Fatigue and quality of life among thyroid cancer survivors without persistent or recurrent disease

Yukari Maki, MD (first author), Department of Pediatric Surgery, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan. Tel: +81-03-3353-8111, E-mail: maki.yukari@twmu.ac.jp

Kiyomi Horiuchi, MD, PhD (corresponding author), Department of Endocrine Surgery, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan. Tel: +81-03-3353-8111, E-mail: horiuchi.kiyomi@twmu.ac.jp

Takahiro Okamoto, MD, MSc, Department of Endocrine Surgery, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan. Tel: +81-03-3353-8111, E-mail: okamoto.takahiro@twmu.ac.jp

Running title: Postoperative fatigue in thyroid cancer

Keywords: Papillary thyroid cancer, Fatigue, Quality of life, Thyroid hormone

3398 words
ABSTRACT

Background: Cancer-related fatigue is one of the most important issues for patients, but research on this topic is sparse. This study aimed to determine the prevalence of fatigue in postoperative patients with papillary thyroid carcinoma (PTC) and to identify the clinical features associated with fatigue.

Methods: We conducted a cross-sectional study on 292 thyroid cancer survivors. Fatigue and quality of life were the study outcomes, measured using the Cancer Fatigue Scale (CFS) and the SF-36 version 2.0. Furthermore, correlations of demographic characteristics and hormonal data with the CFS scores were assessed by univariable and multivariable analyses.

Results: The prevalence of fatigue was 41.8% (95% CI: 36.1, 47.5). The CFS score was significantly correlated the free T3 level (Pearson's r = −0.123, 95%CI: −0.234, −0.008). Multiple regression analysis revealed that the free T3 level and having a job were significant predictors of the CFS score, with unstandardized regression coefficients of −2.52 (95% CI: −4.94, −0.09) and 2.85 (95% CI: 0.49, 5.20), respectively. The median Z-scores were negative for General Health (−0.28) and Vitality (−0.15) subscales of the SF-36. The CFS score was a significant predictor of summary scores of the SF-36. The free T3 level was significantly associated with the physical component summary score with an unstandardized coefficient of 3.20 (95%CI: 0.77, 5.63).

Conclusions: Fatigue was prevalent and associated with poor quality of life among PTC survivors. Thyroid functional status, particularly the level of free T3, may be worth to be considered in alleviating the burden.
INTRODUCTION

Differentiated thyroid carcinoma is the most common malignancy of the endocrine organs and is increasing in incidence (1). In the United States, the age-adjusted incidence of thyroid cancer increased from 3.6 per 100,000 in 1973 to 14.3 per 100,000 in 2009, while the age-adjusted mortality from differentiated thyroid carcinoma has remained unchanged (2-3). The disease burden has followed the same trend in Japan. In 2017, the number of patients newly diagnosed with thyroid cancer was estimated to be 18,090, and its corresponding age-adjusted incidence was 10.8 per 100,000 (4).

Since papillary thyroid carcinoma (PTC) accounts for > 80% of all thyroid cancer cases, the disease burden poses paramount importance for society and individuals. Most patients with PTC have a good prognosis, whereas a few may experience recurrence or even death (5-6). In addition to the oncologic events, subjective sequelae following diagnosis and treatment, such as quality of life or psychological burden, are essential concerns for cancer survivors (7-8). Besides, labelling people with diagnoses may itself could be harmful in psychological well-being (9-10). Some thoughtful clinicians may take these issues into consideration in daily practice, but few clinical researchers have addressed such “soft” outcomes in patients with PTC.

The National Comprehensive Cancer Network defines cancer-related fatigue as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with normal functioning (11-12). Cancer-related fatigue is one of the most common adverse consequences of cancer diagnosis and treatment, with the estimated prevalence ranging from 17% to 99% depending on the definition...
and measurement of cancer-related fatigue, the mode and timing of cancer treatment, and the population (i.e., specific disease) (13-14). Sawka et al. stated in their scoping literature review that long-term fatigue is a common problem among thyroid cancer survivors, with the prevalence ranging from 28% to 62% (15). They argued a need for more research on persistent post-treatment fatigue in thyroid cancer survivors, including studies examining the severity, prevalence, modifying factors, natural history, and associated impact on quality of life. One unresolved question is whether the fatigue is due to thyroid dysfunction. Patients with fatigue often ask, “Does this fatigue have something to do with my thyroid?” Few studies have specifically addressed the relationship between biochemical data and fatigue in thyroid cancer survivors. A randomized controlled trial revealed that restoration of euthyroidism from thyroid-stimulating hormone (TSH) suppression therapy did not affect patient-reported outcomes, as measured by the Multidimensional Fatigue Index-20 (16). A cross-sectional study showed that the levels of free triiodothyronine (fT3) and free thyroxine (fT4) were not significantly associated with the Brief Fatigue Inventory score among thyroid cancer survivors (17). A retrospective longitudinal study found that the complaints, including fatigue or tiredness, of levothyroxine-treated patients were significantly related to a low concentration of fT3 (18).

The objectives of the present study were to determine the prevalence of fatigue among postoperative patients with PTC and to identify the clinical features associated with fatigue. Specifically, our four research questions are as follows: (a) What is the prevalence of fatigue among postoperative PTC patients without recurrence? (b) Is there any relationship between fatigue and clinical characteristics, including thyroid function? (c) Do PTC patients feel impaired in health-related quality of life (HR-QOL) compared
with the general population? (d) What is the magnitude of the association between fatigue and HR-QOL after controlling for other clinical parameters?

MATERIALS AND METHODS

Design and patients

We conducted a cross-sectional study of patients with PTC who visited the outpatient clinic for postoperative follow-up between June 2018 and June 2019. Inclusion criteria were patients who underwent initial treatment at our hospital, had no signs of persistent or recurrent disease, and were 16 years or older at the time of consent. Patients who had persistent/recurrent PTC or a history of other malignant diseases and those deemed unsuitable as study subjects were excluded.

Observations and measurements

At the time of the outpatient follow-up, we asked the participants to fill out two questionnaires, the Cancer Fatigue Scale (CFS) and SF-36 version 2.0, to assess clinical fatigue and HR-QOL, respectively.

The CFS is a 15-item scale used to assess fatigue in cancer patients at the time of the survey (“right now”), with total scores ranging from 0 (no fatigue) to 60 (maximum fatigue). It has three subscales, physical, affective, and cognitive, with maximum scores of 28, 16, and 16, respectively. Okuyama et al. demonstrated the validity and reliability of the CFS (19). They set a cut-off value of 19, which had a sensitivity of 71% and specificity of 74%, for detecting clinical fatigue (20). The CFS showed good reproducibility (test–retest reliability r = 0.69, P < 0.001) and good internal consistency (Cronbach’s α for all 15 items = 0.88) (19).
The SF-36 is a questionnaire to measure generic HR-QOL consisting of 8 subscales translated into three component summary scales. Its Japanese version was developed and validated (21-22). Fukuhara et al. conducted two surveys to establish the national norm, the first using version 1.2 in 1995 and the second using version 2.0 in 2002 (23-25).

We also obtained the following information from each participant on the day of the survey: age, sex, time since initial treatment, TNM class, surgical procedure, use of levothyroxine, use of radioiodine therapy, comorbidities, work status, marital status, cohabitation status, and serum levels of TSH, fT3, and fT4.

Serum levels of TSH, fT3, and fT4 were measured by means of the electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics K.K, Tokyo, Japan). The intra-assay coefficient variations were 0.49-0.99% for TSH assay, 0.97-2.58% for fT3 assay, and 1.24-1.71% for fT4 assay. The reference values were 0.38-4.30 µIU/ml for TSH, 2.40-4.00 pg/ml for fT3, and 0.94-1.60 ng/dL for fT4.

**Statistical analysis**

The sample size was determined to make the width of a 95% confidence interval of the prevalence to be 10%. Based on the normal approximation method, the width of the expected confidence interval was $2 \times 1.96 \times \sqrt{\frac{\pi(1-\pi)}{n}}$, where $n$ denotes the required sample size and $\pi$ the expected prevalence (26). Assuming a 30% prevalence of fatigue based on a literature review, the required sample size was calculated as 323.

We summarized the patient characteristics and scores on the questionnaires using descriptive statistics. For each patient, we calculated the Z score for each subscale of the
SF-36 by referring to the national norms stratified by sex and age (<29, 30–39, 40–49, 50–59, 60–69, and 70–79 years). We defined a significantly impaired SF-36 domain as a subscale Z score ≤ −1.96. To explore the relationships between clinical fatigue and other variables including HR-QOL, we employed the chi-square test (or Fisher’s exact test) for categorical variables and unpaired t-test or correlation analysis using Pearson’s r for numerical variables. A multiple regression model using the CFS score as a dependent variable was used to examine the relationships between clinical fatigue and potential effect modifiers. We further explored the effects of clinical fatigue on the summary scores of the SF-36 using multiple regression analyses. An iterative approach was adopted to select appropriate covariates to maximize adjusted R² values or to minimize the root mean square error of the models. We used jamovi 1.6.23, which is built on top of the R statistical package, for the statistical computations (27). We set a two-sided P-value of <0.05 to indicate statistical significance of type I error.

**Ethical considerations**

The Ethics Committee of Tokyo Women's Medical University approved this study (no. 4791). Each patient provided written informed consent before participation in the study.

**RESULTS**

**Patient and disease characteristics**

Of 321 patients who consented to participating in the study, 29 were excluded for the following reasons: extremely high TSH level (n = 2) and extremely high fT3 level (n = 1) who did not take levothyroxine as prescribed, no measurement of the TSH, fT3, or
fT4 serum level (n = 20), and aged > 80 years (n = 6; national norm data for HR-QOL measurements are not available for this age group). The remaining 292 patients were included in the analysis.

Table 1 shows the clinicopathological characteristics of the study participants. The mean age was 57.0 years (range 23-79 years), and the median time since the initial treatment was 6.3 years (IQR:3.0-12.8). Of the 292 respondents, more than 80% were women, and 79.8% were married; 256 (87.7%) patients were living with family members, 162 (55.5%) had a job, and 172 (58.9%) had comorbidities. More than half of the participants had stage I (59.9%) or pT1/pT2 (64.4%) disease, and 185 (63.4%) patients had pathological lymph node metastasis. Whereas 157 (53.8%) patients underwent less than total thyroidectomy, 206 (70.5%) were on levothyroxine replacement therapy. Approximately 20% of patients received radioactive iodine treatment. Over half (53.1%) of the patients maintained their TSH level within the reference range. The mean levels of fT3 and fT4 were 2.81 pg/ml and 1.47 ng/dl, respectively.

Prevalence of fatigue

Figure 1 shows the distribution of the CFS scores. The mean (SD) and median CFS scores were 18.0 (9.3) and 17.0, respectively. A score ≥ 19 was observed in 122 patients; thus, the prevalence of clinical fatigue was 41.8% (95% CI: 36.1, 47.5). The responses to the first question “Do you become tired easily?” were as follows: “no” by 68 (23.3%) patients, “a little” by 80 (27.4%), “somewhat” by 93 (31.8%), “considerably” by 40 (13.7%), and “very much” by 11 (3.8%).
**Factors associated with fatigue**

None of the following variables showed a statistically significant difference between the patients with clinical fatigue (n = 122) and those without (n = 171): age, time since initial treatment, sex, postoperative stage, TNM pT or TMN pN, extent of thyroidectomy, use of levothyroxine, use of radioiodine therapy, comorbidities, employment status, marital status, cohabitation status, and serum levels of fT3, fT4, and TSH.

Analyses of the correlations between the CFS score and other numerical variables showed that the CFS score was significantly correlated with the fT3 level only (Pearson’s r = −0.123, 95%CI: −0.234, −0.008). Multiple regression analysis of the potential factors associated with the CFS score revealed unstandardized regression coefficients of −2.52 (95% CI: −4.94, −0.09) and 2.85 (95% CI: 0.49, 5.20) for the fT3 level and having a job, respectively (Table 2).

**HR-QOL and its associations with clinical fatigue**

The median Z-scores for each subscale of the SF-36 were as follows: 0.35 for Physical Functioning (PF), 0.36 for Role Physical (RP), 0.12 for Bodily Pain (BP), −0.28 for General Health (GH), −0.15 for Vitality (VT), 0.23 for Social Functioning (SF), 0.18 for Role Emotional (RE), and 0.04 for Mental Health (MH) (Fig. 2). The numbers (%) of patients with a Z-score ≤ −1.96 were 11 (3.8%) for PF, 19 (6.5%) for RP, 18 (6.2%) for BP, 10 (3.4%) for GH, 14 (4.8%) for VT, 18 (6.1%) for SF, 21 (7.2%) for RE, and 12 (4.1%) for MH. Clinical fatigue was associated with impaired HR-QOL in the RP, BP, GH, VT, RE, and MH domains (P < 0.05) (Table 3).

The median component summary score was 49.8 for the physical component summary
(PCS) score, 49.8 for the mental component summary (MCS) score, and 51.2 for the role component summary (RCS) score. The total CFS score was significantly associated with all summary scores, with a Pearson’s $r$ of $-0.255$ for the PCS (95%CI: $-0.360$, $-0.145$), $-0.574$ for the MCS (95%CI: $-0.646$, $-0.492$), and $-0.325$ for the RCS (95%CI: $-0.424$, $-0.218$) (Table 4).

Tables 5 shows the results of multiple regression analyses examining the relationship between the CFS score and the summary scores. The CFS score was a significant predictor of PCS, MCS, and RCS after controlling for the fT3 level, age, and sex. The unstandardized regression coefficient of the CFS score was largest for the MCS ($-0.57$, 95% CI: $-0.67$, $-0.48$), followed by the RCS ($-0.41$, 95% CI: $-0.54$, $-0.27$) and PCS ($-0.26$, 95% CI: $-0.38$, $-0.15$). The fT3 level was significantly correlated with the PCS score, with an unstandardized coefficient of 3.20 (95% CI: 0.77, 5.63).

**DISCUSSION**

Cancer-related fatigue is a distressing and persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer diagnosis and treatment (28). The concept of cancer-related fatigue is multidimensional, consisting of physical (e.g., diminished energy, need to rest), cognitive (e.g., diminished concentration or attention), and affective (e.g., decreased motivation or interest) components (29-30). In a qualitative study, Glaus et al. found that cancer patients perceived fatigue differently from healthy individuals. Cancer survivors felt chronic, unpleasant, distressing, life- and activity-limiting tiredness throughout the day, while
healthy individuals reported a pleasant, acute, normal, regulating phenomenon that disappeared after a good night sleep (29). Cancer-related fatigue can be a significant burden for both patients and caregivers. The Fatigue Coalition in the US reported that 91% of cancer patients with fatigue felt impairment of their “normal” life, and 88% experienced altered daily routines (30). Jones et al. reported that 91% of post-treatment cancer survivors with significant fatigue had moderate to severe disability, compared with 30% of those without significant fatigue (31). This issue is not novel (32), but it may not be appropriately recognized by physicians or other medical staff in daily practice because fatigue is a subjective feeling perceived only by the patient (28)(33).

The mechanism of fatigue in cancer survivors is multifactorial. Piper et al. proposed a framework for conceptualizing fatigue in which physiological, biochemical, and psychological factors play key roles in the development of symptoms (32). As pathophysiological mechanisms of cancer-related fatigue, Morrow et al. proposed the following hypotheses: anemia, adenosine triphosphate dysregulation, vagal afferent nerve activation, and interaction of the hypothalamic–pituitary–adrenal axis/cytokines with serotonin dysregulation (34-35). Of these, Bower focused on the cytokine hypothesis and proposed a model for the release of pro-inflammatory cytokines from tumor cells or surrounding stromal and immune cells induced by cancer diagnosis or treatment, as the critical pathway causing cancer-related fatigue (28). While Bower reviewed evidence corroborating the association between inflammation and fatigue, she also noted tremendous variation in the experience of fatigue at different stages of the cancer continuum, which is not captured by focusing on the mean fatigue level (28). She proposed a model based on predisposing (vulnerability of the individual), precipitating (situational conditions), and perpetuating (sustaining symptoms over time)
factors that may contribute to modifying the key pathway. Of these, predisposing factors include childhood adversity, history of depression, trait anxiety, and loneliness. The perpetuating factors involve a cognitive process characterized by a lack of confidence with an expectation of negative outcomes, reductions in physical activity, and sleep disturbance (28).

Cancer-related fatigue is common among thyroid cancer survivors, as evidenced by the present study and previous reports (36-37). Aside from the proposed mechanisms mentioned above, endocrinological alterations specific to thyroidectomized patients may be relevant as causes of post-treatment fatigue. Alhashemi et al. estimated Spearman’s correlation coefficient between the fT4 level and the Brief Fatigue Inventory score to be 0.132 (P = 0.060), but the biochemical data were not measured on the day of the survey (17). Hughes et al. reported that TSH suppression was associated with substantial fatigue (odds ratio = 1.63) in patients with differentiated thyroid cancer, but the use of TSH suppression was assessed by mail responses, not by actual data (37).

A unique feature of the present study was that we obtained thyroid hormone levels on the day of administering the questionnaires to the patients, which allowed us to examine the relationship between thyroid hormone levels and fatigue more accurately. We found a statistically significant relationship between the fT3 level and CFS score. The association between a low fT3 level and fatigue has also been reported in other populations. Some hypothyroid patients on levothyroxine monotherapy have a low serum fT3 level, and those with a normal serum TSH level were not necessarily euthyroid in terms of energy expenditure, lipid metabolism, dissatisfaction, or quality of life, including fatigue (38-40). A case–control study indicated that the prevalence of a low fT3 level was more frequent in patients with chronic fatigue syndrome (16%).
compared with controls (7%) (41).

A few studies revealed a significantly lower serum tT3 level postoperatively than preoperatively in athyreotic patients on levothyroxine monotherapy (42-43). This is because there is no production of tT3 from the thyroid gland following total thyroidectomy (42-43). Further, a genetic alteration in the type 2 deiodinase pathway and/or thyroid autoimmunity may be involved in the development of perceived symptoms in patients with levothyroxine therapy (38). Ito et al. observed that athyreotic patients with mildly suppressed TSH maintained their levels of tT3, metabolic markers, and subjective symptoms closest to the preoperative levels (43-45). Two crossover trials comparing thyroxine and thyroxine plus triiodothyronine therapies in patients with hypothyroidism showed statistically significant improvements in mood and neuropsychological function during the combination therapy (46-47). However, adequate comparative studies examining the role of adding triiodothyronine to levothyroxine in thyroid cancer survivors are lacking.

Strategies to alleviate fatigue have been explored. A systematic review on the management of fatigue in thyroid cancer survivors included four randomized controlled trials involving the following experimental and control interventions (48):

- triiodothyronine plus levothyroxine versus levothyroxine alone (47), euthyroidism versus TSH suppression (16), predefined exercises versus physical inactivity (48-49).

The randomized controlled trials that compared thyroid hormone therapies showed mixed outcomes depending on the subscales of the specific instruments used (16,47).

Other treatments for cancer-related fatigue, in general, include physical exercise, psychosocial interventions, mind–body interventions, pharmacological interventions, nutritional therapies, integrative therapies, and acupuncture (11,12,50-54). In addition,
observational studies indicated that unemployment or inability to work was associated with fatigue in thyroid cancer patients (17) and other populations (55-56), although fatigue might be a cause rather than a result of being jobless. However, these correlational findings may have limited value in fatigue management because patients’ experiences are quite variable (28). In practice, regular screening, assessment, education, and appropriate medical support are essential for managing cancer-related fatigue (11). To this end, good communication with a patient will facilitate understanding of her/his experience. The American Society of Clinical Oncology Clinical Practice Guideline recommends using a quantitative assessment involving an 11-point numerical rating scale from 0 (no fatigue) to 10 (worst fatigue ever) in clinical practice, when a patient score $\geq 4$ on this scale.

We are aware of several limitations of the present study, particularly a causal role of a low fT3 level for cancer-related fatigue. First, as this was a cross-sectional investigation, we could not confirm temporal relationships between the test results and the outcome. Second, although the correlational analysis indicated an inverse association between the fT3 level and CFS score, this association was not very strong. Finally, our multiple regression analysis of selected explanatory variables predicting the CFS score showed an unstandardized regression coefficient for fT3 of $-2.52$ (95% CI: $-4.94$, $-0.09$) and an adjusted $R^2$ of 0.029, which was small. This observation was in agreement with that of Alhashemi et al., who reported an $R^2$ of 0.177 in their multivariable linear regression model (17). This may indicate that mathematical formulas derived from quantitative research capture only a very small part of the overall picture of cancer-related fatigue.

In conclusion, fatigue was prevalent and associated with poor quality of life among
papillary thyroid carcinoma survivors. Since the mechanism of fatigue development seems to highly depend on the individual, an “on average” approach may fail to alleviate symptoms in some patients. Clinicians need to understand the patient’s view as well as her/his specific circumstances. Thyroid functional status, particularly the level of free T3, may be worth to be considered in alleviating the burden.

Author disclosure statement

No competing financial interests exist.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author Contribution Statement

Yukari Maki: substantial contributions to the conception and design of the work, interpretation of data, statistical analyses, writing and final approval of the version to be published.

Kiyomi Horiuchi: substantial contributions to the conception and design of the work, interpretation of data, statistical analyses, writing and final approval of the version to be published.

Takahiro Okamoto: substantial contributions to the conception and design of the work, interpretation of data, statistical analyses, writing and final approval of the version to be published.

Acknowledgements
The authors are grateful to Yasuko Nozoe for her managerial work. We also thank all participants in this study. It is the patients’ views that provide us deep insights into their experiences.

REFERENCES

1. Welch HG. Overdiagnosed: Making People Sick in the Pursuit of Health. Beacon Press 2011 228p, Boston.

2. Davies L, Welch G. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006 295 2164-2167.

3. Davies L, Welch G. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014 140 317-22.

4. https://ganjoho.jp/reg_stat/index.html (accessed May 1, 2021)

5. Adam MA, Pura J, Lin G, Dinan MA, Tyler DS, Reed SD, Roman SA, Sosa JA. Extent of surgery for papillary thyroid cancer is not associated with survival: An analysis of 61,775 patients. Ann Surg 2014 260 601-607.

6. Dong W, Horiuchi K, Tokumitsu H, Sakamoto A, Noguchi E, Ueda Y, Okamoto T. Time-varying pattern of mortality and recurrence from papillary thyroid cancer: Lessons from a long-term follow-up. Thyroid 2019 29 802-808.

7. Holland JC, Andersen B, Breitbart WS, Compas B, Dudley MM, Fleishman S, Fulcher CD, Greenberg DB, Greiner CB, Handzo GF, et al; NCCN Distress Management Panel. Distress management. J Natl Compr Canc Netw 2010 8 448–485.

8. Harms CA, Cohen L, Pooley JA, Chambers SK, Galvão DA, Newton RU. Quality
of life and psychological distress in cancer survivors: The role of psycho-social resources for resilience. Psychooncology 2019 28 271–277.

9. MacDonald LA, Sackett DL, Haynes RB, Taylor DW. Labelling in hypertension: a review of the behavioural and psychological consequences. J Chron Dis 1984 37 933-942.

10. Li R, Li G, Wang Y, Bao T, Lei Y, Tian L, Li Z, Zhu J, Lei J Tang H. Psychological distress and sleep disturbance throughout thyroid nodule screening, diagnosis, and treatment. J Clin Endocrinol Metab 2021 106 e4221-4230.

11. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, Schnipper HH, Lacchetti C, Ligibel JA, Lyman GH, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: An American Society of Clinical Oncology Clinical Practice Guideline Adaptation. J Clin Oncol 2014 32 1840-1850.

12. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. Nat Rev Clin Oncol 2014 11 597-609.

13. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. Eur J Cancer 2002 38 27-43.

14. Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004 32 40–50.

15. 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. Endoc Metab Clin North Am 2014 43 475-494.

16. Eustatia-Rutten CFA, Corssmit EPM, Pereira AM, Frölich M, Bax JJ, Romijn JA, Smit JWA. Quality of life in longterm exogenous subclinical hyperthyroidism and
the effects of restoration of euthyroidism, a randomized controlled trial. Clin Endocrinol 2006 64 284-291.

17. Alhashemi A, Jones JM, Goldstein DP, Mina DS, Thabane L, Sabiston CM, Chang EK, Brierley JD, Sawka AM. An exploratory study of fatigue and physical activity in Canadian thyroid cancer patients. Thyroid 2017 27 1156-1163.

18. Larisch R, Midgley JEM, Dietrich JW, Hoermann R. Symptomatic relief is related to serum free triiodothyronine concentrations during follow-up in levothyroxine-treated patients with differentiated thyroid cancer. Exp Clin Endocrinol Diabetes 2018 126 546-552.

19. Okuyama T, Akechi T, Kugaya A, Okamura H, Shima Y, Maruguchi M, Hosaka T, Uchitomi Y. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. J Pain Symptom Manage 2000 19 5-14.

20. Okuyama T, Tanaka K, Akechi T, Kugaya A, Okamura H, Nishiwaki Y, Hosaka T, Uchitomi Y. Fatigue in ambulatory patients with advanced lung cancer: prevalence, correlated factors, and screening. J Pain Symptom Manage 2001 22 554-564.

21. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol 1998 51 1037-1044.

22. Fukuhara S, Ware JE Jr, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. J Clin Epidemiol 1998 51 1045-1053.

23. Fukuhara S, Suzukamo Y. Manual of SF-36v2 Japanese version: iHope International Inc. Kyoto, 2015.
24. Ware JE, Kosinski MA, Keller SD. Physical and Mental Health Summary Scales: A User’s Manual, The Health Institute, 1994.

25. Suzukamo Y, Fukuhara S, Green J, Koshinski M, Gandek B, Ware J. Validation testing of a three-component model of Short Form-36 scores. J Clin Epidemiol 2011 64 301-308.

26. Colton T. Statistics in Medicine, Boston: Little Brown & Co, 1974.

27. The jamovi project. 2021 jamovi. (version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org.

28. Bower JE. The role of neuro-immune interactions in cancer-related fatigue: Biobehavioral risk factors and mechanisms. Cancer 2019 125 353-364.

29. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. Eur J Cancer Care 1996 5 8-23.

30. Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, Johnson DH, Miaskowski C, Scherr SL, Portenoy RK, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000 5 353-360.

31. Jones JM, Olson K, Catton P, Catton CN, Fleshner NE, Krzyzanowska MK, McCready DR, Wong RKS, Jiang H, Howell D. Cancer-related fatigue and associated disability in post-treatment cancer survivors. J Cancer Surviv 2016 10 51-61.

32. Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: Developing nursing theory. Oncol Nurs Forum 1987 14 17-23.

33. Vogelzang NJ, Breitbart W, Cella D, Curt GA, Groopman JE, Horning SJ, Itri LM,
Johnson DH, Scherr SL, Portenoy RK. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Semin Hematol 1997 34 4-12.

34. Morrow GR, Paul L R Andrews, Hickok JT, Roscoe JA, Matteson S. Fatigue associated with cancer and its treatment. Support Care Cancer 2002 10 389-398.

35. Ebede CC, Jang Y, Escalante CP. Cancer-related fatigue in cancer survivorship. Med Clin North Am 2017 101 1085-1097.

36. Husson O, Nieuwlaat WA, Oranje WA, Haak HR, Lonneke V van de Poll-Franse, Mols F. Fatigue among short- and long-term thyroid cancer survivors: results from the population-based PROFILES registry. Thyroid 2013 23 1247-1255.

37. Hughes DT, Gastelum RD, Kovatch KJ, Hamilton AS, Ward KC, Haymart MR. Energy level and fatigue after surgery for thyroid cancer: A population-based study of patient-reported outcomes. Surgery 2020 167 102-109.

38. Ettleson MD, Bianco AC. Individualized therapy for hypothyroidism: Is T4 enough for everyone? J Clin Endocrinol Metab 2020 105 e3090–e3104.

39. Saravanan P, Chau W-F, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf) 2002 57 577-585.

40. Peterson SJ, Cappola AR, Castro MR, Dayan CM, Farwell AP, Hennessey JV, Kopp PA, Ross DS, Samuels MH, Sawka AM, et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. Thyroid 2018 28 707-721.

41. Ruiz-Núñez B, Tarasse R, Vogelaar F, Dijck-Brouwer DAJ, Muskiet AJ. Higher
Prevalence of “low T3 syndrome” in patients with chronic fatigue syndrome: A case-control study. Front Endocrinol 2018 9 97.

42. Gullo D, Latina A, Frasca F, Moli RL, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. PLoS One 2011 6 e22552.

43. Ito M, Miyauchi A, Morita S, Kudo T, Nishihara E, Kihara M, Takamura Y, Ito Y, Kobayashi K, Miya A, et al. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. Eur J Endocrinol 2012 167 373-378.

44. Ito M, Miyauchi A, Hisakado M, Yoshioka W, Ide A, Kudo T, Nishihara E, Kihara M, Ito Y, Kobayashi K, et al. Biochemical markers reflecting thyroid function in athyreotic patients on levothyroxine monotherapy. Thyroid 2017 27 484-490.

45. Ito M, Miyauchi A, Hisakado M, Yoshioka W, Kudo T, Nishihara E, Kihara M, Ito Y, Miya A, Fukata S, et al. Thyroid function related symptoms during levothyroxine monotherapy in athyreotic patients. Endocr J 2019 66 953-960.

46. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. NEJM 1999 340 424-429.

47. Bunevicius R, Prange AJ. Mental improvement after replacement therapy with thyroxine plus triiodothyronine: relationship to cause of hypothyroidism. Int J Neuropsychopharmacol 2000 3 167-174.

48. To J, Goldberg AS, Jones J, Zhang J, Lowe J, Ezzat S, Gilbert J, Zahedi A, Segal P, Sawka AM. A systematic review of randomized controlled trials for management of persistent post-treatment fatigue in thyroid cancer survivors. Thyroid 2015 25
Vigário Psos S, Chachamovitz DS, Cordeiro MF, Teixeira Pde F, Castro CL, Oliveira FP, Vaisman M. Effects of physical activity on body composition and fatigue perception in patients on thyrotropin-suppressive therapy for differentiated thyroid carcinoma. Thyroid 2011 21 695-700.

50. Vigário PoS, Chachamovitz DS, Teixeira PeF, Rocque MeL, Santos ML, Vaisman M. Exercise is associated with better quality of life in patients on TSH-suppressive therapy with levothyroxine for differentiated thyroid carcinoma. Arq Bras Endocrinol Metabol 2014 58 274-281.

51. Arring NM, Barton DL, Brooks T, Zick SM. Integrative therapies for cancer-related fatigue. Cancer J 2019 25 349-356.

52. Hilfiker R, Meichtry A, Eicher M, Balfe LN, Knols RH, Verra ML, Taeymans J. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. Br J Sports Med 2018 52 651-665.

53. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, Mohr D, Palesh OG, Peppone LJ, Piper BF, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: A Meta-analysis. JAMA Oncol 2017 3 961-996.

54. Baguley BJ, Bolam KA, Wright ORL, Skinner TL. The effect of nutrition therapy and exercise on cancer-related fatigue and quality of life in men with prostate cancer: A systematic review. Nutrients 2017 9 1003.

55. Chen LM, Yang QL, Duan YY, Huan XZ, He Y, Wang C, Fan YY, Cai YC, Li JM, Chen LP, et al. Multidimensional fatigue in patients with nasopharyngeal
carcinoma receiving concurrent chemoradiotherapy: incidence, severity, and risk factors. Support Care Cancer 2021 29 5009-5019.

56. Castro-Marrero J, Faro M, Zaragozá MC, Aliste L, de Sevilla TF, Alegre J. Unemployment and work disability in individuals with chronic fatigue syndrome/myalgic encephalomyelitis: a community-based cross-sectional study from Spain. BMC Public Health 2019 Jun 28;19(1):840. doi: 10.1186/s12889-019-7225-z

Figure legends

Fig. 1 Distribution of the CFS score

Fig. 2 Median Z-scores of the eight domains

PF: Physical Functioning
RP: Role Physical
BP: Bodily Pain
GH: General Health
VT: Vitality
SF: Social Functioning
RE: Role Emotional
MH: Mental Health
| Characteristic               | Mean (SD) or N (%) |
|-----------------------------|--------------------|
| Age (years)                 | 57.0 (13.7)        |
| Years since initial treatment| 8.7 (7.4)          |
| Sex                         |                    |
| Female                      | 236 (80.8%)        |
| Male                        | 56 (19.2%)         |
| Marital status              |                    |
| Married                     | 233 (79.8%)        |
| Single                      | 59 (20.2%)         |
| Living with a cohabitant    |                    |
| Yes                         | 256 (87.7%)        |
| No                          | 36 (12.3%)         |
| Having a job                |                    |
| Yes                         | 162 (55.5%)        |
| No                          | 130 (44.5%)        |
| Comorbidities               |                    |
| None                        | 120 (41.1%)        |
| ≥ 1                         | 172 (58.9%)        |
| Stage                       |                    |
| I                           | 175 (59.9%)        |
| II                          | 99 (33.9%)         |
| III                         | 18 (6.2%)          |
| TMN pT                      |                    |
| pT1                         | 132 (45.2%)        |
| pT2                         | 56 (19.2%)         |
| pT3                         | 76 (26.0%)         |
| pT4                         | 28 (9.6%)          |
| TMN pN                      |                    |
| pN0                         | 107 (36.6%)        |
| pN1                         | 185 (63.4%)        |
| Extent of thyroidectomy     |                    |
| Less than total             | 157 (53.8%)        |
| Total                       | 135 (46.2%)        |
| Levothyroxine replacement   |                    |
| Yes                         | 206 (70.5%)        |
| No                          | 86 (29.5%)         |
| Radioactive iodine use      |                    |
| Never                       | 232 (79.5%)        |
| Ever                        | 60 (20.5%)         |
| TSH                         |                    |
| Suppressed (< 0.380 µIU/l)  | 102 (34.9%)        |
| Normal (0.380–4.300 µIU/l)  | 155 (53.1%)        |
| Elevated (> 4.300 µIU/l)    | 35 (12.0%)         |
| fT3                         | (reference: 2.40–4.00 pg/ml) 2.81 (0.439) |
| fT4                         | (reference: 0.94–1.60 ng/dl) 1.47 (0.337) |
| Variable    | Unstandardized regression coefficient (95% CI) | P-value | Standardized regression coefficient (95% CI) |
|-------------|-------------------------------------------------|---------|--------------------------------------------|
| fT3         | −2.52 (−4.94, −0.09)                            | 0.042   | −0.23 (−0.23, −0.004)                       |
| Having a job| 2.85 (0.49, 5.20)                               | 0.018   | 0.26 (0.03, 0.28)                           |
| Age         | 0.09 (0.007, 0.18)                              | 0.034   | 0.11 (0.01, 0.26)                           |

Model fit measures: $R^2 = 0.039$, adjusted $R^2 = 0.029$, overall $F = 3.89$ ($P = 0.009$)

CFS: Cancer Fatigue Scale
Table 3. Associations between clinical fatigue and each domains of the SF-36

| Domain | Patients with clinical fatigue (%) | P-value |
|--------|-----------------------------------|---------|
| PF     | Z score > -1.96 116/281 (41.3%)   | 0.383   |
|        | Z score ≤ -1.96 6/11 (54.5%)      |         |
| RP     | Z score > -1.96 108/273 (39.6%)   | 0.003*  |
|        | Z score ≤ -1.96 14/19 (73.7%)     |         |
| BP     | Z score > -1.96 108/274 (39.4%)   | 0.001*  |
|        | Z score ≤ -1.96 14/18 (77.8%)     |         |
| GH     | Z score > -1.96 112/282 (39.7%)   | 0.0001* |
|        | Z score ≤ -1.96 10/10 (100%)      |         |
| VT     | Z score > -1.96 110/278 (39.6%)   | 0.0006* |
|        | Z score ≤ -1.96 12/14 (85.7%)     |         |
| SF     | Z score > -1.96 111/274 (40.5%)   | 0.0866  |
|        | Z score ≤ -1.96 11/18 (61.1%)     |         |
| RE     | Z score > -1.96 105/271 (38.7%)   | 0.0001* |
|        | Z score ≤ -1.96 17/21 (81.0%)     |         |
| MH     | Z score > -1.96 114/281 (40.6%)   | 0.034   |
|        | Z score ≤ -1.96 8/11 (72.7%)      |         |

* P < 0.05

PF: Physical Functioning
RP: Role Physical
BP: Bodily Pain
GH: General Health
VT: Vitality
SF: Social Functioning
RE: Role Emotional
MH: Mental Health
Table 4. Correlations between the SF-36 summary scores and CFS scores

|                      | PCS     | MCS     | RCS     |
|----------------------|---------|---------|---------|
| CFS total            | −0.255* | −0.574* | −0.325* |
| CFS physical         | −0.235* | −0.586* | −0.274* |
| CFS affective        | −0.123* | −0.288* | −0.234* |
| CFS cognitive        | −0.208* | −0.368* | −0.237* |

* P < 0.05

CFS: Cancer Fatigue Scale
PCS: Physical Component Summary
MCS: Mental Component Summary
RCS: Role Component Summary
Table 5. Multiple regression analysis using the PCS, MCS, PCS as a dependent variable.

| Dependent variable | Explanatory variable | Unstandardized regression coefficient (95% CI) | P-value | Standardized regression coefficient (95% CI) |
|--------------------|----------------------|-----------------------------------------------|---------|--------------------------------------------|
| PCS                | CFS score            | −0.26 (−0.38, −0.15)                          | < 0.001 | −26 (−0.37, −0.14)                         |
|                    | fT3 level            | 3.20 (0.77, 5.63)                             | 0.001   | 0.15 (0.019, 0.24)                         |
|                    | Age                  | 0.09 (0.015, 0.17)                            | 0.020   | 0.13 (0.021, 0.24)                         |
|                    | Female               | −2.12 (−0.48, 0.57)                           | 0.122   | −0.087 (−0.2, 0.023)                       |
| PCS                | CFS score            | −0.57 (−0.67, −0.48)                          | < 0.001 | −0.58 (−0.67, −0.48)                       |
|                    | fT3 level            | −0.024 (−2.04, 1.99)                          | 0.981   | −0.001 (−0.097, 0.095)                     |
|                    | Age                  | 0.005 (−0.059, 0.07)                          | 0.87    | 0.0078 (−0.09, 0.10)                       |
|                    | Female               | −0.96 (−3.19, 1.26)                           | 0.395   | −0.041 (−0.14, 0.05)                       |
| PCS                | CFS score            | −0.41 (−0.54, −0.27)                          | < 0.001 | −0.33 (−0.44, −0.22)                       |
|                    | fT3                  | −0.12 (−3.04, 2.80)                           | 0.938   | −0.004 (−0.12, 0.011)                      |
|                    | Age                  | −0.011 (−0.12, 0.082)                         | 0.812   | −0.013 (−0.12, 0.097)                      |
|                    | Female               | −0.92 (−4.14, 2.31)                           | 0.577   | −0.031 (−0.14, 0.079)                      |

Model fit measures (PCS): $R^2 = 0.107$, adjusted $R^2 = 0.0947$, overall $F = 8.61$ ($P < 0.01$)
Model fit measures (MCS): $R^2 = 0.331$, adjusted $R^2 = 0.322$, overall $F = 35.5$ ($P < 0.01$)
Model fit measures (RCS): $R^2 = 0.107$, adjusted $R^2 = 0.094$, overall $F = 8.59$ ($P < 0.01$)

CFS: Cancer Fatigue Scale
PCS: Physical Component Summary
MCS: Mental Component Summary
RCS: Role Component Summary
Fig. 1

338x190mm (96 x 96 DPI)
Fig. 2

338x190mm (96 x 96 DPI)