

Which complaint has the most clinical effect on quality of life of thyroid cancer survivors in long term follow up?

Seyed Rasoul Zakavi¹, Samira Zare Namdar¹, Sousan Shafiei¹, Ramin Sadeghi¹,
Nazanin Fekri¹, Zahra Mazloum Khorasani², Hamideh Sadra¹, Narjess Ayati¹

¹ Nuclear Medicine Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran ² Endocrine Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Introduction: Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. This malignancy generally has an excellent prognosis with more than 90% long term survival. Consequently, life quality improvement is the first priority especially in the young DTC survivors. In classic management of a new DTC patient, each therapeutic modality can significantly induce morbidities. In the current study, we investigated the main complaints in DTC patients during the follow up.

Methods: Clinical symptoms of 300 randomly selected DTC patients were collected during their follow up visiting sessions. Related symptoms were any clinical complaint directly due to DTC or its management. The correlation between the most common complaint and age, gender, TNM staging, RAI therapy, external beam radiotherapy and neck surgery was assessed.

Results: Three hundred randomly selected DTC patients (66 male and 234 female) were included. The mean duration of follow up was 5.18±3.48. External radiotherapy of the neck, frequency of radioiodine therapy and repetitive neck operations were associated with more clinical symptoms during long term follow up. The most frequent DTC related complaint was neck discomfort which was reported in 40% of patients. The main background source of patients' complaints was hypothyroidism followed by subclinical hyperthyroidism ($p<0.01$).

Conclusion: The most common reasons of long term morbidity in DTC patients were related to hypothyroid or subclinical hyperthyroidism. Neck discomfort was the most frequent single complaint with more frequency in patients with repetitive neck operation. The current study could be the first step to discover the unfavorable clinical symptoms of DTC patients.

Key words: Thyroid cancer; Complaints; Quality of life; Clinical symptoms; Complication

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Corresponding author: Dr. Narjess Ayati, Nuclear Medicine Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: ayatin@mums.ac.ir

INTRODUCTION

Thyroid cancer is the most prevalent type of endocrine malignancies showing significant rise in prevalence in the last decades [1]. Papillary and follicular thyroid carcinomas (PTC & FTC) are the most frequent histological subtypes of differentiated thyroid cancer [2-4]. Despite the dramatic rise in the prevalence of DTC in the last 40 years, the prognosis of DTC showed remarkable improvement and the cancer specific death had a decreasing trend [5]. However, this long term survival has led to an increase in cancer-related morbidity. Actually quality of life (QOL) of DTC patients can be impaired substantially due to complications of various treatment modalities and diagnostic tests [6].

Prevalence of DTC in the young and middle aged population, excellent prognosis resulting in long term survival and follow up as well as various therapeutic modalities underscore the importance of more attention to QOL in the DTC survivors.

Although the complications of thyroid surgery, radioiodine therapy and external beam radiotherapy are well-described in the literature, their relative frequency and possible effects on the QOL are not well defined. In developing countries, most of the patients could not afford rhTSH and patients usually have to repetitively face induced severe hypothyroidism because of routine diagnostic and therapeutic procedures. Also a large number of patients with DTC have to be on THS suppression for many years. Both Hypothyroidism and subclinical hyperthyroidism in DTC patient result in dramatic impairment of QOL [7, 8].

In the current study, we identified the most frequent complaints and the most unfavorable clinical symptoms during the long term follow up of DTC patients at our research center.

METHODS

Three hundred randomly selected outpatient DTC patients (out of 2921 DTC files) who had medical records in our department and were regularly followed were included in this study. All patients had

undergone thyroidectomy and radioiodine therapy as the classic protocol of DTC management [9]. In a small number of patients external beam radiotherapy had been performed too. All medical files had complete epidemiologic data as well as pre and post operation information as well as stage of the disease according to the TNM classification. In all visiting sessions the patient's status including appointment date, consumption of drugs, patient's complaints and clinical symptoms, paraclinic results, and findings on physical examination were recorded. The medical records were assessed by two nuclear medicine physicians. The symptoms were divided into "related" and "unrelated" to thyroid cancer subgroups. Related symptoms were defined as clinical complaints due to DTC itself or its management complications (Table 1).

In the next step the complaints which were related to serum thyroid hormones and calcium levels were categorized into three new groups of "hypo and hyper-thyroid and hypoparathyroid related symptoms" (Table 1).

The relationship of the symptoms with the patients' variables (age, gender, pathology (TNM staging), surgery (extension and number of neck operations), RAI therapy and external radiotherapy) was assessed using Mann-Whitney U and Kruskal-Wallis tests. Quantitative variables were expressed as mean±SD. All statistical analyses were performed by SPSS version 11.5.

RESULTS

This retrospective study included 300 randomly selected DTC patients (22% male and 78% female) with the age range of 10 to 87 years at the time of diagnosis (38.8±15.3).

191 patients (63.7%) were at TNM stage 1 of thyroid cancer at the time of diagnosis. Stage 2, 3 and 4 were noted in 9.7%, 9.7% and 14.7% of patients respectively. 27 patients (9.5%) had evidence of distant metastasis in the first 6 month of post thyroidectomy diagnostic work up.

Table 1: Categorization of different complaints related to serum thyroid hormone and calcium levels in to more general categories after TSH and calcium level matching.

Different reported symptoms	New categorization
Palpitation, tremor, sweating, flushing, nervousness, weight loss, hair loss, anxiety, menstrual problems, headache, dyspnea	Hyperthyroid related symptoms
Edema and puffiness, dry skin, generalized bone pain, constipation, fatigue and weakness, headache, depression, sleep problems, lack of concentration, voice dysfunction, generalized bone pain	Hypothyroidism related symptoms
Paresthesia, numbness, carpopedal spasm, seizure, generalized bone pain	Hypoparathyroidism related symptoms

Forty three patients (14.3%) underwent external beam radiotherapy of the neck region as a part of thyroid cancer management during their follow up.

The patients were followed for 1 to 17 years with the mean follow up duration of 5.18 years. They had 2 to 50 recorded visiting sessions during their follow up (15.97 ± 9.19). The mean number of appointment sessions per year was 3.47 ± 1.46 .

Overall, 36 different complaints were recorded among the patients. 26 patients (8.7%) did not have any clinical complaints during follow up while the rest showed 1 to 10 different complaints (median=3) with variable frequencies during their visits. The diversity of complaints was not related to patient's age ($p=0.34$). Female patients showed more symptoms during follow up ($p=0.004$). Presence of regional lymph node involvement or distant metastasis at the time of diagnosis was not related to complaints diversity during long time follow up

($p=0.93, 0.65$ respectively). Also cancer stage and tumor size at the time of diagnosis did not show any statistically meaningful relation with symptoms ($P > 0.86$). Neck radiotherapy, frequency of radioiodine therapy and repetitive neck operations were related to more clinical symptoms during long term follow up. ($p=0.037, 0.021$ & 0.020 respectively). 4.3 % of the total complaints were most probably not related to DTC consequences.

The most frequent DTC-related complaint was neck discomfort. 40% of patients had reported this symptom at least once during their follow up. The next most common symptoms were paresthesia and numbness, tremor and palpitation and emotional disturbance, nervousness and sleep problems respectively. Figure 1 showed the most frequent complaints related to DTC consequences in descending order.

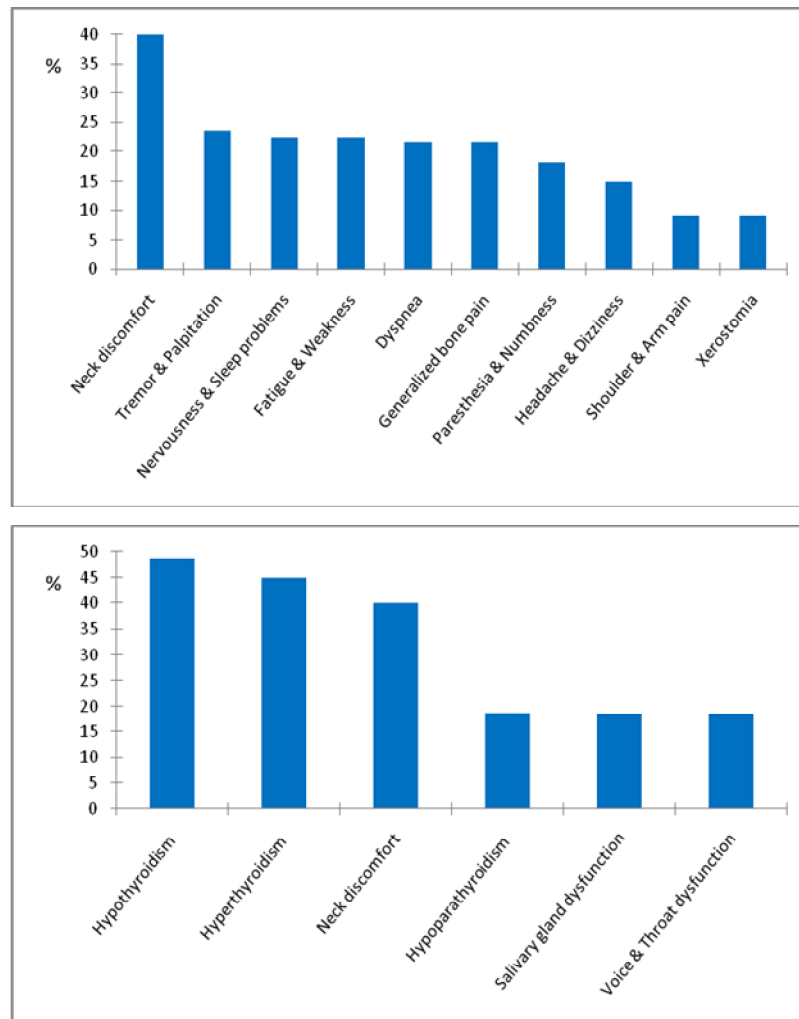


Fig 1. The most frequent complaints related to DTC consequences in descending order (above) and the main sources of related morbidities in DTC patients in descending order (below).

The clinical symptoms were categorized into more general categories based on the possible etiology. (Table 1) Post categorization analysis showed that the main clinical complaints of DTC patients were hypothyroidism related symptoms, hyperthyroidism related symptoms, neck discomfort, hypoparathyroidism related symptoms, salivary gland related problems and voice and throat dysfunction which were reported by 48.6, 45, 39.6, 18.7, 18.6 and 18.6% of patients respectively.

Presence of hyperthyroidism related symptoms was related to patients' TSH level at the time of complain ($p < 0.01$). This finding was also true for hypothyroidism related symptoms ($p < 0.01$).

Age ($p = 0.53$), gender ($p = 0.36$), tumor size ($p = 0.61$), regional lymph node involvement ($p = 0.94$) and neck radiotherapy did not show any relation to neck discomfort. The patients with more than one operation on the neck region were more susceptible to neck discomfort during follow up ($p = 0.02$).

DISCUSSION

Defining the most common clinical symptoms and improving the QOL of life of DTC patients attracts a considerable attention during last decade. Although there are a few studies indicating that the QOL impairment in DTC patients is independent of TSH level [10], the current study showed that the most common source of long term morbidity in DTC patients are hypo- and hyper- thyroid related symptoms. After thyroidectomy, the DTC patients need strong TSH stimulus for diagnostic and therapeutic aims repetitively. If TSH stimulation is achieved by thyroid hormone withdrawal (THW), it can result in many physical and emotional symptoms [11]. In addition, the current trend in thyroid cancer management is intentional suppressive therapy by exogenous thyroid hormone to obtain a $TSH < 0.1$. [8, 12] These two thyroid hormone instability situations make hormone related complications very frequent in DTC patients. Fatigue, weakness, nervousness, sleep problems and emotional susceptibility are some QOL interfering issues that showed strong relevance with TSH level [13]. Anxiety and depressive symptoms have been reported in both conditions with a dramatic effect on patient's QOL [14]. A cross-sectional study in 400 disease-free DTC survivors reported a significant decrease in the QOL mainly because of psychological symptoms including anxiety, depression and fatigue [15]. However another study reported similar mental and physical QOL among DTC patients compared to the healthy Swedish population [16]. Among our patients these symptoms were in the top of the list of patients' complaints. Fatigue and weakness were more common during T4-WD while sleep problems and nervousness were

more commonly reported in patients with subclinical hyperthyroidism during suppressive therapy. Although some studies reported that recombinant human thyrotropin (rhTSH) unlike T4-WD is able to preserve QOL with comparable success rate [17, 18], (rhTSH) as an alternative solution for TSH stimulation is not completely safe [19-22]. Close monitoring of the patients and TSH level could prevent from unnecessary suppressive therapy and probably could decrease hyperthyroid related symptoms.

Neck discomfort including chronic pain, hypersensitivity, numbness and any other chronic non specific symptom in the neck region were the most frequent single complaint among our patients. 40% of our cases experienced one of the above-mentioned discomforts during their follow up. Our data showed that these complaints were independent of gender, age, tumor size, regional lymph node involvement and neck radiotherapy. However patients with more than one operation in the neck region were more susceptible to experience neck discomfort during their follow up. Evaluation of regional lymph nodes before total thyroidectomy could obviate more operations in many patients. Two other complaints are in close association with neck discomfort: voice changes and throat dysfunction. Although the voice changes improves significantly late after operation in many DTC patients [23], it can persist in 14% of patients [24]. Not only laryngeal nerve injury can be responsible for this complaint, the evidence showed that it can occur in the absence of nerve damage as a result of extensive or repetitive neck operations, inexperience of the surgeon or possibly radioiodine therapy and external beam radiotherapy. However, some researchers found no correlation between RIT and voice changes [25]. Due to strong effect of dysphonia on the QOL, voice rehabilitation should be considered in DTC follow up protocol [24].

Hypocalcemia is one of the most common and potentially life-threatening complications in thyroid gland surgery [26]. Although Permanent hypoparathyroidism is rare post thyroid operation, extensive surgery in patients with thyroid malignancy can result in more frequent occurrence of this complication. While the permanent hypoparathyroidism has been reported in 1-4 % of DTC patients [27], our data showed hypoparathyroidism related symptoms in 18.7% of the patients. This considerable discordance is more probably because of our long follow up duration period which consists of both permanent and transient hypocalcemia. The other reason for higher prevalence of hypocalcemia among our cases is in relation to the nature of background pathology for thyroidectomy. The most common reasons of post thyroidectomy hypoparathyroidism are the extent of resection and surgical technique [28, 29]. Our cases

because of their malignant nature of background etiology, needed more extensive surgery (total or near total thyroidectomy) with more chance of parathyroid glands damage.

The current study showed that the frequency of radioiodine therapy was directly related to the number of clinical symptoms during long term follow ups ($p=0.021$). These findings are consistent with previous studies which reported more morbidity in patients who received more than 150 mCi of radioactive iodine therapy [30].

The recorded complaints are based on patients' reports and it is susceptible to bias including patients' tolerance threshold. The other limitation of our study was this fact that each complaint was recorded once in each patient even if the patient reported that symptom several times. If the frequency of each complaint was also calculated in every patient, the influence of that symptom on QOL could potentially be better assessed. Also, some clinical symptoms could have more than one etiology.

CONCLUSION

Our study showed that a significant number of patients with DTC suffer from a variety of symptoms during the follow ups. Preventing over suppression or limiting frequent hypothyroid cycles could be helpful in improving QOL of the patients. Low risk patients may be identified and selected for a less invasive treatment to avoid unnecessary morbidity.

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