ORIGINAL RESEARCH ARTICLE

The impact of cisplatinum-based chemotherapy on ventricular function and cardiovascular risk factors in female survivors after malignant germ cell cancer

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Abstract

Aims Among male cancer survivors, cisplatinum-based chemotherapy (CBCT) is associated with impaired left ventricle (LV) diastolic function, increased risk of metabolic syndrome, and increased cardiovascular morbidity and mortality. Comparable data in females are limited. The long-term effects of cisplatin on right ventricle (RV) function are unknown in both genders. We aimed to investigate the impact of CBCT on cardiovascular risk factors and cardiac function in female survivors after malignant ovarian germ cell tumour (MOGCT).

Methods and results This national cross-sectional follow-up study recruited MOGCT survivors, diagnosed from 1980–09 ($n = 153$). Seventy-four (48%) participated in out-patient visit, of whom 41 had received CBCT (62% of all CBCT): median age, 35 years (range, 18–64 years); median time since CBCT, 14 years (range, 5–31 years). Participants were categorized into high-CBCT ($n = 19$) and low-CBCT ($n = 22$) groups and compared with age-matched healthy females. All participants underwent laboratory tests and echocardiography to determine cardiac function. Compared with low-CBCT participants, the high-CBCT group showed significantly impaired RV function, as evaluated by tricuspid annular plane systolic excursion (22.6 ± 2.4 mm vs. 26.3 ± 3.6 mm; $P < 0.001$); RV S' (10.7 ± 1.9 cm/s vs. 12.4 ± 2.3 cm/s; $P = 0.01$); RV global longitudinal strain ($-23.4 \pm 2.4\%$ vs. $-25.7 \pm 3.7\%$; $P = 0.02$), and tricuspid annular displacement (21 ± 2 mm vs. 24 ± 3 mm; $P = 0.001$). LV diastolic function was impaired in the high-CBCT group compared with controls. Patients and controls exhibited similar metabolic syndrome prevalences.

Conclusions Among long-term survivors of MOGCT, CBCT was associated with impaired RV function and LV diastolic function. Unlike men, women do not appear to have an elevated risk of metabolic syndrome after CBCT.

Introduction

Cisplatinum-based chemotherapy (CBCT) is curative for the overwhelming majority of patients with germ cell malignancies, even in cases with metastases at diagnosis.[1–4] As this cancer most often affects young adults, research has increasingly focused on the long-term effects of cisplatinum-based treatment. Such effects have been most thoroughly investigated in testicular cancer (TC) survivors, with data showing that these patients have increased risks of metabolic syndrome[5,6] and cardiovascular morbidity[7–9] and mortality.[10]

Additionally, cardiovascular dysfunction, evaluated based on left ventricle (LV) diastolic dysfunction, has been demonstrated as early as one year after CBCT[11] as well as at long-term follow-up.[12]

However, little is known about the cardiovascular effects of CBCT in women treated for malignant ovarian germ cell tumours (MOGCT). The lack of data is probably related to the low incidence of this malignancy (0.5 cases per 100 000 womenyears).[13] A 2004 report by de Vos *et al.*[14] indicated that MOGCT survivors who had been treated with CBCT had increased risks of cardiovascular morbidity and metabolic

syndrome. However, their study included only 17 MOGCT survivors, underscoring the need for additional research within this field.

To our knowledge, no study has performed a comprehensive echocardiographic assessment of cardiac function with the aim of investigating the impact of CBCT in female survivors. Consequently, it remains unclear whether the impaired LV diastolic function observed in males also occurs in females. Furthermore, the long-term effects of CBCT on right ventricle (RV) function have not been described in either female or male patients.

In 2013–14, our group performed a cross-sectional national survey of MOGCT survivors. Here, we report our findings related to cardiovascular function and risk factors observed among the surveyed CBCT-treated MOGCT survivors. We anticipated that this explorative study in women would confirm previous findings and extend the current knowledge through additional echocardiographic observations.

Patients and methods

Patient population

Eligibility criteria for the survey were as follows: treatment for MOGCT between 1 January 1980 and 31 December 2009, alive and living in Norway as of June 2012, aged >18 years at survey, and a continuously disease free period of 3 years. Patients were identified in the Cancer Registry of Norway after a review of the histopathology reports confirming a diagnosis of MOGCT. All eligible women were invited to complete a questionnaire and attend an outpatient consultation at Oslo University Hospital, performed between March 2013 and March 2014 including blood sampling and a comprehensive echocardiographic examination. The study complies with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics. Written informed consent was obtained from all study participants.

Treatment

All eligible patients received their MOGCT treatment at one of the four main university hospitals in Norway (Oslo, Bergen, Trondheim, and Tromsoe). Surgery was the initial treatment in all cases, and we categorized surgery as fertility sparing or radical. If possible, young patients (<40 years at diagnosis) underwent fertility sparing surgery. Depending on disease extent, patients received three or four cycles of standard CVB (cisplatinum, vinblastine, bleomycin), BEP (bleomycin, etoposide, cisplatinum), or EP (etoposide, cisplatinum), with cisplatin 20/m^2 administered daily during 5-day cycles every 3rd week.[15] The total cumulative doses of cisplatinum and

bleomycin for each patient were calculated. Based on the median cumulative cisplatinum dose, the patients were stratified into a low-CBCT group and a high-CBCT group.

Study outcomes

Pre-defined outcomes included echocardiographic differences in LV diastolic function, LV systolic function, LV morphology, and RV function between patients and controls. We also assessed the prevalence of components of metabolic syndrome, hypertension, obesity, hypercholesterolemia, and diabetes mellitus.

Echocardiography

After a minimum of 5 min of rest, patients were examined in the left lateral decubitus position, using parasternal and apical projections as recommended.[16] Ultrasound recordings were obtained using digital high-end echocardiographic scanners (Vivid e9; GE Vingmed Ultrasound, Norway). At least three consecutive cineloops were stored for off-line analysis using dedicated software (Echopac version 112; GE).

LV mass (LVM) was calculated according to the Devereux formula[17] and indexed to body surface area (BSA) giving LVMI. Left ventricular ejection fraction (LVEF) was calculated using Simpson's modified biplane rule.[18] LV diastolic parameters were recorded as recommended.[19] Two-dimensional speckle tracking echocardiography was performed in the three standard apical image planes, and global longitudinal strain (GLS) was measured to assess myocardial function in a 16-segment model of the LV.[20] RV GLS was obtained from a dedicated view of the RV in apical four-chamber view. RV function was measured from a focused view of the RV, with measurements performed as recommended.[21] We defined an indication of pulmonary hypertension as maximum tricuspidal regurgitation pressure >30 mmHg obtained by Doppler echocardiography. All data analysis was performed by the same investigator (K. M.) blinded to the patient's treatment status.

Laboratory parameters, blood pressure measurements and comorbidities

Following an overnight fast, blood samples were drawn at 8 a.m. and prior to the echocardiographic examination. Samples were used to measure levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, glycated haemoglobin (HbA1c), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatinine, haemoglobin, and estradiol (<0.09 nmol/L was defined as low).

Metabolic syndrome was defined according to the 2005 guidelines of the American Heart Association/National Heart, Lung, and Blood Institute.[22] Hypercholesterolemia was defined as LDL ≥ 3.6 mmol/L or the use of lipid-lowering agents. Diabetes mellitus was defined as HbA1c ≥ 6.5%, or fasting glucose ≥ 7.0 mmol/L, or the use of antidiabetic medication. In the high-CBCT group, one patient was diagnosed with diabetes mellitus prior to onset of MOGCT and excluded from analyses of HbA1c and glucose. After a minimum of 5-min rest, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the supine position using a Dinamap monitor (GE Medical Systems, USA). At least three consistent measurements were averaged and reported. Hypertension was defined as blood pressure > 140/90 mmHg or the use of antihypertensive agents. Renal dysfunction was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m.[2]

Control group

As a reference population for both echocardiographic parameters and laboratory measurements, 37 age-matched women without known hypertension or diabetes mellitus were randomly recruited from the general Norwegian Population Register.

Statistical analysis

Data are presented as mean ± SD, median (minimum, maximum), or number (%). Patient characteristics and laboratory parameters were compared using independent Student's *t*-tests, and one-way analysis of variance with appropriate post-hoc testing (least significant difference) was used to compare patients with controls. The chi-square test or Fisher's exact tests were used to compare categorical variables. Echocardiographic parameters were compared between the two cisplatin groups and the healthy controls using analysis of variance. The assumption of normality was not violated for echocardiographic parameters or laboratory measurements. Linear regression analysis was used to assess the differences in tricuspid annular plane systolic excursion (TAPSE) among patients, and we tested for factors (age, smoking, body mass index, systolic blood pressure, hypercholesterolemia, kidney function) with a known potential to influence on RV systolic function (by TAPSE) as well as cancer related factors (doses of cisplatinum and bleomycin and time since cancer diagnosis). Factors that were significantly associated or trended towards an association ($P < 0.15$) with TAPSE by univariate regression analysis were included in a multivariable regression model to identify the main predictors of differences in TAPSE. As a surrogate for LV end-diastolic pressure, we controlled for the ratio (E/e') of early transmitral velocity

by pulsed Doppler (E) and the mean of the peak early diastolic velocity (e') at the lateral and septal mitral annulus in the multivariable model. We assessed the intraobserver variability of parameters of LV and RV function by repeated analyses (K. M.) of echocardiograms from 20 randomly selected patients. The repeated analyses were performed with an interval of at least 1 week. The intraobserver variability is presented as intraclass correlation (ICC) with 95% CI. All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

Results

In total, 74 MOGCT survivors (48% of all eligible) consented to participate and met to an outpatient examination, in which 41 had received CBCT (62% of eligible CBCT survivors) (*Figure 1*). More participants received adjuvant chemotherapy compared with non-participants (*Figure 1*); otherwise, age at survey and time since MOGCT-diagnosis did not differ. The median cumulative cisplatinum dose received among participants were 540 mg/m², range 450–1050 mg/m², and 22 MOGCT survivors were categorized into a low-CBCT group with 19 women belonging to the high-CBCT group.

Besides increased blood pressures and bleomycin doses trended higher in high CBCT group, other patient demographics, clinical data, and laboratory measurements did not differ between patients (*Table 1*). In total, four patients used antihypertensive medication (two in low-CBCT group and two in high-CBCT group) and one patient in the high-CBCT group used statin. A subnormal level of estradiol was found in five patients (three in low-CBCT group and two in high-CBCT group).

Echocardiographic parameters

Table 2 presents the echocardiographic results. RV function significantly differed between the high-CBCT group and both the low-CBCT group and the healthy controls, but not between low-CBCT patients and controls. Compared with the low-CBCT group, the high-CBCT group showed significant reductions of most parameters of RV systolic function: TAPSE (*Figure 2*), mean reduction of 14%; tissue Doppler derived tricuspidal lateral annular displacement, mean reduction of 13%; tissue Doppler derived tricuspidal lateral annular peak systolic velocity (RV S'), mean reduction of 14%; and RV GLS, mean reduction of 9%. This phenomenon was observed to an even larger extent when comparing high-CBCT patients with the healthy controls (*Table 2*). Neither patient was observed with truly abnormal RV function nor pulmonary hypertension.

Figure 1 Flow chart of recruitment of eligible survivors after malignant ovarian germ cell tumour (MOGCT) in Norway. CBCT, cisplatinum-based chemotherapy.
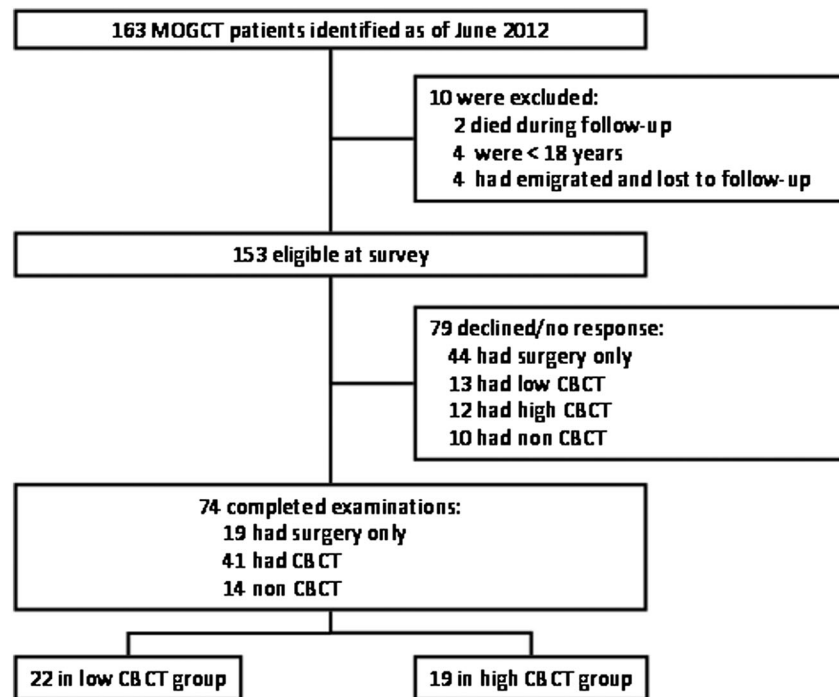
Univariate regression analysis showed that TAPSE was significantly associated with LV myocardial contraction by GLS ($P = 0.03$) and cumulative cisplatinum dose ($P = 0.004$) and trended towards an association with current smoking ($P = 0.08$). These factors were included in a multivariable linear regression model adjusted for E/e', and only cumulative cisplatinum dose remained significantly associated with TAPSE ($P = 0.01$).

Compared with healthy controls, the high-CBCT group showed impaired LV diastolic function, based on observations of higher late mitral peak flow velocity (MV A), increased left atrium area, and a reduced lateral mitral annular diastolic peak early velocity (e' lateral). Correspondingly, the E/e' ratio (a marker of LV filling pressures) was higher in the high-CBCT group.

Furthermore, compared with healthy controls, the high-CBCT group showed significantly greater thickness of the interventricular septum wall and the LV posterior wall. Correspondingly, the high-CBCT survivors had a 12.7% higher LV mass index than controls ($P = 0.01$). Parameters of LV morphology did not differ between the patient groups.

Analysis of LV systolic function did not reveal any differences in LVEF, LV GLS, mitral annular peak systolic velocities (S'), and mitral annulus displacements between the patient groups and the healthy controls

Comorbidities and laboratory measurements

None of the patients had renal dysfunction or known cardiovascular disease. Metabolic syndrome was highly comparable between patients (14.6%) and controls (13.5%) ($P = 0.89$). Furthermore, the frequency of hypercholesterolemia and obesity were equal between patients and controls (*Table 1*). Levels of cholesterol, glucose, HbA1c, and NT-ProBNP did not significantly differ between the two patient groups and the controls (*Table 1*).

Intraobserver variability

Expressed as ICC (95% CI), TAPSE, RV GLS, RV FAC, LVEF, LV GLS, and E/e'-ratio had an intraobserver variability of 0.96 (0.92–0.99), 0.97 (0.92–0.99), 0.87 (0.72–0.95), 0.94 (0.87–0.97), 0.95 (0.90–0.98), and 0.94 (0.86–0.98) (all $P < 0.001$), respectively.

Discussion

The most interesting finding from the present long-term follow-up study of female cisplatinum-treated MOGCT

Table 1 Patient characteristics, clinical data and laboratory measurements

Variable	High CBCT (n = 19)	Low CBCT (n = 22)	Controls (n = 37)	P-value
Age (years)	37 ± 9	37 ± 12	37 ± 4	0.82
Observation time (years)	15 (5, 31)	13 (5, 24)	—	0.16
Body mass index (kg/m^2)	24.8 ± 4.2	24.0 ± 4.2	25.2 ± 4.5	0.59
Heart rate (beats/min)	67 ± 10	64 ± 9	63 ± 10	0.37
Systolic blood pressure (mmHg)	119 ± 14	111 ± 9	113 ± 9	0.04[a]
Diastolic blood pressure (mmHg)	71 ± 9	64 ± 9	71 ± 8	0.01[b]
Comorbidities				
Metabolic syndrome[c]	4 (21%)	2 (9%)	5 (14%)	0.54
Diabetes mellitus[e]	1 (5%)	0	—	0.46
Hypertension[d]	3 (16%)	2 (9%)	—	0.65
Hypercholesterolemia[f]	3 (16%)	4 (18%)	5 (14%)	0.91
Body mass index ≥ 30 kg/m^2	3 (16%)	1 (5%)	5 (14%)	0.47
Current smokers	7 (37%)	4 (18%)	10 (27%)	0.41
Cancer related treatment				
Cumulative cisplatinum dose (mg/m^2)	700 (552, 1050)	505 (450, 540)	—	<0.001
Cumulative bleomycin dose (mg/m^2)	180 (0, 240)	165 (0, 210)	—	0.06
Fertility sparing surgery	14 (74%)	16 (73%)	—	0.95
Laboratory parameters				
Haemoglobin (g/dL)	13.6 ± 1.0	13.3 ± 1.2	—	0.35
Creatinine (μmol/L)	66 ± 10	63 ± 10	—	0.32
N-terminal pro-brain natriuretic Peptide (pmol/L)	6 ± 4	9 ± 8	6 ± 3	0.20
Estradiol (nmol/L)	0.28 ± 0.22	0.35 ± 0.23	—	0.33
Glucose (mmol/L)	5.3 ± 0.5	5.3 ± 0.8	5.4 ± 0.5	0.27
Glycated haemoglobin (%)	5.4 ± 0.4	5.3 ± 0.4	5.4 ± 0.5	0.89
Triglycerides (mmol/L)	1.1 ± 0.5	1.1 ± 0.9	0.9 ± 0.5	0.55
Total cholesterol (mmol/L)	4.7 ± 1.0	4.7 ± 1.0	4.7 ± 0.7	0.96
Low density lipoprotein (mmol/L)	2.9 ± 0.8	2.8 ± 0.9	2.8 ± 0.7	0.96
High density lipoprotein (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	1.6 ± 0.4	0.91

Data are presented as mean ± SD, n (%), or median (range) for observation time and cumulative cisplatinum and bleomycin dose. The P-values for continuous variables were derived from analysis of variance. The P-values for categorical variables were derived from the chi-square test or Fisher's exact tests.
[a]High-dose cisplatin group vs. low-dose cisplatin group.
[b]High-dose cisplatin group and controls vs. low-dose cisplatin group.
[c]American Heart Association/National Heart, Lung and Blood Institute definition from 2005.
[d]Blood pressure > 140/90 mmHg or use of antihypertensive agents.
[e]HbA1c ≥ 6.5%, fasting glucose ≥ 7.0 mmol/L, or the use of antidiabetic medication.
[f]Low density lipoprotein ≥ 3.6 mmol/L or the use of lipid lowering agents.

survivors was that the high-CBCT group exhibited impaired RV function, demonstrated across a wide range of indices of RV systolic function. To our knowledge, this observation has not been reported in studies investigating the cardiac function of testicular cancer survivors after CBCT. We also observed a cisplatinum-dose-dependent reduction in LV diastolic function, and differences in LV morphology between the high-CBCT group and healthy controls, with increased wall thicknesses and consequently higher LV mass index. LV systolic function was assessed using global and regional measures of myocardial contraction and did not differ between patients and controls. Overall, cisplatinum-treated MOGCT survivors showed a low frequency of metabolic syndrome (14.6%) and associated phenomena, such as hypertension, diabetes mellitus, obesity, and hypercholesterolemia, with rates comparable with those in healthy controls when comparisons were applicable.

Little is known about RV function in cancer survivors following CBCT. We found no previous studies with which to compare our present findings of cisplatinum-

dose-related impairment in RV systolic function. One recent publication evaluated RV function by magnetic resonance imaging 3 months after initiation of CBCT for testicular cancer and reported a minor and statistically insignificant decrease in RV ejection fraction compared with baseline values.[23] Our present multivariate regression analysis indicates that related to the cumulative dose, CBCT has an independent deleterious effect on RV function, as evaluated based on TAPSE (a well-validated measure of RV function) even after adjusting for possible confounders. Nevertheless, the significance of our observed reduction in RV function is currently unclear and presumably of subclinical importance, because RV function parameters were within normal range and no patients were found to have reduced RV function.

The pathophysiology for the observed cisplatin-related impairment of RV function remains unclear. An experimental study focusing on RV function demonstrated that RV function indices were associated with right-sided ventricular-arterial coupling rather than with RV contractility.[24] Several studies

Table 2 Echocardiographic parameters in cisplatin-treated groups of patients and in healthy controls

Variable	High CBCT (n = 19)	Low CBCT (n = 22)	Controls (n = 37)	ANOVA P-value	P-value High vs. low	P-value High vs. controls	P-value Low vs. controls
Cardiac morphology							
IVSd (mm)	7.9 ± 0.9	7.6 ± 1.1	7.1 ± 1.2	0.03	0.31	0.009	0.10
LVIDd (mm)	49.2 ± 3.0	49.2 ± 3.8	49.7 ± 3.7	0.87	—	—	—
LVPWd (mm)	7.3 ± 1.2	7.1 ± 1.0	6.4 ± 1.1	0.01	0.61	0.009	0.03
LVMI (g/m^2)	71 ± 9	68 ± 10	63 ± 13	0.03	0.48	0.01	0.07
LV diastolic function							
MV E (m/s)	0.75 ± 0.10	0.76 ± 0.15	0.70 ± 0.12	0.26	—	—	—
MV A (m/s)	0.65 ± 0.14	0.59 ± 0.15	0.52 ± 0.14	0.004	0.16	0.001	0.06
EA-ratio	1.20 ± 0.30	1.34 ± 0.31	1.45 ± 0.42	0.06	—	—	—
MV EdecT (ms)	174 ± 24	173 ± 35	183 ± 32	0.43	—	—	—
IVRT (ms)	77 ± 13	74 ± 15	76 ± 9	0.73	—	—	—
e′ lateral (cm/s)	12.4 ± 3.9	14.7 ± 3.4	14.4 ± 2.8	0.05	0.03	0.03	0.73
e′ septal (cm/s)	9.5 ± 2.6	10.5 ± 2.3	10.1 ± 1.8	0.38	—	—	—
Ee′ ratio	7.3 ± 2.0	6.1 ± 1.2	5.9 ± 1.6	0.01	0.03	0.004	0.59
LA area (cm^2)	18 ± 3	18 ± 3	15 ± 2	<0.001	0.78	<0.001	<0.001
LV systolic function							
EF biplane (%)	61 ± 4	60 ± 4	60 ± 3	0.82	—	—	—
LV GLS (%)	−21.1 ± 1.7	−21.5 ± 1.9	−22.1 ± 1.6	0.09	—	—	—
S′ lateral (cm/s)	9.6 ± 2.1	10.7 ± 2.5	10.1 ± 2.5	0.33	—	—	—
S′ septal (cm/s)	7.9 ± 1.0	7.6 ± 1.3	8.3 ± 1.4	0.17	—	—	—
Displacement lat (mm)	14.0 ± 2.3	14.8 ± 1.7	14.0 ± 2.0	0.31	—	—	—
Displacement sept (mm)	13.9 ± 1.7	14.3 ± 1.6	14.1 ± 1.6	0.73	—	—	—
RV systolic function							
TAPSE (mm)	22.6 ± 2.4	26.3 ± 3.6	25.9 ± 3.5	0.001	<0.001	<0.001	0.65
FAC (%)	43 ± 5	46 ± 6	49 ± 4	0.001	0.12	<0.001	0.03
RV S′ (cm/s)	10.7 ± 1.9	12.4 ± 2.3	12.6 ± 1.7	0.007	0.01	0.002	0.75
RV GLS (%)	−23.4 ± 2.4	−25.7 ± 3.7	−25.2 ± 2.0	0.04	0.02	0.04	0.54
RV Displacement (mm)	21 ± 2	24 ± 3	23 ± 3	0.002	0.001	0.002	0.49
Trp (mmHg)	18 ± 6	19 ± 3	17 ± 30.54	—	—	—	

ANOVA = one-way analysis of variance, appropriate comparisons between groups performed by LSD (least significant difference) post-hoc test.
CBCT, cisplatinum-based chemotherapy; EF, ejection fraction; FAC, fractional area change; GLS, global longitudinal strain; IVRT, isovolumetric relaxation time; IVSd, interventricular septum dimension in end-diastole; LVIDd, left ventricle inner dimension in end-diastole; LVPWd, left ventricle posterior wall dimension in end-diastole; LVMI, left ventricle mass index; MV E, mitral peak early flow velocity; MV A, mitral peak late flow velocity; EA ratio, MV E:MV A-ratio; MV EdecT, mitral valve early deceleration time; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; Trp, maximum tricuspidal regurgitation pressure.

Figure 2 Tricuspid annular plane systolic excursion (TAPSE in mm) in patients and controls. Representative recordings of TAPSE (mm) in patients from the high-cisplatinum-based chemotherapy group (CBCT) (left), low-CBCT (middle), and controls (right). *$P < 0.001$ compared with both other groups.
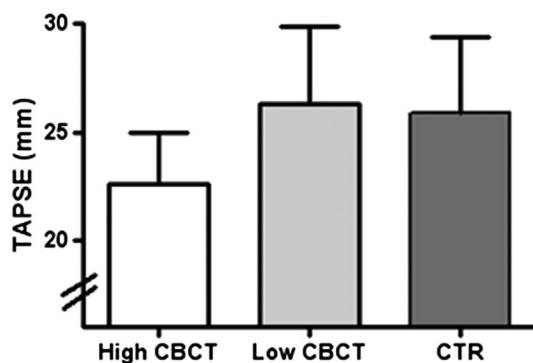
of TC survivors have reported direct vascular injury and consequent endothelial dysfunction secondary to CBCT.[25,26] Therefore, cisplatinum-induced alternation in arterial properties of the pulmonary vasculature could contribute to the impairment of RV systolic function in long-term MOGCT survivors. Bleomycin, widely used in relation to malignant germ cell tumours, has a potential for pulmonary toxicity and further development into pulmonary fibrosis, although occurring infrequently.[27] Consequently, bleomycin may have a negative effect on RV function through reduced pulmonary function. However, in a long term follow-up study in male TC-survivors, bleomycin did not lead to any impairment in pulmonary function,[28] making it less likely to explain our findings. Our observation warrants further studies investigating RV function in CBCT survivors.

Reduced LV diastolic function has been observed in several studies of male survivors after CBCT. Altena et al.[12] observed a gradual decline in LV diastolic function after cisplatinum therapy in TC survivors, and Nuver et al.[26] reported similar findings in a comparable patient group after a median 7-year follow-up. Recently, van Schinkel et al.[23] detected altered LV diastolic function as early as 3 months after CBCT initiation in TC patients. In the present study, we report similar results

among MOGCT survivors, indicating that the unfavourable effect of cisplatinum on LV diastolic function is equal across genders. Even if we observed an impaired LV diastolic function in the high-CBCT group compared with controls, the overall differences were but minor, and likely without significant clinical implications, a notion supported by the fact that NT-proBNP was normal in all patients. However, we observed a significantly higher LVMI of 12.7% in high-CBCT group, which may be related to the altered afterload conditions associated with slightly higher arterial blood pressures and altered diastolic function in these patients. Also in accordance with our present findings in women, cisplatinum treatment is not proven to impair LV systolic function in long-term TC survivors.[12]

Multiple studies have shown that TC survivors are at increased risk of developing metabolic syndrome.[6,7,29] Similar results were observed in a study of 21 women.[14] In contrast, our current sample of 41 long-term cisplatinum-treated MOGCT survivors showed lipid profiles; glucose and HbA1c levels; and the frequency of metabolic syndrome, hypercholesterolemia, and obesity that were highly comparable with those in healthy controls—indicating no increased risk of metabolic syndrome in women after CBCT. The present study used slightly different definitions of these conditions than de Vos *et al.*,[14] making direct comparison difficult. The increased prevalence of metabolic syndrome after CBCT in men is often discussed as a consequence of reduced testosterone levels.[6,29,30] Thus, the presently observed low frequency of metabolic syndrome could be related to gender differences in testosterone levels.

Male CBCT survivors show increased cardiovascular morbidity.[7,9] In females, we observed a reduction in LV diastolic function similar to that previously reported in males. Together with the impaired RV function, our findings indicate that CBCT increases cardiovascular risk in women similarly as in men. On the other hand, we did not observe an increased risk of metabolic syndrome in cisplatinum-treated MOGCT survivors. Consequently, women may have a lower risk of developing cardiovascular disease after CBCT. However, the women in our survey had a median age of less than 40 years, and longer follow-up is required to estimate their risk of clinically significant cardiovascular disease after CBCT.

Study limitations and strengths

Malignant ovarian germ cerm tumours incidence is very low and, thus, study samples are inherently small. Here, we present the largest sample of long-term MOGCT survivors to date for investigation of the long-term impact of CBCT on cardiac function in women. Additionally, our study was nationwide, and thus not affected by the potential biases of single-centre studies. Therefore, we believe these data are robust and provide a unique insight into the long-term cardiovascular effects of CBCT in women. Unfortunately, we did not have data to objectify physical condition. Such data could have highlighted the importance of our observed reduction in RV function and LV diastolic function. Echocardiographic data in the patients at the time of cancer diagnosis would have allowed us to evaluate any progression of cardiac dysfunction after CBCT, but were unfortunately not available in this study.

Conclusion

Long-term MOGCT survivors treated with high-dose CBCT showed significantly impaired RV systolic function compared with both low-CBCT patients and controls. This finding has not been previously reported and warrants further study. Additionally, LV diastolic function was reduced in these women in agreement with observations in men. In contrast to prior findings in men, the frequency of metabolic syndrome was low in female survivors and similar to controls. Therefore, the risk of cardiovascular disease may be lower in women than in men after CBCT.

Funding

Conflict of interest

The authors declare no conflict of interest.

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