significantly depressed SF shortly after doxorubicin therapy, improvement 6 years post-treatment, but progressive impairment of SF 12 years post-treatment. This is in accordance with the results of our study, as we also found unchanged SF at moderate term follow-up and subsequently a further decrease. However, compared with other studies including that of Lipshultz et al., our follow-up was considerably longer: 22 years compared with about 13 years in most other studies [3–6, 11].

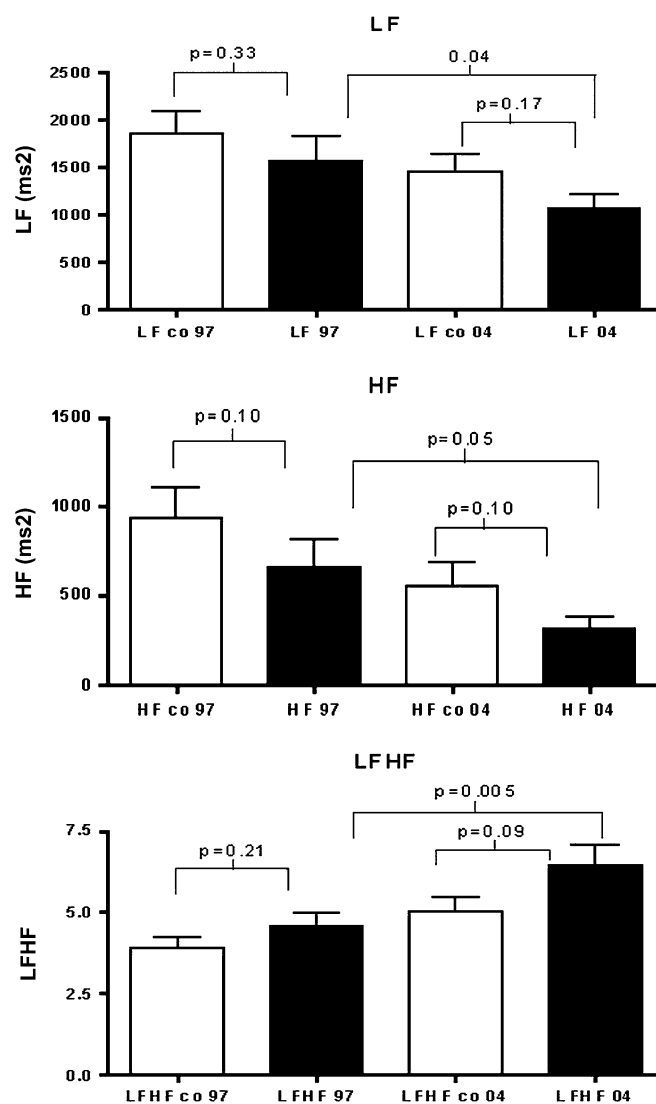
Although the median dimensions decreased significantly compared with earlier measurements, LVEDD and LVESD remained within normal limits. This is in accordance with the results of Lipshultz et al. [6], who found normal left ventricular



**Figure 1.** Time domain parameters. AVGNN, average of all NN-intervals (ms); SDNN, standard deviation of all NN-intervals (ms); rMSSD, root mean square of successive difference (ms); Co, controls; 97, Holter analysis in 1997; 04, Holter analysis in 2004; statistical analyses by non-parametric tests (Wilcoxon's test for paired comparison between parameters measured in patients in 1997 and in 2004 and Mann-Whitney's test for comparison parameters measured in patients and in controls),  $P$  value  $\leq 0.05$ , statistical significant; use of two different control groups, sex- and age-matched with the age of the survivors in 1997 and 2004.

dimensions after cessation of therapy and no further deterioration up to 12 years post-treatment.

At 22 years follow-up we found impairment of diastolic function, measured as E/A ratio, in 45% of the patients. This is in contrast with the findings of Bossi et al., who found no diastolic dysfunction in childhood cancer survivors treated with 214 mg/m<sup>2</sup> doxorubicin and/or daunorubicin [7]. However, our patients received a much higher dose of doxorubicin (median cumulative dose 360 versus 214 mg/m<sup>2</sup> in Bossi's study) and our follow-up was much longer (22 versus 7 years). Therefore our



**Figure 2.** Frequency domain parameters. LF, low frequency power ( $\text{ms}^2$ ); HF, high frequency power ( $\text{ms}^2$ ); LFHF, LF/HF. Co, controls; 97, Holter analysis in 1997; 04, Holter analysis in 2004; statistical analyses by non-parametric tests (Wilcoxon's test for paired comparison between parameters measured in patients in 1997 and in 2004 and Mann-Whitney's test for comparison parameters measured in patients and in controls),  $P$  value  $\leq 0.05$ , statistical significant; use of two different control groups, sex- and age-matched with the age of the survivors in 1997 and 2004.

results suggest that the prevalence of diastolic dysfunction increases with a longer follow-up period. Dorup et al. [21] stated that diastolic dysfunction cannot be described by one index only, but depends on an interaction between several parameters. An interesting new parameter to detect diastolic function is TVI Et, because it is independent of left ventricular filling (load independent) [16, 21]. As far as we know, our study is the first cardiac study in long-term cancer survivors that used TVI Et for measurement of diastolic function. If we consider TVI Et as a parameter of diastolic function, the number of patients with diastolic dysfunction in our study group is even higher (13/22; 59%).

We found no relation between cardiac abnormalities and cumulative dose of doxorubicin, probably because all patients had moderate or high doses of doxorubicin (range 225–550  $\text{mg}/\text{m}^2$ ) and no patient had been treated with lower doses of doxorubicin.

Compared with an age-matched control group, all HRV variables pointed in the same direction: a shift towards sympathetic domination (Figure 1–2). Compared with age-matched controls, none of the HRV variables measured in 2004 showed a statistical difference with the accessory age-matched control group. On the other hand, comparing HRV variables measured in 2004 with variables measured in 1997, a statistical decrease in frequency domain parameters was found (Figure 2). Part of the decrease in HRV variables can probably be explained by the age-related decrease of HRV [19]. A cause for the non-significance for several of the HRV parameters could be the small sample of patients ( $n = 22$ ). Our findings, for example a decreased HRV in combination with diastolic and systolic dysfunction at echocardiography, are in accordance with those of other authors, who found heart failure (either clinical or subclinical) to be associated with a decrease in HRV [22–24].

Our study has some limitations. First, the small number of patients may have compromised statistical evaluation. Secondly, patients reported no cardiac symptoms, but this was not confirmed by exercise tests. Finally, the results of the current study are not completely comparable with those of the previous ones. In the current study we used WMSI and TVI Et to determine cardiac function. These techniques are superior to those used in the previous studies, but were not available at that time.

In conclusion, longitudinal assessment of cardiac function in anthracycline-treated survivors of a malignant bone tumour showed a high rate of systolic and diastolic dysfunction (27% and 45%, respectively). Moreover, cardiac dysfunction was progressive in 9–22 years follow-up. Our results suggest that after treatment with anthracyclines there is an ongoing deterioration of cardiac function and no extinction is anticipated. Therefore, anthracycline-treated cancer survivors are considered for life-long cardiac surveillance.

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