

Psychological Status and Quality of Life Associated with Radioactive Iodine Treatment of Patients with Differentiated Thyroid Cancer: Results of Hospital Anxiety and Depression Scale and Short-Form (36) Health Survey

Abstract

Purpose: The objective is to investigate psychological status and quality of life (QoL) using Hospital Anxiety and Depression Scale (HADS) and Short-Form (36) Health Survey (SF-36) questionnaires in patients with proven differentiated thyroid cancer (DTC) who are referred for radioactive iodine (RAI) ablation before, during, and after treatment. **Methods:** Of patients who underwent total thyroidectomy with a pathologically proven DTC (papillary and follicular types) referred for RAI treatment to our department in 2018, 150, in whom the diagnosis was newly established, were referred for the first course of RAI treatment and were consecutively enrolled in the study. The patients received an oral dose of radioiodine (3700 or 5550 MBq). For evaluation of anxiety, depression, and QoL, all patients are given two standard questionnaires, HADS, and SF-36 and are requested to answer them at four time points. First one was at 1 month before RAI, second was at the time of RAI treatment. Third and fourth ones were 1 week and 6 months later, respectively. **Results:** The mean age of patients was 39.17 (± 12.95) years and 121 (80.7%) were female and 29 (19.3%) were male. Values of HADS and SF-36 scores at corresponding time points were significantly correlated using Pearson correlation (HADS and SF-36 scores at 1 month before RAI: $r = -0.56$, $P < 0.001$; at time of RAI: $r = -0.71$, $P < 0.001$; 6 months after RAI: $r = 0.19$, $P = 0.021$). Using paired-sample *t*-test, for HADS, except for difference between time points of 1 month before RAI and time of RAI, pairwise difference between scores of other time points was statistically significant after Bonferroni correction. For SF-36, pairwise difference between scores of all three time points was statistically significant. Interaction of age, gender, RAI dose, and thyroid-stimulating hormone level at the time of RAI on HADS and SF-36 scores did not show statistical significance. **Conclusion:** Trend in scores over several-months' time discloses gradual improvement of QoL and merits close observation but limited psychiatric intervention.

Keywords: Differentiated thyroid cancer, Hospital Anxiety and Depression Scale, psychological status, quality of life, radioactive iodine, short-form (36) health survey

Introduction

Differentiated thyroid cancers (DTCs), including papillary and follicular types, as one of the most common malignancies of the endocrine system reveal a growing incidence but concomitantly decreased mortality and longer survival over the past decade.^[1-3] Treatment and follow-up of such patients are seriously challenging for health-care practitioners and may exert a massive impact on the psychological status and quality of life (QoL) of patients and their families. Assessment of QoL in such patients may improve the status of care provided after surgical operation

of the neck and radioactive iodine (RAI) therapy as the two major therapeutic options. To date, there is little evidence regarding the impact of initial treatment and subsequent follow-up on the QoL in these patients, of which most of the studies have employed other questionnaires for psychological and QoL assessments.^[4-6] It seems that no acceptable tool exists for the evaluation of QoL, particularly in patients with DTCs. It is clearly evident that the QoL in patients who underwent treatment for DTCs is much lower than that in the normal population. Taken together, the need exists for a standardized tool for

Seyedshahab Banihashem, Mehdi Arabzadeh, Reyhaneh Sadat Jafarian Bahri, Mohsen Qutbi¹

Departments of Psychosomatic Medicine and ¹Nuclear Medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Address for correspondence:

Dr. Mohsen Qutbi,
Department of Nuclear
Medicine, Taleghani Hospital,
Yaman Street, Velenjak, Tehran
1985711151, Iran.
E-mail: mohsen.qutbi@gmail.
com, mohsen.qutbi@sbm.u.ac.ir

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psychological assessment and strategies to improve the status of QoL during the treatment and thereafter. Research on the QoL in the Iranian patients with DTCs has been scarcely conducted. However, Short-Form (36) Health Survey (SF-36) questionnaires are validated in healthy Iranian population.^[7] Hospital Anxiety and Depression Scale (HADS), as a standard questionnaire for evaluation of hospital-related anxiety and depression in patients with general medical conditions, is currently a widely used tool in medical research because of its distinct advantages in the assessment of anxiety and depression which occur concomitantly.^[8,9] In the present study, it aimed to investigate the psychological status and QoL in patients with proven DTC (papillary or follicular types) who underwent total thyroidectomy and are referred for RAI ablation before, during, and after treatment.

Methods

Patient population

Of patients who underwent near-total or total thyroidectomy with a pathologically proven differentiated thyroid cancer (papillary and follicular types) referred for radioiodine treatment to our department, 150 were selected and enrolled in the study, with the following criteria: newly established diagnosis and being referred for the first course of radioiodine treatment and eligibility to receive a fixed dose of 3700 or 5550 MBq. Informed consent was obtained from all patients included in the study. Patients aged under 18 and above 70 years are excluded to reduce the potential confounding effect of age on the psychological assessments. All individuals with a prior major medical condition or psychological/psychiatric disorder or on psychotropic drugs were also excluded from the study.

Radioactive iodine treatment

After surgical removal of the thyroid gland, patients who were on thyroxine therapy postoperatively were asked to withdraw ingesting levothyroxine tablets for 3–4 weeks and maintain a low-iodine diet for 2 weeks before treatment. Patients in whom the postoperative thyroxine therapy was not started were only requested to complete the 3–4-week period of withdrawal and 2-week period of the low-iodine diet. The patients were hospitalized and received an oral fixed dose of radioiodine (3700 or 5550 MBq). After 2 days of isolation, based on dosimetry results, patients were discharged with necessary instructions for radiation safety and protection. Levothyroxine replacement therapy was also started at the time discharge.

Assessment of psychological status

For evaluation of anxiety, depression, and QoL, all patients were given two standard questionnaires, HADS and SF-36, and are requested to answer them. For the evaluation of QoL, the SF-36 is employed which is a validated measure of the status of health. This questionnaire contains 36

items that the patients were expected to report.^[10,11] HADS, another validated and widely used questionnaire, is used for the evaluation of anxiety and depression in patients with a medical condition.^[9] Assessment of psychological status of patients using the aforementioned questionnaires was conducted at three and four time points for SF-36 and HADS questionnaires, respectively. The first one (SF-36₍₁₎ and HADS₍₁₎) was at 1 month before RAI administration (i.e., the start of levothyroxine withdrawal) and the second (SF-36₍₂₎ and HADS₍₂₎) was at the time of hospitalization for RAI treatment. The third (HADS₍₃₎) and the fourth (SF-36₍₃₎ and HADS₍₄₎) ones were 1 week and 6 months after receiving the dose, respectively. At 1 week after RAI, the SF-36 questionnaire was not used. At the first, third, and fourth time points, the questionnaires were filled in by one psychology practitioner. However, for the second time point, i.e., at the time of hospitalization, the patients were asked to fill the forms. Where appropriate, the items and questions were further clarified by the same practitioner.

Statistical analysis

Descriptive and analytical statistical methods were employed for the analysis of the variables using a SPSS software package, IBM® SPSS® Statistics for Windows, Version 24.0, Chicago, IL, United States. For evaluation of the correlation between values of scores of SF-36 and HADS questionnaires at each time point, a Pearson correlation test was used. Then, a paired sample *t*-test was used to compare the values of scores of each questionnaire at different time points. This pairwise comparison was performed for all time points, and for assessing statistical significance, a Bonferroni correction was used. Concomitantly, General Linear Model and Repeated Measures were utilized for the analysis of the scores of the patients in HADS and SF-36 questionnaire at several time points. The variables, gender and RAI dose, were also included into the model, separately or simultaneously, to evaluate the interaction of these variable on scores of SF-36 and HADS. Moreover, finally, the variables, age and thyroid-stimulating hormone (TSH) level at the time RAI administration, were used and entered into the model as covariates. A level of 0.05 for *P* values was considered as statistically significant.

Results

The basic characteristic data of the patients recruited in the study are summarized in Table 1. The mean values of the HADS and SF-36 scores are presented in Table 2, and the corresponding error bar plot as well as the plots separated by gender and RAI dose are presented in Figures 1 and 2, respectively. Values of HADS and SF-36 scores at corresponding time points were significantly correlated using Pearson correlation (HADS and SF-36 scores at 1 month before RAI: $r = -0.56$, $P < 0.001$; at time of RAI: $r = -0.71$, $P < 0.001$; and at 6 months

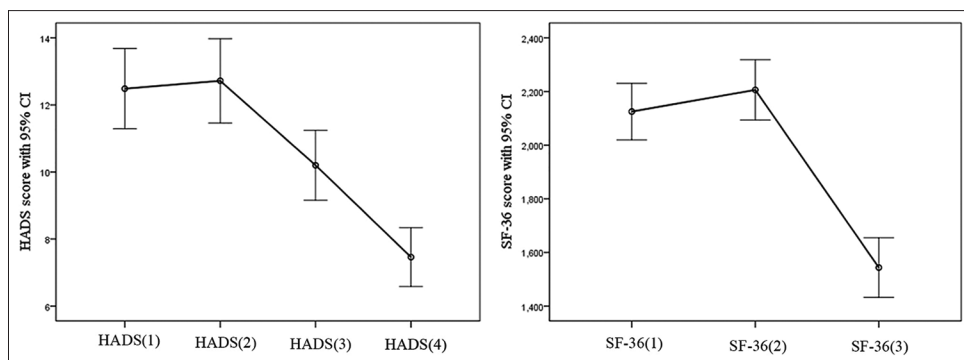


Figure 1: The error bar plot with the line connecting the means at different time points of Hospital Anxiety and Depression Scale and Short-Form (36) Health Survey scores. Nearly similar pattern is observed in these two questionnaires

Table 1: Basic characteristic data of the patients recruited in the study

Description	Value (n=150)
Age	
Female	38.21±12.53 ^a
Male	43.14±14.15
Total	39.17±12.95
Range	19-75
Gender (female:male), n (%)	121 (80.7):29 (19.3)
Tumor type, n (%)	
Papillary	142 (94.7)
Follicular	5 (3.3)
Hurtle cell	3 (2.0)
RAI dose, n (%)	
3700 MBq	65 (43.3)
5550 MBq	85 (56.7)
TSH	72.04±31.86 (75.00) ^b

^aMean±SD, ^bMean±SD (median). SD: Standard deviation, RAI: Radioactive iodine, TSH: Thyroid-stimulating hormone

Table 2: Mean values of Hospital Anxiety and Depression Scale and Short-Form-36 scores at different time points

Description	Mean±SD
HADS	
HADS ₍₁₎	12.49±7.42 ^a
HADS ₍₂₎	12.72±7.79
HADS ₍₃₎	10.20±6.47
HADS ₍₄₎	7.46±5.44
SF-36	
SF-36 ₍₁₎	2125.33±652.63
SF-36 ₍₂₎	2206.23±698.04
SF-36 ₍₃₎	1543.33±688.88

^aMean±SD. HADS: Hospital Anxiety and Depression Scale, SF-36: Short-form-36, SD: Standard deviation

after RAI: $r = 0.19$, $P = 0.021$). The scatter plots are demonstrated in Figure 3. By performing paired sample t -test, for HADS questionnaire, except for the difference between time points of 1 month before RAI and at time of RAI, the pairwise difference between scores of other time points were statistically significant, even after Bonferroni correction. For SF-36 questionnaire, the pairwise difference

between scores of all three time points was statistically significant [Table 3].

Parallel to paired sample t -test, tests of within-subjects effects (in analysis of general linear model/repeated measures) showed a significant difference in HADS scores in four time points ($F_{(2.098,306.364)} = 42.871$, $P < 0.001$, $\eta^2 = 0.227$) as well as in SF-36 scores in three time points ($F_{(1.411,206.15)} = 54.661$, $P < 0.001$, $\eta^2 = 0.272$).

The interaction of HADS scores with gender and RAI dose and also with concomitant consideration of gender and RAI dose was not statistically significant ($P = 0.344$ for gender, $P = 0.492$ for RAI dose, and $P = 0.752$ for concomitant consideration of gender and RAI dose). In tests of between-subjects effects, differences in HADS scores in different subgroups of gender (female/male), RAI dose (100 or 150 mCi), and gender/RAI dose were not statistically significant ($P = 0.096$ for gender, $P = 0.477$ for RAI dose, and $P = 0.391$ for gender/RAI dose). The interaction of SF-36 scores with gender and RAI dose and also with concomitant consideration of gender and RAI dose was not statistically significant ($P = 0.505$ for gender, $P = 0.583$ for RAI dose, and $P = 0.865$ for concomitant consideration of gender and RAI dose). In tests of between-subjects effects, differences in HADS scores in different subgroups of gender (female/male), RAI dose (3700 or 5550 MBq), and gender/RAI dose were not statistically significant ($P = 0.247$ for gender, $P = 0.081$ for RAI dose, and $P = 0.121$ for gender/RAI dose).

For the effect of age and TSH level at the time of RAI administration on the HADS scores, entering these variables as covariates did not show statistical significance ($P = 0.071$ for age and $P = 0.542$ for TSH level). For the effect of age and TSH level at the time of RAI administration on the SF-36 scores, entering these variables as covariates did not show statistical significance ($P = 0.071$ for age and $P = 0.614$ for TSH level).

Discussion

The present study was conducted to investigate the psychological status and QoL in patients with thyroid

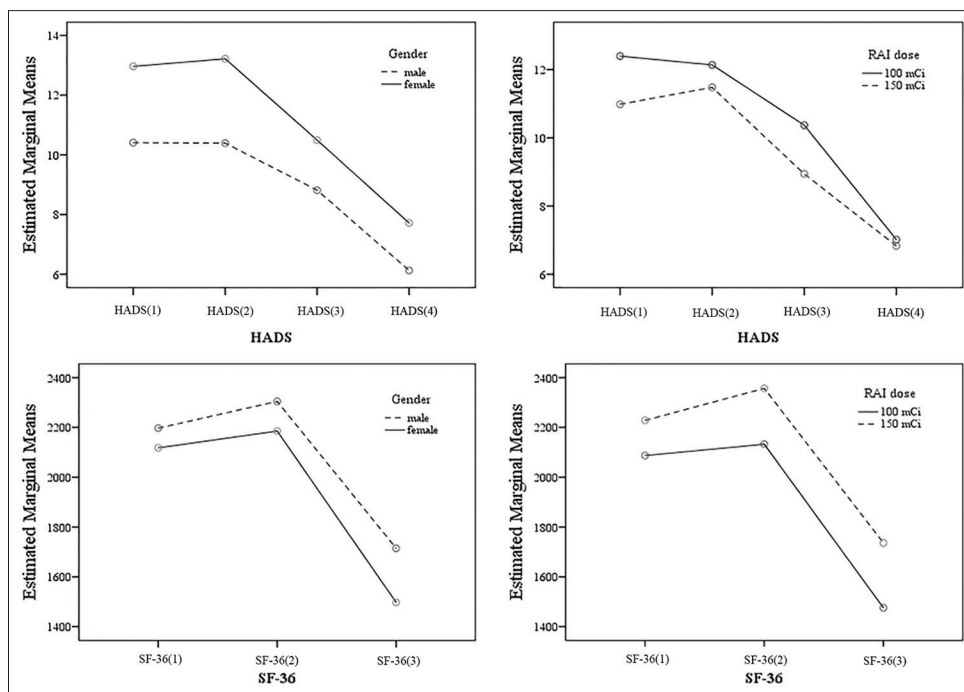


Figure 2: The error bar plot of Hospital Anxiety and Depression Scale (upper panel) and Short Form (36) Health Survey (lower panel) questionnaires separated by gender and radioactive iodine dose

Table 3: Mean difference and 95% confidence interval				
Description (difference)	Mean±SD	95% CI	P	
HADS				
HADS ₍₁₎ - HADS ₍₂₎	-0.23±3.33	-0.77-0.30	0.392	
HASD ₍₁₎ - HADS ₍₃₎	2.29±4.45	1.57-3.00	0.000	
HADS ₍₁₎ - HADS ₍₄₎	5.03±6.01	4.06-6.00	0.000	
HADS ₍₂₎ - HADS ₍₃₎	2.52±4.04	1.87-3.17	0.000	
HADS ₍₂₎ - HADS ₍₄₎	5.26±5.64	4.35-6.17	0.000	
HADS ₍₃₎ - HADS ₍₄₎	2.74±4.30	2.05-3.43	0.000	
SF-36				
SF-36 ₍₁₎ - SF-36 ₍₂₎	-80.90±378.09	-141.90--19.89	0.010	
SF-36 ₍₁₎ - SF-36 ₍₃₎	582.00±717.66	466.21-697.79	0.000	
SF-36 ₍₂₎ - SF-36 ₍₃₎	662.90±737.04	543.98-781.82	0.000	

Numbers in the parentheses as indices represent the time points of the HADS or SF-36 scores as follows: (1): 1 month before RAI; (2): At time of RAI; (3): 1 week after RAI and (4): 6 months after RAI. HADS: Hospital Anxiety and Depression Scale, SF-36: Short-form-36, SD: Standard deviation, CI: Confidence interval, RAI: Radioactive iodine

cancer who underwent a RAI treatment. For measurement of QoL, a SF-36 questionnaire was used at three time points: 1 month before RAI, at the time of RAI, and then 6 months later. Moreover, to evaluate anxiety and depression, a HADS questionnaire was employed at four time points: 1 month before RAI, at the time of RAI, and then 1 week and 6 months later. For patients who have undergone total thyroidectomy and are candidates for RAI treatment, a 4-week period of thyroid hormone withdrawal is recommended before scheduled RAI treatment. During this period, patients become hypothyroid. As the hypothyroid status may bear a significant effect on

the psychological status and QoL and can be considered as the most important factor in reducing QoL, the first assessment (SF-36₍₁₎ and HADS₍₁₎) was conducted at the beginning of this period as the baseline status and the second assessment (SF-36₍₂₎ and HADS₍₂₎) was performed at the time of hospitalization to receive RAI to assess the effect of induced hypothyroidism. The latter was done to evaluate how the QoL is influenced by iatrogenic hypothyroidism. After administration of RAI, acute adverse effects of RAI treatment, including xerostomia, discomfort in salivary glands, and gastrointestinal problems, will emerge within 24–48 h. A week later, patients were assessed for the third time (HADS₍₃₎). At this time point, the focus is on the assessment of QoL influenced by limitations of 2-day isolation and acute adverse effects of RAI treatment. Patients generally resume consumption of levothyroxine on the 3rd day. By this time, the hypothyroidism mitigates to some extent. At this time point, the assessment of QoL by SF-36 questionnaire was not performed, owing to the slow pace of changes in QoL indices and thus irrelevance and lower applicability of such evaluation. Assessment 6 months later (SF-36₍₃₎ and HADS₍₄₎), is conducted when the acute adverse effects of RAI have eliminated, and the metabolic status and serum level of thyroid hormones have stabilized. To alleviate the potential confounding effect of experience from previous episodes of treatment in patients with prior history of RAI therapy, we only included the individuals who were newly diagnosed and were referred for RAI treatment for the first time.

Our results demonstrated that the lowest value of SF-36 scores was at 6 months after RAI and the highest value was

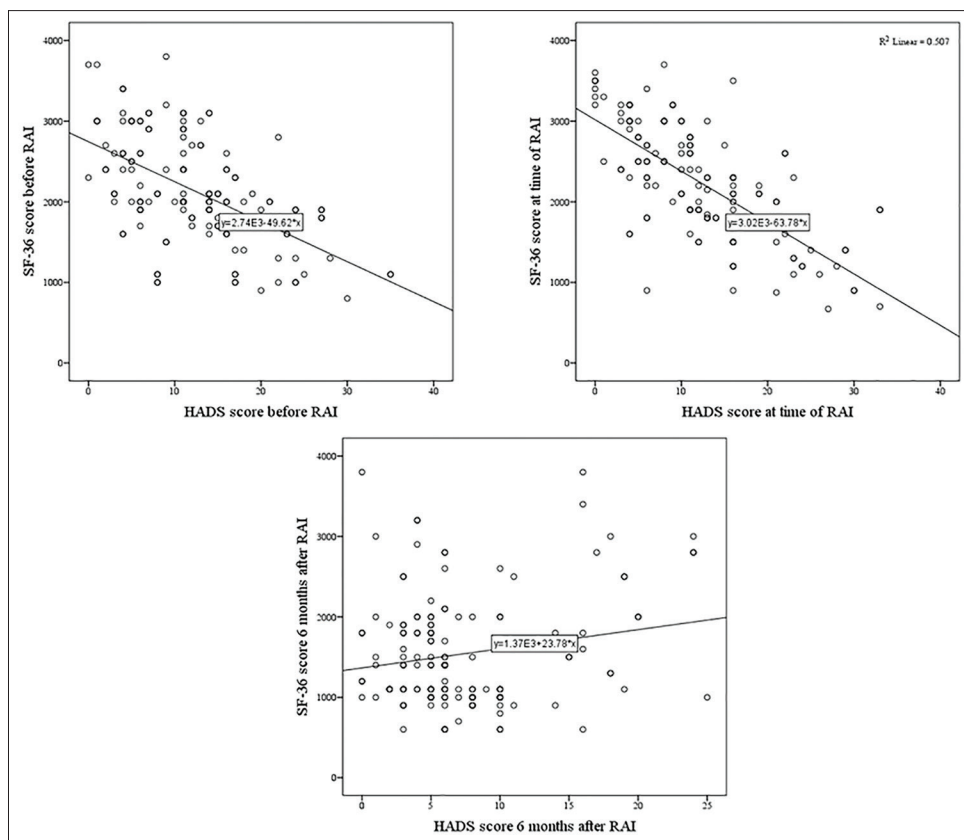


Figure 3: Scatter plots of Hospital Anxiety and Depression Scale and Short-Form (36) Health Survey scores at three time points

at the time of RAI treatment. It seems that the main culprit factor for such deterioration of QoL is hypothyroidism induced by thyroxine withdrawal. This is in accordance with the results of previous studies. However, at 6 months later, the SF-36 scores decreased to a much lower values indicating an improvement in QoL. In a study,^[12] QoL was assessed in different subscales using SF-36 questionnaire and finally showed a decrease in QoL against the control group. The highest change in the QoL was spotted at peak thyroxine withdrawal in another study.^[13] Similar findings were observed in another study, and the results were attributed to distress from thyroxine withdrawal.^[14] We did not find any association between the level of TSH and the QoL. However, this association was also contradictory in other studies.

The mean values of HADS scores were similar 1 month before and at the time of RAI. However, the scores decreased to lower values at 1 week after RAI and predominantly 6 months later. This pattern of gradual decrease, as presented in Figure 2, indicates the promotion of psychological status or diminution of depression and anxiety; the same results were found by Haraj *et al.*^[15] who compared the patients with DTC against control cohorts. In another investigation, in which psychological and behavioral interventions were implemented, an improvement in the QoL and mental health status was observed in patient cohorts who were receiving those

services versus the groups who received only conventional nursing care.^[6]

A significant agreement was found between the pattern of decrease in anxiety and depression (measured by HADS questionnaire) and QoL (measured by SF-36 questionnaire) as is evident in Figure 1. It can be hypothesized that similar factors may be involved in and underlie the changes in anxiety and depression and also QoL. Moreover, an improvement exists over a 6-month period. Unfortunately, this favorable improvement has not been found in other indices, including fatigue and role functioning over longer follow-ups. Olga *et al.* conducted a population-based survey to investigate the fatigue in thyroid cancer survivors. They showed a higher level of fatigue in both short- and long-term survivors.^[16] We did not assess the fatigue in our study, however, we found an impaired QoL only in a shorter period time before RAI and shortly thereafter.

The number of patients with DTCs (follicular and Hurtle cell) was so insufficient compared to papillary cancer. Therefore, the comparison between HADS and SF-36 scores in patients with different pathological types of cancer was not accomplished. On the effect of RAI dose (3700 or 5550 MBq) on the anxiety and depression and QoL, we did not find any association. However, another study showed that the cohort of patients who received higher

RAI doses (higher than 5550 MBq) tended to achieve unfavorable results.^[17]

Conclusion

Lowest values of HADS and SF-36 scores were recorded at 6 months after RAI as compared to those at time of RAI. The latter may be consequences of levothyroxine withdrawal and side effects of RAI. Trend in scores over several-months' time discloses gradual improvement of QoL and merits close observation but limited psychiatric intervention.

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Conflicts of interest

There are no conflicts of interest.

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