# The Effect of Thyroid Hormone Withdrawal, Performed to Evaluate the Success of I-131 Ablation, On Quality of Life in Female Patients With Low-Risk Differentiated Thyroid Cancer

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# Abstract

**Objective:** There is a need to evaluate the treatment response in patients who have undergone radioiodine treatment (RIT) for differentiated thyroid cancerDiagnostic tests that are used for this purpose include radioiodine whole body scan (sWBS) and serum thyroglobulin (Tg) measurement which are most accurate during thyroid-stimulating hormone (TSH) stimulation. However temporary discontinuation of thyroid hormone therapy to increase TSH (withdrawal) may be associated with the morbidity of hypothyroidism The aim of our study was to show the effects of thyroid hormone withdrawal (THW), on quality of life and psychological symptoms in female patients with low-risk, well-differentiated papillary thyroid cancer.

**Methods:** We applied the short form-36 (SF-36) and *Symptom Checklist-90-R* (*SCL-90-R*) questionnaires to the patients in the euthyroid state who were referred a median of 9 months (6-13 months) after RIT, to perform a dWBS and to evaluate stimulated Tg. We applied the same questionnaire again when thyroid-stimulating hormone (TSH) was > 30 μIU/mL 4 weeks after THW (hypothyroid state). We evaluated the changes in questionnaire scores using the paired-samples t test or the Wilcoxon signed rank test.

**Results:** Our study included  52 patients (median age 48 years, range 23-65 years) with differentiated cancer. Forthy –two (%) of these patients received 3700 MBq I-131 wheras 7 (%) patients received 1850 MBq. . Ablation success based on the dWBS only was 96.2%, based on Tg only was 98% and based on thyroglobulin antibodies (TgAb) only was 88.5%. There was statistically significant worsening in anxiety, psychosis, additional items and general symptom index symptoms with the SCL-90-R questionnaire, and physical functioning, role limitation due to physical health, energy/fatigue, emotional well-being, social function, general health and health change with the SF-36 questionnaire.

**Conclusions:** THW worsened the patients' psychological symptoms and quality of life. Our findings show that stimulated Tg and the dWBS may have side effects that outweigh benefits in patients with low-risk differentiated thyroid cancer without TgAb interference and access to ultrasonography.


# Introduction

Differentiated thyroid cancers (DTC) originate from from epithelial folliculararcells and generally have a good prognosis. The standard treatment for DTC is total thyroidectomy, with cervical lymph node dissection if necessary, followed by radioiodine treatment (RIT). The survival rate of patients with thyroid cancer is > 90%, although it varies among disease subgroups [1, 2]. Administration of iodine 131 (I-131) after total thyroidectomy has three main goals: (1) to destroy possibly benign residual thyroid tissue, which increases the specificity of serum thyroglobulin (Tg) measurement during follow-up; (2) to eliminate suspected but unidentified residual disease or known persistent or recurrent disease that may decrease disease-free survival (DFS) and overall survival (OS); and (3) to perform a highly sensitive post-treatment whole-body scan (WBS) [3]. In patients undergoing ablation, diagnostic whole body scans (dWBS) with stimulated Tg test are performed 6–12 months after treatment to evaluate treatment success, [4]. Although the sensitivity of a dWBS in demonstrating residual normal thyroid tissue is high, its success in demonstrating metastatic disease is limited. For this reason, the use of this method has steadily

decreasedespecially in low-risk patients. In addition, evaluation of the treatment response without a dWBS can also be done with stimulated thyroid-stimulating hormone (TSH). Tg levels [5–8]. However both tests require TSH stimulation for optimal sensitivityTSH stimulation can be performed by thyroid hormone withdrawal (THW) or administration of recombinant human thyrotropin (thyrotropin alfa) [9]. THW is cheap, readily available method of TSH stimulation However, it is associated with clinical hypothyroidism, which consists of a wide variety of side effects, including drowsiness, constipation, weakness, myalgia, emotional dysfunction and physical discomfort [10, 11]. While improving survival is important in cancer patient management, QoL preservation should also be one of the ultimate goals. Altough temporary hypothyroidism reduces the quality of life (QoL) [12, 13]. Several studies have been published on the deterioration of QoL in patients with thyroid cancer [14–17]. The 36-item Short Form Health Survey (SF-36) is a validated questionnaire on general health and well-being, and has also been used in studies on thyroid diseases. The Symptom Checklist 90–Revised (SCL-90-R) is a questionnaire evaluating psychological symptoms and has been used in studies on hypothyroidism [19, 20]. The aim of our study was to determine the effects of THW, which was created to evaluate the treatment response after I-131 administration, on QoL and psychological symptoms in female patients with low-risk, well-differentiated papillary thyroid cancer.

## Materials And Methods

# Patient selection

Our study was carried out in accordance with the Declaration of Helsinki with the approval of the ethics committee of our institution (40465587-102.01-274, 2019/191). All patients provided written informed consent.

# Inclusion criteria

We included female patients aged 18–65 years who underwent RIT for differentiated thyroid cancer. After RIT, regular TSH, free thyroxine (fT4), Tg and thyroglobulin antibody (TgAb) levels were followed up until the dWBS.

# Exclusion criteria

We excluded patients with diabetes mellitus, chronic kidney disease, chronic liver disease, chronic rheumatic disease, chronic musculoskeletal disease, and patients with non-thyroid cancer. We also excluded patients who were using active psychiatric drugs at that time. After RIT, some patients did not have regular TSH and fT4 level follow-up; hence, there were patients with overt hypothyroidism and hyperthyroidism, and we excluded them.

# TSH, fT4, Tg and TgAb measurements

fT4, TSH and TgAb levels were measured on an Abbott Architect i2000 analyser (Abbott Diagnostics, Santa Clara, CA, USA) with the chemiluminescent immunoassay (CLIA) method. The TgAb analytical

measurement range is 1-1000 IU/ml and the reference range is < 4.11 IU/ml. The coefficient of variation (CV) values are < 8.2%. The fT4 analytical measurement range is 0.40-5.00 ng/dL and the reference range is 0.70–1.48 ng/dl. The CV values are < 7.8%. The TSH analytical measurement range is 0.01–100 µIU/ml and the reference range is 0.35–4.94 µIU/ml. The CV values are < 5.3%. The Tg levels were analysed with a Beckman Coulter Access 2 analyser (Beckman Coulter, Brea, CA, USA) with the CLIA method. The reportable range for Tg is 0.1–500 ng/ml and the reference range is 1.59-50 ng/ml. The CV values are < 6.6%. All the above-mentioned values are from the manufacturers' documents.

# Treatment protocol

# Surgical treatment

Less than half of our patients were operated on in our centre; more than half of them were operated on in other centres and referred to our centre for RIT. Total thyroidectomy (TT) was performed in 18 patients (36.4%), and total thyroidectomy plus central neck dissection (CND) was performed in 5 patients (9.6%). Near-total thyroidectomy (nTT) was performed in 15 patients (28.8%) and sub-total thyroidectomy (sTT) was performed in 14 patients (26.9%). The surgeon who performed the operations in our centre (SK) is experienced in thyroid surgery (12 years of experience with endocrine surgery). The total number of patients operated on in our centre was 23 (18 patients TT, 5 patients TT + CND). CND was performed in patients when there was either biopsy-proven lymph node metastases (n = 1) or suspicious findings were found preoperatively on neck ultrasound (n = 4). None of the patients underwent lateral neck dissection.

# Pre-ablation scanning with technetium-99m and neck ultrasonography

Pre-ablation screening with technetium-99m was performed to assess the size of the residual mass when TSH was at least 30 µIU/mL. Evaluations were made by a nuclear medicine specialist (OK). Pre-ablation neck ultrasonography was performed in all patients after surgery and before I-131 ablation using the Toshiba Aplio 300 (Toshiba Medical Systems Corporation, Tochigi, Japan) by one radiologist (HG) and one nuclear medicine specialist (OK). Peripheral vascularisation, microcalcification, cystic component, hyperechogenicity (thyroid tissue like), round shape and hilum absence in lymph nodes were classified as suspicious for metastasis. The decision was made by consensus.

# I-131 administration decision

Pathology results; TSH, Tg and Tg-Ab levels; pre-ablation technetium-99m scintigraphy; and ultrasonography results of the patients were evaluated in the council consisting of pathologists, endocrinologists, surgeons, radiologists and nuclear medicine specialists, and the treatment was decided by a consensus.

# I-131 administration

I-131 administration was initiated 2–4 months after surgery. Patients received 1.85 or 3.7 GBq of I-131 approximately 4 weeks after THW 2–3 week period of a low iodine-diet. At the time of I-131 administration,

serum TSH levels were > 30 μIU/mL in all patients.

# Post-ablation I-131 whole-body scintigraphy

Approximately seven days (4–12 days) after I-131 administration, the post-ablation planar whole-body scintigraphy was performed in anterior and posterior projections using a dual-head camera (Mediso AnyScan S SPECT, Mediso Medical Imaging Systems, Budapest, Hungary) equipped with high-energy, parallel-hole collimators. The images were evaluated by a nuclear medicine specialist (OK) who was blinded to the patient's identity, pathology results and Tg levels. The absence of radioiodine uptake in the thyroid bed or central-lateral lymph node compartment was considered a negative scan. We evaluated the presence of radioiodine distribution in the pyramidal lobe or thyroglossal duct located in the thyroid bed or superior midline as residual tissue.

# Research protocol

A nuclear medicine specialist (OK) and two thyroid endocrinologists (ŞA and UA) reviewed the staging and initial risk stratification of each patient, based on the clinical, surgical and pathological information as well as the post-ablation scintigraphy findings.

# Risk stratification

We classified the tumours using TNM staging according to the criteria of the American Joint Committee on Cancer (AJCC) 8th edition [21]. The risk classification of the patients and the RIT response were made according to the 2015 American Thyroid Association (ATA) criteria [9].

# Clinical outcome, dWBS, neck ultrasonography and questionnaire administration

After the I-131 administration, the patients were followed up in the endocrinology clinic. The patients were referred to the nuclear medicine clinic for the dWBS and evaluation of stimulated Tg at a median of 9 months (6–13 months) after RIT. We evaluated the TSH and fT4 levels of the patients. We informed the patients without overt hyperthyroidism and hypothyroidism about the questionnaire and administrated the SF-36 and SCL-90-R under the guidance of an expert (OK) (questionnaire 1: euthyroid state). We terminated the patients' LT4 use. After four weeks, the patients were given an appointment to receive 185 MBq via an oral I-131 capsule. They were recommended to consume a low-iodine diet for two weeks. We measured TSH, Tg, TgAb and fT4 levels when they arrived four weeks later. The same specialist applied the SF-36 and SCL-90-R questionnaires again to the patients with serum TSH > 30 μIU/mL (questionnaire 2: hypothyroid state). Ultrasonography was performed on the patients by OK and HG. We evaluated the absence of residue in the thyroid bed and the absence of pathological lymph nodes in the central/lateral neck compartment as a negative result. We then administered 185 MBq via an oral I-131 capsule to the patients. Two days after I-131 administration, a planar dWBS was performed in anterior and posterior projections using a dual-head camera equipped with high-energy, parallel-hole collimators. The dWBSs were evaluated by the same specialist (OK), who was blinded to the patients' Tg, TgAb levels, clinical findings and post-ablation WBS images. Radioiodine uptake in the thyroid bed, midline superior

thyroglossal duct cyst/pyramidal lodge and the central and lateral neck compartment was evaluated as residual disease.

# Treatment response assessment

An excellent response was negative imaging and either supressed Tg < 0.1 ng/ml or TSH-stimulated Tg < 1 ng/ml. A biochemically incomplete response was negative imaging and supressed Tg ≥ 1 ng/ml or stimulated Tg ≥ 10 ng/ml or elevated TgAb levels. A structurally incomplete response was structural or functional evidence of disease with any Tg level with or without TgAb. An indeterminate response was non-specific findings on imaging studies; faint uptake in the thyroid bed on radioactive iodine scanning; non-stimulated Tg detectable but < 1 ng/ml; stimulated Tg detectable but < 10 ng/ml; or TgAb stable or declining in the absence of structural or functional disease [9].

# Measurement of QoL

We applied the SF-36 to evaluate the patients' QoL. We also applied the SCL90-R psychological symptom screening test. We calculated the total score of these tests for each patient.

The SF-36 scale was developed by Ware et al. [22]. The validity and reliability study of the SF-36 in the Turkish population was performed by Koçyiğit et al. [23]; we used this Turkish version of the scale in our study. The SF-36 consists of 36 items and provides measurements of eight symptoms: physical functioning, role limitation due to physical health, energy/fatigue, emotional well-being, social functioning, pain, general health and health changes. The total score is obtained by adding the points given for each sub-scale, with a total score of 100. A decrease in the numerical score indicates deterioration in health.

The SCL-90-R psychological symptom screening test is a self-assessment instrument. The psychopathological symptoms are scored from 0 to 4 for 90 items, and the sub-scale scores – somatisation, anxiety, depression, obsession, intersensitivity, anger, paranoid, psychoticism, phobia, general symptom index and additional items (symptoms related to sleep disorders, appetite disorders and guilt) – are calculated [24]. The validity and reliability study of the SLC-90-R in the Turkish population was performed by Dağ et al. [25]; we used this Turkish version in our study.

# Statistics

Statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics of categorical variables are reported as frequency and percentages within the group (n, %). Continuous variables were subjected to normality analysis to determine their distributions. Changes between questionnaires 1 and 2 were evaluated with the paired-samples t test or the Wilcoxon signed rank test. The mean ± standard deviation (SD) and t values of the normally distributed variables or the median (min-max) and Z values of the non-normally distributed variables are presented. The limit of significance was accepted as $p < 0.05$.

## Results

## Study cohort

We included 52 female patients who underwent RIT between March 2017 and November 2017 (median age 48 years, range 23-65 years). TT was performed in 18 patients, nTT was performed in 15 patients, sTT was performed in 14 patients and TT + CND was performed in 5 patients. Metastatic lymph nodes were detected in 5 patients who underwent CND (17 metastatic lymph nodes with mean size 8.4 mm [range 4-11 mm]). The mean time between surgery and RIT was 60.85 ± 17.34 days. All patients had papillary thyroid carcinoma. Only 1 patient (2%) had stage 2 disease according to the TNM classification; all other patients had stage 1 disease. Forty-eight patients (92%) were in the low-risk group according to the ATA risk classification. Four patients (8%) were in the intermediate group. For treatment, 1850 MBq was administered to 7 patients and 3700 MBq I131 was administered to 45 patients. The main characteristics of the study population are shown in Table 1.

### *Pre-ablation Tc-pertechnetate scintigraphy and ultrasonography*

Tc-pertechnetate scintigraphy showed residual disease in 39 patients (75%). We could detect the residue by ultrasonography in 28 of these 39 patients. We did not detect residues by ultrasonography in the patients whose Tc-pertechnetate scintigraphy did not show residue.

### *Post-ablation whole body scan*

We observed iodine uptake in the thyroid bed in 46 patients (88.5%). In 6 patients (11.5%), iodine uptake was not observed in the thyroid bed in the neck. At the time of I-131 administration, there were 24 patients (46%) with stimulated Tg >1 ng/ml; 4 of these patients had TgAb detectable (> 4.1 IU/ml). There were 4 patients (8%) with stimulated Tg >10 ng/ml (19.5, 18.9, 21.7 and 10.4 ng/ml) at the time of I-131 administration. Stimulated TgAb was not detectable in any of these patients (all < 4.1 IU/ml). At the time of I-131 administration, stimulated TgAb was detectable (> 4.1 IU/ml) in 22 patients (42%) (median 11.98, range 4.4-502 IU/ml). Stimulated Tg was > 1 ng/ml in 4 of these 22 patients, and stimulated Tg was < 1 ng/ml in 18 patients. While TSH was suppressed, Tg was < 0.1 ng/ml in all patients. While TSH was suppressed, TgAb was detectable (> 4.1 IU/ml) in 4 patients.

The median time between the dWBS and post-ablative WBS was 9 months (6-13 months). While radioactive iodine uptake was not observed in the thyroid bed and central-lateral compartment in 50 patients (96.2%) based on the dWBS, low, faint radioiodine uptake was observed in the thyroid bed in 2 patients (3.8%). At the time of I-131 administration, all 4 patients with stimulated Tg >10 ng/ml had stimulated Tg < 1 ng/ml at the time of the dWBS. At the time of the dWBS, stimulated Tg was > 1 ng/ml in only 1 patient (2%) (4.20 ng/ml; at the time of I-131 administration, stimulated Tg was 8.6 ng/ml). At the time of I-131 administration, stimulated TgAb values of 22 patients were detectable, while stimulated TgAb values of 16 patients (73%) were undetectable at the time of the dWBS. In 6 patients (27%), TgAb levels decreased but were still detectable (median 30.95, range 4.91-76.74 IU/ml). TgAb of 2 patients with faint radioiodine uptake in the thyroid bed was detectable at the time of the dWBS (76.74 and 60.70 IU/ml).

While the treatment response was excellent in 45 patients (86.5%), there was an indeterminate response in 7 patients (13.5%); characteristics of these 7 patients are given in Table 2. At the time of TSH suppression, TgAb was detectable in 4 of these 7 patients (6.4, 14, 34 and 42 IU/ml). While 2 of the patients with an indeterminate response were in the intermediate risk group, the remaining 5 patients were in the low-risk group. Ablation success based on the dWBS only was 96.2%, based on Tg only was 98% and based on TgAb only was 88.5%. All patients underwent neck ultrasonography at the time of the dWBS, and no residual tissue or pathological lymph node was observed in the neck.

### SCL-90-R analysis

Between questionnaire 1 and questionnaire 2, there was significant worsening in anxiety ($Z = -2.052$, $p = 0.040$), psychoticism ($Z = -2.187$, $p = 0.029$), additional items ($Z = -2.306$, $p = 0.021$) and the general symptom index ($Z = -2.086$, $p = 0.037$). None of the other symptoms showed a significant change (depression, $t = -1.390$, $p = 0.171$; somatisation, $Z = -1.453$, $p = 0.146$; obsession, $Z = -0.700$, $p = 0.484$; intersensitivity, $Z = -1.194$, $p = 0.232$; paranoia, $Z = -0.261$, $p = 0.794$; anger, $Z = -1.115$, $p = 0.265$; phobia, $Z = -0.834$, $p = 0.404$) (Fig. 1).

### SF-36 analysis

Between questionnaire 1 and questionnaire 2, there was significant worsening in physical functioning ($t = 2.588$, $p = 0.013$), role limitation due to physical health ($Z = -2.677$, $p = 0.007$), energy/fatigue ($Z = -2.502$, $p = 0.012$), emotional well-being ($Z = -3.618$, $p < 0.0001$), social function ($Z = -3.179$, $p = 0.001$), general health ($Z = -2.397$, $p = 0.017$) and health change ($Z = -1.996$, $p = 0.046$). There was worsening of the pain symptom, but it was not statistically significant ($t = 1.234$, $p = 0.223$) (Fig. 2). A summary of the questionnaire data is given in Table 3.

## Discussion

There is a need to evaluate the treatment response in patients who have undergone RIT for differentiated thyroid cancer. This is usually done by evaluating the dWBS or stimulated Tg. However, hypothyroidism that we have created with THW causes some complaints in patients and negatively affects QoL. In this study, we performed LT4 THW to evaluate treatment response with a dWBS and stimulated Tg at 6–12 months after RIT in patients with low-risk, well-differentiated thyroid cancer. Using questionnaires, we found that hypothyroidism adversely affected QoL (based on the SF-36) and worsened psychological symptoms (based on the SCL-90-R). With the SF-36, we found significant worsening in physical functioning, role limitation due to physical health, energy/fatigue, emotional well-being, social function, general health and health change symptoms at the time of the dWBS. There was a worsening of the pain symptom, but it was not statistically significant. With the SCL-90-R, we detected significant worsening in anxiety, psychoticism, additional items, and general symptom index symptoms at the time of the dWBS. Although other symptoms worsened, the results were not statistically significant. Banihashem et al. [26] investigated the psychological status and QoL of 150 patients who had undergone thyroidectomy for differentiated thyroid cancer. They evaluated the patients at four different times: 1 month before RIT, at the

time of RIT and 1 week and 6 months after RIT. Differently from our study, they used the Hospital Anxiety and Depression Scale (HADS) to measure the psychological state of the patients. The SF-36 was applied to determine QoL. According to the SF-36 survey, they determined that the greatest deterioration in QoL was during the period of RIT. They stated that the reason for this was hypothyroidism caused by LT4 withdrawal [26]. Botella-Carretero et al. [27] investigated psychometric functionality and QoL in patients with DTC. Fifty female patients with differentiated thyroid carcinoma were compared with 18 healthy female patients in the same age group. At the time of the dWBS, when in the hypothyroid state, a comparison was made with healthy female patients in the control group, and impairment was found in QoL and cognitive performance [27]. Tagay et al. [28] applied QoL assessments to 136 patients with thyroid cancer while they were in a hypothyroid state in preparation for radioiodine administration. The available results were compared with German population reference values. All values of the SF-36 were lower than the reference values of the population [28]. One of the differences from our study is that we have compared the QoL scores in the hypothyroid period with the QoL scores of the same patients in the euthyroid period 4 weeks before, not with the reference values of the population. We tried to evaluate the effects of deep hypothyroidism, which we developed in a short time, on QoL, free from all factors. To eliminate the gender factor, we did not include male patients, and we excluded patients with chronic diseases known to impair QoL as well as patients using chronic pain medication. When comparing a patient's QoL with community reference values, it should be taken into account that there may be differences in QoL within the society due to social, cultural, economic and regional reasons.

Thyrotropin alfa has been used for a long time to prepare thyroid cancer patients before radioiodine administration to reduce the adverse effects of LT4 THW on QoL, to reduce the radiation dose to the body and perhaps to reduce the cost of the treatment by shortening the hospital stay [10, 11, 29–31]. In two prospective studies evaluating the ablation success of low-dose and high-dose I-131 administration in patients with low risk differentiated thyroid cancer, QoL deteriorated in the group of patients who had undergone THW. The authors reported that there was no deterioration in QoL in the group administered thyrotropin alfa or the deterioration was much less compared with the LT4 withdrawal group, and this effect was independent of the applied radiation dose. They stated that thyrotropin alfa is superior to LT4 withdrawal in terms of radiation exposure and side effects [29, 32]. Because the aim of our study was to evaluate whether the hypothyroidism we created adversely affected QoL, we did not administer thyrotropin alfa. In addition, thyrotropin alpha is imported in Turkey, access to it is not always possible and it is an expensive product, approximately €684, which is too high for developing countries. We can only administer thyrotropin alfa to select patients who have comorbidities and cannot tolerate hypothyroidism.

In a multicentre prospective randomised study published in 2012, patients with low-risk, well-differentiated thyroid cancer were treated with low-dose (30 mCi) and high-dose (100 mCi) I-131 and the treatment response was evaluated with a dWBS 6–12 months later. The treatment response rates were high (88.9%) and there was no significant difference in the treatment response between the low-dose and the high-dose groups. As a result, the authors stated that 30 mCi was sufficient for ablation success in low-risk patient groups. Neck pain and nausea were more common in the high-dose group [29]. Another prospective, multicentre, randomised study published in the same year evaluated treatment response in patients treated

with 30 or 100 mCi I-131. The authors did not include patients with aggressive histological variants and TgAb detectable patients. At the time of I-131 administration, the proportion of patients with a stimulated Tg > 1 ng/ml was only 4.8% (compared with 46% in our study). The treatment response success rate was 92%. There was no statistically significant difference between the treatment response rates between the low-dose and high-dose I-131 groups. They explained the high success rate as follows: all patients underwent total thyroidectomy, resulting in a lower remnant volume. As another reason, they did not consider faint uptake, which is frequently observed with a dWBS and which they thought had no clinical impact [32]. Our treatment success rate was 86.5%, which is similar to the two studies. We applied 3700 MBq to 45 patients and 1850 MBq to 7 patients. However, there were some differences not only in the dose of RIT we applied, but also in our patient population. In our study, the rate of patients with stimulated Tg > 1 ng/ml at the time of I-131 administration was 46%, which suggests that postoperative remnant tissue is at a considerable level. In addition, we did not exclude aggressive histological variants such as tall cell and oncocytic. Approximately 10% of our patients had lymph node metastases and we had patients with positive surgical margins. Unlike our study, the authors excluded patients stimulated TgAb detectable at the time of ablation, whereas 42% of our patient group consisted of TgAb-detectable patients [32]. They ignored patients with faint uptake in dWBS on the grounds that faint uptake had no clinical impact [8, 33]. Our 2 patients had faint uptake and we defined it as an indeterminate response. One of the reasons for high-dose I-131 administration to our patients is that our patient group was heterogeneous, and studies have indicated that high-dose administration may be more effective than low-dose administration in ablating large, normal thyroid remnants and eliminating micrometastases [34–36].

TgAb can be detected at diagnosis or treatment in approximately 25% of patients with differentiated DTC. When TgAb is present, it interferes with Tg measurement, causing falsely low or undetectable Tg values that can mask the disease [37]. Transient elevation or de novo appearance of TgAb is seen 4–8 weeks after thyroidectomy, prior to radioiodine therapy in approximately 40% of patients. This increase appears to be unrelated to the preoperative Tg or TgAb concentration or the risk of recurrence and is most likely an immune response to the acute release of large amounts of Tg antigen by surgical trauma. It has been shown that the change in TgAb over time after RIT during the diagnosis and treatment process rather than its absolute values has a prognostic significance [38]. For these reasons, we did not analyse the effect of TgAb on treatment response success. At the time of I-131 administration, TgAb was detectable in 22 of our patients. The remaining 30 patients had stimulated TgAb that was undetectable at the time of ablation. We wanted to study the effect of the stimulated Tg level at the time of I-131 administration on the success of the treatment response, but none of these 30 patients had any residuals on the dWBS (regardless of whether stimulated Tg < 1 vs > 1 ng/ml or < 10 vs > 10 ng/ml). While TSH was suppressed, Tg was < 0.1 ng/ml in all of our patients, and none of the patients had residuals on the dWBS. While TSH was suppressed, non-stimulated TgAb was detectable in 4 patients, 2 of whom had residuals on the dWBS. It is known that the stimulated Tg level at the time of the dWBS is highly sensitive in predicting the success of the treatment response [39]. Studies have shown a correlation between the dWBS findings and the stimulated Tg level at the time of the dWBS; in fact, the stimulated Tg level is more sensitive than the dWBS [40–42]. In our study, there was a similar relationship between the dWBS and the stimulated Tg

level. In 29 of 30 patients with TgAb absence at the time of ablation, the stimulated Tg level was < 0.1 ng/ml at the time of the dWBS, and none of these patients had residuals on the dWBS.

Our study has some limitations. The main limitation is that it is from a single centre. Another limitation is that all surgeries were not performed in the same centre, so a standard surgical procedure was not applied. Perhaps our most important limitation is why patients were not administered low-dose (1.1 GBq) I-131. Some of our patients had aggressive histological variants, tumours at the surgical margin and lymph node metastases. In addition, due to the fact that TT was not performed in all patients, the relatively high residuals in the pre-ablation evaluations was one of the reasons for our high dose application. One of the reasons why we administer high doses in our clinic is that Turkey is one of the countries that has been affected by the Chernobyl nuclear accident. The incidence of thyroid cancer has increased in our country, similarly to other countries [43, 44]. Moreover, thyroid cancer may have a worse prognosis in areas affected by the Chernobyl nuclear accident [45, 46]. Multicentre, prospective, randomised studies were published for the first time in 2018 and 2019 on the association of low- and high-dose administration with recurrence in patients with low-risk differentiated thyroid cancer. The median follow-up was 6.5 and 5.4 years. As a result, it was stated that low-dose and high-dose application did not have a statistically significant effect on recurrence, and low-dose application caused fewer side effects [47, 48]. Our study group consisted of patients who received high-dose treatment in 2017. After these last two articles were published, low-dose administration in patients with low-risk thyroid cancer became more preferred in our centre, as in many centres in our country. Another limitation was the small number of patients and faint uptake in only 2 patients in dWBS. For these reasons, we could not study the prognostic value of Tg levels stimulated at the time of administration and at the time of TSH suppression in in terms of the presence of residue in dWBS.

In conclusion, our RIT ablation success rate was similar to ablation success rates with different doses of I-131 administration. Unfortunately, we have shown with the questionnaires we applied during the euthyroid and hypothyroid periods that hypothyroidism, which we created for stimulated Tg examination and dWBS application in low-risk female patients, adversely affects QoL and worsens psychological symptoms. Our findings show that evaluations that involve the stimulated Tg level and dWBS may have side effects rather than contribution in patients with low-risk differentiated thyroid cancer without TgAb interference and access to USG.

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# Tables

| Parameter | N (%) |
|---|---|
| Surgery | |
| • TT | 18 (36.4) |
| • nTT | 15 (28.8) |
| • sTT | 14 (26.9) |
| • TT +CND | 5(9.6) |
| Histology | |
| Classical | 33 (63.5) |
| Mixt+classical | 3 (5.8) |
| Folicular | 13 (25) |
| Tall cell | 2 (3.8) |
| Oncositic | 1 (1.9) |
| Multifocality | 39 (75) |
| Tumor at surgery margin | 6 (11.5) |
| Microcarcinoma | 21 (40.4) |
| Vascular invasion | 2 (3.8) |
| TNM stage 1 | 51 (98) |
| T1 | 37 (71.2) |
| T1a | 20 (38.5) |
| T1b | 17 (32.7) |
| T2 | 13 (25) |
| T3a | 2 (3.8) |
| N0 | 46 (88.4) |
| N0a | 10 (19.2) |
| N0b | 36 (69.2) |
| N1a | 5 (9.6) |
| Nx | 1 (1.9) |
| M0 | 52 (100) |
| ATA low risk | 48 (92.3) |
| ATA intermediate risk | 4 (7.7) |
| Iodine-131 dose | |
| 1850 MBq | 7 (13.5) |
| 3700 MBq | 45 (86.5) |
| Treatment response | |
| Excellent | 45 (86.5) |
| Indeterminate | 7 (13.5) |

Table 1. The haracteristics of the study population.

Abbreviations: TT, total thyroidectomy; nTT, near total thyroidectomy; sTT, sub-total thyroidectomy; CND, central neck dissection; ATA, American thyroid Association.

| Patient no | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Age | 54 | 50 | 50 | 42 | 43 | 64 | 25 |
| Surgery | sTT | TT | nTT | sTT | TT | TT | TT+CND |
| pTN | T2N0a | T1bN0b | T1bN0b | T1bN0b | T1aN0b | T1bN0b | T1bN1a |
| Tumor Size (cm) | 3 | 1.6 | 1.2 | 1.2 | 0.9 | 1.4 | 1.2 |
| Multifocality | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Tumor presence at surgery margin | No | No | No | Yes | Yes | No | No |
| Vascular invasion | Yes | No | No | No | No | No | No |
| Lymph node metastasis | No | No | No | No | No | No | Yes |
| Histology | Classic | Classic | Follicular | Mixt+classic | Classic | Classic | Tall cell |
| Post-ablation iodine uptkae | Tiroid bed | Tiroid bed | Tiroid bed | Tiroid bed | Tiroid bed | Tiroid bed | Tiroid bed |
| TSH level at the time ofI-131 administration µIU/mL | 46.8 | 100 | 36.7 | 100 | 56.9 | 82.8 | 100 |
| Tg level at the time ofI-131 administration ng/mL | 4.29 | 0.4 | 0.1 | 0.1 | 0.1 | 0.1 | 8.6 |
| TgAb level at the time ofI-131 administration IU/mL | 85.2 | 9.96 | 502.2 | 470.7 | 47.4 | 10.86 | 2 |
| dWBS iodine uptake | Tiroid bed | No Uptake | No Uptake | Tiroid bed | No Uptake | No Uptake | No Uptake |
| TSH level at the time of dWBS µIU/mL | 55.8 | 100 | 30.4 | 100 | 38.7 | 93.8 | 100 |
| Tg level at the time of dWBS ng/mL | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 4.2 |
| TgAb level at the time of dWBS IU/mL | 76.7 | 4.91 | 27.4 | 60.7 | 6.99 | 8.99 | 1.8 |
| TgAb level at the time of TSH supression IU/mL | 42 | 1 | 14 | 34 | 2 | 6.4 | 1 |
| Tg levels at the time of TSH supression ng/mL | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 |

Table 2. Characteristics of 7 patients with indeterminate response.

Abbreviations: TT, total thyroidectomy; nTT, near total thyroidectomy; sTT, sub-total thyroidectomy; CND, central neck dissection; dWBS, diagnostic whole body scan.

| SCL-90 mean±SD/median (min-max) | | | | SF-36 mean±SD/median (min-max) | | | |
|---|---|---|---|---|---|---|---|
| **Sypmthoms** | **Questionnaire1** | **Questionnaire2** | **p** | **Sypmthoms** | **Questionnaire1** | **Questionnaire2** | **p** |
| **Depression** | 0.814±0.580 | 0.903± 0.605 | 0.171 | **Energy fatique** | 60 (0-100) | 50 (5-100) | **0.012** |
| **Somatisation** | 1.0 (0.25-2.75) | 0.958 (0.083-3.0) | 0.146 | **Physical function** | 80 (10-100) | 70 (5-100) | **0.013** |
| **Anxiety** | 0.450 (0.0-2.1) | 0.600 (0.0-2.0) | **0.04** | **Phsical health (role limit)** | 83.350 (0-100) | 50 (0-100) | **0.007** |
| **Obsession** | 0.850 (0.1-3) | 0.900 (0.0-2.8) | 0.484 | **Emotional well-being** | 68 (12-100) | 60 (24-92) | **0.0001** |
| **intersensitivity** | 0.666 (0.00-3.11) | 0.666 (0.00-3.22) | 0.232 | **Social function** | 75 (38-100) | 75 (13-100) | **0.001** |
| **Psycotic** | 0.200 (0.00-2.00) | 0.250 (0.00-1.7) | **0.029** | **Health change** | 62.50 (25-100) | 50 (0-100) | **0.046** |
| **Paranoid** | 0.333 (0.00-2.17) | 0.333 (0.00-1.83) | 0.794 | **Pain** | 72.75±25.52 | 68.43±22.66 | 0.223 |
| **Anger** | 0.416 (0.00-1.67) | 0.500 (0.00-1.83) | 0.265 | **General health** | 60 (0-90) | 55 (0-95) | **0.017** |
| **Phobic** | 0.285 (0-1.28) | 0.285 (0-1.42) | 0.404 | | | | |
| **Additional items** | 0.857 (0-2.57) | 1.0 (0.0-2.571) | **0.021** | | | | |
| **General Sympthom index** | 0.583 (0.06-2.02) | 0.767 (0.78-1.82) | **0.037** | | | | |

Table 3. The summary of SF-36 and SCL-90-R questionnaires

# Declarations

Competing interests: All authors declare that they have no conflict of interest.

# Figures

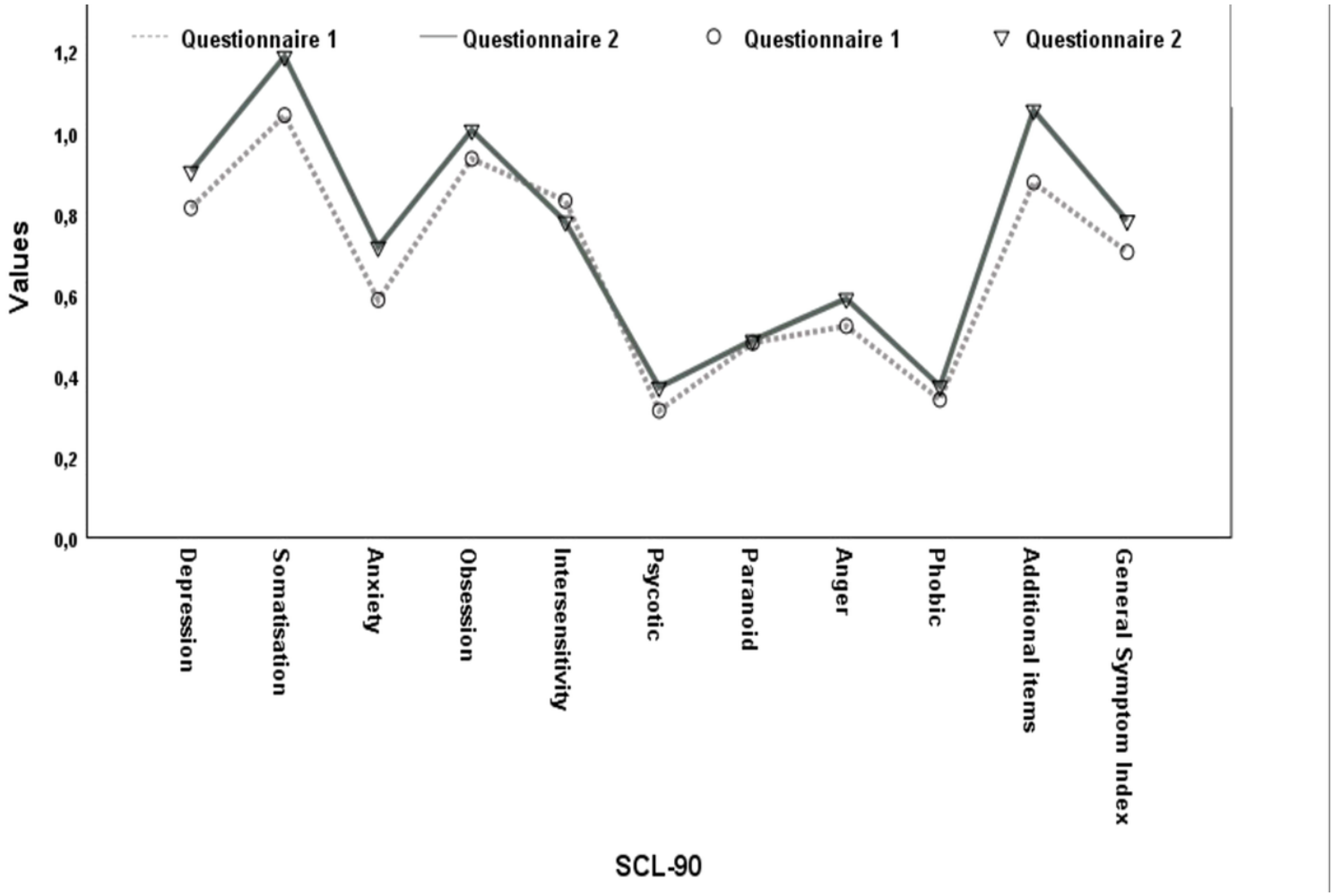
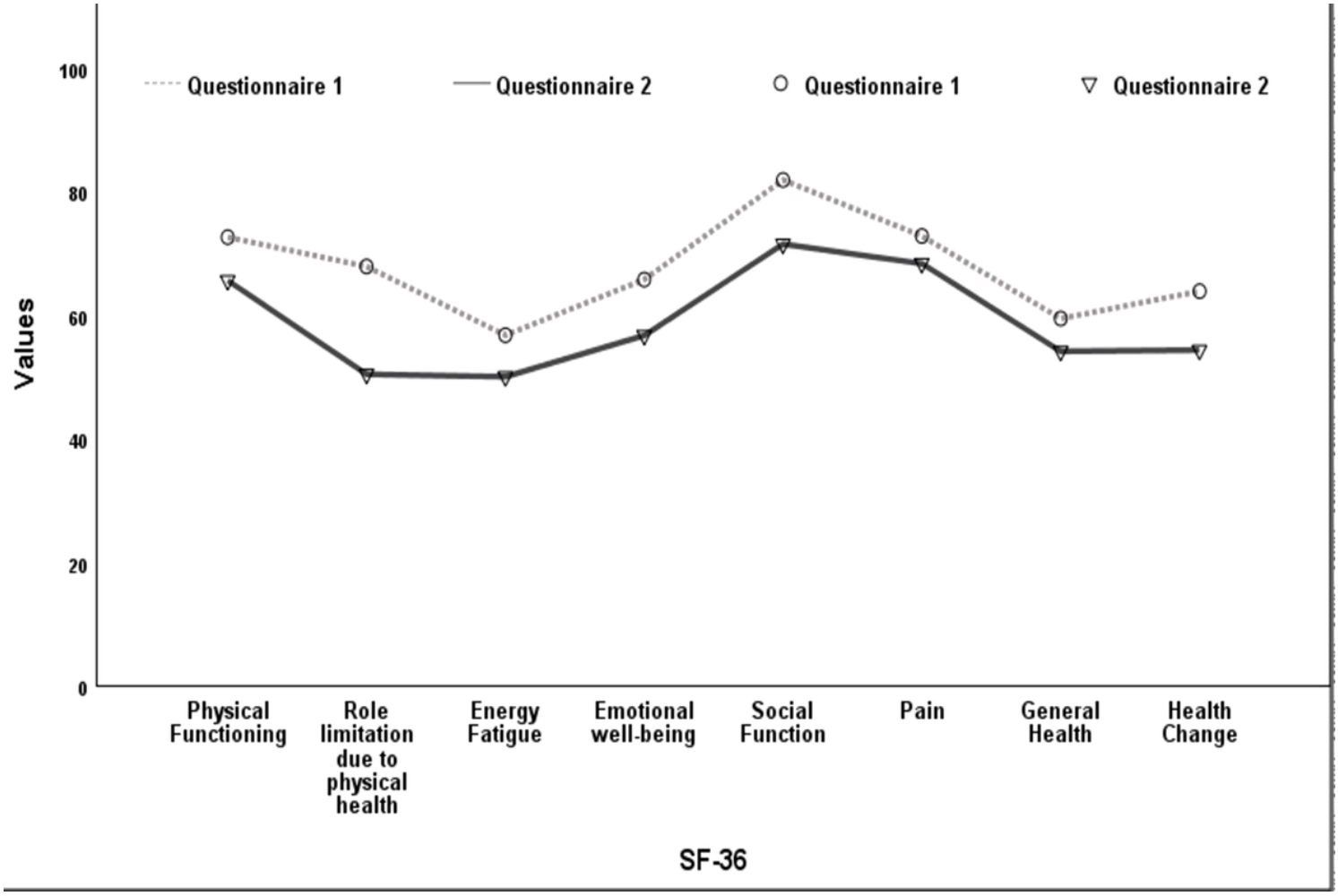



**Figure 1**

Graph showing the differences in The Symptom Checklist-90-Revised symptoms between questionnaire 1 and questionnaire 2.




## Figure 2

Graph showing the differences in Short form-36 symptoms between questionnaire 1 and questionnaire 2.