Long-Term Quality of Life in Adult Survivors of Pediatric Differentiated Thyroid Carcinoma

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Context: Little is known about long-term quality of life (QoL) of survivors of pediatric differentiated thyroid carcinoma. Therefore, this study aimed to evaluate generic health-related QoL (HRQoL), fatigue, anxiety, and depression in these survivors compared with matched controls, and to evaluate thyroid cancer–specific HRQoL in survivors only.

Design: Survivors diagnosed between 1970 and 2013 at age ≤18 years, were included. Exclusion criteria were a follow-up <5 years, attained age <18 years, or diagnosis of DTC as a second malignant neoplasm (SMN). Controls were matched by age, sex, and socioeconomic status. Survivors and controls were asked to complete 3 questionnaires [Short-Form 36 (HRQoL), Multidimensional Fatigue Inventory 20 (fatigue), and Hospital Anxiety and Depression Scale (anxiety/depression)]. Survivors completed a thyroid cancer–specific HRQoL questionnaire.

Results: Sixty-seven survivors and 56 controls. Median age of survivors at evaluation was 34.2 years (range, 18.8 to 61.7). Median follow-up was 17.8 years (range, 5.0 to 44.7). On most QoL subscales, scores of survivors and controls did not differ significantly. However, survivors had more physical problems ($P = 0.031$), role limitations due to physical problems ($P = 0.021$), and mental fatigue ($P = 0.016$) than controls. Some thyroid cancer–specific complaints (*e.g.*, sensory complaints and chilliness) were present in survivors. Unemployment and more extensive disease or treatment characteristics were most frequently associated with worse QoL.

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Abbreviations: 131-I, radioactive iodine; DTC, differentiated thyroid carcinoma; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; MFI-20, Multidimensional Fatigue Inventory 20; QoL, quality of life; SF-36, Short-Form 36; SMN, second malignant neoplasm; THYCA-HRQoL, thyroid cancer–specific health-related quality of life; TSH, thyrotropin.

Conclusions: Overall, long-term QoL in survivors of pediatric DTC was normal. Survivors experienced mild impairment of QoL in some domains (physical problems, mental fatigue, and various thyroid cancer–specific complaints). Factors possibly affecting QoL need further exploration. (***J Clin Endocrinol Metab*** **102: 1218–1226, 2017)**

The diagnosis and treatment of childhood cancer constitute a major life event that may influence psychosocial functioning and quality of life (QoL) long after initial treatment has been completed. Pediatric differentiated thyroid carcinoma (DTC) is a rare malignancy with an excellent survival rate (1, 2). The incidence of this disease is rising (3, 4). At present there is an increased focus on the long-term consequences of this disease and its treatment. After initial treatment, which most often consists of a total thyroidectomy followed by radioactive iodine (131-I) administration, life-long follow-up is initiated (5). Moreover, about a third of the pediatric DTC survivors in The Netherlands have postoperative complications, including permanent hypoparathyroidism, which also require medical support (2). Both hypothyroidism and hypoparathyroidism have been described as negatively affecting the QoL of DTC survivors (6, 7).

The available data on QoL in survivors of pediatric DTC are limited. Most studies evaluate QoL in survivors of adolescent and adult DTC. QoL in survivors of adolescent DTC was found to be normal compared with control groups (8, 9). Survivors of adult DTC reported lower health-related QoL (HRQoL) and higher levels of fatigue, anxiety, and depression compared with healthy controls (5, 10–12). For DTC survivors, thyroid cancer–specific complaints may arise after treatment and during follow-up. Most long-term survivors of adult DTC with a median follow-up period of 9.6 years experienced disease-specific symptoms (13). In survivors of pediatric DTC, thyroid cancer–specific complaints have not yet been evaluated.

QoL studies performed in survivors of other childhood cancers showed conflicting results. QoL varied from no differences to lower QoL in survivors, compared with a control or comparison group; this may be explained by the differences in specific clinical characteristics of the different types of cancers in which this has been studied (14–20).

Several specific survivor characteristics may influence QoL during follow-up. QoL may improve in survivors of adult DTC after a longer time following diagnosis, especially $\geq$5 years after diagnosis (10, 21). Employment and a higher educational level were found to be associated with better QoL in survivors of adult DTC (12, 21, 22). Young adult survivors reported other thyroid cancer–specific complaints than did older survivors. For example, young adult survivors reported more scar complaints, but less voice complaints (22). QoL in DTC survivors seems to be independent of thyrotropin (TSH) levels (8, 10).

So far, information is limited on long-term QoL in survivors of pediatric DTC. Therefore, the first aim of our study was to evaluate QoL by means of the self-reported levels of generic HRQoL, fatigue, anxiety, and depression in adult survivors of pediatric DTC compared with those of matched controls. The second aim was to evaluate thyroid cancer–specific HRQoL in adult survivors of pediatric DTC. Our third aim was to evaluate whether long-term generic HRQoL, fatigue, anxiety, depression, and thyroid cancer–specific HRQoL were associated with survivor, tumor, treatment, or follow-up characteristics.

Materials and Methods

Survivors

Adult survivors of pediatric DTC who participated in a nationwide follow-up study were asked to participate in this substudy (2). Inclusion criteria for the nationwide study were: diagnosis of DTC between January 1970 and December 2013 at the age of $\leq$18 years, and treatment in The Netherlands [as described earlier (2)]. Exclusion criteria for this substudy were: follow-up $<$5 years after diagnosis, attained age $<$18 years, diagnosis of DTC as a second malignant neoplasm, lack of command of the Dutch language, and 131-I administration within 3 months before evaluation.

Controls

To include controls, survivors were asked to approach 1 or 2 persons of similar sex and age ($\pm$5 years of the survivor's age) at time of follow-up. The only exclusion criterion for controls was having a medical history of malignancy. Preferably, peers were included as controls, trying to match on socioeconomic status. If this was not possible, siblings were allowed to be matched controls.

Participants

All survivors and controls gave informed consent before participating in the study. The Institutional Review Board of the University Medical Center Groningen approved the study on behalf of all participating institutions.

Medical data

Data on survivor and tumor characteristics (tumor–node–metastasis classification, histology, and age at diagnosis), treatment (surgical complications, *i.e.*, hypoparathyroidism and recurrent laryngeal nerve injury, and cumulative 131-I dose), and follow-up (follow-up time; outcome, *i.e.*, remission, recurrence, or persistent disease; and level of TSH suppression during follow-up) were retrieved from medical records. Data on

marital status, job status, and level of education were retrieved from a questionnaire.

QoL assessment

Generic HRQoL, fatigue, anxiety, and depression questionnaires were assessed for survivors and controls. The thyroid cancer-specific HRQoL questionnaire was assessed for survivors only. The questionnaires delineated below were used to assess QoL.

Short-Form 36

The Short-Form 36 (SF-36) (23) is a 36-item health survey, validated for the Dutch population (24). This questionnaire measures self-reported HRQoL on 8 domains: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Scores of domains are presented on a scale from 0 to 100. A higher score indicates better HRQoL. The scores of the 8 subscales were converted into the physical and mental component scales by means of the algorithm of Ware and Kosinski (25), based on Dutch norms (24). An example of a question in the SF-36 questionnaire is, "In general, would you say your health is…." Possible answers are "poor," "fair," "good," "very good," "excellent."

Multidimensional Fatigue Inventory 20

The Multidimensional Fatigue Inventory 20 (MFI-20) (26) self-report instrument was designed to measure fatigue. Fatigue is scored on 5 domains: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. The MFI-20 was proven to be valid for the Dutch population (26). The total score, ranging from 20 to 100 (higher scores indicating more fatigue), is calculated as the sum of the 5 domains, and each domain (range, 4 to 20) is the sum of 4 items. Each domain includes 4 items on a 1- to 5-point scale ranging from "no, that is not true" to "yes, that is true." An example of an item is "thinking requires effort."

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (27) is a 14-item self-assessment scale measuring levels of depression and anxiety. This questionnaire has been validated for Dutch subjects (28). Scores on subscales range from 0 to 21. Scores for the total scale can range from 0 to 42. A higher score indicates a higher level of anxiety and/or depression. Answers can be given on a 4-point Likert scale. For example, for "I feel tense or 'wound up'," possible answers are "not at all," "from time to time, occasionally," "a lot of the time," or "most of the time."

Thyroid cancer–specific HRQoL

The thyroid cancer–specific HRQoL (THYCA-QoL) (29) questionnaire was designed to assess treatment- and cancer-specific side effects of thyroid cancer. For a time frame dealing with the previous week (except in the case of the sexual interest item, which refers to the previous 4 weeks), items can be scored on a 4-point scale ranging from 1 ("not at all") to 4 ("very much"). Items are summarized and translated into 7 scales (neuromuscular, voice, concentration, sympathetic, throat/mouth, psychological, and sensory problems) and 6 single items (problems with scar, felt chilly, tingling hands/feet, gained weight, headache, interest in sex). Scales range from 0 to 100. A higher score on this scale indicates more complaints. An example of a question in the THYCA-QoL questionnaire is "Have you had a dry mouth?"

Statistical analysis

Characteristics of survivors included in the QoL study were compared with characteristics of the excluded survivors from the nationwide study and to the eligible, but not included, survivors in the QoL study. Characteristics of survivors and controls were compared to evaluate whether controls were a good comparison group for the included survivors. Scores on HRQoL, fatigue, anxiety, and depression of survivors and matched controls were compared. Scores on thyroid cancer–specific HRQoL were analyzed using descriptive statistics. Associations between survivor, tumor, treatment, and follow-up characteristics and scores on QoL were assessed. Single items of the THYCA-QoL were dichotomized (not at all = no; a little; quite a bit; and very much = yes) before testing these associations. Comparisons were made using χ^2 tests or a Fisher's exact test (if >20% of the cells had an expected count of <5) in case of categorical variables. Mann–Whitney *U* and Kruskal–Wallis tests were performed because normality and homogeneity assumptions of dependent variables had been violated. For analyses of possible correlations between 2 variables with ordinal scales, the Spearman rank correlation coefficient was used. The TSH level for each year of follow-up was expressed as the geometric mean of the observed TSH values during that year, as published previously (30).

Missing or unknown values were excluded (listwise deletion) from analyses or, in case of the 4 questionnaires, imputed using questionnaire-specific guidelines. For SF-36 and the THYCA-QoL, scores were imputed when ≤50% values of the scores for this subscale were missing. For MFI-20 and HADS, scores were imputed when ≥2 values of the subscale were not missing. When these criteria were not met, survivors or controls were excluded from analyses of the relevant subscale. IBM SPSS Statistics for Windows version 23 (IBM, Armonk, NY) was used for statistical analyses. Differences were considered statistically significant at $P < 0.05$. To adjust for the multiple testing, a significance level of 1% ($P < 0.01$) was used for the tested associations between survivor, tumor, treatment, and follow-up characteristics and QoL.

Results

Characteristics of survivors of pediatric DTC and matched controls

Out of 105 survivors participating in the nationwide study (2), 75 survivors were eligible for this long-term QoL substudy, 67 of whom (89.3%) agreed to participate. Eight survivors eligible for the QoL study were not included (Fig. 1). As expected, survivors of the nationwide study, excluded for the QoL study, and participating survivors in the QoL study differed in age at evaluation (median 19.1 vs 34.2 years, respectively; $P < 0.001$) and follow-up duration (median 2.8 vs 17.8 years, respectively; $P < 0.001$). For all other survivor, tumor, treatment, or follow-up characteristics, survivors of the 3 groups did not differ (Supplemental Table 1).

Table 1 shows the demographic characteristics of the survivors and their matched controls. Median age of survivors at evaluation was 34.2 years (range, 18.8 to 61.7). Most survivors were female (86.6%), were married or in a relationship (64.2%), and had a paid job or were full-time students (91.0%). Tumor, treatment, and follow-up

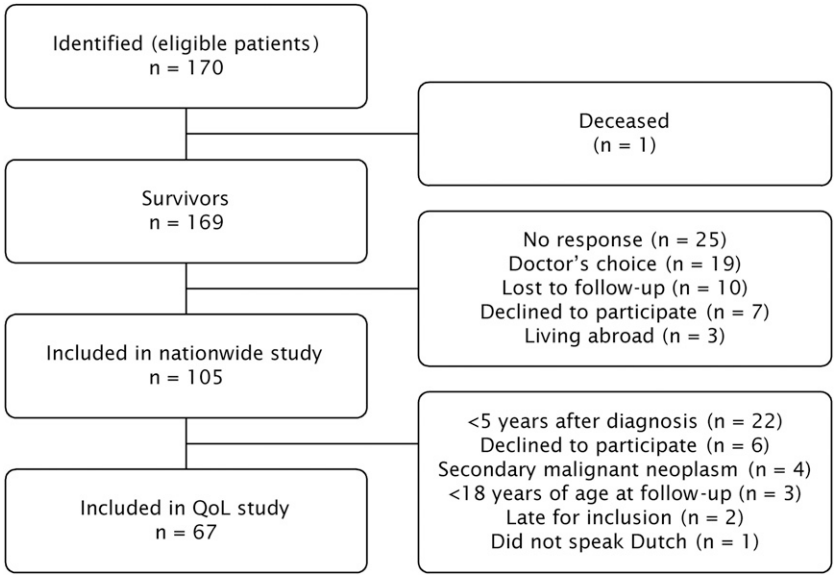

Figure 1. Flowchart of inclusion of adult survivors of pediatric DTC in the QoL study.

characteristics of survivors are shown in Supplemental Table 1. Survivors had a median follow-up time of 17.8 years (range, 5.0 to 44.7) after diagnosis. All survivors underwent a total thyroidectomy and 131-I was administered to 97.0%. Of the survivors, 82.1% remained in remission during follow-up. Ten percent had recurrence of the disease and 7% had persistent disease.

The 67 survivors gathered 59 controls. Three controls were not included because matching criteria were not met. The survivor and control groups did not differ significantly with respect to sex, age, marital status, employment/education, nationality, or completed education (Table 1). Almost 14% of the controls were siblings of the survivors.

QoL in adult survivors of pediatric DTC (vs matched controls)

Table 2 summarizes self-reported QoL measurements in survivors and controls. For the subscales of the questionnaires, survivors had significantly lower scores on physical functioning and role limitations due to physical problems as compared with controls ($P = 0.031$ and $P = 0.021$; lower scores represent worse HRQoL) [Fig. 2(A) and 2(B)]. Mental fatigue scores were significantly higher in survivors ($P = 0.012$; higher scores represent more fatigue) [Fig. 2(C)]. Scores on the remaining SF-36 and MFI-20 subscales and all HADS subscales did not differ significantly between survivors and controls. In 12 out of 15 subscales on

Table 1. Characteristics of Adult Survivors of Pediatric DTC and Matched Controls

	Survivors (n = 67)	Controls (n = 56)	*P* Value
Sex, n (%)			0.878[a]
Female	58 (86.6)	49 (87.5)	
Male	9 (13.4)	7 (12.5)	
Age at evaluation, y			0.431[b]
Median (range)	34.2 (18.8–61.7)	34.0 (19.4–60.2)	
Age at diagnosis, y			n.a.
Median (range)	15.8 (7.9–18.8)	—	
Follow up duration, y			n.a.
Median (range)	17.8 (5.0–44.7)	—	
Nationality, n (%)			n.a.
Dutch	67 (100)	56 (100)	
Marital status, n (%)			0.129[a]
Relationship	43 (64.2)	43 (76.8)	
No relationship	24 (35.8)	13 (23.2)	
Completed education, n (%)			0.128[a]
Low level	16 (23.9)	6 (10.7)	
Medium level	25 (37.3)	21 (37.5)	
High level	26 (38.8)	29 (51.8)	
Employment, n (%)			0.743[a]
Employed or full-time student	61 (91.0)	50 (89.3)	
Unemployed and no full-time student	6 (9.0)	6 (10.7)	
Relationship with survivor, n (%)			n.a.
Peer	—	48 (85.7)	
Sibling	—	8 (14.3)	

Abbreviation: n.a., not applicable.

[a] χ^2 Test.

[b] Mann–Whitney *U* test.

Table 2. QoL in Adult Survivors of Pediatric DTC and Matched Controls

Questionnaire	Survivors (n = 67)		Controls (n = 56)	*P* Value
Survivors vs controls				
SF-36, median (p25, p75)				
Physical functioning	95 (85, 100)[a]		100 (95, 100)[b]	0.031[c]
Role limitations due to physical problems	100 (75, 100)[a]		100 (100, 100)[b]	0.021[c]
Bodily pain	84 (72, 100)[a]		100 (74, 100)[d]	0.104
Social functioning	88 (63, 100)		100 (81, 100)	0.065
Mental health	84 (72, 92)[a]		84 (76, 92)	0.723
Role limitations due to emotional problems	100 (67, 100)[a]		100 (67, 100)[b]	0.711
General health perceptions	72 (57, 87)[a]		77 (67, 89)	0.231
Vitality	65 (50, 78)[a]		70 (60, 80)	0.194
Mental component summary scale	54 (41, 56)[e]		53 (47, 56)[b]	0.961
Physical component summary scale	53 (47, 57)[e]		57 (53, 59)[b]	0.024[c]
MFI-20, median (p25, p75)				
General fatigue	10 (8, 15)		9 (5, 12)	0.075
Physical fatigue	8 (5, 12)		6 (4, 10)	0.083
Reduced activity	8 (5, 11)		8 (5, 11)	0.613
Reduced motivation	6 (4, 9)		6 (4, 9)	0.879
Mental fatigue	9 (5, 15)		7 (4, 10)	0.012[c]
Total	41 (31, 57)		36 (27, 54)	0.129
HADS, median (p25, p75)				
Anxiety	4 (2, 9)		3 (2, 6)	0.317
Depression	1 (0, 4)		1 (0, 3)	0.964
Total	6 (2, 11)		4 (3, 9)	0.392
Survivors only				
THYCA-QoL scales, median (p25, p75)				
Neuromuscular	11 (0, 22)			
Voice	0 (0, 17)			
Concentration	0 (0, 17)			
Sympathetic	0 (0, 17)			
Throat/mouth	11 (0, 22)			
Psychological	8 (0, 17)			
Sensory	17 (0, 33)			
THYCA-QoL single items, n (%)	*No*	*A Little*	*Quite a Bit*	*Very Much*
Problems with scar[a]	56 (84)	8 (12)	2 (3)	0 (0)
Felt chilly	39 (58)	13 (19)	9 (13)	6 (9)
Tingling hands/feet	42 (63)	19 (28)	5 (8)	1 (2)
Gained weight	47 (70)	16 (24)	3 (5)	1 (2)
Headache	34 (51)	29 (43)	2 (3)	1 (2)
Interested in sex	8 (12)	37 (55)	21 (31)	1 (2)

For SF-36, higher scores indicate a better HRQoL; subscales range from 0 to 100. For MFI-20, higher scores indicate more fatigue; subscales range from 4 to 20; the total scale ranges from 20 to 100. For HADS, higher scores indicate higher levels of anxiety and/or depression; subscales range from 0 to 21; the total scale ranges from 0 to 42. For THYCA-QoL, a higher score indicates more symptoms; subscales range from 0 to 100.

[a] n = 66 because 1 survivor filled in the questionnaire erroneously.

[b] n = 54 because 2 controls filled in the questionnaire erroneously.

[c] $P < 0.05$. Scores on the SF-36, MFI-20, and HADS were compared using the Mann–Whitney *U* test.

[d] n = 53 because 3 controls filled in the questionnaire erroneously.

[e] n = 65 because 2 survivors filled in the questionnaire erroneously.

generic HRQoL, fatigue, anxiety, and depression, the interquartile range of scores was larger for survivors than for controls; for none of the 15 subscales was the interquartile range of scores for controls larger than that for the survivors. For the component scales, scores on the physical component scale were significantly lower in survivors compared with controls ($P = 0.024$; lower scores represent worse HRQoL). Scores of other summary scales (mental component scale, total MFI-20, and total HADS scores) did not differ significantly between survivors and controls. Scores of survivors with a second malignant neoplasm (SMN) are reported in Supplemental Table 2. Three survivors developed a SMN after DTC. Scores of QoL of the 2 women diagnosed with breast cancer were similar compared with the survivors that were not diagnosed with a SMN. For 1 woman diagnosed with a high-grade cervical intraepithelial neoplasia, QoL scores were lower compared with the survivors that were not diagnosed with a SMN after DTC. Siblings of survivors did not differ significantly from nonsiblings in scores on questionnaires (data not shown). For thyroid cancer–specific QoL, scores of

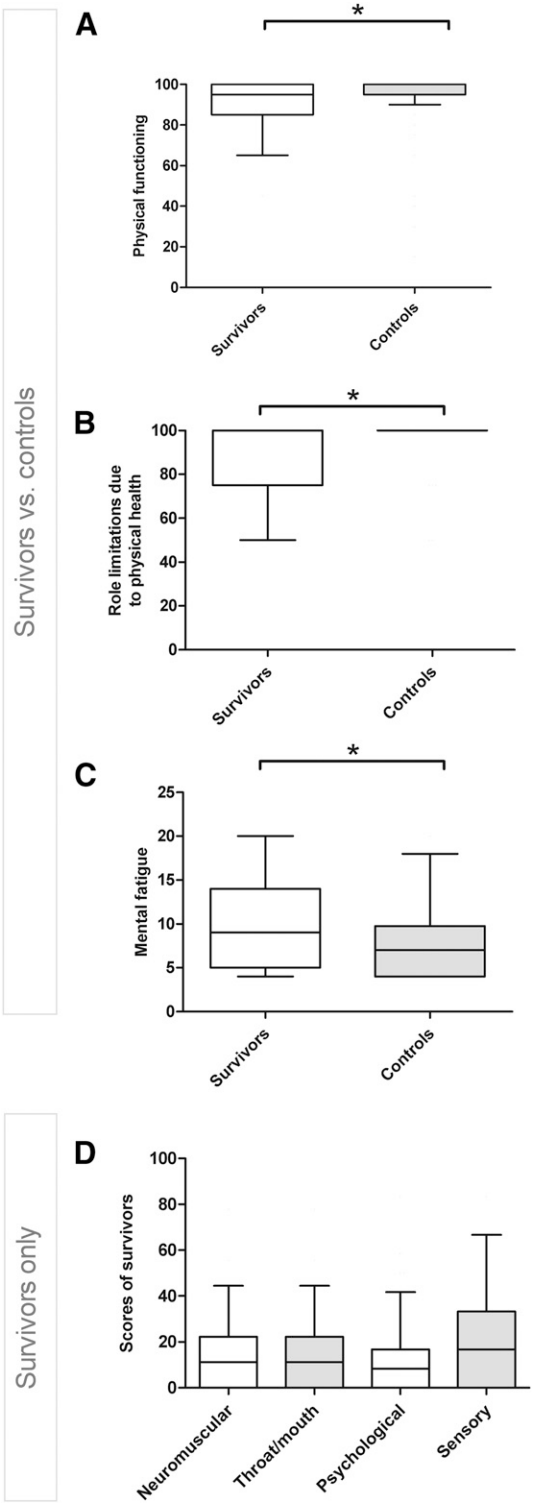

Figure 2. QoL scores in survivors of pediatric DTC. (A–C) Scores of survivors vs controls. (A) Physical functioning (SF-36, HRQoL) scores of survivors of vs matched controls. Scale ranges from 0 to 100. A higher score indicates a better QoL. (B) Limitations in role functioning due to physical health (SF-36, HRQoL) scores of survivors vs matched controls. Scale ranges from 0 to 100. A higher score indicates a better QoL. (C) Mental fatigue (MFI-20, fatigue) scores of survivors vs matched controls. Scale ranges from 4 to 20. A higher score indicates a worse QoL. (D) Scores of survivors only. Scores of survivors on neuromuscular, throat/mouth, psychological, and sensory complaints are shown. Scales range from 0 to 100. A higher score indicates a worse QoL.

survivors are shown in Table 2 and Fig. 2(D). Most frequently reported were neuromuscular, throat/mouth, psychological, and sensory complaints, feeling chilly, and headache.

Characteristics associated with QoL in adult survivors of pediatric DTC

Characteristics that were possibly associated with QoL in adult survivors of pediatric DTC are shown in Supplemental Table 3. Male survivors reported higher levels of reduced motivation and more depression than did females ($P = 0.007$ and $P = 0.009$). Unemployment was associated with lower scores on physical functioning and the physical component scale ($P = 0.005$ and $P = 0.003$) and higher levels of general fatigue, physical fatigue, and total fatigue ($P = 0.009$, $P = 0.009$, and $P = 0.004$, respectively).

Treatment with a higher cumulative dose of 131-I was associated with more complaints of headache ($P = 0.006$). Survivors with recurrent or persistent disease and survivors with a higher level of TSH suppression reported more complaints about the scars in their necks ($P < 0.001$ and $P = 0.002$).

Marital status at follow-up, educational level, age at follow-up, all tumor characteristics (*i.e.*, age at diagnosis, tumor–node–metastasis stage, and histology), surgical complications (permanent hypoparathyroidism and recurrent laryngeal nerve injury), and follow-up duration showed no significant associations with QoL (HRQoL, fatigue, anxiety, depression, and/or thyroid cancer–specific HRQoL).

Discussion

In the present study, we focus on long-term QoL in adult survivors of pediatric DTC, and our results show overall normal HRQoL, fatigue, anxiety, and depression in these survivors compared with matched controls. This normal QoL is similar to that found in studies performed in survivors of adolescent DTC (8, 9). Although survivors reported more physical problems, role limitations due to physical problems, and mental fatigue, the overall scores of survivors on these domains were still within the normal range. Thyroid cancer–specific complaints were present in some survivors, but most survivors reported relatively few or no complaints [Table 2; Fig. 2(D)]. Another reflection of the normal QoL of the survivors is their full participation in society, exemplified in most of these survivors by high employment and relationship rates and an educational level comparable to matched controls. Thereby, most (88%) of the survivors reported to have an interest in sex.

Remarkably, the overall QoL in survivors of pediatric DTC seems to be better than the QoL of survivors diagnosed with DTC at older ages. HRQoL, fatigue,

anxiety, and depression were reported as worse in both short- and long-term survivor studies in adult DTC compared with controls (10, 11). Additionally, survivors of (young) adult DTC seem to experience more severe thyroid cancer–specific complaints than do survivors of pediatric DTC (5, 13, 22).

Although overall QoL is normal in pediatric DTC survivors compared with controls, physical problems seemed to be relatively more prominent in the survivor group compared with controls. The impaired physical functioning observed in survivors of pediatric DTC has been described previously in other childhood cancer survivors (18, 19). Also in adult DTC survivors, the largest differences in scores between survivors and the general population were observed for physical complaints and complaints of fatigue (11).

Besides physical obstacles, survivors in the present study experienced mental constraints, in particular mental fatigue, entailing the inability to stay concentrated. Husson *et al.* (5) proposed that (mental) fatigue in survivors of (adult) DTC might be due to a suboptimal TSH level suppression target or could otherwise be explained by the presence of cancer-related fatigue (31). The present data provided no support for a possible relationship between TSH levels and fatigue, which is consistent with findings in DTC survivors diagnosed at older ages (8, 10).

Normal anxiety and depression levels as we found in the survivors of pediatric DTC were similar to the reported similar levels of emotional distress found in survivors of other childhood cancers (*e.g.*, acute lymphatic leukemia, renal tumor, non-Hodgkin lymphoma, and other types of cancer) and controls (32).

Survivors reported neuromuscular, throat/mouth, psychological, and sensory problems to be most present in the symptom scale items. Headache and feeling chilly were reported most frequently in the single items. Complaints most often reported in survivors of adult DTC were sympathetic complaints, neuromuscular complaints, and complaints of fatigue (13). Physicians underestimate the incidence of several thyroid cancer–specific complaints in survivors (21). For example, although 40% of the survivors reported voice problems, for only 15% of the survivors, recurrent laryngeal nerve injury was reported in their medical records (Supplemental Table 1). Because only 3 survivors were diagnosed with a SMN after DTC (Supplemental Table 2), general conclusions regarding QoL in this specific group of survivors cannot be drawn.

QoL is more variable in survivors compared with controls, as shown by the wider distribution toward worse QoL in survivors [Fig. 2(A–C)]. It would be of great value to be able to portend QoL (variability) based on predictors. Therefore, the present study evaluated whether long-term generic HRQoL, fatigue, anxiety, depression, and thyroid cancer–specific HRQoL were associated with survivor, tumor, treatment, or follow-up characteristics. Of all possible predictors of QoL, unemployment was most frequently associated with worse QoL on many domains. However, the retrospective design of the study does not allow us to make statements regarding the causality of this impairment. This means that employment could influence QoL or *vice versa*. Socioeconomic factors could play a role in the level of QoL, as has been described previously in studies evaluating QoL in survivors of adult DTC (21, 22). Adddditionally, we found evidence for a more impaired QoL among survivors undergoing more extensive treatment or survivors with a more extended disease. Survivors with a worse outcome may report more complaints due to their more active disease and treatment. Lower QoL in female survivors of DTC compared with male survivors has been reported by several authors (21, 22). However, owing to the limited number of male survivors in the present study, conclusions regarding associations between sex and QoL could not be drawn. Adverse late effects on physical functioning have been described after administration of 131-I to survivors of adult DTC (33, 34). An association between worse QoL and higher doses of 131-I in survivors of adult DTC has previously been described (35). The present data on survivors of pediatric DTC also show an association between higher cumulative doses of 131-I and worse QoL. In contrast, QoL in survivors of pediatric DTC was shown to be independent of other tumor or treatment characteristics, which confirms findings of studies in survivors of adult DTC (10, 21). Survivors of adult DTC showed an increasing QoL >5 years after diagnosis (21). The normal QoL in the present survivors may be explained by their long-term follow-up, but the present results do not confirm this hypothesis: a longer follow-up period was not associated with better QoL.

The present study has both strengths and limitations. This study considers the QoL of adult survivors of both pediatric and adolescent DTC. Moreover, survivors were compared with sex-, age-, and socioeconomic-matched controls. Because of the cross-sectional design of the study ≥ 5 years after diagnosis, short-term QoL was not evaluated. Because pediatric DTC is uncommon, gathering a larger group of survivors is difficult. Owing to nonnormally distributed data and the limited number of survivors included in this study, multivariable regression or stratified analysis was not feasible. To make more conclusive statements, international collaboration in prospective studies assessing QoL in pediatric DTC survivors is urgently needed. Moreover, to identify characteristics that predict QoL, longitudinal prospective studies would be more appropriate.

Finally, the results of this study were based only on quantitative data. Combining quantitative and qualitative

elements to assess QoL in survivors of pediatric DTC could help to evaluate perceived physical and mental limitations and parameters that could in turn predict QoL more clearly; such methodology has also been applied in studies of survivors of adult DTC (36).

To identify vulnerable childhood cancer survivors early and offer them the care they need, regular measurement of QoL parameters should be implemented during follow-up. This is in accordance with Dutch evidence-based guidelines for follow-up of childhood cancer survivors (37). Additionally, measurements at baseline and during treatment should also be performed to evaluate individual alterations in QoL. In our opinion, follow-up regarding monitoring QoL is necessary in survivors of pediatric DTC.

In conclusion, this study shows that, in general, long-term adult survivors of pediatric DTC function well in society, with relatively good HRQoL and levels of fatigue, anxiety, and depression that are similar to matched controls. Various thyroid cancer–specific complaints were present (*e.g.*, sensory complaints, headache, and chilliness), but mostly in mild forms. However, physical problems and mental fatigue seemed to be relatively more prominent in the survivor group compared with controls. Thereby, scores on QoL in survivors are widespread, indicating individual differences between survivors. Factors most frequently associated with worse QoL were unemployment and more extensive disease or treatment characteristics. These predictors will have to be further explored in future studies. We recommend evaluating changes in the QoL of individual pediatric DTC patients from diagnosis to long-term follow-up, using a prospective screening program to be able to provide early and individualized care to prevent long-term alterations in QoL.

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References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016;**26**(1):1–133.
2. Klein Hesselink MS, Nies M, Bocca G, Brouwers AH, Burgerhof JG, van Dam EW, Havekes B, van den Heuvel-Eibrink MM, Corssmit EP, Kremer LC, Netea-Maier RT, van der Pal HJ, Peeters RP, Schmid KW, Smit JW, Williams GR, Plukker JT, Ronckers CM, van Santen HM, Tissing WJ, Links TP. Pediatric differentiated thyroid carcinoma in The Netherlands: a nationwide follow-up study. *J Clin Endocrinol Metab*. 2016;**101**(5):2031–2039.
3. Vergamini LB, Frazier AL, Abrantes FL, Ribeiro KB, Rodriguez-Galindo C. Increase in the incidence of differentiated thyroid carcinoma in children, adolescents, and young adults: a population-based study. *J Pediatr*. 2014;**164**(6):1481–1485.
4. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001–2009. *Pediatrics*. 2014;**134**(4):e945–e955.
5. Husson O, Nieuwlaat WA, Oranje WA, Haak HR, van de Poll-Franse LV, Mols F. Fatigue among short- and long-term thyroid cancer survivors: results from the population-based PROFILES registry. *Thyroid*. 2013;**23**(10):1247–1255.
6. de Oliveira Chachamovitz DS, dos Santos Vigário P, Nogueira Cordeiro MF, de Castro CL, Vaisman M, dos Santos Teixeira PdeF. Quality of life, muscle strength, and fatigue perception in patients on suppressive therapy with levothyroxine for differentiated thyroid carcinoma. *Am J Clin Oncol*. 2013;**36**(4):354–361.
7. Sikjaer T, Moser E, Rolighed L, Underbjerg L, Bislev LS, Mosekilde L, Rejnmark L. Concurrent hypoparathyroidism is associated with impaired physical function and quality of life in hypothyroidism. *J Bone Miner Res*. 2016;**31**(7):1440–1448.
8. Oren A, Benoit MA, Murphy A, Schulte F, Hamilton J. Quality of life and anxiety in adolescents with differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2012;**97**(10):E1933–E1937.
9. Metallo M, Groza L, Brunaud L, Klein M, Weryha G, Feigerlova E. Long-term quality of life and pregnancy outcomes of differentiated thyroid cancer survivors treated by total thyroidectomy and I^{131} during adolescence and young adulthood. *Int J Endocrinol*. 2016;**2016**:7586482.
10. Hoftijzer HC, Heemstra KA, Corssmit EP, van der Klaauw AA, Romijn JA, Smit JW. Quality of life in cured patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab*. 2008;**93**(1):200–203.
11. Gamper EM, Wintner LM, Rodrigues M, Buxbaum S, Nilica B, Singer S, Giesinger JM, Holzner B, Virgolini I. Persistent quality of life impairments in differentiated thyroid cancer patients: results from a monitoring programme. *Eur J Nucl Med Mol Imaging*. 2015;**42**(8):1179–1188.
12. Lee JI, Kim SH, Tan AH, Kim HK, Jang HW, Hur KY, Kim JH, Kim KW, Chung JH, Kim SW. Decreased health-related quality of life in disease-free survivors of differentiated thyroid cancer in Korea. *Health Qual Life Outcomes*. 2010;**8**:101.
13. Husson O, Haak HR, Buffart LM, Nieuwlaat WA, Oranje WA, Mols F, Kuijpens JL, Coebergh JW, van de Poll-Franse LV. Health-related quality of life and disease specific symptoms in long-term thyroid cancer survivors: a study from the population-based PROFILES registry. *Acta Oncol*. 2013;**52**(2):249–258.
14. Sawka AM, Naeem A, Jones J, Lowe J, Segal P, Goguen J, Gilbert J, Zahedi A, Kelly C, Ezzat S. Persistent posttreatment fatigue in thyroid cancer survivors: a scoping review. *Endocrinol Metab Clin North Am*. 2014;**43**(2):475–494.

15. Langeveld N, Ubbink M, Smets E; Dutch Late Effects Study Group. "I don't have any energy": the experience of fatigue in young adult survivors of childhood cancer. *Eur J Oncol Nurs*. 2000;**4**(1):20–28.
16. van Santen HM, Aronson DC, Vulsma T, Tummers RF, Geenen MM, de Vijlder JJ, van den Bos C. Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience. *Eur J Cancer*. 2004;**40**(11):1743–1751.
17. Jóhannsdóttir IM, Hjermstad MJ, Moum T, Wesenberg F, Hjorth L, Schrøder H, Mört S, Jónmundsson G, Loge JH. Increased prevalence of chronic fatigue among survivors of childhood cancers: a population-based study. *Pediatr Blood Cancer*. 2012;**58**(3):415–420.
18. Rueegg CS, Gianinazzi ME, Rischewski J, Beck Popovic M, von der Weid NX, Michel G, Kuehni CE. Health-related quality of life in survivors of childhood cancer: the role of chronic health problems. *J Cancer Surviv*. 2013;**7**(4):511–522.
19. Sundberg KK, Doukkali E, Lampic C, Eriksson LE, Arvidson J, Wettergren L. Long-term survivors of childhood cancer report quality of life and health status in parity with a comparison group. *Pediatr Blood Cancer*. 2010;**55**(2):337–343.
20. Frederick NN, Kenney L, Vrooman L, Recklitis CJ. Fatigue in adolescent and adult survivors of non-CNS childhood cancer: a report from project REACH. *Support Care Cancer*. 2016;**24**(9):3951–3959.
21. Aschebrook-Kilfoy B, James B, Nagar S, Kaplan S, Seng V, Ahsan H, Angelos P, Kaplan EL, Guerrero MA, Kuo JH, Lee JA, Mitmaker EJ, Moalem J, Ruan DT, Shen WT, Grogan RH. Risk factors for decreased quality of life in thyroid cancer survivors: initial findings from the north American thyroid cancer survivorship study. *Thyroid*. 2015;**25**(12):1313–1321.
22. Goldfarb M, Casillas J. Thyroid cancer specific quality of life and health related quality of life in young adult thyroid cancer survivors. *Thyroid*. 2016;**26**(7):923–932.
23. Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;**30**(6):473–483.
24. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;**51**(11):1055–1068.
25. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: Health Insitute, New England Medical Center; 1994.
26. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;**39**(3):315–325.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;**67**(6):361–370.
28. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med*. 1997;**27**(2):363–370.
29. Husson O, Haak HR, Mols F, Nieuwenhuijzen GA, Nieuwlaat WA, Reemst PH, Huysmans DA, Toorians AW, van de Poll-Franse LV. Development of a disease-specific health-related quality of life questionnaire (THYCA-QoL) for thyroid cancer survivors. *Acta Oncol*. 2013;**52**(2):447–454.
30. Klein Hesselink EN, Klein Hesselink MS, de Bock GH, Gansevoort RT, Bakker SJ, Vredeveld EJ, van der Horst-Schrivers AN, van der Horst IC, Kamphuisen PW, Plukker JT, Links TP, Lefrandt JD. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. *J Clin Oncol*. 2013;**31**(32):4046–4053.
31. Berger AM, Abernethy AP, Atkinson A, Barsevick AM, Breitbart WS, Cella D, Cimprich B, Cleeland C, Eisenberger MA, Escalante CP, Jacobsen PB, Kaldor P, Ligibel JA, Murphy BA, O'Connor T, Pirl WF, Rodler E, Rugo HS, Thomas J, Wagner LI. Cancer-related fatigue. *J Natl Compr Canc Netw*. 2010;**8**(8):904–931.
32. van der Geest IM, van Dorp W, Hop WC, Neggers SJ, de Vries AC, Pieters R, Aarsen FK, van den Heuvel-Eibrink MM. Emotional distress in 652 Dutch very long-term survivors of childhood cancer, using the hospital anxiety and depression scale (HADS). *J Pediatr Hematol Oncol*. 2013;**35**(7):525–529.
33. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, Eftekhari M. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. *Nucl Med Commun*. 2014;**35**(8):808–817.
34. Klein Hesselink EN, Links TP. Radioiodine treatment and thyroid hormone suppression therapy for differentiated thyroid carcinoma: adverse effects support the trend toward less aggressive treatment for low-risk patients. *Eur Thyroid J*. 2015;**4**(2):82–92.
35. Almeida JP, Vartanian JG, Kowalski LP. Clinical predictors of quality of life in patients with initial differentiated thyroid cancers. *Arch Otolaryngol Head Neck Surg*. 2009;**135**(4):342–346.
36. Applewhite MK, James BC, Kaplan SP, Angelos P, Kaplan EL, Grogan RH, Aschebrook-Kilfoy B. Quality of life in thyroid cancer is similar to that of other cancers with worse survival. *World J Surg*. 2016;**40**(3):551–561.
37. Dutch Childhood Oncology Group. Guidelines for Follow-up in Survivors of Childhood Cancer 5 Years After Diagnosis. Den Haag/Amsterdam, The Netherlands (2010).