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Chemotherapy for testicular cancer induces acute alterations in diastolic heart function

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Background: After treatment with cisplatin-based chemotherapy for testicular cancer (TC), patients have higher prevalence of cardiovascular complications after long-term follow up. Little is known about acute cardiovascular effects of cisplatin-based chemotherapy. The aim of this study was to explore acute effects of chemotherapy on cardiac function in patients treated for TC.

Methods: Fourteen TC patients (age 34.6 ± 12.3 years) were studied before and 3 months after start with cisplatin-based chemotherapy. Cardiac function was assessed with magnetic resonance imaging. Fasting glucose and insulin levels were measured and insulin sensitivity, reflected by the quantitative insulin sensitivity index (Quicki index), was calculated.

Results: Left ventricular (LV) end-diastolic volume and LV stroke volume (SV) significantly decreased from 192 ± 27 to 175 ± 26 ml ($P<0.05$) and 109 ± 18 to 95 ± 16 ml ($P<0.05$), respectively. The ratio of early and atrial filling velocities across the mitral valve, a parameter of diastolic heart function, decreased after chemotherapy from 1.87 ± 0.43 to 1.64 ± 0.45 ($P<0.01$). Metabolic parameters were unfavourably changed, reflected by a decreased Quicki index, which reduced from 0.39 ± 0.05 to 0.36 ± 0.05 ($P<0.05$).

Conclusion: Chemotherapy for TC induces acute alterations in diastolic heart function, paralleled by unfavourable metabolic changes. Therefore, early after chemotherapy, metabolic treatment may be indicated to possibly reduce long-term cardiovascular complications.

Testicular cancer (TC) is the most frequent form of cancer in young men. The prognosis of TC is good, with high cure rates since the introduction of treatment with cisplatin-based chemotherapy (International Germ Cell Consensus Classification, 1997; Einhorn, 1997). Because of the increasing number of survivors with a long life expectancy, understanding and prevention of short-term and long-term cardiovascular effects of chemotoxicity is very important.

Treatment of TC with cisplatin, bleomycin and etoposide (BEP) combination chemotherapy is associated with acute vascular toxicity and subacute changes in cardiac function (Stefenelli *et al*, 1988; Altena *et al*, 2009), as well as with long-term cardiovascular disease (Bajraktari *et al*, 2006; Battiprolu *et al*, 2010). Previous studies showed that cisplatin and bleomycin induce alterations in endothelial function and endothelial damage *in vitro* (Montiel *et al*, 2009; Nuver *et al*, 2010). These findings suggest direct toxic effects of chemotherapy on the cardiovascular system. Little is known about acute effects of cisplatin-based chemotherapy on cardiac function. More insight in the pathophysiology of the direct toxic effects of cisplatin-based chemotherapy on the cardiac function and vessel wall is relevant to possibly prevent long-term cardiovascular disease. One previous study reported subacute deterioration of diastolic function, assessed with echocardiography 10 months after cisplatin-based chemotherapy (Altena *et al*, 2009).

Indirect effects of chemotherapy also seem to have a role in the increased risk of cardiovascular complications. For example, early

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after treatment with cisplatin-based chemotherapy changes in serum lipids have been described (Raghavan *et al*, 1992). In addition, higher incidences of hypercholesterolaemia, hypertension, microalbuminuria, obesity, elevated insulin-glucose ratio and thereby metabolic syndrome have been reported at least 3 years after chemotherapy (Battiprolu *et al*, 2010; Dinh *et al*, 2010; Devaraj *et al*, 2011). The acute effects of chemotherapy, defined as effects occurring 3 months after start of chemotherapy, on these risk factors are largely unknown. The aforementioned indirect risk factors are all independently associated with a higher risk of cardiovascular disease and may contribute to the overall increased risk of cardiovascular complications after treatment with cisplatin-based chemotherapy. The increased risk of cardiovascular disease in cured TC patients after cisplatin-based chemotherapy is probably a combination of direct and indirect effects of chemotherapy (Einhorn, 1997; Devaraj *et al*, 2011). Early changes in cardiac function and risk factors may have prognostic value for long-term development of cardiovascular complications (Altena *et al*, 2011). Magnetic resonance (MR) imaging is a highly reproducible imaging modality to assess cardiac function. Furthermore, myocardial triglyceride (TG) content can be measured with proton (^{1}H)MR spectroscopy (van der Meer *et al*, 2007). In addition, abdominal visceral and subcutaneous fat volume can be accurately assessed with MRI (Rijzewijk *et al*, 2008). Therefore, the purpose of this study was to investigate acute changes in cardiac function and myocardial TG, in relation to body fat distribution and metabolic parameters 3 months after start with chemotherapy for TC, assessed with MR-techniques.

MATERIALS AND METHODS

This study was approved by the local medical ethics committee, and all subjects gave written informed consent. Metastatic TC patients, scheduled for first-line curative cisplatin-based combination chemotherapy in the Leiden University Medical Center were included between 2007 and 2009. Exclusion criteria were comorbidities, including cardiovascular disease and diabetes mellitus.

Patients received three or four cycles of standard BEP-chemotherapy repeated every 3 weeks. Each cycle consisted of intravenously administered etoposide ($100\,mg\,m^{-2}$ over 1 h, days 1–5), cisplatin ($20\,mg\,m^{-2}$ over 4 h, days 1–5) and bleomycin (30 IUSP over 30 min) at days 2, 8 and 15. According to Dutch oncological guidelines, TC patients with good prognosis were treated with three cycles of BEP and patients with intermediate prognosis were treated with four cycles BEP. One patient, in addition received paclitaxel ($175\,mg\,m^{-2}$) on day 1 of each of his four chemotherapy cycles as part of a randomized phase III study comparing paclitaxel BEP and standard BEP in patients with intermediate prognosis TC. All patients were orchidectomised before adjuvant chemotherapeutic treatment.

Body mass index was determined at baseline and after chemotherapy. Fasting serum glucose, insulin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and TGs were determined. Insulin resistance was assessed with the quantitative insulin sensitivity index (Quicki index), which is calculated using the formula: $1/(\log(\text{fasting insulin } \mu U\,ml^{-1}) + \log(\text{fasting glucose } mg\,dl^{-1}))$ (Katz *et al*, 2000). Renal function defined as estimated glomerular filtration rate was calculated with the Modification of Diet in Renal Disease (MDRD) equation: $186 \times (\text{serum creatinine } \mu mol\,l^{-1}/88.4)^{-1.154} \times (\text{age})^{-0.203}$.

Patients underwent MRI before start and shortly after the last chemotherapy cycle, which was approximately 3 months after start of chemotherapy.

Blood pressure and heart rate were measured during MRI using a semiautomated sphygmomanometer (Dinamap, Critikon, Tampa, FL, USA).

We have included part of a study group from a previous study, describing metabolic changes and MRI assessment of hepatic TG content, aortic pulse wave velocity and abdominal fat mass in TC patients undergoing curative chemotherapy at 3 and 9 months after start of chemotherapy (submitted).

Magnetic resonance imaging protocol

Left and right ventricular function. Cardiac imaging was performed using a 1.5 Tesla whole-body MRI scanner (Gyroscan ACS-NT15; Philips Medical Systems, Best, The Netherlands) after a night fast. The heart was imaged in short-axis orientation, using electrocardiographically gated breath-hold cine steady-state free-precession sequences as previously described (Lamb *et al*, 1996). Imaging parameters were: repetition time (TR) 3.4 ms, echo time (TE) 1.7 ms, flip angle (FA) 35°, field of view (FOV) 400×320 mm, slice thickness 10 mm, no slice gap was used. To assess LV and RV systolic function, endocardial contours were manually drawn, using MASS software (Medis, Leiden, The Netherlands). Left ventricular and RV ejection fraction (EF), SV, end-diastolic volume (EDV) and end-systolic volume were assessed. Epicardial contours of the LV were drawn to calculate LV end-diastolic mass.

To assess LV and RV diastolic function, the flow across mitral and tricuspid valve was measured using an electrocardiographically gated gradient echo sequence with velocity-encoding. Scan parameters were: TR = 9.1 ms, TE = 1.0 ms, FA = 20°, slice thickness = 8 mm, FOV = 350 mm^2 and matrix = 256×256 pixels. Flow velocities in early diastole (E) and at atrial contraction (A) were measured and peak flow ratio was calculated (E/A ratio) using FLOW software (Medis). The downslope of the early filling phase (E deceleration peak) and LV filling pressures (E/Ea) were calculated (Pattynama *et al*, 1993; Paelinck *et al*, 2005)

Myocardial TG content. Myocardial ^{1}H-MR spectra were obtained as described before (van der Meer *et al*, 2007). A voxel was positioned in the myocardial interventricular septum in end-systole. ECG triggering and respiratory pencil beam navigator were used during acquisition. Spectra with water suppression were acquired with TE = 26 ms and TR $\geqslant$ 3000 ms. A total of 1024 data points were collected using a 1000 Hz spectral width and averaged over 128 acquisitions. Spectra without water suppression with TR = 10 s and four averages were obtained without changing other parameters. Spectroscopic data were fitted using validated software (jMRUI version 2.2, Leuven, Belgium; Naressi *et al*, 2001). Myocardial TG content was calculated as (amplitude of TG signal/amplitude water signal) $\times$ 100%.

Pericardial fat. Pericardial fat was quantified as described previously using electrocardiographically gated breath-holds with balanced turbo-field echo MR sequence (Jonker *et al*, 2010). Imaging parameters were: TR = 3.2 ms, TE = 1.60 ms, FA = 50°, slice thickness = 10 mm and FOV = 400 mm^2. The four-chamber view was analysed, with the plane of respiratory mitral and tricuspid valves as margins. To quantify periventricular fat volume, contours around pericardial fat were drawn manually at end-systole and multiplied by the thickness of the slice. We used MASS for postprocessing.

Visceral and subcutaneous fat. Visceral and subcutaneous fat volumes were imaged using a turbo spin echo imaging sequence (Rijzewijk *et al*, 2008). During one breath-hold, three consecutive transversal slices of 10 mm thickness were scanned at the fifth

lumbar vertebrae. Imaging parameters were: TR = 168 ms, TE = 11 ms and FA = 90°. Contours were drawn around visceral and subcutaneous abdominal fat depots using MASS. Visceral and subcutaneous fat areas of each slice were multiplied by the slice thickness to acquire a volume, the volumes of all three slices were summed.

Statistical analysis. Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). We used two-tailed paired *t*-tests to compare the two study time points, as all data were normally distributed. To determine which significantly changed parameters influenced the differences of the other cardiac parameters, univariate regression analyses were performed. In these regression analyses, the delta of the significantly changed parameter (the difference of the parameter before and after chemotherapy) was the independent variable and the delta of the cardiac parameter of interest was the dependent variable. In case of a significant influence, the corrected difference between baseline and follow-up was extracted from the regression analysis. A *P*-value of <0.05 was considered statistically significant. Data are expressed as mean ± s.d.

RESULTS

Forty consecutive patients were asked to participate. Twenty-one patients could not participate, based on logistic reasons ($N=5$), refusal or non-eligibility ($N=16$). These patients had unwillingness to undergo frequent blood drawings during chemotherapy or MRI. Nineteen patients underwent baseline MRI. Five patients missed the follow-up MRI due to treatment-related sickness ($N=2$), study withdrawal ($N=2$) and treatment-related death ($N=1$). Accordingly, 14 patients were included in data analysis of the present study. Three HDL concentration and one insulin concentration were missing.

Table 1 shows the tumour characteristics and staging. Table 2 shows the patient characteristics at baseline and after chemotherapy. Average age was 34.6 ± 12.3 years. Average time between the two MRI scans was 2.6 ± 0.5 months. Time between the last day of chemotherapy and the MRI after chemotherapy was 18 ± 18 days. Weight, BMI and blood pressure did not change during follow-up. Heart rate increased significantly from 64 ± 9 to 76 ± 15 b.p.m. ($P=0.007$). Laboratory parameters at baseline and at follow-up are described in Table 2. The Quicki index decreased, from 0.39 ± 0.05 to 0.36 ± 0.05 ($P=0.018$), reflecting greater insulin resistance.

Left and right ventricular function. Owing to technical difficulties, two diastolic LV and RV scans and one systolic RV were missing. Left ventricular EDV and SV significantly decreased, respectively, from 192 ± 27 to 175 ± 26 ml ($P=0.012$) and from 109 ± 18 to 95 ± 16 ml ($P=0.025$) (Table 3). Although LV EDV and SV were significantly influenced by the increased heart rate, the difference between baseline and follow-up remained significant

Table 1. Tumour and staging characteristics of the patients

Histology; *n* (%)	
Seminoma	4 (28.6)
Non-seminoma	2 (14.3)
Combined tumour	8 (57.1)
TNM tumour staging; *n* (%)	
Stage II (para-aortic lymph node metastasis)	7 (50)
Stage III (distant metastasis)	7 (50)

Table 2. Patient characteristics at baseline and after chemotherapy

	Baseline	After chemotherapy
Systolic blood pressure (mmHg)	123 ± 17	118 ± 11
Diastolic blood pressure (mmHg)	73 ± 11	70 ± 12
Heart rate (b.p.m.)	64 ± 9	76 ± 15†
Weight (kg)	83.3 ± 15.5	84.5 ± 18.5
Body mass index (kg m^{-2})	24.4 ± 4.0	24.7 ± 4.6
Cholesterol (mmol l^{-1})	4.7 ± 1.3	5.5 ± 1.5†
Estimated GFR (MDRD), ml min^{-1}	102 ± 16	113 ± 18†
HDL (mmol l^{-1})	1.30 ± 0.31	1.36 ± 0.25
LDL (mmol l^{-1})	3.12 ± 1.15	3.74 ± 1.41*
Triglycerides (mmol l^{-1})	1.16 ± 0.60	1.64 ± 1.11
Fasting glucose (mmol l^{-1})	5.1 ± 0.5	5.2 ± 0.6
Insulin (mU l^{-1})	6.2 ± 5.0	9.8 ± 6.8
Quicki index	0.39 ± 0.05	0.36 ± 0.05*

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; MDRD = Modification of Diet in Renal Disease; Quicki index = quantitative insulin sensitivity index. *$P<0.05$. †$P<0.01$. Data are mean ± s.d.

Table 3. Parameters of myocardial function, assessed with MRI at baseline and after chemotherapy

	Baseline	After chemotherapy
Left ventricle		
Systolic function		
EDV (ml)	192 ± 27	175 ± 26*
ESV (ml)	84 ± 16	80 ± 14
SV (ml)	109 ± 18	95 ± 16*
CO (ml min^{-1})	6816 ± 1112	7050 ± 1160
EF (%)	56.6 ± 5.3	54.3 ± 5.1
Diastolic function		
E peak filling rate (ml s^{-1})	657 ± 119	662 ± 122
E deceleration (ml s^{-2} × 10^{-3})	6.3 ± 2.2	6.0 ± 1.7
A-peak filling rate (ml s^{-1})	362 ± 78	425 ± 111*
E/A-peak ratio	1.87 ± 0.43	1.64 ± 0.45†
E/Ea	6.8 ± 2.0	6.8 ± 2.0
Right ventricle		
Systolic function		
EDV (ml)	210 ± 32	196 ± 38*
ESV (ml)	105 ± 29	103 ± 25
SV (ml)	105 ± 14	93 ± 16*
CO (ml min^{-1})	6595 ± 927	6976 ± 851
EF (%)	49.9 ± 6.7	47.9 ± 4.6
Diastolic function		
E peak filling rate (ml s^{-1})	415 ± 55	406 ± 60
E deceleration (ml s^{-2}x10^{-3})	3.7 ± 1.9	3.0 ± 1.2
A-peak filling rate (ml s^{-1})	311 ± 57	325 ± 100
E/A-peak ratio	1.37 ± 0.25	1.32 ± 0.31

Abbreviations: A = atrial diastolic wave; CO = cardiac output; E = early diastolic wave; E/Ea = estimated left ventricular filling pressure; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; MRI = magnetic resonance imaging; SV = stroke volume. *$P<0.05$, †$P<0.01$. Data are mean ± s.d.

after correction for heart rate. The other systolic LV parameters did not change after chemotherapy (Table 3).

Left ventricular E/A ratio decreased significantly after chemotherapy from 1.87 ± 0.43 to 1.64 ± 0.45 ($P = 0.009$). In addition, the atrial peak filling rate increased significantly after chemotherapy. The LV E/A ratio and the atrial peak filling rate were not significantly influenced by the increased heart rate, thus correction for heart rate was not required. Other LV diastolic function parameters did not change after chemotherapy.

Right ventricular EDV and SV decreased significantly from 210 ± 32 to 196 ± 32 ml and from 105 ± 14 ($P = 0.011$) to 93 ± 16 ($P = 0.038$), respectively. Both parameters were influenced by the increased heart rate. After the correction for heart rate, the difference between baseline and follow-up remained statistically significant. All other RV parameters, systolic or diastolic, remained unchanged after chemotherapy (Table 3).

Fat distribution

Myocardial TG content. Baseline and follow-up data from eight myocardial ^{1}H-MR spectra were present. Myocardial TG content did not significantly change after chemotherapy. At baseline TG content was 0.69 ± 0.41%, after chemotherapy 0.74 ± 0.35% ($P = 0.742$).

Pericardial fat. Pericardial fat volume did not change significantly after chemotherapy, 27.0 ± 3.9 ml at baseline and 28.1 ± 5.5 ml early after chemotherapy ($P = 0.343$).

Visceral and subcutaneous fat. One waist fat MRI scan was missing. Visceral fat volume increased significantly from 186 ± 125 to 227 ± 162 ml ($P = 0.039$), whereas subcutaneous fat volume did not change. The visceral/subcutaneous fat ratio did significantly increase from 0.38 ± 0.11 to 0.42 ± 0.12 ($P = 0.025$).

DISCUSSION

The main finding of this study is that LV diastolic function is decreased 3 months after start of cisplatin-based chemotherapy for TC. Decreased diastolic function was accompanied by an unfavourable change in metabolic profile as measured by increased serum LDL and total cholesterol and decreased insulin sensitivity. In addition, visceral fat volume and visceral/subcutaneous fat ratio increased. Several studies reported increased cardiovascular risk factors, increased incidence of cardiovascular disease and diminished cardiac function as long-term complications years after treatment with cisplatin-based chemotherapy (Meinardi *et al*, 2000; Huddart *et al*, 2003; Nuver *et al*, 2005a; Haugnes *et al*, 2010; Altena *et al*, 2011). Only few studies report on the subacute cardiovascular effects of cisplatin-based chemotherapy (Nuver *et al*, 2005b; Altena *et al*, 2009; Nuver *et al*, 2010). To the best of our knowledge, we are the first to investigate the acute effects of chemotherapy on cardiac function. Altena *et al* (2009) showed deterioration of diastolic heart function assessed with echocardiography ~10 months after chemotherapy. In contrast, we assessed cardiac function immediately after completion of chemotherapy.

In the present study, the LV E/A ratio decreased, reflecting deterioration in diastolic LV function. As the E/A ratio is load dependent and thus influenced by the filling status of the patient, an estimation of LV filling pressure was determined (E/Ea) (Paelinck *et al*, 2005), which did not change after chemotherapy. Therefore, the decreased E/A ratio after chemotherapy presumably reflects disturbed intrinsic relaxation of the LV, rather than change in LV filling pressure. A previous study showed progressive deterioration of diastolic heart function, 10 months and 6.9 years after cisplatin-based chemotherapy (Haas de *et al*, 2013). Therefore, acute changes in diastolic function observed in the present study might be of prognostic clinical significance. Long-term follow-up data of our patient group would be interesting to have some information of the predictive value of these early cardiac changes. Left ventricular EF (LVEF), an important parameter of systolic function, did not change. Change in the LV diastolic function with preserved LVEF after treatment with cisplatin-based chemotherapy is in line with previous studies (Nuver *et al*, 2005a; Altena *et al*, 2009; Altena *et al*, 2011). It is known that diastolic dysfunction precedes a decline in systolic function and can be regarded as an important prognostic marker of ongoing disease (Naressi *et al*, 2001; Nuver *et al*, 2010). For future studies, it would be interesting to combine echocardiography with cardiac MRI, as previous studies suggest that early impairment of systolic function may also be detected using strain echocardiography and that it could be predictive of subsequent reduction in LVEF (Monsuez, 2012). Furthermore, in further studies biomarkers such as N-terminal pro-brain natriuretic peptide and troponin I could be determined, because determination of these biomarkers may be useful in the evaluation of early cardiac toxicity (Monsuez, 2012).

Cisplatin can directly injure cardiomyocytes through oxidative stress and mitochondrial damage (Nuver *et al*, 2004). In addition, cisplatin and bleomycin cause decreased endothelial cell survival and induce apoptosis of endothelial cells *in vitro* (Nuver *et al*, 2010). These endothelial changes may promote inflammation and atherosclerosis, which can contribute to chemotherapy-induced vascular toxicity. In addition, endothelial cells at the endocardium have an obligatory role in maintaining cardiac function (Brutsaert, 2003). Cisplatin-based chemotherapy may also indirectly lead to cardiovascular disease, via increased prevalence of cardiovascular risk factors (de Haas *et al*, 2010; Haugnes *et al*, 2010). Increased prevalence of cardiovascular risk factors, such as dyslipidemia, central obesity and insulin resistance, can lead to accelerated atherosclerosis (Nuver *et al*, 2004). In this study, the follow-up time is presumably too short for these indirect effects of chemotherapy to contribute to impaired cardiac function. We could not establish a direct relationship between cardiac function and metabolic profile. However, already 3 months after start of chemotherapy, we identify a shift to an unfavourable metabolic profile: visceral fat volume, visceral/subcutaneous fat ratio, low-density lipoprotein-cholesterol and total cholesterol were increased and insulin sensitivity decreased. Visceral fat is more deleterious than subcutaneous fat and is associated with the metabolic syndrome and cardiovascular disease (Despres and Lemieux, 2006; Mathieu *et al*, 2008; de Haas *et al*, 2010). The metabolic syndrome consists of a cluster of risk factors: dyslipidemia, hypertension, central obesity and insulin resistance. This syndrome is associated with a long-term increased risk for atherosclerotic disease (Alberti *et al*, 2006; de Haas *et al*, 2010), with cardiovascular disease as one of the major complications. Via insulin resistance and the concomitant increased release of adipokines such as resistin, the metabolic syndrome is associated with endothelial dysfunction (Verma *et al*, 2003). High C-reactive protein (CRP) levels are associated with the metabolic syndrome and endothelial dysfunction (Devaraj *et al*, 2011). In this study we did not measure CRP levels unfortunately, but in subsequent studies these levels should be measured. A recent study showed that the metabolic syndrome is more prevalent and develops at earlier age in TC survivors, treated with cisplatin-based chemotherapy (Haas de *et al*, 2013). Visceral adipose tissue contributes to insulin resistance (Mathieu *et al*, 2008), which is associated with decreased cardiac function (Battiprolu *et al*, 2010; Rijzewijk *et al*, 2009; Voulgari *et al*, 2010), even in the absence of diabetes mellitus (Bajraktari *et al*, 2006; Dinh *et al*, 2010). In the metabolic syndrome, insulin resistance and (visceral) adiposity is correlated with myocardial TG accumulation, which might negatively influence cardiac function (Kankaanpaa *et al*, 2006;

Hammer *et al*, 2008). In this study, we did not find a difference between myocardial TG content before and after chemotherapy. The number of measurements of myocardial TG ($N = 8$) content is probably too small to draw firm conclusions regarding myocardial TG changes early after chemotherapy. Another explanation could be that the follow-up period is too short, so the oxidative capacity of the myocardium is still sufficient, preventing storage of TG in the myocardium.

Diastolic cardiac function progressively deteriorates in TC survivors treated with cisplatin-based chemotherapy (Altena *et al*, 2011). Subclinical changes in cardiac diastolic function may therefore precede late clinical dysfunction. If these early changes are predictive for later abnormalities in cardiac function, such changes may be used to monitor patients more specifically. Furthermore, patients treated with cisplatin-based chemotherapy are at increased risk of developing an unfavourable cardiovascular risk profile, which can contribute to development of long-term cardiac failure. Accordingly, early detection of risk factors for cardiovascular disease is important, as treatment of the unfavourable metabolic changes with lifestyle intervention or medication can contribute to an improved long-term prognosis in patients treated with cisplatin-based chemotherapy.

In conclusion, treatment with cisplatin-based chemotherapy for TC induces acute alterations in diastolic cardiac function, paralleled by unfavourable metabolic changes. Although the predictive significance of the diastolic cardiac changes for long-term cardiovascular morbidity is not clear at present, it seems plausible that they may eventually lead to overt cardiovascular disease. As the detrimental metabolic changes can contribute to the development of cardiovascular disease, these risk factors should be monitored and treated if necessary.

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