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Progressive diastolic dysfunction in survivors of pediatric differentiated thyroid carcinoma

Antoinette D Reichert[1,*], Marloes Nies[1,*], Wim J E Tissing[2,3], Anneke C Muller Kobold[4], Mariëlle S Klein Hesselink[1], Adrienne H Brouwers[5], Bas Havekes[6], Marry M van den Heuvel-Eibrink[3,7], Helena J H van der Pal[8,9], John T M Plukker[10], Hanneke M van Santen[3,11], Eleonora P M Corssmit[12], Romana T Netea-Maier[13], Robin P Peeters[14], Eveline W C M van Dam[15], Johannes G M Burgerhof[16], Peter van der Meer[17], Gianni Bocca[18] and **Thera P Links[1]**

[1]Department of Endocrinology, University of Groningen, University Medical Center Groningen, Internal Medicine, Groningen, the Netherlands, [2]University of Groningen, Beatrix Children's Hospital, Paediatric Oncology, University Medical Center Groningen, Groningen, Groningen, [3]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands, [4]Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, [5]Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, [6]Division of Endocrinology, Department of Internal Medicine, Maastricht University Medical Center, Maastricht, the Netherlands, [7]Department of Pediatric Oncology, Sophia Children's Hospital, Erasmus Medical Center, Rotterdam, the Netherlands, [8]Department of Pediatric Oncology, Emma Children's Hospital, Amsterdam UMC, Amsterdam, the Netherlands, [9]Department of Medical Oncology, Academic Medical Center, Amsterdam UMC, Amsterdam, the Netherlands, [10]Department of Surgical Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, [11]Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands, [12]Leiden University Medical Center, Division of Endocrinology, Department of Internal Medicine, Leiden, the Netherlands, [13]Radboud University Medical Center, Division of Endocrinology, Department of Internal Medicine, Nijmegen, the Netherlands, [14]Erasmus Medical Center, Department of Internal Medicine and Erasmus MC Academic Center for Thyroid Disease, Rotterdam, the Netherlands, [15]Department of Endocrinology, Internal Medicine, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands, [16]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, [17]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, and [18]University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Pediatric Endocrinology, Groningen, the Netherlands

[*](A D Reichert and M Nies contributed equally to this work)

Correspondence should be addressed to T P Links
Email
t.p.links@umcg.nl

Abstract

Background: Pediatric differentiated thyroid cancer (DTC) has an excellent prognosis but unknown late effects of treatment. The initial cardiac evaluation showed subclinical diastolic dysfunction in 20% of adult survivors. The objective of this follow-up study was to determine the clinical course of this finding.

Methods: This multicenter study, conducted between 2018 and 2020, re-evaluated survivors after 5 years. The primary endpoint was echocardiographic diastolic cardiac function (depicted by the mean of the early diastolic septal and early diastolic lateral tissue velocity (e' mean)). Secondary endpoints were other echocardiographic parameters and plasma biomarkers.

Results: Follow-up evaluation was completed in 47 (71.2%) of 66 survivors who had completed their initial evaluation. Of these 47 survivors, 87.2% were women. The median age was 39.8 years (range: 18.8–60.3), and the median follow-up after the initial diagnosis was 23.4 years (range: 10.2–48.8). Between the first and second evaluation, the e' mean significantly decreased by 2.1 cm/s (S.D. 2.3 cm/s, $P < 0.001$). The median left ventricular ejection fraction did not significantly change (58.0% vs 59.0%, *P= NS*). In the best explanatory model of e' mean, multivariate linear regression analysis showed that BMI and age were significantly associated with e' mean (β coefficient: −0.169, 95% CI: −0.292; −0.047, $P = 0.008$ and β coefficient: −0.177, 95% CI: −0.240; −0.113, $P < 0.001$, respectively).

Conclusions and relevance: In these relatively young survivors of pediatric DTC, diastolic function decreased significantly during 5-year follow-up and is possibly more pronounced than in normal aging. This finding requires further follow-up to assess clinical consequences.

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Introduction

Worldwide, the incidence of pediatric differentiated thyroid carcinoma (DTC) shows a sustained increase (1). Fortunately, its prognosis is excellent, with a 15-year overall survival rate exceeding 95% (2). Treatment consisting of surgery and the administration of radioactive iodine can be followed by thyroid-stimulating hormone (TSH) suppression therapy. The aim of this therapy is to suppress the growth-promoting effect of TSH on the thyroid cells, thereby preventing the (re)growth of possible remnant malignant cells (3). However, TSH suppression therapy is associated with adverse long-term effects.

In survivors of 'adult' DTC, diastolic dysfunction and an increased risk of cardiovascular disease and cardiovascular mortality were observed in patients treated with TSH suppression therapy (4, 5). In our initial cross-sectional cardiac evaluation of long-term survivors of 'pediatric DTC, one out of five survivors had diastolic dysfunction without cardiac arrhythmias or overt systolic dysfunction (6). Compared to sex- and age-matched controls, survivors were found to have significantly worse diastolic function, but no differences between these groups were found for systolic function. The aim of this study was to assess the clinical course of this finding by re-evaluating cardiac function after 5years in these long-term survivors of pediatric DTC.

Subjects and methods

Study design and population

All 66 survivors of pediatric DTC participating in the initial evaluation were invited to complete a second evaluation. This follow-up evaluation was similar to the initial evaluation (6).

Clinical and cardiac evaluation

In short, this 5-year follow-up evaluation consisted of a physical examination (blood pressure, waist and hip circumference, heart rate, height, and body weight), fasting serum measurements (cholesterol, glucose, and N-terminal pro–B-type natriuretic peptide (NT-proBNP)), and echocardiography. For serum measurements, glucose was analyzed on a Roche cobas C system using the hexokinase-based assay. Reference values ranged from 4.4 to 5.5 mmol/L. Cholesterol was analyzed on a Roche cobas C system using an enzymatic, colorimetric method. A cholesterol value below 5.0 mmol/L was considered normal. NT-proBNP was analyzed by sandwich electrochemiluminescence immunoassay 'ECLIA' on the Roche cobas e immunoassay analyzer. An NT-proBNP level of <125.0 ng/L was considered normal. The echocardiographic evaluation involved imaging of systolic and diastolic function, left ventricle ejection fraction (LVEF), dimensions, wall thickness, tissue Doppler I, and tissue velocity imaging. Diastolic function was marked by the diastolic septal (e' septal) and lateral tissue velocity (e' lateral), and the E/A ratio. Because none of the survivors had atrial fibrillation upon first evaluation, the 24-h Holter electrocardiography was not repeated. Smoking status was obtained from a questionnaire completed by the survivor. Details regarding treatment and medical history were obtained from survivors' medical records.

Study definitions

Differences (deltas) in cardiac function between both evaluations were calculated as the value of the second evaluation minus the value from the first evaluation. Diastolic function was considered abnormal when values were less than two standard deviations (S.D.) of the mean age-adjusted reference data (7). The e' mean as marker of diastolic dysfunction was calculated by the mean of the early diastolic septal and early diastolic lateral tissue velocity.

The mean TSH level represents the area under the curve (AUC) for survivors with at least one available TSH measurement per year from diagnosis to second evaluation to obtain a representative impression of the TSH suppression. TSH values measured before radioactive iodine treatment during thyroid hormone withdrawal as well as stimulation by recombinant human TSH were excluded from analyses. If a reported value was below the relevant assay detection limit, the TSH value of the detection limit was taken for analysis.

Statistical analysis

Missing or unknown cases were listwise excluded from statistical testing. Two-sided P values <0.05 were considered statistically significant. Data are shown as the mean ± S.D., or as median and range or interquartile range (IQR). Mann–Whitney U tests were performed for non-normally distributed continuous variables. Categorical variables were compared with Fisher's exact test because conditions for chi-square tests had not been met. The deltas of some cardiovascular risk factors were

Table 1 Clinical and treatment characteristics in survivors of pediatric differentiated thyroid carcinoma. Data are presented as *n* (%) or as median (range).

Characteristics	Survivors		*P* value
	Non-participating	Participating	
n	19	47	
Sex (female)	16 (84.2%)	41 (87.2%)	0.709[a]
Age upon diagnosis, years	15.0 (7.9–18.3)	16.1 (8.7–18.9)	0.295[b]
Follow-up since diagnosis, years	-	23.4 (10.2–48.8)	n.a.
Histology			0.716[a]
Papillary	15 (78.9%)	40 (85.1%)	
Follicular	4 (21.1%)	7 (14.9%)	
Total thyroidectomy	19 (100%)	47 (100%)	n.a.
Radioiodine treatment	18 (94.7%)	45 (95.7%)	1.000[a]
Cumulative activity, GBq	4.8 (1.2–23.9)	5.8 (1.3–35.2)[c]	0.561[b]
TSH levels, mU/L			
Total follow-up period, AUC	-	0.5 (0.2–2.8)[d]	n.a.
Till first evaluation, AUC	-	0.6 (0.1–3.9)[e]	n.a.
TNM stage, *n* (%)			
T			0.301[a]
T1–T2	14 (73.7%)	27 (57.4%)	
T3–T4	2 (10.5%)	11 (23.4%)	
Tx	3 (15.8%)	9 (19.1%)	
N			0.173[a]
N0	11 (57.9%)	20 (42.6%)	
N1a–N1b	8 (42.1%)	22 (46.8) %	
Nx	0 (0%)	5 (10.6%)	
M			0.170[a]
M0	16 (84.2%)	40 (85.1%)	
M1[f]	3 (15.8%)	2 (4.3%)	
Mx	0 (0%)	5 (10.6%)	
Disease remission	-	47 (100.0%)	n.a.
Time between evaluations, years	-	5.5 (4.7–6.7)	n.a.

No significant difference ($P<0.05$) were observed.
[a] Fisher's exact test. [b] Mann–Whitney U test. [c] $n = 45$; two survivors did not receive radioiodine treatment. [d] $n = 10$, 37 survivors had incomplete TSH levels. [e] $n = 22$ survivors, 25 survivors had incomplete TSH levels. [f] All lung metastases.
TSH, thyroid-stimulating hormone; AUC, mean area under the curve; TNM, tumor node metastasis; n.a., not applicable.

not normally distributed and were therefore analyzed using the Wilcoxon signed-rank test. Categorical values with more than two categories were compared using the McNemar–Bowker test. The differences (deltas) of the echocardiographic measurements between the first and second evaluations were normally distributed and were taken into analysis using paired t-tests. A univariate linear regression analysis was performed to evaluate whether attained age, sex, smoking, diastolic blood pressure, waist circumference, BMI, or TSH were significant predictors of diastolic function (e' mean) (8). Variables significantly associated ($P < 0.1$) with diastolic function were included in a multivariate analysis. Based on reported literature, TSH and sex were added to the multivariate model (8, 9). All variables associated with e' mean were entered into a multivariate model. Thereafter, variables with the highest *P* values were removed from each subsequent model. In the multivariate models, the final model represented the best explanatory model for e' mean.

IBM SPSS Statistics (version 23.0, IBM Corp) was used for statistical analysis. The Institutional Review Board of the University Medical Center Groningen approved the study on behalf of all participating institutions (ABR NL40572.042.12, file number 2012/183) and registered in the Netherlands Trial Register (Trial NL3280). Written informed consent was obtained from all survivors.

Results

Participants

Supplemental Figure 1 shows the flowchart of inclusion for this follow-up evaluation. Of the 66 survivors who completed the first cardiac evaluation, 47 (71.2%) completed the second evaluation (10). When clinical and treatment characteristics and cardiovascular risk factors were compared between the non-participating and the participating survivors, only systolic blood pressure and

Table 2 Cardiovascular risk factors in survivors ($n = 47$) of pediatric differentiated thyroid carcinoma.

Cardiovascular risk factors	Survivors		Difference†	*P* value
	First evaluation*	Second evaluation*		
Age upon evaluation, years	34.3 (18.8–60.3)	39.8 (24.6–65.9)	5.5 (5.2 to 6.2)	n.a.
Heart rate, bpm	68.2 (43.5–93.7)	66.0 (52.7–88.8)	2.1 (−7.8 to 7.1)	0.878[a]
Body mass index, kg/m^2	24.0 (18.9–40.4)	25.6 (19.3–39.4)	1.5 (−0.1 to 2.4)	**<0.001**[a]
Overweight‡, *n* (%)	21 (44.7)	24 (51.1)		0.219[b]
Body surface area, m^2	1.8 (1.6–2.4)	1.9 (1.6–2.4)	0.0 (−0.0 to 0.1)[c]	**<0.001**[a]
Smoking[d], *n* (%)				0.317[e]
No	32 (74.4)	31 (72.1)		
Current	1 (2.3)	1 (2.3)		
Past	10 (23.3)	11 (25.6)		
NT-proBNP[f], ng/L	51.5 (7.0–225.0)	62.5 (5.0–653.0)	8.5 (−12.0 to 31.0)	**0.023**[a]
NT-proBNP ≥125 ng/L, *n* (%)	5 (10.9)	8 (17.4)		0.508[b]
Fasting glucose[g], mmol/L	4.9 (4.2–5.8)	5.3 (3.7–6.9)	0.4 (0.0 to 0.7)	**<0.001**[a]
Cholesterol, mmol/L	4.6 (3.2–7.1)	5.1 (3.8–7.6)	0.3 (−0.1 to 0.8)	**0.002**[a]
Systolic blood pressure[h], mmHg	120.0 (100.0–145.0)	121.0 (98.0–173.0)	0.1 (−5.4 to 10.9)	0.249[a]
Diastolic blood pressure[h], mmHg	77.0 (53.0–100.0)	78.0 (57.0–105.0)	1.0 (−1.5 to 5.9)	0.056[a]
Waist circumference[i], cm	83.0 (67.0–123.0)	87.0 (67.0–123.0)	1.5 (−2.5 to 7.1)	**0.044**[a]
Hip circumference[j], cm	102.0 (77.0–134.0)	104.0 (79.0–132.0)	0.5 (−2.5 to 5.0)	0.404[a]

P values in bold indicate significant difference (<0.05).
*Variables shown as median (range). Difference values between the two evaluations calculated as second evaluation minus first evaluation. †Difference values are shown as median (interquartile range); ‡BMI ≥ 25 kg/m^2; [a] Wilcoxon signed-rank test. [b] McNemar test. [c] Unrounded median difference: 0.04 (−0.01–0.08) m^2. [d] $n = 43$; four survivors excluded from analysis for inconsistent answers. [e] McNemar–Bowker test. [f] $n = 46$; blood sample too small in one participant. [g] $n = 45$; blood sample too small in one participant and non-fasting glucose in one participant. [h] $n = 44$; three survivors lacked complete physical examination. For two survivors, blood pressure at first or second evaluation measured using right arm only. This measurement was taken into analysis. [i] $n = 42$; waist circumference was not measured in four survivors; measured incorrectly in one survivor. [j] $n = 43$; hip circumference not measured in four survivors.
IQR, interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Table 3 Echocardiographic measurements of survivors ($n = 47$) of pediatric differentiated thyroid carcinoma.

Echocardiographical measurement	Survivors		Difference†	*P* value
	First evaluation*	Second evaluation*		
Dimensions and volumes				
Left ventricular end diastolic diameter, mm	47.0 (39.0–58.0)	47.0 (39.0–54.0)	−1.4 ± 3.2	**0.006**
Left ventricular mass at end diastole, g	121.0 (71.0–226.0)	124.0 (78.0–208.0)	7.2 ± 24.7	0.052
Left ventricular mass at end diastole index, g/m^2	66.2 (41.0–106.0)	65.9 (44.9–114.4)	2.5 ± 13.2	0.196
Left ventricular end systolic diameter, mm	31.0 (22.0–46.0)	30.0 (23.0–38.0)	−1.5 ± 4.4	**0.026**
Left atrial volume index[a], mL/m^2	28.1 (12.0–46.0)	28.5 (16.0–38.0)	0.5 ± 6.3	0.596
Systolic function				
Left ventricular ejection fraction, *n* (%)	58.0 (51.0–73.0)	59.0 (51.0–70.0)	1.5 ± 5.6	0.084
Diastolic function				
Early diastolic mitral valve inflow, m/s	0.8 (0.4–1.2)	0.8 (0.5–1.2)	−0.1 ± 0.1[b]	**0.009**
Late diastolic mitral valve inflow, m/s	0.5 (0.3–0.9)	0.6 (0.3–1.1)	0.0 ± 0.1[c]	0.124
Deceleration time of mitral valve early inflow, m/s	195.4 (137.8–329.4)	184.9 (76.0–337.3)	−11.4 ± 55.2	0.163
E/A ratio	1.6 (0.7–3.3)	1.4 (0.7–3.2)	−0.2 ± 0.4	**0.002**
E/e' ratio[d]	6.1 (3.7–9.5)	5.9 (2.8–9.3)	−0.3 ± 1.4	0.133
Early diastolic septal tissue velocity[d], cm/s	12.6 (5.6–19.9)	10.2 (5.1–15.7)	−2.1 ± 2.3	**<0.001**
Early diastolic lateral tissue velocity, cm/s	15.9 (6.1–24.6)	13.4 (5.8–23.3)	−1.7 ± 2.9	**<0.001**
Mean of septal and lateral early diastolic tissue velocity[d], cm/s	14.5 (6.3–20.4)	11.7 (5.5–18.2)	−1.9 ± 2.2	**<0.001**

P values in bold indicate significant difference (<0.05).
*Variables shown as median (range). Difference values between the two evaluations calculated as second evaluation minus first evaluation. †Difference values shown as mean ± S.D. and compared using paired t-tests [a]Left atrial volume index available for 40 patients. [b]Unrounded mean difference: −0.06 m/s. [c]Unrounded mean difference: 0.003 m/s. [d]$n = 46$; for one survivor, required echocardiographic image was missing.

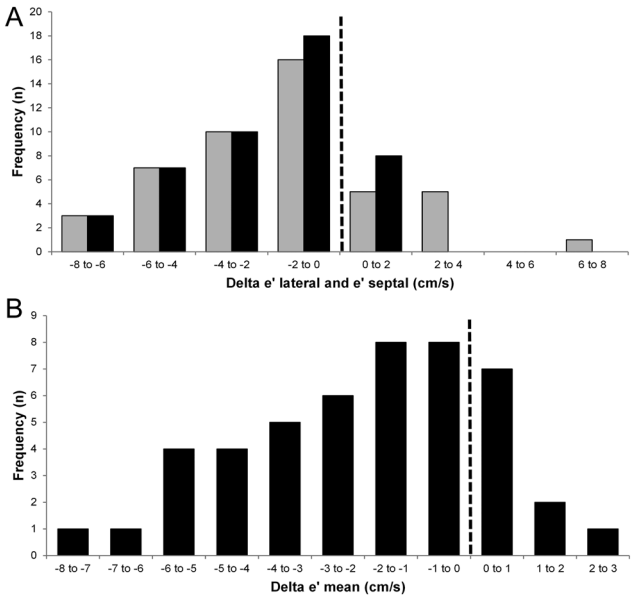

Figure 1

Difference (delta) in diastolic function in 47 survivors of childhood differentiated thyroid carcinoma over a median period of 5 years. Dashed vertical line displays difference of 0 cm/s between evaluations. Negative values indicate decrease in diastolic function. (A) Difference in early diastolic lateral (gray bars, n = 47) and septal (black bars, n = 46) tissue velocity in cm/s, plotted against frequency. (B) Difference in mean of early diastolic lateral and septal tissue velocity in cm/s (black bars, n = 46), plotted against frequency. e' lateral, early diastolic lateral tissue velocity; e' septal, early diastolic septal tissue velocity. For one survivor, there was no data regarding e' septal.

e' lateral significantly differed (114.7 vs 120.0 mmHg, respectively; P = 0.049 and 17.0 vs 15.9 cm/s, respectively; P = 0.035) (Table 1 and Supplemental Table 1) (10).

Of the 47 participating survivors, 41 were women (87.2%). Upon second evaluation, the median age of survivors was 39.8 (range: 18.8–60.3) years, and the median follow-up was 23.4 (range: 10.2–48.8) years after initial diagnosis. Additional treatment characteristics are shown in Table 1. Ten survivors (21.3%) had at least one TSH measurement per year during their total follow-up period. The median AUC for TSH levels during their total follow-up period was 0.5 mU/L.

Cardiovascular risk factors

Table 2 shows the cardiovascular risk factors during the first and second evaluations, i.e., the factors revealed by physical examination, serum measurements, and smoking status. In the median 5.5-year (range: 4.7–6.7) follow-up period, median BMI significantly increased from 24.0 to 25.6 kg/m^2 (P < 0.001), NT-proBNP levels significantly increased from 51.5 to 62.5 ng/L (8.5 ng/L (IQR: −12.0–31.0) P = 0.023), fasting glucose significantly increased from 4.9 to 5.3 mmol/L (0.4 mmol/L (IQR: 0.0–0.7) P < 0.001), and cholesterol significantly increased from 4.6 to 5.1 mmol/L (0.3 mmol/L (IQR: −0.1–0.8) P = 0.002). All other cardiovascular risk factors did not significantly differ between the two evaluations.

Echocardiography

Echocardiographic characteristics are shown in Table 3. Between the first and the second evaluation, the mean e' septal decreased by 2.1 cm/s (S.D. 2.3 cm/s, P < 0.001), the e' lateral decreased by 1.7 cm/s (S.D. 2.9 cm/s, P < 0.001), the e' mean decreased by 1.9 cm/s (S.D. 2.2 cm/s, P < 0.001), and the E/A ratio decreased by 0.2 (S.D. 0.4, P = 0.002). For e' lateral as well as e' septal, 20 survivors (42.6%) showed a decrease of 2 cm/s or more (Fig. 1). Twenty-one out of 46 survivors (45.7%) with available measurements had a decrease in e' mean of 2 cm/s or more. Figure 2 shows the individual differences in e' mean over time for each survivor. E' mean decreased in the majority of the survivors. Upon first evaluation, 21 survivors (45.7%) and 12 survivors (26.0%) scored below the −1 S.D. and −2 S.D. values compared to the derived age-adjusted reference values (7). For the second evaluation, respectively, 32 (69.6%) and 11 (23.9%) of the survivors scored below the −1 S.D. and −2 S.D.. The LVEF did not significantly change over time (58.0%, range 51–73% vs 59.0%, range 51–70%, respectively; P = 0.084) (7).

In the univariate linear regression, age upon evaluation, diastolic blood pressure, BMI, waist circumference, and cholesterol were significantly associated with e' mean (Table 4). In the best explanatory multivariate model, BMI and attained age were significantly associated with e' mean (β coefficient: −0.169, 95% CI: −0.292; −0.047, P = 0.008, and β coefficient: −0.177, 95% CI: −0.240; −0.113, P < 0.001, respectively). The median AUC of the TSH values was not significantly associated with the e' mean.

Discussion

In this longitudinal study of cardiac function in these relatively young survivors of childhood DTC, we found a deterioration of the diastolic function. The possible clinical consequences of these findings require continued follow-up since the development of diastolic dysfunction

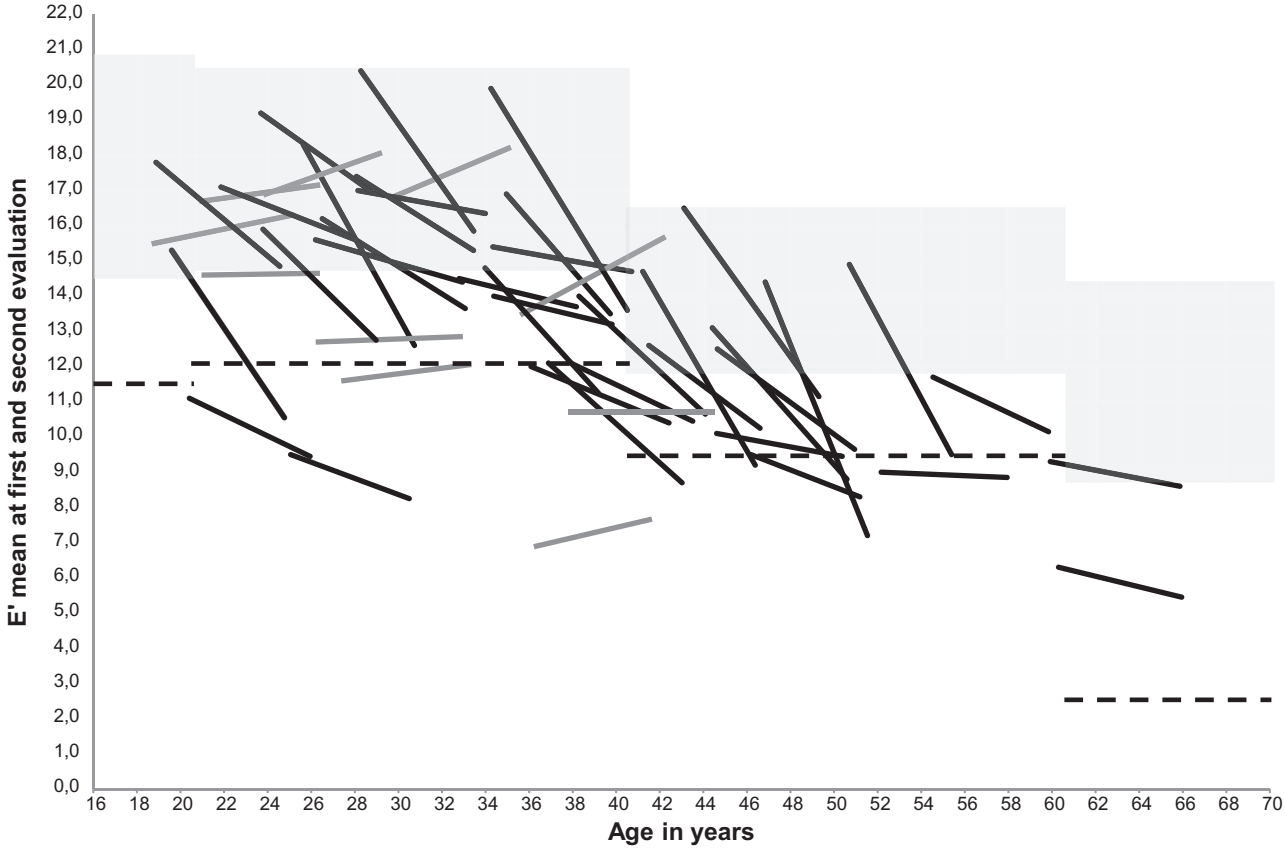

Figure 2

Difference (delta) in diastolic function in 46 survivors of childhood differentiated thyroid carcinoma, presented as the e' mean in the first and second evaluation plotted against the age in years. The black lines (n = 36) represent a decline in the e' mean between the first and second evaluation, whereas the gray lines (n = 10) represent an increase in the e' mean between the first and second evaluation. The horizontal gray bars represent the ±1 S.D. range derived from the age-adjusted reference values for e' mean (7). The striped horizontal bars represent the −2 S.D. cut-off. E' mean was unknown in one patient. e' mean, mean of early diastolic lateral and septal tissue velocity in cm/s.

is a known risk factor for heart failure and accelerated cardiac aging (8, 9, 11, 12). The LVEF did not change during the 5-year follow-up period.

This is the first study that shows long-term data on cardiac function in pediatric DTC survivors. Evaluation of long-term effects of treatment is relevant since most children will survive their disease (13, 14). Age is a significant predictor of diastolic function, and the decrease in diastolic function in the current survivors was considerably greater than would have been expected based on extrapolation of data in non-affected individuals (7, 15). Although no control group is available, the finding of an impaired diastolic function at the first cross-sectional measurement and the decrease that has been observed intra-individually over a period of 5 years may be of importance in this patient group. Compared to the age-adjusted reference values (7), deterioration of diastolic function seems to be more pronounced in survivors of pediatric DTC than in the general population: the precise clinical significance of this finding needs to be determined.

In survivors of 'adult' DTC, the prolonged subclinical hyperthyroidism – induced by TSH suppression therapy – is associated with disturbed myocardial relaxation, which can eventually result in diastolic dysfunction (4, 16) and increased risk of cardiovascular disease and mortality (17, 18, 19, 20). Strikingly, in our study, TSH levels were not associated with diastolic function. This might be due to the fact that yearly TSH measurements were only available in half of the patients, creating an incomplete representation of the applied TSH suppression therapy. This underestimation of the actual suppression is inherent to the design of this unique study. The median of the available TSH values during the total follow-up period of

Table 4 Univariate and multivariate linear regression models for diastolic function (e' mean) among 47 survivors of pediatric DTC.

Variable	*n*	Coefficient β^a (95% CI)	*P* value	R^2	Constant B
Univariate models					
Attained age, years		−0.199 (−0.264; −0.133)	**<0.001**	0.462	20.032
Sex		−1.072 (−3.917; 1.773)	0.452	0.013	12.239
TSH – till first evaluation, mU/L	22	−0.948 (−2.277; 0.381)	0.152	0.100	14.297
TSH – between evaluations, mU/L	19	0.070 (−2.023; 2.163)	0.944	0.000	12.046
Diastolic blood pressure, mmHg	44	−0.169 (−0.267; −0.070)	**0.001**	0.225	25.240
Current smoking (yes)		5.134 (−1.358; 11.626)	0.118	0.056	12.016
BMI, kg/m^2		−0.258 (−0.410; −0.106)	**0.001**	0.211	19.021
Waist circumference, mm	42	−0.109 (−0.172; −0.046)	**<0.001**	0.237	21.784
Glucose, mmol/L	45	−0.031 (−1.902; 1.840)	0.973	0.000	12.306
Cholesterol, mmol/L	45	−1.588 (−2.681; −0.495)	**0.005**	0.166	20.248
Multivariate models					
Model 1	18		**0.112**	0.588	26.060
Attained age		−0.168 (−0.315; −0.021)	**0.028**		
Diastolic blood pressure		−0.028 (−0.240; 0.184)	0.774		
BMI		−0.134 (−0.700; 0.432)	0.613		
Sex		−1.651 (−6.056; 2.754)	0.427		
TSH – till first evaluation		−0.102 (−1.714; 1.510)	0.891		
Cholesterol		−0.173 (−2.302; 1.955)	0.8861		
Waist circumference		*−0.003 (−0.227; 0.221)*	*0.978*		
Model 2	20		**0.030**	0.588	26.027
Attained age		−0.169 (−0.294; −0.043)	**0.012**		
Diastolic blood pressure		−0.029 (−0.210; 0.152)	0.739		
BMI		−0.140 (−0.423; 0.143)	0.307		
Sex		−1.657 (−5.444; 2.131)	0.364		
TSH – till first evaluation		*−0.101 (−1.488; 1.287)*	*0.879*		
Cholesterol		−0.177 (−1.997; 1.642)	0.838		
Model 3	42		**<0.001**	0.587	26.251
Attained age		−0.171 (−0.241; −0.101)	**<0.001**		
Diastolic blood pressure		−0.029 (−0.134; 0.076)	0.580		
BMI		−0.139 (−0.303; 0.026)	0.096		
Sex		−1.596 (−3.745; 0.553)	0.141		
Cholesterol		*−0.223 (−1.216; 0.771)*	*0.653*		
Model 4	42		**<0.001**	0.585	25.739
Attained age		−0.175 (−0.242; −0.107)	**<0.001**		
Diastolic blood pressure		*−0.032 (−0.135; 0.071)*	*0.537*		
BMI		−0.148 (−0.305; 0.009)	0.064		
Sex		−1.732 (−3.770; 0.307)	0.094		
Model 5	45		**<0.001**	0.580	24.294
Attained age		−0.180 (−0.242; −0.118)	**<0.001**		
BMI		−0.177 (−0.296; −0.058)	**0.004**		
Sex		*−1.805 (−3.735; 0.125)*	*0.066*		
Model 6	45		**<0.001**	0.545	23.719
Attained age		−0.177 (−0.240; −0.113)	**<0.001**		
BMI		−0.169 (−0.292; −0.047)	**0.008**		

[a] Unstandardized coefficient β.

DTC, differentiated thyroid carcinoma; TSH, thyroid-stimulating hormone. *P* values in bold represent statistically significant values. Variables in italics in multivariate models represent variable excluded in successive model.

23 years was not in the suppressed range. Hypothetically, the strict TSH suppression therapy pursued during the first years after initial treatment may have initiated the observed cardiac damage.

Especially considering the lack of specific studies evaluating the added value of TSH suppression in children (21), re-evaluating the need for TSH suppression, while bearing in mind its possible adverse effects, would be of great value. The possible cardiac damage affects the observed patients at a relatively young age, even though thyroid cancer has an excellent prognosis. These pediatric survivors are expected to have a normal life span with very low disease-specific deaths (2). More knowledge regarding both TSH suppression therapy and its adverse effects is required in order to reach a balanced conclusion regarding the harms and benefits of this treatment.

Another explanation for the observed cardiac deterioration is that diastolic dysfunction has also been described in patients with subclinical hypothyroidism (9), suggesting that profound hypothyroidism (as present in thyroid hormone withdrawal periods before the administration of radioactive iodine) may also play a role in the pathophysiology. However, this hypothesis cannot be confirmed in the current data.

Other possible explanations of the decrease in diastolic function in these survivors of childhood DTC seem less likely. We found no clinically relevant increase in cardiovascular risk factors between the two evaluations that could explain the substantial decrease in diastolic function. BMI was strongly associated with diastolic function but increased between the first and second evaluation with a median of only 1.5 kg/m^2 (representing a median gain of 4 kg), resulting in slightly overweight survivors. Therefore, we do not assume that the increase in BMI solely explains the observed decrease in the e' mean. The 50% of survivors considered to be overweight is comparable to the general population of the Netherlands ().

In addition to the decrease in diastolic function in the majority of the participants, we observed an increase in e' mean in ten participants. This increase could not be explained by a decrease in BMI; we found that the BMI increased in six participants and decreased in four patients. Unfortunately, we do not have information regarding medication possibly affecting diastolic function.

Strengths and limitations

No other cohorts of survivors of 'pediatric' DTC have been evaluated for (long-term) cardiac function. This is the first study to evaluate longitudinal cardiac function in a substantial group of survivors treated for this rare disease. The evaluation consisted of an elaborate assessment of parameters of cardiac function. Unfortunately, age- and gender-specific reference values or a control group for the decrease of diastolic function over time in non-affected individuals are lacking and comparison with time valid definitions has limited us to draw tough conclusions.

Conclusions

This study showed a significant decrease in diastolic function in survivors of pediatric DTC after a median follow-up of 23 years following diagnosis. Although the pathophysiological mechanisms and clinical consequences are yet to be assessed, this outcome requires attention since impaired diastolic function is associated with accelerated cardiac aging and the survivors included in our study had a median age of only 40 years. Further research and follow-up, including echocardiography, are needed to evaluate the diastolic function and its potential long-term consequences.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
Reichert and Nies had full access to all data used in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Reichert, Nies, Tissing, Burgerhof, Bocca, Links. Acquisition, analysis, or interpretation of data: Reichert, Nies, Tissing, Muller Kobold, Klein Hesselink, Burgerhof, van der Meer, Corssmit, Netea-Maier, Peeters, van Dam, Bocca, Links. Drafting of the manuscript: Reichert, Nies, Tissing, Bocca, Links. Critical revision of the manuscript for important intellectual content: Muller Kobold, Klein Hesselink, Brouwers, Havekes, van den Heuvel-Eibrink, van der Pal, Plukker, Ronckers, van Santen, Corssmit, Netea-Maier, Peeters, van Dam. Statistical analysis: Reichert, Nies, Burgerhof. Obtained funding: Nies, Tissing, Klein Hesselink, Bocca, Links. Administrative, technical, or material support: Reichert, Nies, Tissing, Muller Kobold, Klein Hesselink, Burgerhof, van der Meer, Corssmit, Netea-Maier, Peeters, van Dam, Bocca, Links. Study supervision: Tissing, van der Meer, Bocca, Links. Final approval of the version to be published: all authors.

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